

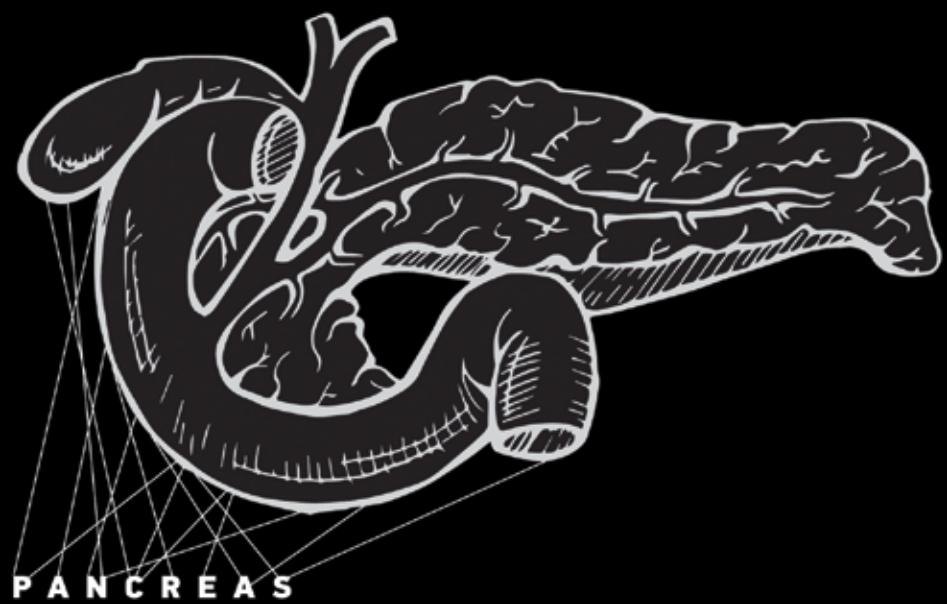


Academic Forensic Pathology

The Official Publication of the National Association of Medical Examiners

Christopher Milroy MD LLB LLM FRCPC EDITOR-IN-CHIEF

Nicholas I. Batalis MD ASSOCIATE EDITOR-IN-CHIEF



HEPATOBILIARY

Volume Eight • Issue Two • June 2018



**Neuropathology specimens photograph
just as nicely as this dragon fruit.**

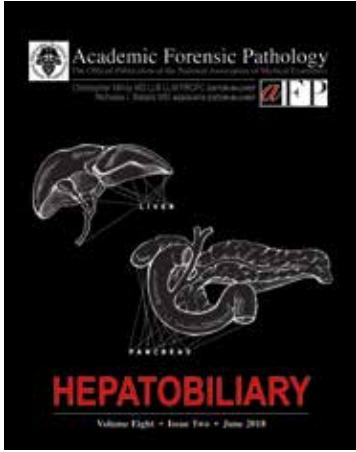
We just don't advertise with them.

Expert dissections and consultations in neuropathology, cardiovascular pathology, forensic gynecologic pathology, and bone pathology.

- Guaranteed 21 calendar day turnaround time
- All reports are peer reviewed
- All-inclusive, predictable pricing
- SUID/SIDS brains and hearts are always FREE
- Free custom secure shipping containers
- Professional photography
- CLIA-accredited histology, including special stains
- CAP-accredited immunostains, including APP
- Ultra secure laboratory
- NIST-level data protection

www.naagpathology.com • 1-800-985-5346 ext. 3 • consults@naagpathology.com

NAAG Pathology Labs PC • A California Professional Medical Corporation



On the Cover

Adapted from "Human organ anatomy set. Hand drawing illustration for a textbook on medicine. Heart, kidney, lung, stomach, intestines, brain, liver, pancreas." Used under license from www.shutterstock.com.

On the Scholarly Content Cover Page

"Liver, fatty, not yet cirrhosis - sirius ." Original image provided by Dr. Christopher Milroy.

Editor-In-Chief Christopher Milroy MD LLB LLM FRCPath FRCPC DMJ

Associate Editor-In-Chief Nicholas I. Batalis MD

Special Guest Editor Laura D. Knight MD

Publisher Emma O. Lew MD

Executive Director Evan W. Matshes MD FRCPC

Director of Operations Don Downey BA PMT

Editorial Director Lori Selanders BSc MSc

IT Consultant Tom Moore

Research Associate Casey P. Bitting DO

Medical Illustrator Diana Kryski

Web Support Roundbrix

Executive Offices

6540 Lusk Blvd, Suite C260
San Diego, CA
92121
1-888-909-7856
[email admin@academicfp.com](mailto:email.admin@academicfp.com)

www.academicfp.com

www.afpjurnal.com

<https://store.academicfp.com>

Editorial Board Members

Russell T. Alexander MD, Assistant Medical Examiner, Office of the Chief Medical Examiner, State of Maryland, Baltimore, MD, USA

Sam W. Andrews MD, Deputy Medical Examiner, Travis County Medical Examiner's Office, Austin, TX, USA

Jonathan L. Arden MD, President, Arden Forensics, PC, McLean, VA, USA

Philip S.L. Beh MBBS DMJ FHKAM(Pathology) FHKCPath FFPLM, Associate Professor (Forensic Pathology), Department of Pathology Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China (SAR)

Ryan Blumenthal MD PhD, Forensic Pathologist, Department of Forensic Medicine, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa

Andreas Büttner MD, Professor, Director, Institute of Forensic Pathology/Legal Medicine, University Medical Center, Rostock, Germany

Jim Caruso MD, Chief Medical Examiner, Denver Office of the Medical Examiner, Denver, CO, USA

Kim A. Collins MD FCAP, Forensic Pathologist, Newberry Pathology Associates, Newberry, SC, USA

David Fowler MBChB MMed Path (Forens), Chief Medical Examiner, Office of the Chief Medical Examiner, State of Maryland, Baltimore, MD, USA

James Gill MD, Chief Medical Examiner, Office of the Chief Medical Examiner, Farmington, CT, USA

Thomas P. Gilson MD, Medical Examiner, Cuyahoga County Medical Examiner's Office, Cleveland, OH, USA

Leslie E. Hamilton MD, Neuropathologist/Autopsy Pathologist and Neuropathology Residency Program Director, Calgary Laboratory Services and University of Calgary, Calgary, AB, Canada

Jennifer Hammers DO, Deputy Chief Medical Examiner, Brooklyn Campus, Office of the Chief Medical Examiner, New York, NY, USA

Walter Kemp MD PhD, Associate Professor, University of North Dakota School of Medicine and Health Sciences, Grand Forks, ND, USA

Laura D. Knight MD, Chief Medical Examiner, Washoe County Regional Medical Examiner's Office; and Associate Professor, Departments of Pathology and Pediatrics, University of Nevada-Reno School of Medicine, Reno, NV, USA

Kelly C. Lear MD, Coroner/Forensic Pathologist, Arapahoe County Coroner's Office, Centennial, CO, USA

Dianne Little MBBS FRCPA, Forensic Pathologist, Gold Coast University Hospital, Queensland Health Forensic and Scientific Services, Southport, Queensland, Australia

Owen Middleton MD, Assistant Chief Medical Examiner, Hennepin County Medical Examiner's Office, Minneapolis, MN, USA

Melissa A. Pasquale MD, Deputy Chief Medical Examiner, Brooklyn Campus, Office of the Chief Medical Examiner, New York, NY, USA

Kathy Pinneri MD, Director, Montgomery County Forensic Services, Conroe, TX, USA

Reade Quinton, Deputy Chief Medical Examiner, Southwestern Institute of Forensic Sciences, Dallas, TX, USA

Robert Stoppacher MD, Chief Medical Examiner, Onondaga County Medical Examiner's Office, Syracuse, NY, USA

Alfredo E. Walker MB BS FRCPath DMJ (Path) MFPLM MCSFS Dip Teach Train, Forensic Pathologist, Ontario Forensic Pathology Service, Ottawa, ON, Canada



TABLE OF CONTENTS

aFP

ACADEMIC FORENSIC PATHOLOGY:

The Official Publication of the National Association of Medical Examiners

June 2018 • Volume Eight • Issue Two • Hepatobiliary

EDITORIALS

Letter from the Editor-In-Chief	vi
Christopher M. Milroy	
Letter from the NAME President	viii
Kim A. Collins	
Letter from the Guest Editor.....	x
Laura D. Knight	

BIOGRAPHIES

Biography for the Editor-In-Chief.....	xii
Biography for the Associate Editor-In-Chief.....	xiii
Biographies for the Editorial Board.....	xiv

INVITED REVIEWS

The Forensic Pathology of Liver Trauma	184
Christopher B. Rogers, Ronald Devera	
The Adult Pancreas in Trauma and Disease	192
Alfredo E. Walker	
The Pancreas in Child Abuse	219
Katherine Callahan, Laura D. Knight	
Sudden Death Due to Acute Pancreatitis	239
Robert Stoppacher	
Differential Diagnosis of Hepatic Necrosis Encountered at Autopsy.....	256
Daniel C. Butler, David N. Lewin, Nicholas I. Batalis	
Fatty Liver and the Forensic Pathologist.....	296
Christopher M. Milroy	
Postmortem Serum Amylase and Lipase Analysis in the Diagnosis of Acute Pancreatitis	311
Theodore T. Brown, Joseph A. Prahlow	
The Utility of Bile in Postmortem Forensic Toxicology	324
Jolene Bierly, Laura M. Labay	



TABLE OF CONTENTS

AFP

REVIEW ARTICLES

- Autopsy Biosafety: Recommendations for Prevention of Meningococcal Disease328**

Erin G. Brooks, Suzanne R. Utley-Bobak, National Association of Medical Examiners Ad Hoc Committee for Bioterrorism and Infectious Disease

ORIGINAL ARTICLES

- Fatal Mitragynine-Associated Toxicity in Canada: A Case Report and Review of the Literature340**

Carol Wang, Alfredo E. Walker

METHODS AND PROCEDURES

- Improving Forensic Pathologic Investigation of Sudden Death in the Young: Tools, Guidance, and Methods of Cardiovascular Dissection from the Sudden Death in the Young Case Registry347**

Sam P. Gulino, Kristin Burns, Wendy M. Gunther, Heather MacLeod

CASE OF THE MONTH

- A Case Series of Anterograde and Retrograde Vascular Projectile Embolization392**

Jennifer Chao, Jeffrey Barnard, Joyce L. deJong, Joseph A. Prahlow

- A Case of Severe Cardiac Sarcoidosis with Minimal Pulmonary Involvement: A Case Report with Literature Review.....407**

Mark R. Fowler, Nobby C. Mambo

IMAGES IN FORENSIC PATHOLOGY

- Coronary Artery Aneurysms and Thrombosis in Kawasaki Disease416**

Linda J. Szymanski, Julie Huss-Bawab, James K. Ribe



TABLE OF CONTENTS

AFP

COPYRIGHT NOTICE

This publication and its content is copyright of Academic Forensic Pathology International ©2018. All rights reserved.

Subscribers may download and print-off Journal articles for their own personal use. Subscribers may distribute articles for scholarly purposes only. Subscribers may not receive payment in exchange for reproducing an article published in the Academic Forensic Pathology journal. As per the AFPI Author Rights (see below), although an author assigns AFPI copyright of their manuscript, they retain the right to use, teach with, and in a limited fashion distribute their manuscript for scholarly purposes. However, any individual, group, institution or corporation who does not have authorship over an AFP Journal article, but intends to distribute that article in any fashion (including distribution at meetings, educational sessions, etc.), must obtain an offprint license from AFPI directly or risk copyright violations. Inquiries should be directed to the Publisher.

Authors retain the following rights:

1. The right to make print or electronic copies of the article for their own personal use. Personal uses extend to the classroom where an author is granted the right to distribute print or electronic copies to students.
2. The right to distribute print or electronic copies of the article to colleagues, strictly for scholarly use. This expressly excludes commercial uses including fee-for-service consultations. The author may not receive any form of payment in exchange for provision of a print or electronic copy of the article.
3. The right to present the substance of the article at scientific meetings and to distribute a copy of that article to meeting attendees.
4. The right to provide a copy of the article to the author's employer or home institution.
5. The right to prepare derivative works from the article, including books, so long as full acknowledgement of the original publication is provided.

DISCLAIMER

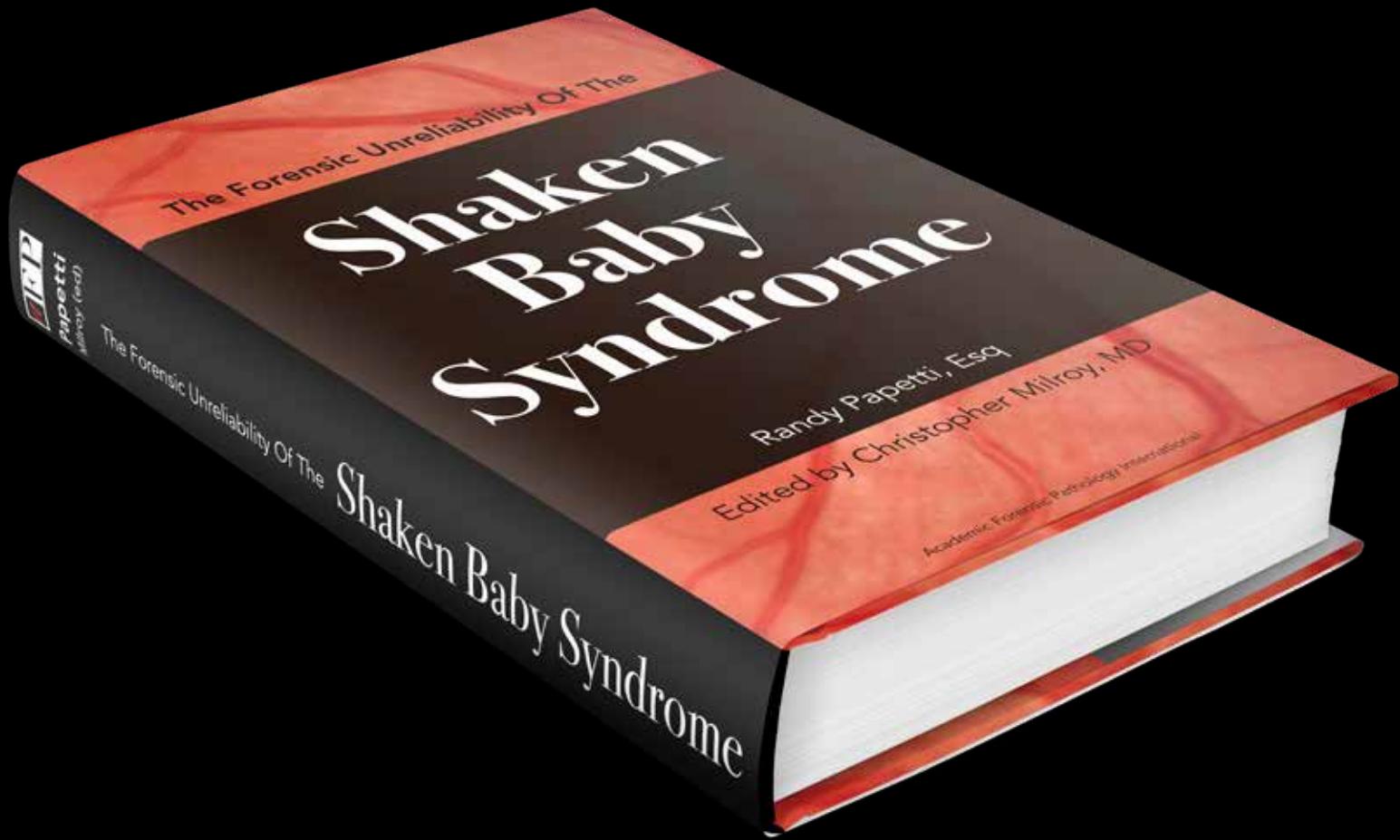
The Publisher (Academic Forensic Pathology International), The Editor-In-Chief (Dr. Christopher Milroy) and the sponsoring society (National Association of Medical Examiners) are committed to the publication of high quality, timely and relevant scholarly forensic pathology materials, and take every effort to ensure that the information presented within the Journal are precise and accurate. However, errors can occur and readers must carefully evaluate the literature and decide how to best integrate it into their own practice. Please report any errors directly to the Publisher (publisher@academicfp.com) or the Editor-In-Chief (editor@academicfp.com). The Publisher shall not be liable or responsible for any direct or indirect losses or damages of any kind whatsoever, whether based in contract, tort, strict liability, or otherwise, arising out of or in any way connected with: your use of or inability to use this website; the provision of or failure to provide services; any information, products, services, software or graphics obtained through this site. The Editor-In-Chief and the Publisher do not assume any responsibility for any injury and/or damage to persons or property related to any use of the content contained herein. Publication of an advertisement or other product mention in Academic Forensic Pathology: The Official Publication of the National Association of Medical Examiners is not an endorsement of either the product or the manufacturer's claims and should not be construed as such.

The Forensic Unreliability Of The Shaken Baby Syndrome

SHIPPING NOW

USD \$150

www.sbsbook.com



Randy Papetti Esq • ISBN: 978-0-9989043-0-6 • 340 pages

Release: March 10, 2018 • Retail price \$150 USD

Free shipping within North America

www.sbsbook.com

Letter From the Editor-In-Chief



Christopher M. Milroy MBChB MD LLB BA LLM FRCPath FFFLM FRCPC DMJ
Editor-In-Chief

Academic Forensic Pathology was founded in 2011 with Dr. Keith Pinckard as its first Editor-In-Chief. Since its inception, it has been the Official Journal of the National Association of Medical Examiners. Throughout the last eight years, Dr. Pinckard has guided the Journal through from its birth to maturity. In this period, four issues have been published each year with hundreds of articles written, both reviews and new papers, with many papers written by people new to publishing. The Journal has proven a great success and it is a singular honor to take over from Keith as the Interim Editor-In-Chief. Keith moves on to become Editor Emeritus. The Associate Editor and edi-

torial board remain the same. This will be the second issue published under the association with Sage Journals. The concept of the Journal remains the same, and themed issues will continue to be published. With Sage Journals, the reach of the Journal is expanding.

In this issue, the liver and pancreatico-duodenal system is the focus of the papers published. This is an anatomical area that involves many diseases, toxins, and trauma that the forensic pathologist has to interpret and, as usual with papers in *Academic Forensic Pathology*, there is much practical information. As ever, not all papers are invited reviews and once more I in-



vite all authors to consider submitting their work for publication in the Journal, whether reviews, images in forensic pathology, or new research. Forensic pathology remains a vibrant specialty with an academic

base. This Journal has a central role as the academic journal of death investigation and it is my intention to build on the work of Dr. Pinckard and keep this journal as the Journal for and by forensic pathologists.

Letter From the NAME President



Kim A. Collins MD FCAP
NAME President 2018

How many times have you heard someone ask, “What is forensic pathology?” Then when you begin to explain, they instantly draw upon a preconceived notion derived from televisions and movies. Yes, as forensic pathologists and medicolegal death investigators, we do attend death scenes, work on homicide cases, testify in court, and are involved in other activities within the crime and legal arena. But, there is so much more to the knowledge base of a forensic pathologist and the practice of forensic pathology. We are physicians, have extensive training, have patients, and perform medical procedures. Our patients may be a high profile murder victim, an abused child, or the victim of

a motor vehicle collision. However, the expertise of a forensic pathologist and medicolegal death investigator goes far beyond examining what many view as the “typical” or “routine” forensic case. Often, the most challenging patients we examine and autopsy are those who die from complications of a natural disease(s) or a natural disease that is a complication of trauma. Approaching these cases requires knowledge of all body systems, male and female, from the unborn fetus to the aged. Pathology draws upon all the basic sciences and branches of clinical medicine. Often called “The Doctor’s Doctor,” pathologists are an integral part of the patient care team; diagnosing,



treating, and preventing disease. The forensic pathologist takes all of this knowledge and experience and uses it to investigate injury and death, natural and unnatural, to certify the cause and manner of death, and use findings to improve public health and safety. This issue of *Academic Forensic Pathology* focuses on one of these body systems, the hepatobiliary system including the pancreas. Hepatic necrosis, pancreatitis, and fatty liver as well as the hepatobiliary system in cases of sudden death and child abuse are discussed.

Gross and microscopic findings with clinicopathologic correlation and ancillary studies such as chemistry and toxicology are presented. The topics are pertinent, and the respective authors proficient.

As you read through this issue, don't overlook the other sections such as methods and procedures, case of the month, and images in forensic pathology. This journal is unique and one of a kind for our specialty. Cover to cover, it cannot be beat!

Letter From the Guest Editor

A handwritten signature in black ink that reads "Laura D. Knight MD".

Laura D. Knight MD
Guest Editor

Key organ systems in forensic pathology that spring to mind most often in the differential diagnosis of likely cause of death prior to autopsy are 1) the heart, and 2) the brain, because of their frequent involvement in the pathophysiology of sudden deaths. Perhaps the lungs also, with their pulmonary thromboemboli, would be near the top of the list. The liver and pancreas, however, are the focus of this issue, and the hepatobiliary system is one rich in potential pathology, including lethal and other forensically-relevant pathology. Overlooking this organ system in any autopsy would be a grave error, and it is only fitting that it be the featured theme for an issue of *Academic Forensic Pathology*.

The particular pathologic entities in the hepatobiliary system most relevant to forensic pathology tend to be those related to trauma, including child abuse; hepatic necrosis; alcohol-related pathologies of the liver like cirrhosis, alcoholic hepatitis, and fatty liver; nonalcoholic fatty liver disease and metabolic syndrome/diabetes mellitus; and acute and chronic pancreatitis (whether related to alcohol or other disease processes). Four invited reviews in this issue address the pancreas. Dr. Alfredo Walker's exhaustive review of the adult pancreas in disease and trauma describes the myriad of pancreatic conditions that may be encountered during a forensic autopsy, along with his-



tory, pathophysiology, diagnostic features, and significance. Forensic pathologists will find the description and history of the finding of vacuolation of pancreatic acinar cells particularly interesting. Dr. Robert Stoppacher reviews acute pancreatitis and its relationship to sudden death addresses the diagnosis of acute pancreatitis, including hemorrhagic pancreatitis, and its differentiation from postmortem autolysis type changes, with diagnostic gross and histologic images. Dr. Katherine Callahan and I provide a critical evaluation of pancreatic injuries in children and an evidence-based look at which injuries are most specific for child abuse, with an illustrative case presentation. Finally, Dr. Theodore Brown and coauthor Dr. Joseph Prahlow discuss the utility of postmortem serum amylase and lipase testing in the diagnosis of pancreatitis.

Three articles focus on the liver, and injury and disease states highly relevant to forensic pathologists. Dr. Christopher Milroy reviews fatty liver disease, and tackles the question of whether “fatty liver” is a competent cause of death or has a direct role in sudden death. (Spoiler alert: Yes, fatty liver has been associated with sudden death; however, one should look closer for the exact mechanism and other related causes). Dr. Christopher Rogers presents a look at patterns of liver trauma, with a focus on appropriate documentation of injuries at autopsy in sufficient detail to provide the information needed by trauma surgery teams in their morbidity and mortality reviews and related scoring of the survivability of the patient’s cumulative

injuries. This is an important collaboration between forensic pathology and clinical medicine. A review on various patterns and causes of hepatic necrosis, with excellent gross and microscopic photos, by Dr. Daniel Butler and coauthors Dr. David Lewin and Dr. Nicholas Batalis rounds out the coverage of the liver.

Finally, Laura Labay PhD, of NMS Laboratories, reviews the usefulness of bile in toxicology analysis. Bile is not a routinely tested matrix, and this article is useful in pointing out the occasions that bile may come in handy in the realm of forensic toxicology.

Having a journal with content that is of high quality, relevant, and timely, specific to forensic pathology, is extremely valuable to our specialty. Each issue is crafted by the efforts of our colleagues, and any coordinated endeavor of this scale takes much time and effort from all involved. My sincere thanks go to the authors in this issue, who kindly agreed to take time away from work, family, and other valued activities to create the invited, themed content in this issue for the edification of their colleagues near and far. For me personally, this has been a richly rewarding intellectual endeavor, and a fantastic opportunity to work more closely with colleagues well-known to me, as well as some I have gotten to know better through this process.

May your autopsy suites be well-lit, appropriately supplied, and very adequately staffed.



**INTERIM EDITOR-IN-CHIEF
CHRISTOPHER M. MILROY**

Dr. Christopher Milroy is a forensic pathologist and is the Director of the Eastern Ontario Forensic Pathology Unit in Ottawa, Canada. He is a Full Professor at the University of Ottawa.

He qualified in medicine from the University of Liverpool, UK. After completing training in anatomical pathology at University College London, he trained in forensic pathology with a fellowship at the University of Sheffield, UK, and then became a Staff Pathologist in Sheffield in 1991. He was a Full Professor at the University of Sheffield.

In 2008, he moved to Ottawa, Canada. He is a Fellow of the UK Royal College of Pathologists and the Royal College of Physicians of Canada. He currently chairs the Royal College of Physicians of Canada committee of examiners in Forensic Pathology.

Dr. Milroy also holds law degrees (LLB, LLM) from the University of London. He currently serves on the Board of Directors of NAME and its executive committee. He has published over 100 articles and chapters on forensic pathology and has particular interests in the pathology of alcoholism, diabetes, drug misuse, and the history of forensic pathology.



**ASSOCIATE EDITOR-IN-CHIEF
NICHOLAS I. BATALIS**

Dr. Nicholas I. Batalis is a Professor in the Department of Pathology and Laboratory Medicine at the Medical University of South Carolina (MUSC) in Charleston, South Carolina.

Dr. Batalis received his Bachelor of Science degree from Butler University and his Doctor of Medicine degree from the Indiana University School of Medicine, then completed a residency in anatomic and clinical pathology at MUSC before attaining fellowship training in forensic pathology at the Southwestern Institute of Forensic Sciences/Dallas County Medical Examiner's Office in Dallas, Texas.

Upon completion of his training Dr. Batalis returned to MUSC where he has been on faculty since 2008 and is certified by the American Board of Pathology in anatomic, clinical, and forensic pathology. Dr. Batalis also serves as Director for the Pathology residency program and Forensic Pathology fellowship program at MUSC and has received several teaching awards from the medical school.

Dr. Batalis is an active member of several local and national pathology organizations including the American Academy of Forensic Sciences, the American Society for Clinical Pathology, the College of American Pathologists, and the National Association of Medical Examiners.

**ALEXANDER, RUSSELL**

Dr. Russell Alexander is a board-certified anatomic and forensic pathologist practicing as an Assistant Medical Examiner at the Office of the Chief Medical Examiner for the State of Maryland. He earned his bachelor's degree from Johns Hopkins University, a master's degree from the University of California, Santa Barbara, and his medical degree from Albert Einstein College of Medicine. He completed a residency in anatomic pathology at Duke University, and then a fellowship in forensic pathology at the Office of the Medical Investigator in Albuquerque. Dr. Alexander has been active on various committees for the National Association of Medical Examiners, and currently is chair of the research committee. He has received various teaching and research awards including most recently the Susan P. Baker Public Health Impact Award. Dr. Alexander's publications include the use of a geographic information system to analyze an epidemic of fentanyl deaths, toxicology, modeling of burn injuries, infant deaths, cardiovascular pathology, neuropathology, and the origin of faults on the seafloor near mid-ocean ridges.

**ANDREWS, SAM**

Dr. Sam Andrews is a board-certified anatomic and forensic pathologist practicing as a Deputy Medical Examiner at the Travis County Medical Examiner's Office in Austin, Texas. He completed his MD and anatomical pathology residency training at the University of Alberta, and his forensic fellowship training at the New Mexico Office of the Medical Investigator. His interests include quality improvement in forensic pathology and the use of advanced postmortem imaging.



**ARDEN, JONATHAN L.**

Dr. Jonathan Arden is a board-certified anatomic and forensic pathologist. He is currently President of Arden Forensics, PC, which provides consultation and expert witness services in forensic pathology and medicine. He also holds a part-time appointment as a forensic pathologist with the State of West Virginia. Dr. Arden received his MD degree from the University of Michigan. He completed training in anatomic pathology at the New York University Medical Center, and in forensic pathology at the Office of the Chief Medical Examiner for the State of Maryland. He is certified in both anatomic and forensic pathology by the American Board of Pathology. He has served as a medical examiner in Suffolk County, NY and the State of Delaware. He worked for the Office of Chief Medical Examiner for the City of New York where he finished his tenure as the First Deputy Chief Medical Examiner. He also served as the Chief Medical Examiner for the District of Columbia. Dr. Arden is an active member of the National Association of Medical Examiners. He currently serves as the Vice President of NAME, and is also a member of NAME's Board of Directors, and on the Board's Executive Committee. He also chairs NAME's By-Laws committee.

**BLUMENTHAL, RYAN**

Dr. Ryan Blumenthal is an Associate Professor at the University of Pretoria's Department of Forensic Medicine, South Africa. He graduated as a medical doctor from the University of Pretoria in 1998. He then started and completed a full-time five-year training program in forensic pathology at the University of Pretoria earning his master of medicine in forensic pathology in 2005. In the same year, he obtained his forensic pathology fellowship through the Colleges of Medicine of South Africa. In 2015, he obtained his PhD through the Department of Electrical and Information Engineering at the University of the Witwatersrand, in Johannesburg. His fields of interest include lightning and electrothermal injuries. He has been involved in the publication of numerous articles and textbooks on the forensic aspects of lightning and electro-thermal injuries. He is an international corresponding member of NAME and serves on NAME's International Relations Committee. He has a particular interest in international forensic capacity development.



**BÜTTNER, ANDREAS**

Dr. Andreas Büttner is a board-certified forensic pathologist and is the Director of the Institute of Legal Medicine / Forensic Pathology at the Rostock University Medical Center, Germany. He is a Full Professor at the University of Rostock. In addition, he is the Chairman of the Ethical Commission at the Medical Faculty. Before his medical study, he completed training as an autopsy technician in Berlin and Munich. He qualified in medicine at the University of Munich, Germany and completed his MD in neuropathology. After residency training in neurosurgery and neuropathology, he completed full-time training in forensic pathology and his professorial thesis at the Institute of Legal Medicine at the University of Munich. Subsequently, he moved to Rostock after appointment as Chair of Legal Medicine / Forensic Pathology. Dr. Büttner is an active member of several professional organizations and expert advisory boards including the German Society of Legal Medicine, German Society of Neuropathology and Neuroanatomy, and Euro-CNS. In addition, he serves on the editorial boards and as a reviewer of several national and international journals. He has published numerous scientific journal articles and textbook chapters on forensic pathology and neuropathology. His major interests includes forensic autopsy, histology and immunohistochemistry; forensic neuropathology, and alcohol and drug abuse.

**CARUSO, JAMES**

Dr. Jim Caruso is a board-certified anatomic, clinical, and forensic pathologist practicing as the Chief Medical Examiner for Denver, Colorado. Dr. Caruso received both his undergraduate and medical degrees from the University of Illinois, completed pathology training at Duke University Medical Center, and undertook forensic pathology fellowship training at the Office of the Chief Medical Examiner for Maryland and the Office of the Armed Forces Medical Examiner. He spent 12 years as an Armed Forces Medical Examiner, including tours as Chief Deputy Armed Forces Medical Examiner and Regional Armed Forces Medical Examiner for Asia and the Pacific. Dr. Caruso's forensic interests include water-related deaths, aviation mishaps, and combat-related ballistic and blast injuries. Dr. Caruso holds Navy Diving Medical Officer and Navy Flight Surgeon certifications and he also completed fellowship training in diving and hyperbaric medicine at Duke. He represents the College of American Pathologists (CAP) at the American Medical Association, he is a member of the CAP Toxicology Resource Committee, and has chaired of the Pathology/Biology Section of the American Academy of Forensic Sciences. He has numerous book chapters, scientific journal articles, and formal presentations to his credit.



**COLLINS, KIM A.**

Dr. Kim A. Collins serves as a forensic pathologist with Newberry Pathology Associates and is a Medical Director for Sharing Hope SC, the organ and tissue donation services for South Carolina. After receiving her BS in microbiology, magna cum laude Phi Beta Kappa, from the University of Georgia, Athens, Dr. Collins earned her MD from the Medical College of Georgia, Augusta. Following medical school, Dr. Collins completed an anatomic and clinical pathology residency at Wake Forest University/Bowman Gray School of Medicine. After residency, she completed a forensic fellowship at the Medical University of South Carolina where she remained on faculty as a Professor of Pathology and Laboratory Medicine, Director of Forensic and Autopsy Pathology, and Chief Medical Examiner. Dr. Collins is a Diplomat of the American Board of Pathology, board-certified in anatomic pathology, clinical pathology, and forensic pathology. She is a member of the College of American Pathologists and past Chair of the Autopsy Committee. She is past President of the South Carolina Society of Pathologists, and past Chair for the Pathology/Biology section of the American Academy of Forensic Sciences. She serves on the Board of Directors and is President of the National Association of Medical Examiners.

**FOWLER, DAVID**

Dr. David Fowler is a board-certified anatomic and forensic pathologist practicing as Chief Medical Examiner for the State of Maryland. He graduated from the University of Cape Town in 1983 and did a year of general medical and surgical internship, followed by a year of pediatric pathology at the Red Cross Children's Hospital in Cape Town. He then started and completed a five-year full-time training program in forensic pathology at the University of Cape Town earning his master of medicine in forensic pathology. Following this, he did additional training in the United States at the University of Maryland and the Office of the Chief Medical Examiner for the state of Maryland. Dr. Fowler is an Associate Professor at the University of Maryland in the departments of pediatrics and pathology, faculty at the National Study Center for Trauma and EMS, and is a visiting professor at both Tongji Medical School and Fudan University in the People's Republic of China. Dr. Fowler is active on multiple committees in the National Association of Medical Examiners and is a past president of that organization. He has numerous book chapters, scientific journal articles, and formal presentations to his credit.



**GILL, JAMES**

Dr. Gill is the Chief Medical Examiner of Connecticut and a Clinical Assistant Professor in the Department of Pathology at Yale. He is a graduate of MIT and the University of Connecticut School of Medicine. He did his pathology training at Yale and Memorial Sloan-Kettering Cancer Center and his forensic pathology fellowship at the New York City Office of Chief Medical Examiner. Prior to Connecticut, he was the Deputy Chief Medical Examiner for Bronx County in New York City. He is a member of several professional organizations including the National Association of Medical Examiners (Board of Directors), American Academy of Forensic Sciences, the College of American Pathologists (Forensic Pathology Resource Committee), the Organization of Scientific Area Committee's subcommittee on Medicolegal Death Investigation, and the forensic pathology test-writing committee for the American Board of Pathology. In addition to *Academic Forensic Pathology*, he serves on the editorial boards of the *Journal of Forensic Sciences* and *Forensic Science, Medicine, and Pathology*.

**GILSON, THOMAS**

Dr. Thomas Gilson is the Medical Examiner of the Cuyahoga County Medical Examiner's Office, the Executive Director of the Cuyahoga County Regional Forensic Laboratory and Clinical Associate Professor of Pathology at Case Western Reserve University School of Medicine. Dr. Gilson is certified by the American Board of Pathology in Anatomic, Clinical, and Forensic Pathology. He received his medical degree from the Medical College of Pennsylvania and performed his pathology residency at the University of Cincinnati Medical Center before completing a forensic pathology fellowship at the Office of Chief Medical Examiner for the City of New York. Prior to his current position in Cleveland, Dr. Gilson served as Chief Medical Examiner for Rhode Island and Deputy Chief Medical Examiner for the City of New York and the States of Connecticut and New Hampshire. He is a member of the National Association of Medical Examiners, American Academy of Forensic Sciences, and the College of American Pathologists (Histocompatibility and Identification Testing Committee). Dr. Gilson's research interests focus on the integration of forensic pathology with public health.



**HAMILTON, LESLIE**

Dr. Leslie Hamilton is a board-certified anatomic, neuro-, and forensic pathologist practicing as a neuropathologist and hospital autopsy pathologist at Calgary Laboratory Services/Foothills Medical Center in Calgary, Alberta. In addition, she is a Clinical Assistant Professor and Program Director for the Neuropathology Residency Training program at the University of Calgary. She is also the Director of Neuropathology for the National Autopsy Assay Group. Dr. Hamilton graduated from the University of Alberta and Queen's University prior to completing anatomic pathology and neuropathology residency training at the University of Calgary and is board-certified by the Royal College of Physicians and Surgeons of Canada and the American Board of Pathology in both anatomic and neuropathology. Subsequently she attained a forensic pathology fellowship at the New Mexico Office of the Medical Investigator in Albuquerque, New Mexico. Her interests include autopsy neuropathology, cardiac pathology, and sudden natural death in children and young adults.

**HAMMERS, JENNIFER L.**

Dr. Jennifer L. Hammers is a board-certified anatomic, clinical, and forensic pathologist. Following her forensic pathology and forensic cardiac pathology and neuropathology fellowship training at the New York City Office of Chief Medical Examiner, she worked as a Medical Examiner in Boston, Massachusetts before returning to New York City to serve as the Fellowship Program Director and then Deputy Chief Medical Examiner of the Brooklyn Campus. Dr. Hammers currently works at a private forensic pathology practice in Pittsburgh, Pennsylvania. Dr. Hammers has a particular interest in cardiac pathology and actively participates in research related to chronic traumatic encephalopathy.



**KEMP, WALTER L.**

Dr. Walter L. Kemp is a board-certified anatomic, clinical, and forensic pathologist, and is currently an Associate Professor of Pathology at the University of North Dakota School of Medicine and Health Sciences. He was born and raised in Libby, Montana, attended Carroll College in Helena, Montana for his BA in Biology and Creighton University School of Medicine in Omaha, Nebraska for his MD. He completed his residency training in anatomic and clinical pathology at the University of Texas Southwestern Medical Center (UTSW) in Dallas, Texas, and his fellowship training in forensic pathology at the Dallas County Medical Examiner's Office and UTSW. He was an Assistant Professor of Pathology for two years at UTSW prior to becoming the Deputy State Medical Examiner for Montana for ten years, during which time he earned his MA and PhD in Anthropology, both from the University of Montana in Missoula. During his career, he has taught a variety of groups including medical students, residents, coroners, law enforcement agencies, emergency medical technicians, medical and radiologic technologists, and junior high, high school, and college students. Other than teaching, his main interests are cardiovascular pathology and forensic anthropology.

**KNIGHT, LAURA**

Dr. Laura Knight is a board-certified anatomic, clinical, and forensic pathologist practicing as Chief Medical Examiner and Coroner at the Washoe County Regional Medical Examiner's Office in Reno, NV, which serves 19 counties in Northern Nevada and California. She holds dual appointments at the rank of Associate Professor in the departments of Pathology and Pediatrics at the University of Nevada Reno School of Medicine. Dr. Knight earned her medical degree from the University of Louisville School of Medicine, completed residency training in anatomic and clinical pathology at the Medical University of South Carolina, and completed fellowship training in forensic pathology at the New Mexico Office of the Medical Investigator. Dr. Knight is a member of the Board of Directors for the National Association of Medical Examiners, and is the current Chairperson of the NAME Self-Assessment Modules/Maintenance of Certification Subcommittee. Her professional interests include pediatric forensic pathology, sudden infant death, forensic toxicology, organ/tissue donation, and death certification, and she has published numerous scientific journal articles, textbook chapters, and educational modules.



**LEAR, KELLY**

Dr. Kelly Lear is a board-certified anatomic, clinical, and forensic pathologist serving as the elected Coroner for Arapahoe County, Colorado (serving portions of the Denver metropolitan suburbs and eastern plains), and is an assistant clinical professor with the Department of Pathology at the University of Colorado School of Medicine. She graduated with her Bachelor of Arts degree in biology, biochemistry, and molecular biology from Cornell College and received her Doctor of Medicine degree from University of Colorado School of Medicine. She completed her anatomic and clinical pathology residency and surgical pathology fellowship at the University of Colorado Hospital, and her forensic pathology fellowship at the New Mexico Office of the Medical Investigator. Dr. Lear's forensic interests include investigation of child deaths, prevention of prescription drug-related deaths, and management of mass fatalities. She is an active member of multiple professional organizations including the National Association of Medical Examiners, College of American Pathologists (CAP), American Academy of Forensic Sciences, Colorado Society of Clinical Pathologists, Colorado Coroners Association, and Colorado Homicide Investigators Association. She has previously been lead editor for the CAP Forensic Pathology Resource Committee case series, is a member of the Sudden Unexpected Death in Childhood Medical and Investigative Advisory Board and Research Collaborative, and sits on multiple local and regional boards and committees with an emphasis on child death prevention and mass fatality planning.

**LITTLE, DIANNE**

Dr. Dianne Little is a forensic pathologist practicing in the Gold Coast, Queensland, Australia. She received her medical degree from the University of Sydney, Australia and subsequently trained in pathology in Sydney, including at the Department of Forensic Medicine. She then worked in Vancouver, Canada as a fellow in forensic pathology, followed by time at the San Francisco Medical Examiners Office. She returned to Australia to work as a forensic pathologist in the Department of Forensic Pathology at Westmead in Sydney from 1989 to 2009, before relocating to Queensland in 2009. Dr. Little has been the Chief Examiner in Forensic Pathology for the Royal College of Pathologists of Australasia since 2014. She has been a member of various committees of the National Association of Medical Examiners (NAME) and is currently a member of the NAME Board of Directors. She also serves on the editorial board of the *Journal of Forensic Sciences*. Her professional interests include pediatric forensic pathology, cardiac pathology, occupational health and safety in the mortuary, and disaster victim identification.



**MIDDLETON, OWEN**

Dr. Owen Middleton is a board-certified anatomic, clinical, and forensic pathologist practicing as the Assistant Chief Medical Examiner for the Hennepin County Medical Examiner's Office in Minneapolis, Minnesota. He graduated from Vanderbilt University with a bachelor's degree in biology, and then obtained his medical degree from the University of Arkansas College of Medicine, where he also completed anatomic and clinical pathology residency training. His forensic pathology fellowship training was through the Jefferson County Coroner/Medical Examiner's Office in Birmingham, Alabama. Currently on the Board of Directors for the National Association of Medical Examiners, his service also includes participation on several committees and he is coauthor on multiple NAME position papers. He also serves on the editorial board for the *Journal of Forensic Sciences* and as a consultant for the Case Reports education series on forensic pathology for the American Society for Clinical Pathology.

**PASQUALE, MELISSA**

Dr. Melissa Pasquale is a board-certified forensic pathologist and Deputy Chief Medical Examiner in the Brooklyn office at the Office of Chief Medical Examiner of the City of New York. Originally from Michigan, she graduated from Wayne State University School of Medicine in Detroit, Michigan and completed an anatomic pathology residency at Jackson Memorial Hospital in Miami, FL. She did forensic pathology fellowships at the Miami-Dade County Medical Examiner Office and at the Wayne County Medical Examiner Office in Detroit, MI. She has also worked as a medical examiner in Detroit and Atlanta. She has presented at forensic conferences and published on topics including poisoning, death in custody, child abuse, and sudden infant death investigation.



**PINNERI, KATHRYN**

Dr. Kathryn Pinneri is a board-certified anatomic and forensic pathologist serving as Director of Forensic Services for Montgomery County, Texas. Prior to this, she worked for the Harris County Institute of Forensic Sciences as Assistant Deputy Chief Medical Examiner in Houston, Texas. She received her Doctor of Medicine degree from the University of Texas Southwestern Medical School in Dallas, completed an anatomic and clinical pathology residency at the University of Tennessee Medical Center in Knoxville, and completed a forensic pathology fellowship at the University of Texas Southwestern Medical School at Dallas. Dr. Pinneri is the Chief Medical Officer for the Region III Disaster Mortuary Operational Response Team (DMORT) and is an active member of multiple organizations, serving on the board of directors for the National Association of Medical Examiners (NAME) and past chair of the Pathology/Biology section of the American Academy of Forensic Sciences (AAFS). She is a member of multiple committees for NAME, AAFS, and the American Society of Clinical Pathologists (ASCP). Her interests include child abuse, blunt trauma, anthropology, death investigation, and mass fatality response/preparedness.

**QUINTON, READE A.**

Dr. Reade A. Quinton is a board-certified anatomic, clinical, and forensic pathologist practicing as Deputy Chief Medical Examiner of the Southwestern Institute of Forensic Sciences in Dallas, Texas. He obtained his MD from LSU Medical Center in New Orleans, Louisiana and completed his pathology residency training and forensic pathology fellowship at the University of Texas Southwestern Medical Center at Dallas, where he is currently an Associate Professor in the Department of Pathology. Dr. Quinton is responsible for the instruction of medical students, pathology residents, and forensic pathology fellows, and he is the director of the forensic pathology training program. His interests include sudden infant death investigation, child abuse, and fellowship training. Dr. Quinton is an active member of the National Association of Medical Examiners (NAME), the American Academy of Forensic Sciences, and the College of American Pathologists (CAP). He currently sits on the CAP Forensic Pathology Resource Committee, the NAME Forensic Pathology Training Subcommittee, and the Association of Pathology Chairs Fellowship Chairs Ad Hoc committee.



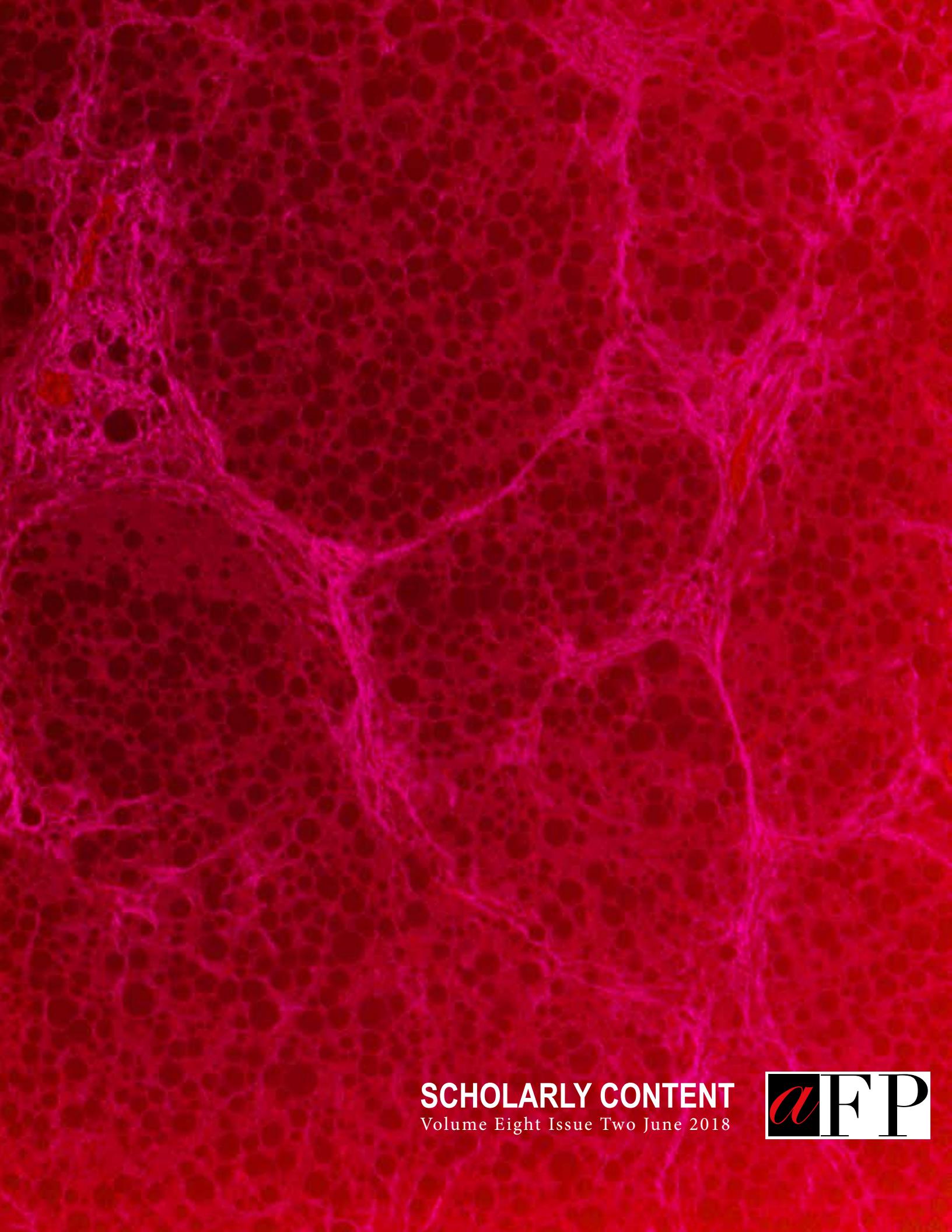
**STOPPACHER, ROBERT**

Dr. Stoppacher is board-certified in anatomic, clinical, and forensic pathology and is the Chief Medical Examiner at the Onondaga County Medical Examiner's Office in Syracuse, New York. He also holds the position of associate professor in the Upstate Medical University Hospital Department of Pathology where he serves as the director of autopsy services. In addition, he is a professor of forensic science at the Syracuse University Forensic and National Security Sciences Institute, where he also serves on the advisory board. Dr. Stoppacher received his undergraduate degree in biology from Union College, his graduate degree in physiology from Georgetown University, and his medical degree from the University of Vermont. He also trained in pathology at the University of Vermont prior to completing his forensic training at the Milwaukee County Medical Examiner's Office. Dr. Stoppacher is a member of the College of American Pathologists, the American Academy of Forensic Sciences, and the National Association of Medical Examiners, where he serves as the chairman of the Scientific Presentation Awards committee.

**WALKER, ALFREDO E.**

Dr. Alfredo E. Walker is a registered forensic pathologist of the Ontario Forensic Pathology Service (OFPS) based within its Eastern Ontario Forensic Pathology Unit at the General Campus of The Ottawa Hospital, Ottawa, Canada. He holds an academic appointment of Assistant Professor, University of Ottawa, within its Department of Pathology and Laboratory Medicine. He is also an appointed Visiting Lecturer in Forensic Pathology at the University of the West Indies, Mona campus, Jamaica. His medical degree was obtained from the School of Medicine, University of the West Indies, St. Augustine campus, Trinidad and Tobago. Prior to his current post, Dr. Walker was a consultant forensic pathologist with the UK government Forensic Science Service. He pursued postgraduate training in histopathology (anatomical pathology) and sub-specialty training forensic pathology in the United Kingdom and holds fellowship of the Royal College of Pathologists of the United Kingdom and the Diploma in Medical Jurisprudence (Pathology) from the Society of Apothecaries, London, UK. He is a member of the Faculty of Forensic and Legal Medicine (MFFLM) and the Chartered Society of Forensic Sciences of the United Kingdom. Internationally, Dr. Walker has presented at, developed, and organized international and regional conferences in forensic pathology, legal medicine and forensic science. He also spearheaded the formation of the Caribbean Association of Forensic Sciences and was the Founding President. His areas of interests are expert witness training, quality assurance, the use of computer-generated images for the courtroom, and forensic toxicology. He acts as an invited reviewer for academic journals of forensic pathology and science.





SCHOLARLY CONTENT
Volume Eight Issue Two June 2018





The Forensic Pathology of Liver Trauma

Christopher B. Rogers, Ronald Devera

ABSTRACT

The forensic pathologist is an integral part of the trauma surgery team. Trauma surgeons depend on autopsy descriptions for accurate measurement of the severity of trauma and determination of the chance of mortality. The outcome of liver injury improved greatly during the 20th century, primarily due to improved diagnostic and management techniques. In many trauma cases, survival depends on injuries to areas other than the liver.

Measurement of the severity of liver trauma often uses the TRISS (Trauma and Injury Severity Score) method, which depends on the nature, location, and size of injuries. Injuries produced by blunt trauma depend on the direction of the force and its interaction with the anatomic structures that surround the liver. Sharp force and gunshot injuries depend on the portions of the liver involved and the amount of kinetic energy transmitted to the tissue. The liver is susceptible to injury from resuscitation, although these injuries are usually not severe. *Acad Forensic Pathol.* 2018 8(2): 184-191

AUTHORS

Christopher B. Rogers MD MBA, Los Angeles County Coroner

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, principal investigator of the current study, general supervision.

Ronald Devera BS MS, Ross University School of Medicine

Roles: Data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work.

CORRESPONDENCE

Christopher B. Rogers MD MBA, 1104 N. Mission Rd., Los Angeles CA 90033, crogers@coroner.lacounty.gov

ETHICAL APPROVAL

As per Journal Policies, ethical approval was not required for this manuscript

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies conducted with animals or on living human subjects

STATEMENT OF INFORMED CONSENT

No identifiable personal data were presented in this manuscript

DISCLOSURES & DECLARATION OF CONFLICTS OF INTEREST

The authors, reviewers, editors, and publication staff do not report any relevant conflicts of interest

FINANCIAL DISCLOSURE

The authors have indicated that they do not have financial relationships to disclose that are relevant to this manuscript

KEYWORDS

Forensic pathology, Liver, Trauma

INFORMATION

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

©2018 Academic Forensic Pathology International • (ISSN: 1925-3621) • <https://doi.org/10.23907/2018.014>

Submitted for consideration on 27 Feb 2018. Accepted for publication on 22 Apr 2018



INTRODUCTION

The liver is the largest internal organ in the body, and the most commonly injured in abdominal trauma (1). With the increase in sophistication of the treatment of liver injuries has come an increase in the need for forensic pathologists to provide a detailed description of these injuries. Trauma surgeons can translate an autopsy description of liver injuries into a quantitative injury score, thus retrospectively determining how severely the decedent was injured. This information, in turn, provides an assessment of quality assurance of trauma care—if the injury score shows a high probability of survival, why did the decedent die?

Injury scoring depends on the degree of trauma to all parts of the body, as well as clinical factors such as blood pressure. However, the scope of this review is limited to autopsy assessment of injuries of the liver.

DISCUSSION

Trauma Scales

Injury scoring was developed over many years of trauma surgery (2). Although there have been many attempts to quantify the severity of trauma, the first scale usable for traffic accidents was the Abbreviated Injury Scale (AIS), developed in 1969 and updated several times (3). **Table 1** summarizes the 2008 update of the 2005 AIS (4). The AIS ranks the severity of injury to individual organs, but does not give a quantitative scale. Thus, the difference between AIS 1 and 2 is not necessarily the same as the difference between AIS 3 and 4.

Table 1: Abbreviated Injury Scale (4)

Severity Code	Severity Category
1	Minor
2	Moderate
3	Serious
4	Severe
5	Critical
6	Maximal

There have been several methods used to increase the precision of trauma scoring in patients with multiple injuries. One common method is the use of the Injury Severity Score (ISS) (5). To calculate the ISS, trauma surgeons take the highest AIS from the three most severely injured areas, and then add their squares. The highest possible ISS is 75. The ISS is not linear and some values occur more frequently than others. However, the ISS is reasonably correlated with the probability of survival (5). For example, in patients less than 50 years of age, an injury severity score of 20 is associated with less than 5% mortality, while an injury severity score of 40 is associated with about 50% mortality.

Another approach is to include physiological variables. The Revised Trauma Score (RTS) includes respiratory rate, systolic blood pressure, and Glasgow coma scale score, each of which is correlated with survival (6). Finally, the Trauma Score and Injury Severity Score (TRISS) combines measures of anatomical injury (ISS), physiological derangement (RTS), and the patient's age (7).

A recent survey showed 258 models for trauma assessment, of which 103 were externally validated (8). While there have been many attempts to improve the ability of the TRISS score to predict mortality, none is a clear improvement.

Describing Liver Trauma

The Organ Injury Scales were developed by the Organ Injury Scaling Committee of the American Association for the Surgery of Trauma (AAST) starting in 1987. Each injury is placed on a scale from 1 (minor) to 6 (fatal). Specific scales for liver injury were developed in 1989 and modified in 1995 and 2008 (**Table 2**) (4, 9, 10).

The description of the liver injuries needed to determine the injury score includes the percent of the hepatic lobe involved, length and depth of lacerations, size of hematoma, and number of Couinaud segments involved. The Couinaud classification divides the liver into eight segments, each of which has its own



vascular inflow, outflow, and biliary drainage. The right hepatic vein divides the right lobe into anterior (segment 8) and posterior (segment 7) portions. The middle hepatic vein divides the liver functionally into right (segments 8 and 5) and left portions (segment 4) along Cantlie's line, which connects the inferior vena cava superiorly to the gallbladder fossa inferiorly. The falciform ligament divides the liver anatomically into right (segment 4) and left (segments 2 and 3) lobes (**Figure 1**) (11).

Mechanism of Liver Injury

The liver is covered with peritoneum, except for a patch on the superior surface called the bare area. The falciform ligament and the round ligament (ligamentum teres hepatis, the remnant of the umbilical vein) on its free edge connect the midline of the liver with the anterior abdominal wall and the diaphragm. These ligaments prevent displacement of the liver to the right. Additional ligaments (the right and left lateral ligaments and the coronary ligament) connect the superior surface of the liver to the diaphragm and prevent caudal displacement of the liver (12).

The abdominal organs are mostly covered by peritoneum, and peritoneal fluid lubricates the organs, re-

ducing friction. The liver, although somewhat mobile, is tethered in place by the inferior vena cava and ligaments. The ribs and spine protect the liver from outside forces, though trauma can overcome these protective mechanisms, resulting in predictable patterns of injury (13). Injuries are often due to movement of the liver while the inferior vena cava and ligaments remain relatively fixed. The most common types of trauma include blunt injury (acceleration, deceleration, and crush injury) and penetrating injury (sharp force trauma and gunshot wounds). Another common mechanism of trauma is for the liver to be compressed between the anterior aspects of the ribs and spine.

Acceleration injuries occur when there is a new external force (such as from a collision) that suddenly changes the direction the liver is moving. Acceleration injuries are most commonly due to forces from the lateral right side, as seen in a side impact collision of two automobiles. The force displaces the liver in the coronal plane. The right lateral ligament fixes the liver between Couinaud segments 7 and 8, making segment 7 relatively fixed while segments 5 and 8 continue to move. This creates lacerations between the anterior and posterior portions of the right lobe. Another type of acceleration injury occurs when the blunt force comes from the right front, as in a head-on

Table 2: Liver Injury Scale (4, 9, 10)

Grade*	Injury type	Description of Injury	AIS
I	Hematoma	Subcapsular, < 10% surface area	2
	Laceration	Capsular tear, < 1 cm parenchymal depth	2
II	Hematoma	Subcapsular, 10% to 50% surface area; intraparenchymal < 10 cm in diameter	2
	Laceration	Capsular tear 1 to 3 cm parenchymal depth, < 10 cm in length	2
III	Hematoma	Subcapsular, > 50% surface area of ruptured subcapsular or parenchymal hematoma; intraparenchymal hematoma > 10 cm or expanding	3
	Laceration	> 3 cm parenchymal depth	3
IV	Laceration	Parenchymal disruption involving 25% to 75% hepatic lobe or 1 to 3 Couinaud's segments	4
V	Laceration	Parenchymal disruption involving > 75% of hepatic lobe or > 3 Couinaud's segments within a single lobe	5
	Vascular	Juxtahepatic venous injuries, i.e., retrohepatic vena cava/central major hepatic veins	5
VI	Vascular	Hepatic avulsion	6

* Advance one grade for bilateral injuries up to grade III

AIS - Abbreviated injury scale

collision of two automobiles. In this case, the vena cava serves as a fixed point, while the rest of the right lobe is pushed posteriorly. This results in a vertical laceration along Cantlie's line. A third type of acceleration injury occurs when the blunt force is to the front of the chest, as in a resuscitative injury. The left lobe of the liver is displaced backwards, causing lacerations adjacent to the falciform ligament (14).

In deceleration injuries, such as injuries to a passenger in an automobile striking a fixed object, the liver is compressed either against the anterior chest wall, resulting in injury of the anterior segments, or against the posterior chest wall, resulting in injury of the posterior segments. In a crush injury, the liver is compressed between the anterior and posterior chest walls, as might occur in an unbelted automobile occupant in a low-speed collision. The impact with the dashboard or back of the front seat results in laceration of both anterior and posterior segments (13, 15).

Liver lacerations have been created experimentally by blunt cardiac impact at a velocity of 12-18 m/sec (16). The mechanism of these injuries is believed to be "ex-

traordinarily high venous pressure that develops at the instant of impact" (16).

Decedents who fall from a height may sustain deceleration-type injuries, but the pattern of injury depends greatly on factors such as the height of the fall, the landing surface, the occurrence of secondary impacts, and the area of the body involved in the first impact (17). In a study of suicidal falls from height, rib fractures were present in more than 90% of cases, resulting in possible laceration of the liver by the fractured ribs. Liver injuries were significantly less common in victims who weighed less than 50 kg and in falls less than 12 m (17).

In primary blast injury to the abdomen with the pressure wave traveling through air, liver injuries are present in about 20% of victims (18). These injuries are associated with a very high intensity of the primary blast wave and proximity of the decedent to the blast. The injury can occur on any surface of the liver, depending on the surface struck by the primary blast wave.

While there is an association between liver injury and rib fractures in general (19), the severity of the liver injury does not correlate with the number of fractured ribs (20). The liver injury may or may not be caused by laceration from the fractured ribs.

Several forensic textbooks report that livers with significant fatty infiltration are more susceptible to trauma, but this is not statistically supported. In a study of 171 cases of blunt trauma, Molina divided the cases into those with and without hepatic trauma, and also rated the degree of fatty change (21). There was no statistical correlation between the degree of fatty change and the presence of liver trauma.

Penetrating trauma of the liver, in cases of simple stab wounds or low-velocity gunshot wounds, is often associated with minimal tissue damage, and may not require surgical intervention (22). However, stab wounds involving major vessels or gunshot wounds involving high kinetic injury may cause extensive liver injury and exsanguinating hemorrhage.

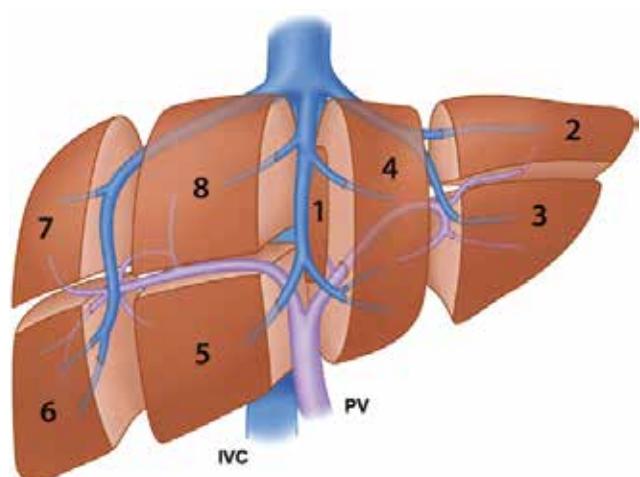


Figure 1: Couinaud segments of the liver. Hepatic vein branches are shown in blue, and portal vein branches, in purple.
 PV - Portal Vein
 IVC - Inferior vena cava
 Image used under a Creative Commons Attribution 4.0 License (11).



In one study, cardiopulmonary resuscitation resulted in liver laceration or hematoma in 0.6% of patients (23). The most common site of laceration was the left lobe, suggesting that there may be a relationship between liver laceration and incorrect placement of the hands over the xiphoid process during resuscitation. Hemorrhage from liver laceration may be exacerbated by use of thrombolytics or preexisting coagulopathy in some patients.

Outcome of Liver Injury

In a study of 348 cases admitted to a trauma surgery unit, there was no mortality among patients with grade I-II liver injury (24). The mortality rate was 3.8% in patients with grade III injury, 13.2% with grade IV, and 62.2% with grade V. Risk factors for death included grade of injury, mechanism of injury (blunt injury was worse than penetrating injury), presence of retrohepatic venous injury, presence of other injuries, shock, high transfusion requirements, and coagulopathy.

A comparison of patients with isolated liver injuries and concomitant injuries of liver and other organs showed that in many cases the trauma to other organs was more significant than the trauma to the liver (25). Mortality from liver injuries has improved from 60-80% before World War I to about 6% at the end of the 20th century. This progress is attributed to a change in common mechanism of injury from blunt trauma to stab wounds, use of more precise diagnostic tools, such as computed tomography (CT) scan, and availability of new techniques, such as arteriographic embolization of bleeding vessels (26).

Death from liver injury within two days of admission is most often due to hemorrhagic shock and coagulopathy (27). After this time, significant liver-related complications include sepsis (abscess of the right subphrenic, subhepatic, or intrahepatic areas), bile leak (28), and hemobilia due to hepatic artery pseudoaneurysms.

The Medical Examiner and the Trauma Surgeon

Trauma surgery has a well-developed system of quality assurance. At our trauma center, each incoming case receives a trauma score (often a TISS score), and the expected probability of survival is calculated. This enables the surgeons to determine whether there is discordance between the expected survival and the actual survival (29). Cases are later reviewed at morbidity and mortality conference to determine whether there should be any changes in procedure.

The medical examiner assists this process in many ways. The medical examiner performs expedited complete autopsies on cases that the trauma center designates as high priority. Ideally, a single forensic pathologist is assigned as a liaison with the trauma center coordinator. This insures that the injury descriptions are uniform. The medical examiner also fills out a preliminary draft of the AIS. This gives the trauma coder a more accurate idea of how to code individual injuries. For example, if the forensic pathologist describes the most severe injury as a 5 cm capsular laceration, the coder would assign an AIS score of 3 (see **Table 2**). The autopsy report provides a precise description of the injuries including measurements, percent of the liver parenchyma damaged, etc. Additionally, the AIS documents are sent to the trauma center on the date of the autopsy, providing findings and rapid feedback to the surgeons. A representative from the coroner/medical examiner's office also attends the trauma morbidity and mortality conference to provide feedback and improve the quality of trauma patient care. The main benefit of following this procedure is that the forensic pathologist provides information to the surgeons in a format that is usable for trauma coding. Thus, the surgeons can draw accurate conclusions about whether mortality rates exceed expected numbers. While the forensic pathologist must make a time commitment of a few hours a month, the more precise autopsy descriptions make the medical examiner's reports much more clinically useful.



CASE EXAMPLE

A 30-year-old woman was admitted to a Level 1 trauma center after being struck by a vehicle as a pedestrian. The initial pulse was 155, blood pressure 150/110, and respirations agonal. The Glasgow coma score was 3. She became bradycardic and a left thoracotomy was done and the aorta cross clamped. No thoracic injury was identified. Upon open cardiac massage, the pulse returned and she was taken for emergency laparotomy.

At surgery, she had lacerations of the liver, spleen, and left kidney. There was injury to the right internal iliac artery and vein. After the lacerations were packed and the left kidney removed, there was no significant abdominal bleeding. Her condition continued to be unstable and she was believed to have a significant brain injury; however, CT scan could not be performed because of her need for emergency treatment. The left tibia was fractured. Her pulse and blood pressure were unstable and she died about one hour after admission.

The case was sent to the morbidity and mortality review conference to establish whether the decedent had a significant brain injury or whether her death was due to a missed injury.

At autopsy, the major injuries included subdural and subarachnoid hemorrhage, partial transection of the cerebral peduncles, cardiac laceration and contusion, left kidney laceration, spleen laceration, and multiple fractures of the legs and ribs.

The liver showed a 17 cm long by 0.6 cm deep laceration of the anterior aspect of the right lobe, a small subcapsular hematoma of the right lobe, (**Image 1**), and a 9 cm superficial laceration of the inferoposterior aspect of the right lobe. **Table 2** indicates that a capsular tear of less than 1 cm parenchymal depth is a grade I injury (AIS score of 2), which would have a 10% expected mortality if it were the only injury (4). However, the decedent's brain injury was not survivable. The conclusion of the conference was that the decedent's injuries were so severe that treatment would not have improved the outcome.

CONCLUSION

In cases of fatal liver injury, the forensic pathologist is responsible for providing a clinically relevant description of the trauma. The relevant items include length and depth of lacerations, size of subcapsular hematomas, extent of parenchymal disruption, and the nature of vascular injuries. These elements are not always present in forensic autopsy reports, but a detailed description of injuries is important in determining whether the injury is survivable and whether there was an error in treatment.

The Los Angeles County Department of Medical Examiner-Coroner has established a relationship with a nearby trauma surgery team. This allows the medical examiner to prepare autopsy reports that are clinically relevant and useful in quality assurance. The interaction with the trauma surgeons has been mutually beneficial.

REFERENCES

- 1) Parikh MS, Pachter HL. Current therapy of trauma and surgical critical care. Philadelphia: Mosby; 2008. Chapter 51, Liver injury; p. 385-99.
- 2) Yates DW. Measuring the severity of injury. In: Vincent JL, editor. Yearbook of intensive care and emergency medicine. Berlin: Springer-Verlag; 1992. p. 682-90
- 3) Rating the severity of tissue damage. I. The abbreviated scale. *JAMA*. 1971 Jan 11; 215(2):277-80. PMID: 5107365.
<https://doi.org/10.1001/jama.1971.03180150059012>.
- 4) Tinkoff G, Esposito TJ, Reed J, et al. American Association for the Surgery of Trauma organ injury scale I: spleen, liver and kidney, validation based on the National Trauma Data Bank. *J Am Coll Surg*. 2008 Nov; 207(5):646-55. PMID: 18954775.
<https://doi.org/10.1016/j.jamcollsurg.2008.06.342>.
- 5) Baker SP, O'Neill B, Haddon W Jr, Long WB. The injury severity score, a method for describing patients with multiple injuries and evaluating emergency care. *J Trauma*. 1974 Mar; 14(3):187-96. PMID: 4814394.
<https://doi.org/10.1097/00005373-197403000-00001>.
- 6) Champion HR, Sacco WJ, Copes WS, et al. A revision of the trauma score. *J Trauma*. 1989 May;29(5):623-9. PMID: 2657085.
<https://doi.org/10.1097/00005373-198905000-00017>.
- 7) Boyd CR, Tolson MA, Copes WS. Evaluating trauma care: the TRISS method. Trauma score and the injury severity score. *J Trauma*. 1987 Apr; 27(4):370-8. PMID: 3106646.
<https://doi.org/10.1097/00005373-198704000-00005>.
- 8) deMunter L, Polinter S, Lansink KW, et al. Mortality prediction models in the general trauma population: a systemic review. *Injury*. 2017 Feb; 48(2):221-229. PMID: 28011072.
<https://doi.org/10.1016/j.injury.2016.12.009>.

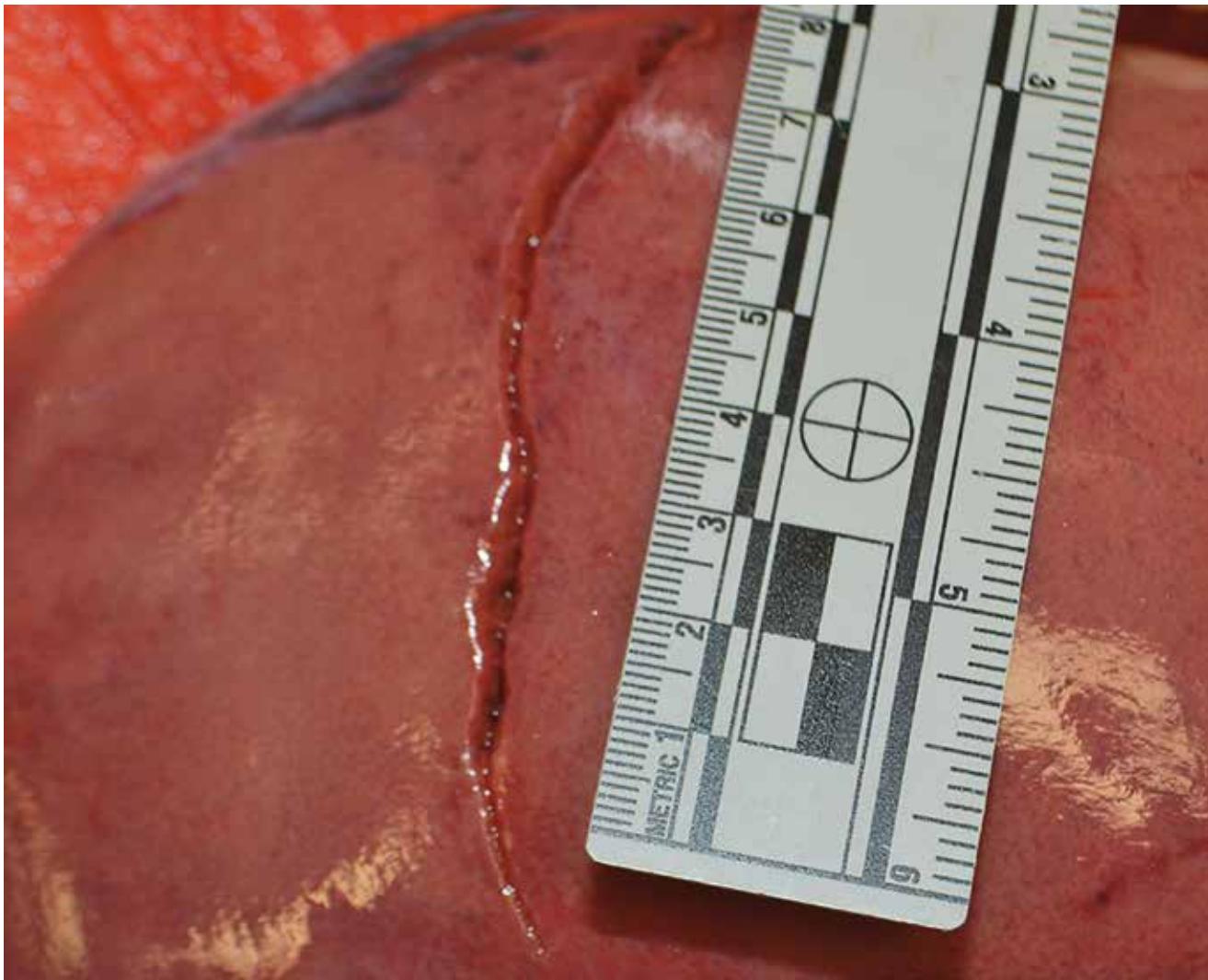


Image 1: Liver showing a small subcapsular hematoma and a 17 cm laceration.

- 9) Moore EE, Shackford SR, Pachter HL, et al. Organ injury scaling: spleen, liver and kidney. *J Trauma*. 1989 Dec;29(12):1664-6. PMID: 2593197. <https://doi.org/10.1097/00005373-198912000-00013>.
- 10) Moore EE, Cogbill TH, Jurkovich MD, et al. Organ injury scaling: spleen and liver (1994 revision). *J Trauma*. 1995 Mar; 38(3):323-4. PMID: 7897707. <https://doi.org/10.1097/00005373-199503000-00001>.
- 11) Orcutt ST, Kobayashi K, Sultenfuss M, et al. Portal vein embolization as an oncosurgical strategy prior to major hepatic resection: anatomic, surgical, and technical considerations. *Front Surg*. 2016 Mar 11; 3:14. PMID: 2704696. PMCID: PMC4786552. <https://doi.org/10.3389/fsurg.2016.00014>.
- 12) Gray H. Anatomy, descriptive and surgical. New York: Bounty Books; 1977. 1257 p.
- 13) Rouhana SW. Accidental injury: biomechanics and prevention. New York: Springer; 2002. Chapter 17, Biomechanics of abdominal trauma; p.405-53.
- 14) Jin W, Deng L, Lv H, et al. Mechanisms of blunt liver trauma patterns: an analysis of 53 cases. *Exp Ther Med*. 2013 Feb; 5(2):395-398. PMID: 23404632. PMCID: PMC3570073. <https://doi.org/10.3892/etm.2012.837>.
- 15) Slotta JE, Justinger C, Kollmar O, et al. Liver injury following blunt abdominal trauma: a new mechanism-driven classification. *Surg Today*. 2014 Feb; 44(2):241-6. PMID: 23459788. PMCID: PMC3898124. <https://doi.org/10.1007/s00595-013-0515-7>.
- 16) Stein PD, Sabbah HN, Hawkins ET, et al. Hepatic and splenic injury in dogs caused by direct impact to the heart. *J Trauma*. 1983 May; 23(5):395-404. PMID: 6854675. <https://doi.org/10.1097/00005373-198305000-00007>.
- 17) Casali MB, Battistini A, Blandino A, Cattaneo C. The injury pattern in fatal suicidal falls from a height: an examination of 307 cases. *Forensic Sci Int*. 2014 Nov; 244:57-62. PMID: 25194643. <https://doi.org/10.1016/j.forsciint.2014.08.004>.



- 18) Wani I, Parry FQ, Seikh T, et al. Spectrum of abdominal organ injury in a primary blast type. *World J Emerg Surg.* 2009 Dec 21; 4:46. PMID: 20025766. PMCID: PMC2803452. <https://doi.org/10.1186/1749-7922-4-46>.
- 19) Subedi N, Yadav BN, Jha S. Liver and spleen injuries and associated rib fractures: an autopsy study. *J Forensic Res.* 5:240. <https://doi.org/10.4172/2157-7145.1000240>.
- 20) Swaid F, Peleg K, Alfici R, et al. The severity of liver injury following blunt trauma does not correlate with the number of fractured ribs: an analysis of a national trauma registry database. *Surg Today.* 2015 Jul; 45(7):846-50. PMID: 24996646. <https://doi.org/10.1007/s00595-014-0975-4>.
- 21) Molina DK. Is steatosis a risk factor for hepatic blunt force injury? *Am J Forensic Med Pathol.* 2011 Sep; 32(3):263-5. PMID: 24042070. <https://doi.org/10.1097/paf.0b013e3181d8e3bc>.
- 22) Ackroyd FW. The liver, pancreas, spleen and gallbladder. In: Tedeschi CD, Eckert W, Tedeschi LG, editors. *Forensic medicine: a study in trauma and environmental hazards*, Volume 1. Philadelphia: WB Saunders; 1977.
- 23) Meron G, Kurkciyan I, Sterz F, et al. Cardiopulmonary resuscitation-associated major liver injury. *Resuscitation.* 2007 Dec; 75(3): 445-53. PMID: 17640792. <https://doi.org/10.1016/j.resuscitation.2007.05.023>.
- 24) Gao JM, Du DY, Zhao XJ, et al. Liver trauma: experience in 348 cases. *World J Surg.* 2003 Jun; 27(6):703-8. PMID: 12733001. <https://doi.org/10.1007/s00268-003-6573-z>.
- 25) Yazici P, Aydin U, Sozbilen M. Comparison of isolated and concomitant liver injuries: is hepatic trauma entirely responsible for the outcome? *Acta Chir Belg.* 2010 Nov-Dec; 110(6):598-602. PMID: 21337840.
- 26) Richardson JD. Changes in the management of injuries to the liver and spleen. *J Am Coll Surg.* 2005 May; 200(5):648-69. PMID: 15848355. <https://doi.org/10.1016/j.jamcollsurg.2004.11.005>.
- 27) Fabian TC, Croce MA, Stanford GG, et al. Factors affecting morbidity following hepatic trauma. A prospective analysis of 482 injuries. *Ann Surg.* 1991 Jun; 213(6):540-7; discussion 548. PMID: 2039284. PMCID: PMC1358571. <https://doi.org/10.1097/00000658-199106000-00003>.
- 28) Bala M, Gazalla SA, Faroja M, et al. Complications of high grade liver injuries: management and outcome with focus on bile leaks. *Scand J Trauma Resusc Emerg Med.* 2012 Mar 23; 20:20. PMID: 22444252. PMCID: PMC3352307. <https://doi.org/10.1186/1757-7241-20-20>.
- 29) Teixeira PER, Inaba K, Hadjizacharia P, et al. Preventable or potentially preventable mortality at a mature trauma center. *J Trauma.* 2007 Dec; 63(6):1338-46; discussion 1346-7. PMID: 18212658. <https://doi.org/10.1097/ta.0b013e31815078ae>.



The Adult Pancreas in Trauma and Disease

Alfredo E. Walker

ABSTRACT

The spectrum of traumatic and natural disease that can affect the adult pancreas is multiple and varied. Some entities are more commonly encountered in routine forensic pathology practice and the forensic pathologist needs to be very familiar with their pathological features and development from a pathophysiological perspective. However, many of the conditions are extremely rare and may never be encountered in the professional lifetimes of an individual pathologist. Still, forensic pathologists need to be aware of them in case they are one day faced with these entities as possible diagnoses to be established at postmortem examination. This can be the result of clinical concerns raised in life, potential natural disease explanations for unexpected biochemical results, and sudden, unexpected or otherwise unexplained deaths where criminal concern about the exogenous administration of a substance must be considered. *Acad Forensic Pathol.* 2018 8(2): 192-218

AUTHOR

Alfredo E. Walker MB BS FRCPath DMJ (Path) MFPLM MCSFS Dip Teach Train, Eastern Ontario Regional Forensic Pathology Unit - Department of Pathology and Laboratory Medicine - University of Ottawa

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, principal investigator of the current study.

CORRESPONDENCE

Alfredo E. Walker MB.BS, 501 Smyth Road, Ottawa ON K1H 8L6, aewalker@toh.on.ca

ETHICAL APPROVAL

As per Journal Policies, ethical approval was not required for this manuscript

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies conducted with animals or on living human subjects

STATEMENT OF INFORMED CONSENT

No identifiable personal data were presented in this manuscript

DISCLOSURES & DECLARATION OF CONFLICTS OF INTEREST

The author, reviewers, editors, and publication staff do not report any relevant conflicts of interest

FINANCIAL DISCLOSURE

The author has indicated that he does not have financial relationships to disclose that are relevant to this manuscript

KEYWORDS

Forensic pathology, Pancreatic injury, Pancreatitis, Chronic pancreatitis, Alcoholic and obstructive pancreatitis, Pancreatic trauma

INFORMATION

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

©2018 Academic Forensic Pathology International • (ISSN: 1925-3621) • <https://doi.org/10.23907/2018.015>

Submitted for consideration on 1 Apr 2018. Accepted for publication on 7 May 2018



INTRODUCTION

Anatomy of the Pancreas

The pancreas is an elongated, soft, tan-grey digestive gland of 12-15 cm length, which is located more or less transversely in the retroperitoneal space across the posterior abdominal wall in the upper part of the abdomen, within the epigastric and left hypochondrial regions. It has both exocrine and endocrine functions. Its exocrine function is manifested in its production of pancreatic juice which enters the duodenum via the pancreatic duct to aid in digestion, and its endocrine function is reflected in its production of glucagon and insulin which enter the bloodstream (1).

The pancreas crosses the midline plane of the body and consists of a head, neck, body, and tail. Its passage across the midline unevenly divides it into left and right segments with its right segment lying across the bodies of the L1 to L3 vertebrae. Its head is located within the C-curve of the duodenum and is embraced by it. The head of the pancreas rests posteriorly on the inferior vena cava, the right renal vessels, and the left renal vein, and exhibits a superior prolongation called the uncinate process.

The neck of the pancreas is about 2 cm long and is continuous with the head and merges imperceptibly into the body. The body of the pancreas extends slightly superiorly as it extends to the left side of the body across the aorta and superior lumbar vertebra. The body of the pancreas is intimately related to the stomach. The tail of the pancreas is its narrow, leftward-end that crosses the upper pole of the left kidney and ends in the hilum of the spleen. The splenic artery runs along the superior border of the pancreas towards the spleen (**Figures 1 and 2**).

The exocrine function of the pancreas is facilitated by secretions into the main pancreatic duct. The pancreatic duct begins in the tail of the pancreas and runs through its parenchyma from left to right and is joined by tributaries along its course. Within the pancreatic head, the main pancreatic duct turns inferiorly and comes into close relationship with the common bile

duct. The pancreatic and common bile ducts pierce the posteromedial wall of the second part of the duodenum in an oblique manner near its middle, usually uniting to form a short dilated hepatopancreatic ampulla (ampulla of Vater), which usually opens via a common channel into the duodenum at the summit of the major duodenal papilla.

DISCUSSION

Traumatic Injury of the Pancreas

Pancreatic injury occurs in less than 5% of major abdominal injuries (2). Pancreatic injury may occur from blunt force trauma (e.g., assaults, motor vehicular accidents) or penetrating injury (e.g., gunshot wounds or stabbings) (3).

The posterior position of the pancreas within the abdomen and its considerable distance from the anterior abdominal wall preclude it from frequent blunt force injury. As such, the duodenum and pancreas are relatively well protected because of their deep location in the abdomen. Consequently, injury of the pancreas and duodenum is often associated with severe injuries of other structures (4).

However, since the third part of the duodenum, neck, and body of the pancreas are located immediately in front of the rigid bony vertebral column, they are very susceptible to crushing injuries with the application of blunt force along the anteroposterior plane, with resultant compression of these structures against the rigid bony vertebrae such that laceration and/or contusion of these structures occur (5).

The second part of the duodenum is also vulnerable to blows to the central abdomen, since deep to that area the duodenum also crosses the midline and is liable to be sandwiched between the compressed anterior abdominal wall and the promontory of the lumbar spine with resultant perforation or laceration.

The application of a severe, localized blunt force to the epigastrium can result in pancreatic injury. The pancreatic injury can be sustained at the point where

the pancreas overlies the lumbar vertebra. On receipt of a direct blow to the abdomen, the pancreas is prone to percuss the rachidian relief. Since the pancreas is closely connected to adjoining organs, it is relatively fixed and does not benefit from any shock absorption effect and can be severely injured or even ruptured when forced against the vertebral column (6). Contusions, lacerations, and transections can occur. Spill-

age of pancreatic secretions into the abdominal cavity secondary to lacerations of the pancreas will result in chemical peritonitis as a concomitant sequela of associated injury to the pancreatic ducts.

Clinically, traumatic pancreatic lesions are classified according to the Hervé and Arrighi classification as follows:

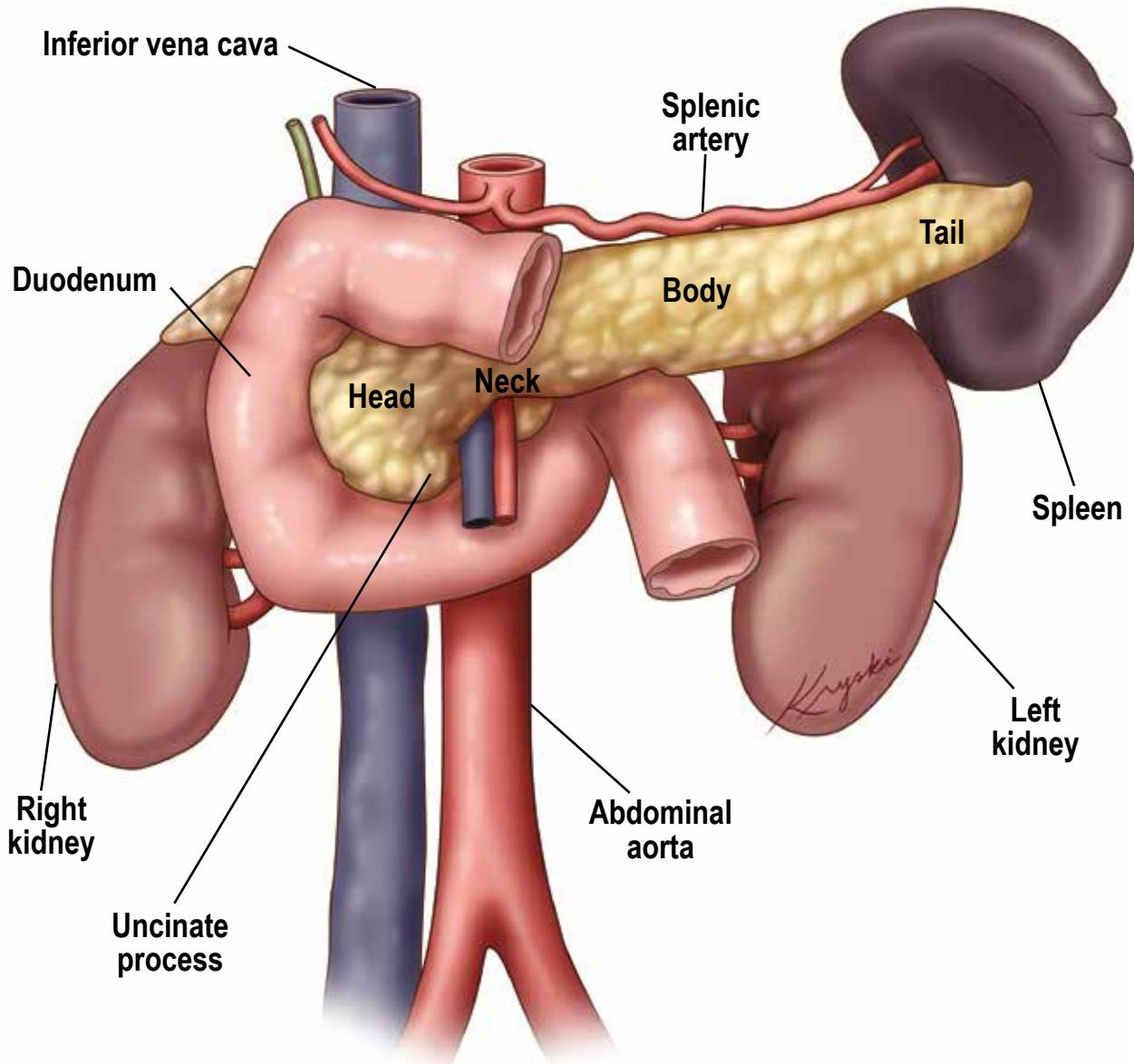


Figure 1: Diagrammatic representation of the pancreas and its relation to neighboring structures (anterior view). Created under contract by professional medical illustrator Diana Kryski.

Grade I: Contusion/hematoma with integrity of the duct system.

Grade II: Distal rupture of the gland.

Grade III: Proximal rupture of the gland with duct lesions or cross cutting without blow on the duodenum.

Grade IV: Laceration of the cephalic part of the pancreas.

The type of lesion sustained may primarily depend on the impact angle. Direct blows to the abdomen will result in median grade III injuries, whereas lateral impact will cause injuries of either the head or body of the pancreas from either right- or left-sided trauma, respectively (2).

The diagnosis of traumatic pancreatic lesions is often delayed. However, rapid death can occur and when it does, it is generally ascribed to the associated lesions through hemorrhagic shock or peritonitis (7), which would account for a death rate of more than 20% (8).

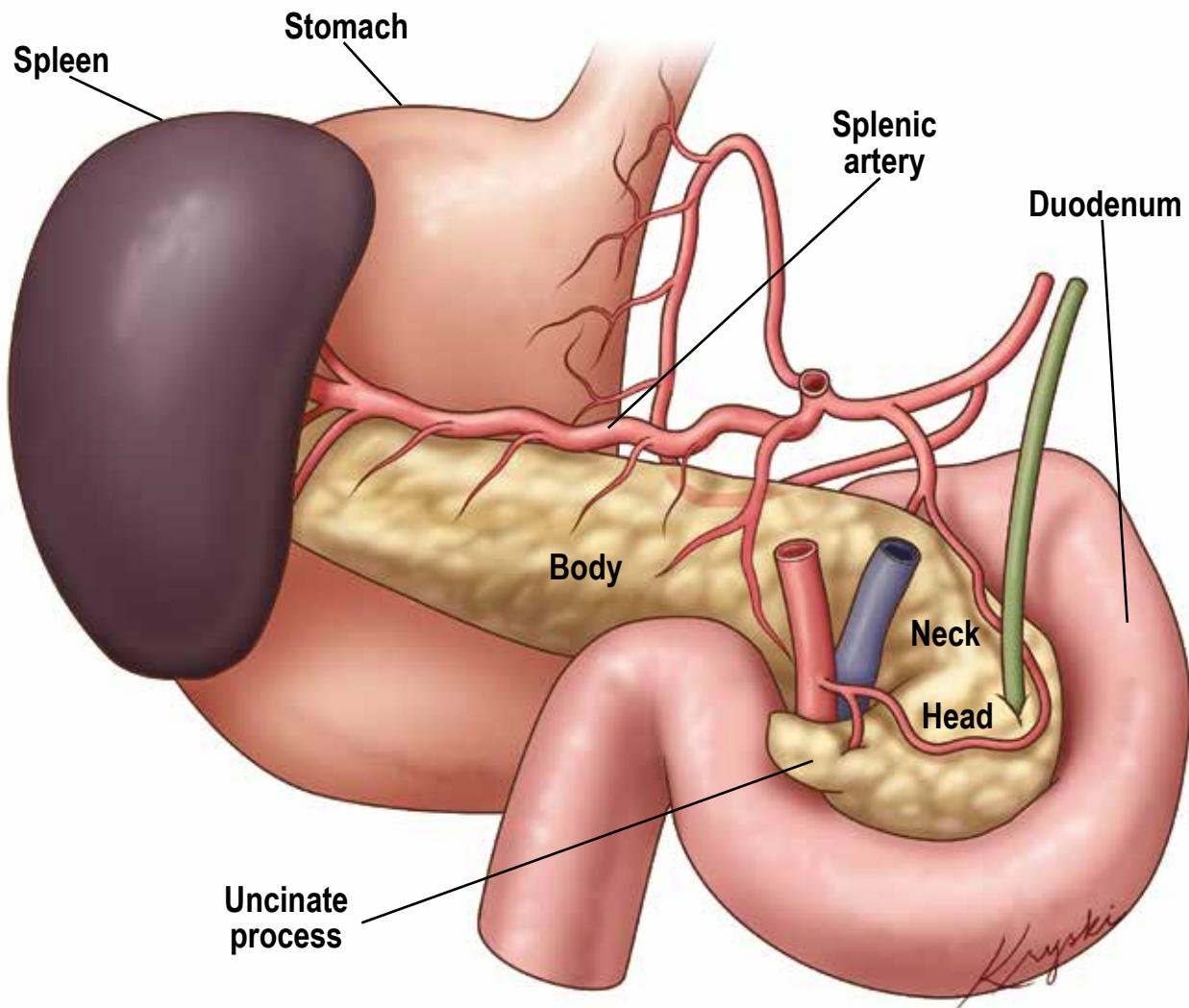


Figure 2: Diagrammatic representation of the pancreas and its relation to neighboring structures (posterior view). Created under contract by professional medical illustrator Diana Kryski.

Several authors have stated that isolated trauma of the pancreas cannot be responsible for a rapid death (8–10) but can result in numerous complications in 19–25% of cases (11, 12) from fistula formation, acute pancreatitis, pancreatic pseudocyst, and abscess formation with an estimated rate of delayed death of 9% (10, 13). The predictable complications are explained by a combination of rupture of the proximal acini with associated partial digestion of the gland by release of its enzymes. It has been reported that this phenomenon may be delayed for 12 days and up to six months, and is classically not involved in premature deaths (8, 10, 11).

Rougé-Maillart et al. reported a case of fatal blunt pancreatic trauma secondary to assault and battery in which complete destruction of the pancreatic head with massive necrosis of the gland resulted in death six to eight hours after the victim had been hit (6). In their opinion, their case confirmed the reports of others that pancreatic lesions caused by direct trauma to the abdomen, especially from blows in the context of violence, may be rapidly fatal even if isolated because of the high severity of the necrosis they may induce (6, 14, 15). As such, an isolated pancreatic injury can result in rapid death because of the particular type of pancreatic rupture frequently involved (6).

Peripancreatic and intrapancreatic pseudocysts can be

a complication of pancreatic injury (16, 17). A pancreatic pseudocyst is filled with blood and pancreatic secretions and accumulates around the pancreas in the form of a peripancreatic hematoma that resolves to give a cystic lesion filled with clear fluid, the wall of which is devoid of an epithelial lining. This is in contrast to a neoplastic or congenital cyst, which will have an epithelial lining. The wall of the pseudocyst will contain numerous hemosiderin-laden macrophages within fibrous connective tissue. Intrapancreatic pseudocysts develop from intrapancreatic hematomas as a result of intrapancreatic hemorrhage, but again their walls are devoid of an epithelial lining and will contain hemosiderin (16).

Because of its close anatomical relationship with the duodenum, traumatic injury of the pancreas may co-exist with traumatic injury of the duodenum and this is reflected in the American Association for the Surgery of Trauma (AAST) classifications of duodenal and pancreatic injury where combined pancreatic and duodenal disruption has been classified as a grade 4 lesion under both categories (18, 19).

Direct blows to the abdomen in the form of stamping, kicking, forceful blows with a clenched fist, impact from bicycle handle bars, and compression from the lap belt portion of seatbelts are all capable of causing injury (**Image 1**). Severe or fatal intraabdominal in-

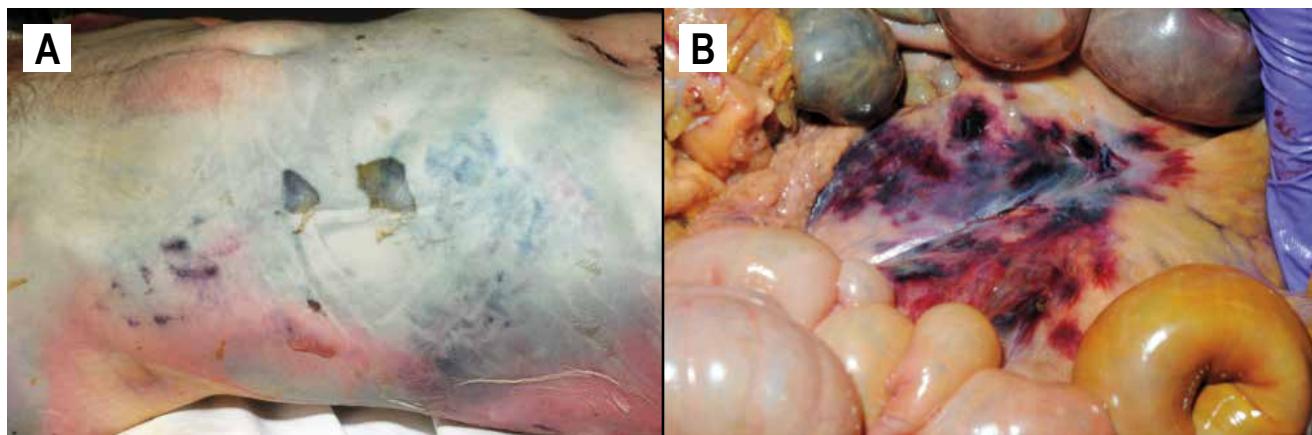


Image 1: **A)** Patterned footwear mark on the lateral aspect of the abdomen of a decomposed male decedent who died from blunt force head injury with a large acute subdural hematoma. **B)** A large contusion of the mesentery was evident on internal examination. (Images courtesy of Dr. Matt Lyall, Home Office Pathologist, United Kingdom).



jury can exist without any discernible external signs of injury, especially if the blunt impact blow has been inflicted through clothing or has been applied over a large area (20). However, injury may be manifested as either cutaneous and/or subcutaneous bruising.

Pancreatic injuries are much less common in children but may occur in vehicular collisions due to the incorrect placement of seatbelts. Although death in the setting of pancreatic trauma is more often due to injuries elsewhere (for example head and chest), pancreaticoduodenal injuries can be lethal in themselves (21). In pediatric pathology, injuries of the duodenum account for less than 5% of intra-abdominal injuries, due to its relatively protective position in the retroperitoneal and duodenal hematomas. Lacerations and perforations should raise concern about the possibility of inflicted injury if no plausible explanation can be provided (22, 23). Pancreatic injury in children is dealt with elsewhere in this edition (24).

Mallick and Thoufeeq reported a case of a 40-year-old woman with a thin body habitus who presented with a two-day history of constant epigastric pain that radiated to her back (25). There was no history of alcohol ingestion or abdominal trauma. Abdominal tenderness and guarding of the epigastrium were evident on physical examination. Blood investigations revealed a normal white cell count but an elevated serum amylase concentration of 404 IU/L (normal range: 0-70 IU/L). A provisional diagnosis of acute pancreatitis was made. Ultrasonography of the abdomen identified a collection of fluid between the spleen and the diaphragm; no gallstones were evident. Computed tomography scans of the abdomen identified a vertical tear in the tail of the pancreas with an intact main pancreatic duct. The other abdominal viscera were normal. She was hemodynamically stable and was managed conservatively with an excellent outcome without complications. Although she had initially denied any history of abdominal trauma, further questioning unearthed an incident two days prior to her onset of symptoms in which she had accidentally collided into the edge of a door frame whilst carrying a medical textbook in front of her abdomen. She had considered the incident to be too trivial to report at

the time of initial presentation. As this was the only plausible traumatic event that she could relate to the onset of her symptoms, the medical team ascribed this incident as the underlying cause of her presentation, but in my opinion the validity of this association is highly dubious.

Mechanism of Pancreatic and Duodenal Injury

The application of blunt force to the body involves inward displacement of the tissues as the primary mechanism of energy transfer. Experimental animal models have shown that blunt impact to the torso produces very little rebound velocity, thereby inferring that bodies are viscous and this can be extrapolated to the human body, which is considered viscoelastic. This viscoelasticity means that displacement upon impact is rate-dependent with the rate and magnitude of the distortion of the body wall determining the nature and severity of the internal injury. Little or no injury may develop on a slow velocity of compression, even with severe inward displacement, while rapid compression may produce severe internal injury with compression of only a small area, although it is recognized that prolonged compression may also be associated with severe injury (26).

Mechanical compromise of the affected tissues in the propagation of different types of waves (e.g., stress, shock, and shear waves) into the body are the factors that determine the likelihood of injury being sustained, as well as crush injury (27). More damage will occur when a localized force is applied in contrast with diffuse application of a force of the same magnitude. As a general principle, solid abdominal organs are more susceptible to blunt force injury than hollow organs. The application of large, relatively static loads to the body give rise to crush injuries as can occur with compression of the anterior abdominal wall towards the retroperitoneum (27).

Shock waves are high-pressure, high velocity waves that travel faster than the speed of sound and can be encountered in explosions (28). Stress (compression) waves are the most common mechanism of injury in high-speed collisions in which impact speeds are

greater than 106 kph, or 66 mph. Shear waves are transverse waves of longer duration but low velocity in which injuries arise from the collision of viscera against non-elastic structures, the asynchronous motion of adjacent connected structures, or stretching (strain) at the site of attachment. This mechanism of injury may be associated with contusions or lacerations of the mesentery, splenic pedicle, the liver at the falciform ligament, and the aorta at the ligamentum arteriosum. Shear wave injury is the most common type of impact injury seen at lower velocity (less than 53 kph or 33 mph) motor vehicular collisions (27). Crush injuries arise from the application of large, relatively static loads to the body (27).

Blunt force injury of the pancreas may be frighteningly symptom-free but the more common scenario will consist of the clinical manifestation of severe peritoneal irritation (3). As such, blunt force injuries of the pancreas may not be picked up immediately and can result in higher rates of morbidity and mortality (3). The biochemical determination of the serum amylase concentration is notorious for being manifestly unreliable in making the diagnosis and can even be normal, even in the presence of disruption of the pancreatic ductal system (3). Injury of the distal aspect of the pancreas carries a much better prognosis than proximal injury, especially when there is associated breach of the major pancreatic ductal system (28).

The complications of pancreatic injury are bleeding, abscess formation, recurrent pancreatitis, fistula formation, and pancreatic pseudocysts (29). Death is usually from sepsis, late hemorrhage, and pancreatic necrosis secondary to acute pancreatitis. As previously stated, pancreatic pseudocysts may complicate blunt abdominal trauma (16, 17).

Complications of Pancreatic Injury – Illustrative Case

The author has seen a case of a 20-year-old young woman who died in an overseas jurisdiction where a forensic postmortem examination had been performed. Her body was repatriated to her home country where a second postmortem examination was conducted at the

request of the local coroner. The circumstances of the death were such that the decedent had been admitted to a hospital with a four-day history of constipation and dehydration. It was alleged that she had fallen onto a drinking glass or bottle eight days prior to her presentation to hospital, but had only began to feel unwell four days prior to presentation. An emergency laparotomy was performed but she died the following day in the intensive care unit. The forensic postmortem examination listed her cause of death as biliary peritonitis due to contusion of the head of pancreas due to abdominal injuries and the manner of death was classified as homicide. The decedent's boyfriend was arrested, charged, and prosecuted in relation to her death and was subsequently found guilty at trial. The account provided by her boyfriend was that the decedent had been out drinking with friends and had fallen onto a glass to cause the injuries. Later, that account was changed to indicate that she had fallen onto her elbow whilst she had been adjusting her clothes and her own fist had inadvertently rammed into her abdomen as a result.

At the first postmortem examination, two wide bruises with an “arch-like shape” and dark colored edges were identified on the anterior abdominal wall and were attributed to having been caused by a dull object. The abdominal cavity exhibited diffuse white-yellow, chalky fat necrosis of the peripancreatic fat, the omentum, and mesentery with a mesenteric bruise (**Images 2 and 3**). A recent surgically repaired traumatic lacer-

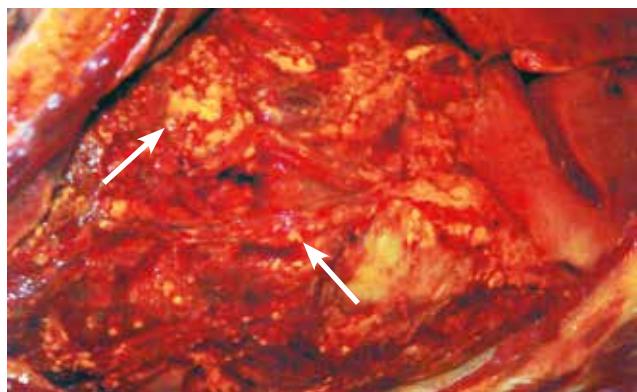


Image 2: Inflammation of the peritoneum with fat necrosis (saponification) (arrows) of the mesentery.

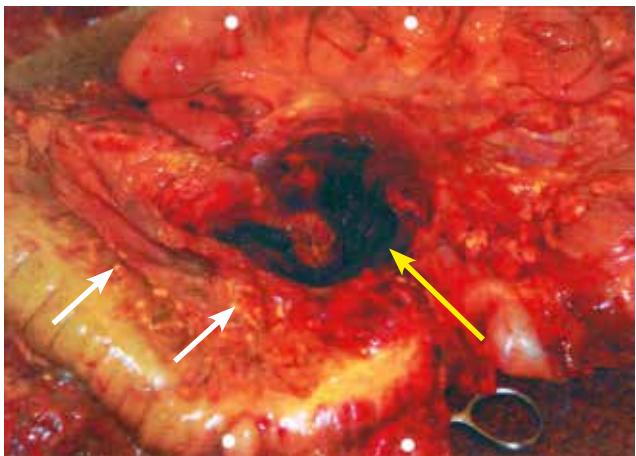


Image 3: Mesenteric bruise (yellow arrow) and fat necrosis (saponification) (white arrows) of the mesentery.

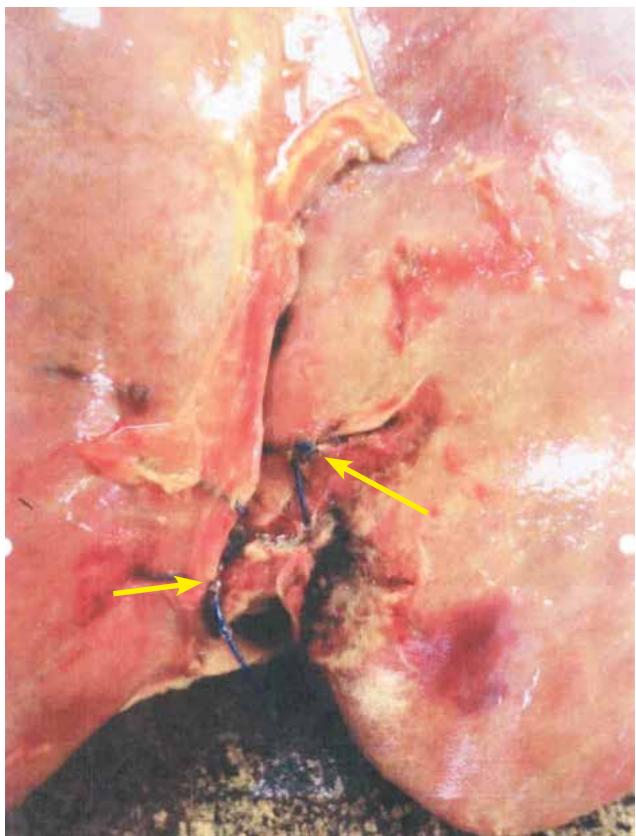


Image 4: Sutured laceration of the liver.

ation of the liver close to the round ligament (**Image 4**) and lacerations of the head of the pancreas with rupture of the major pancreatic duct close to the ampulla of Vater were identified, with extensive hemorrhagic infiltration and fat necrosis on sectioning. There was a wide communication between the lesser omental pouch and the retroperitoneum that contained a collection of 400 mL of bile stained fluid within the retroperitoneum.

Retrospective review of the translated medical/surgical notes indicated that the decedent had undergone an emergency laparotomy in which rupture of the cystic duct and liver had been diagnosed intraoperatively and cholecystostomy, suturing of the liver, and abdominal washout had been performed. Intraoperative cholangiography had raised the possibility of rupture of the cystic duct and that investigation was followed by intraoperative gastroscopy which had supported that impression.

Images of the multi-slice CT scans of the abdomen and pelvis, which had been performed on admission to hospital (without and with contrast enhancement), were obtained, reviewed, and reported on by a radiologist in the jurisdiction of repatriation. The radiological findings and opinions were that there was a clear complex laceration of the pancreatic head and neck with significant retroperitoneal fluid almost obliterating the perinephric fat. The body and tail of the pancreas appeared normal. There was extensive free fluid in the peritoneal cavity which had extended retroperitoneally downwards on the right side to the right paracolic gutter and right pelvic side wall. The small bowel loops appeared rather thick-walled from either inflammation or ischemia. No free intraperitoneal gas was present. The liver, spleen, kidneys, and bones were uninjured. The CT findings were considered entirely in keeping with the findings demonstrated at initial postmortem examination, which consisted of a pancreatic laceration and extension of free fluid throughout the abdomen and was quite compatible with an extensive bile leak. The extensive retroperitoneal collections around the right kidney and in the right flank, which had spread downwards extra-peritoneally, to the right pelvic side wall, were interpret-

ed as collections of bile attributable to a putative late presentation some seven days after the injury.

The second postmortem examination was performed on the repatriated, previously autopsied body without the benefit of the medical/surgical notes, the detailed postmortem reports, and postmortem photographs were subsequently obtained.

External examination of the body at the second postmortem examination identified a large area of healing abrasions of the back of the right elbow (**Image 5**) with healing, smaller, short linear abrasions on the back of the right forearm. No cutaneous or subcutaneous bruising of the center of the upper abdomen/epigastrium was evident; only a 2 x 1.5 cm recent subcutaneous bruise of the upper right quadrant of the abdomen was identified. Internal examination revealed features of biliary peritonitis associated with an apparent large mesenteric contusion. Some pancreatic tissue with a previously opened segment of common bile duct was identified but that pancreatic tissue did not exhibit any signs of inflammation or injury; however, the head of the pancreas was absent.

All the major organs and tissues appeared to have been repatriated with the body, but the esophagus and duodenum were not identified and the kidney and pancreas were incomplete. The duodenum and head of pancreas were believed to have been either excised at laparotomy or retained at postmortem examination for formalin fixation and histological examination. No cutaneous or subcutaneous bruise of the central abdominal area was identified at second examination to account for the internal abdominal injuries.



Image 5: Abrasions on the back of the right elbow.

Microscopic examination of the tissues taken for histological examination at the second examination confirmed acute biliary peritonitis with lipolytic fat necrosis of the abdominal cavity. No chronic or acute pancreatitis was evident in the examined sections of normal-looking pancreatic tissue that was present in the body. Histological examination of the areas of tissue hemorrhage in the abdominal wall and mesenteric tissue confirmed extravasation of red blood cells but no associated inflammatory reaction was evident and iron stains were negative. If any of those areas had represented true bruising, they would have had to have been sustained within two to three days, and given that the decedent had undergone abdominal surgery and postmortem examination in the overseas jurisdiction, these areas were considered unrelated to any abdominal impact five or more days prior to death. The histological sections from the original postmortem examination were not provided for review because of the criminal trial in that jurisdiction, despite official requests for the same to be obtained.

The conclusions of the second postmortem examination were in concert with those of the initial examination in that the young woman had died from the systemic complications of biliary peritonitis that had developed from traumatic blunt force impact of the abdomen with injuries of the head of the pancreas in the form of contusions and lacerations, which had been sustained by the application of a severe degree of blunt force to the anterior abdomen. The surgically diagnosed rupture of the cystic duct had permitted leakage of bile into the peritoneal cavity with the resultant bile-induced inflammatory response of the peritoneum (biliary peritonitis).

The mechanism of injury was the application of a severe degree of blunt force to the anterior abdominal wall that resulted in compression of the abdominal wall and underlying intraabdominal viscera against the rigid vertebral column in a “hammer and anvil manner” to effect crush injury on the liver and head of pancreas. Severe forceful blow(s) to the abdomen in the form of stamp(s) with a shod foot, kick(s), or a clenched fist were the most likely cause of the spectrum of injury but other mechanisms of forceful compressive blows



to the abdomen were also possible. It was not conceivable that a fall from a standing height onto either a drinking glass, a bottle, or the decedent's clenched fist could have generated enough force to produce the spectrum of severe injuries identified intraoperatively or adequately explain their development.

The alleged fall onto a bottle or her own fist four days prior to her reported symptoms of feeling unwell appeared to be a rather long delay in presentation and was considered an atypical presentation of the spectrum of intraabdominal injuries sustained. If the fall onto a bottle were a feasible cause of the intraabdominal injuries, the expected clinical presentation of the peritonitis should have developed over the course of a few hours and not after four days, but it was recommended that the clinical opinion of a consultant general surgeon should be sought in that regard. From the available information gathered at the second postmortem examination, the cause of death was given as biliary peritonitis due to contusion and laceration of the head of the pancreas due to blunt force trauma of the abdomen.

A third postmortem examination was performed by another forensic pathologist in the jurisdiction of repatriation acting on the instructions of a lawyer who was seeking the interest of the accused in the overseas jurisdiction. That forensic pathologist concluded that the cause of death was straightforward from a medical point of view and agreed that the decedent had died from complications of traumatic injury of the head of the pancreas secondary to a substantial impact to the front of the abdomen. He opined that the causative impact could have been a punch or a fall onto an object or other projecting surface. It was stated that there was no convincing medical evidence of abdominal wall bruising attributable to the original impact and stated that the naked eye and microscopic autopsy findings indicated that the causative impact had occurred days prior to death, with five to eleven days being within the possible timescale, but with the caveat that the clinical history may further assist in determining a likely timescale. It must be noted that this expert opinion had also been provided without the benefit of reviewing the histology sections from the original postmortem examination.

The expert opinion of a professor of upper gastrointestinal tract, pancreatic, and biliary surgery was sought. That opinion stated that the alleged account of how the injury was sustained was plausible. In providing that opinion, the accounts of eight friends and the decedent's boyfriend were considered. It was stated in that expert report that the decedent had allegedly fallen twice on the same day. The description of the first fall was the decedent had tripped and fallen forwards whilst she had been out drinking with friends. She had apparently fallen full length without attempting to break the fall. It appears that she may have had a drinking glass in her right hand at the time of the fall and had been attempting to adjust her clothes with her hand, which was inside her belt. After the fall, she complained that she had hurt her right side but had carried on drinking before going home. The account of the second fall was more speculative in that she may have fallen on a set of spiral stairs in her apartment on arrival home. The professor of general surgery stated in his report that:

...the likely mechanism involved was that the decedent's arm had been driven upwards into her right upper quadrant to cause the pancreatic injury by the force of the impact. The effect of the alcohol that she had drank had contributed to her failure to react to save herself in the fall and had probably dulled the response of the abdominal muscles, thereby reducing the protection given to the internal organs.

Three years later, the professor of surgery produced an addendum to his initial report where it was stated he had now seen evidence that the decedent had not fallen onto the glass she had been allegedly holding in her right hand at the time of the fall. However, he reiterated his conclusion that a fall onto her elbow whilst inebriated could have pushed her hand into the right upper quadrant of her abdomen with sufficient force to injure the pancreas and stated this mechanism was most consistent with the clinical picture and development of the illness over the following eight to ten days. In his opinion, in the absence of any other documented injuries, this allegedly witnessed fall remained the only possible cause of the pancreatic injury and explanation for her death.

The overseas court rejected the defense of a fall being responsible for the injury and found the boyfriend guilty of murder. A coronial inquest subsequently occurred in the jurisdiction in which the body had been repatriated at the request of the defendant and the outcome of the inquest was in line with the determination of the overseas court at the criminal trial.

Spectrum of Natural Disease and Nontraumatic Conditions in the Adult Pancreas

Autolysis and the Pancreas

Postmortem autolysis is defined as the spontaneous destruction of cells or tissues by lysosomal enzymes after death (30). The pancreas is well known to be one of the organs most susceptible to postmortem autolysis due to its abundant content of enzymes. Its autolysis can be rapid and interfere with histological examination of pancreatic lesions. It is rare for the pancreas to be extremely well preserved at postmortem (**Image 6**). While not a disease, autolysis must be distinguished from disease.

Morphologically, autolysis is determined by degeneration of the cells without an associated inflammatory reaction, especially a lack of neutrophils (31). Cellular necrosis is adjudged by the combination of either nuclear pyknosis, karyorrhexis, or karyolysis, and increased eosinophilia of the cytoplasm (31). In general

terms, greater degrees of autolysis are seen in lengthened postmortem intervals (32).

The changes in cell nuclei after death generally indicate the breakdown of nucleoproteins by enzymes, although no trypsin activity in the pancreatic tissue has been reported to occur during *in vitro* postmortem autolysis (33). One of the most important enzymes is cathepsin, an intracellular proteinase found in most animal tissues and is most abundant in the liver, kidney, and spleen (34). Cathepsin is inactivated by formalin and formalin fixation of tissues prevents further autolysis by inactivation of intracellular enzyme activity (34).

Postmortem autolysis is influenced by both the body and environmental temperatures and is delayed by low temperatures (30). It has also been suggested that the degree of autolysis is influenced by several other factors including the cause of death (35).

Shimizu et al. assessed the histological features of the pancreas for autolysis in 92 autopsy cases by sections taken from the head, body, and tail (32). They classified the degree of autolysis as zero degree (no autolysis), first degree (up to $\frac{1}{3}$ of the section), second degree (between first and third degree), and third degree (greater than $\frac{2}{3}$ of the section), with the final degree of autolysis expressed as the mean value for three sampled sites (head, body and tail). The degree of autolysis

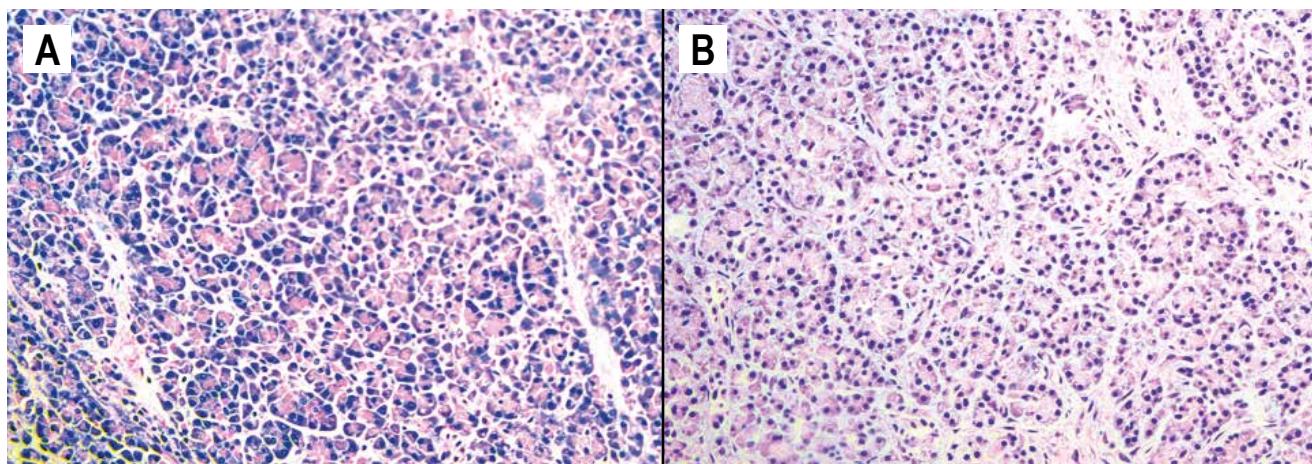


Image 6: Sections of well preserved pancreas **A**) and **B**) (H&E, x50).

ysis was then compared against the clinical data and other information for every case. Their findings supported the generalization that more extensive autolysis is seen with lengthening of the postmortem interval but some outliers were also observed. The pancreas was either unexpectedly well preserved or poorly preserved in a few cases, irrespective of the postmortem intervals (e.g., 40 hours versus two hours), and these cases were removed from their overall statistical analysis. The multiple correlation coefficient was obtained for the degree of autolysis and their results suggested that the mode of death, temperature at the time of death, cause of death, and clinical conditions all need to be considered for those cases of unexpected autolysis for postmortem interval. The extent of autolysis was most significantly related to the postmortem interval. With respect to mode of death, there was a statistical significance between acute and chronic death.

The pancreas has been investigated immunohistochemically as a tool in establishing the postmortem interval based on the immunoreactivity with antibodies to glucagon (36). The pancreas from 214 corpses (for which the time since death was known to be between one and 21 days \pm one day from police investigations) were stained with antibodies to glucagon. The circumstances in which the bodies were recovered were all different with respect to environmental parameters (e.g., site of discovery, temperature, and humidity).

It was demonstrated that pancreatic α -cells exhibited positive immunoreactions for glucagon in all cases up to six days old but no corpse older than 14 days exhibited a positive reaction. The interpretation was that a positive immunoreaction indicates a time of death less than seven days prior to postmortem examination and absence of glucagon immunoreactivity in the specimen indicated that the time of death must be at least 13 days earlier. However, a negative immunoreaction could occur earlier and a positive immunoreaction could occur later under different environmental conditions.

The differentiation of pancreatic autolysis from acute pancreatitis should be relatively straightforward with lack of an acute inflammatory response being one of the main discriminating features for autolysis (**Images 7 and 8**) and the presence of an acute inflammatory response pointing towards acute pancreatitis (**Image 9**).

The Pancreas in Diabetes Mellitus

Pathological changes in the pancreas are evident in both type 1 and type 2 diabetes mellitus. Type 1 diabetes is a multifactorial disease that develops from a complex interplay of host genetics, the immune system, and the environment with resultant destruction of the insulin-producing beta cells of the islets of Langerhans.

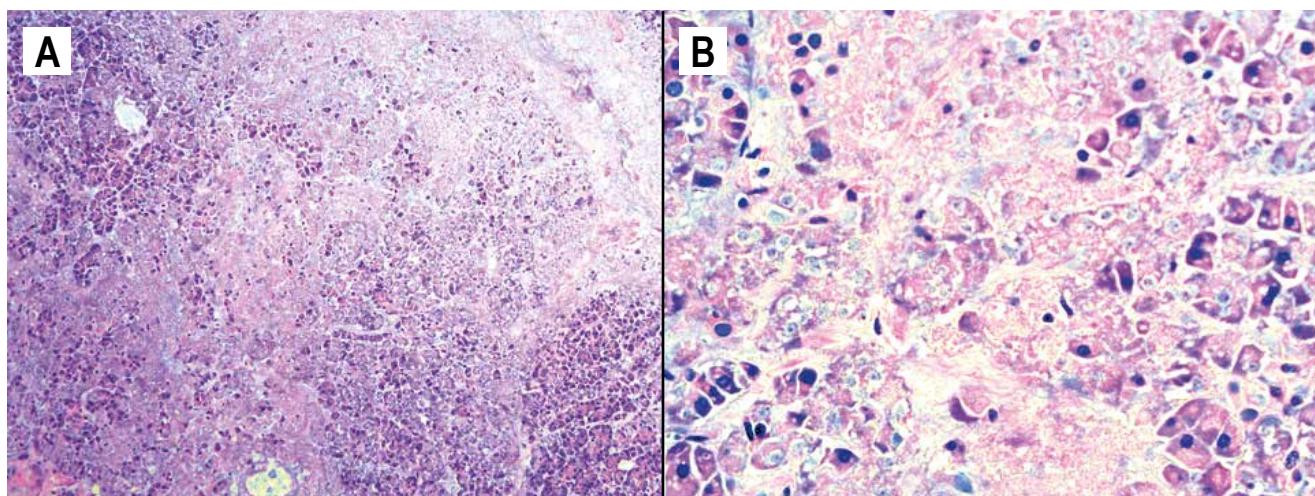


Image 7: A) Mild autolysis (H&E, x20) and B) (H&E, x400).

Islets in the commonly sampled body and tail of the pancreas contain four main endocrine cell types. Approximately 80% of the cells are insulin-secreting β cells, 15% glucagon-secreting α cells, 4% somatostatin-secreting δ cells, and 1% contain pancreatic polypeptide (PP) (37).

The presence of insulitis in the islets of the pancreas of a predominantly lymphocytic inflammatory infiltrate was reported in the 1965 seminal article by Willy Gepts who had identified it in 68% of autopsies (15 of 22 persons) performed on decedents who were under

the age of 30 years and had died within six months of a diagnosis of diabetes (38). A larger collection of samples in the UK confirmed these findings, where 47 out of 60 (78 %) of young patients under the age of 20 years were found to have insulitis (39).

Gepts had also noted that the pancreas in persons who had been afflicted with the disease for many years was characterized by an almost complete lack of insulin-secreting beta cells, and this was reported before the advent of immunohistochemistry. Two hypotheses for the islet cell inflammation flowed out of this,

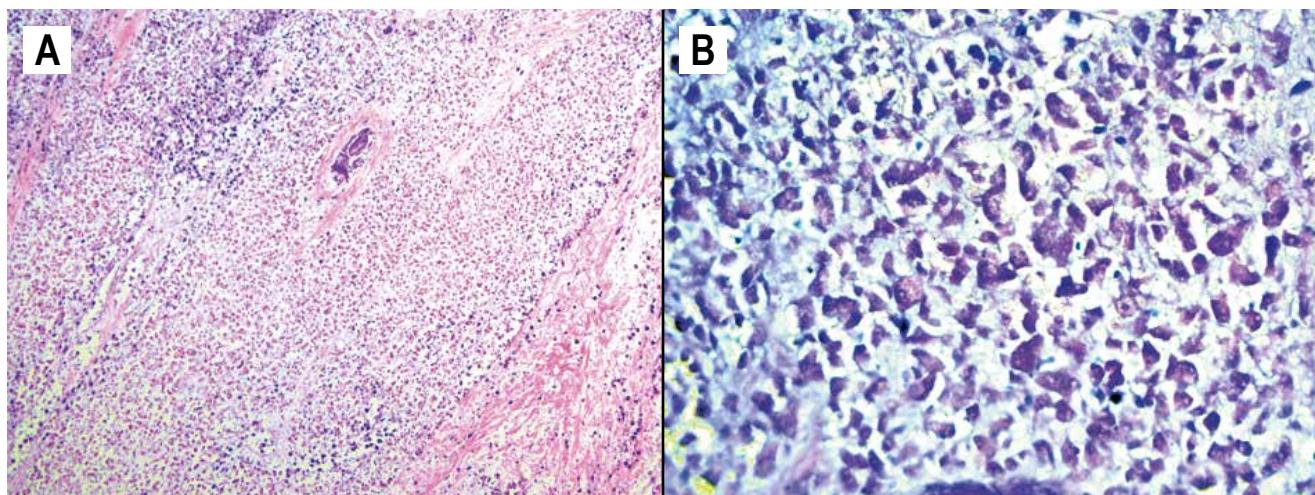


Image 8: Severe autolysis of the pancreas **A**) (H&E, x10) and **B**) (H&E, x400).

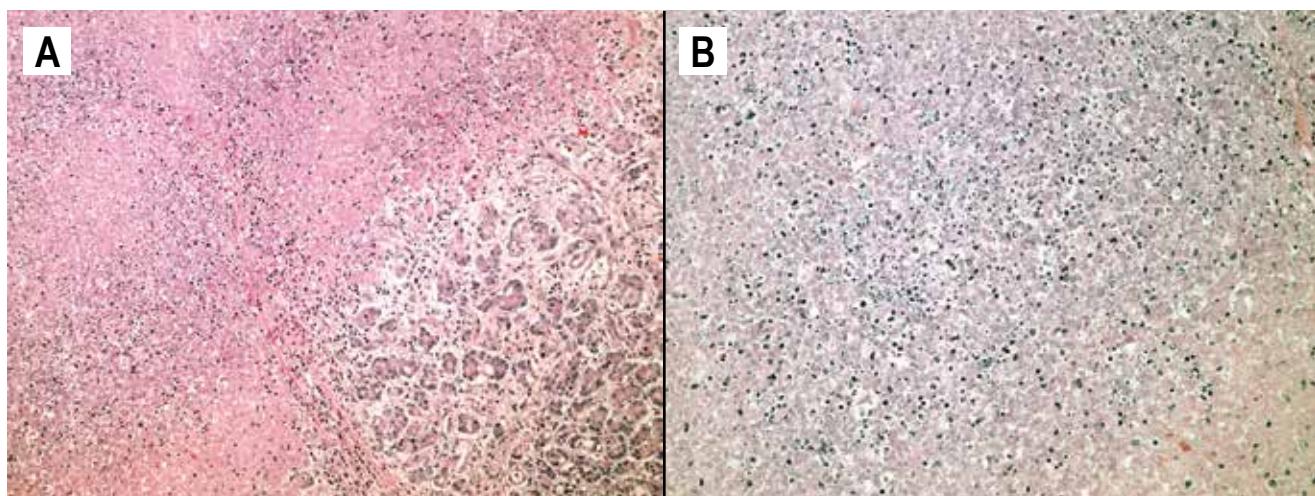


Image 9: Acute pancreatitis **A**) (H&E, x100) and **B**) (H&E, x200).



namely that the islet inflammation could be secondary to a viral infection of beta cells, or could represent an autoimmune process.

Support for both theories was obtained when it was shown that patients with recently diagnosed type 1 diabetes were more likely than controls to have antibodies to Coxsackie viruses (40), and Coxsackie B4 virus was cultured from the pancreas of a 10-year-old boy who had died at clinical presentation of type 1 diabetes (41). As the virus was also cultured from the brain of the child, it was stated that this case may have been exceptional in that there was a possibility of an incidental viremia. In 1974, two separate groups reported the presence of islet cell autoantibodies in patients with type 1 diabetes (42-44), which led to a subsequent reclassification of the disease as an organ-specific autoimmune disease that targeted the insulin-secreting beta cells of the islets.

The use of immunohistochemistry on paraffin-embedded tissue has shown that most islets (70%) were small and had no beta cells in children dying at clinical presentation of their disease (45). However, a normal complement of glucagon-secreting alpha cells, somatostatin-secreting delta cells, and pancreatic polypeptide-secreting PP cells were identified and these cases were termed insulin-deficient islets (IDI). The remainder of the islets had residual beta cells and were called insulin-containing islets (ICI). Insulitis affected 18% of ICI but only 1% of IDI, which provided the first evidence that insulitis affected ICI primarily and lent support to the idea that it represented an immunologically driven destruction of beta cells (45). Importantly, a lobular distribution of the disease was also noted, where a seemingly unaffected lobe, or one where ICI with insulitis could be observed, was frequently surrounded by lobes containing only IDI.

Histological examination of the pancreas in decedents with long-standing type 1 diabetes mellitus will essentially reveal an absence of β cells; however, there will be a normal number of islets containing normal numbers of α , δ , and PP cells (39).

In well-developed insulitis, lymphocytes outnumber macrophages by ten to one, and there are more T cells than β cells (46). CD8 T cells outnumber CD4 cells (47). In most cases, there are islets which appear histologically normal and contain normal numbers of endocrine cells, and are not inflamed. These three populations of islets, therefore, represent examples of islets before, during, and after destruction of β cells in the insulitis process.

The pancreas in middle-age-onset and early-age-onset type 2 diabetics will contain lesions in the islets and exocrine pancreas (48). The lesions of the exocrine pancreas are represented by stromal inflammatory changes, atrophy of the acinar tissues, interstitial fibrosis of lobules, fatty infiltration of the lobules and interlobular areas, arteriosclerotic changes of nutrient arteries, and ductal lesions. Ductal lesions are represented by obstruction or dilatation, with or without epithelial hyperplasia with the possibility of transformation into dysplastic changes. Vascular abnormalities can consist of atherosclerotic and hyaline changes with associated narrowing of lumina.

Although the pathological changes in the pancreas in middle-age-onset diabetes mellitus have been well known for years, the pathological findings of the pancreas in early-onset type 2 diabetes mellitus were only first characterized in 2017. The salient features identified were marked atrophy of the pancreatic parenchyma, ductal obstruction or dilatation (with epithelial hyperplasia) and dysplasia, interstitial fibrosis, fat infiltration, reduction of volume and mass of the β cells, and marked amyloid deposition in the islets.

Although it is generally accepted that pancreatic atrophy is common in type 1 diabetes mellitus (49-51), it is still controversial in middle-age-onset type 2 diabetes mellitus (52-54).

Pancreatitis

Inflammation of the pancreas (pancreatitis) can develop as an acute phenomenon (acute pancreatitis) in response to a variety of parenchymal insults (e.g., alcohol, gall stones, trauma, drugs, scorpion stings,

hypothermia) or can be recurrent, chronic, and relapsing (chronic pancreatitis). Acute pancreatitis has been dealt with in the accompanying article on the topic (55) and will not be dealt with further here, except to remark on the gross appearance of lipolytic fat necrosis, which is most times apparent as focal chalky white spots of saponification in the omentum and mesentery on opening the abdominal cavity (**Image 10**).

Chronic Pancreatitis

Chronic pancreatitis is characterized by the persistent and relentless progression of pancreatic lesions with diverse manifestations and complications (56). It is these characteristics that distinguish chronic from acute pancreatitis, the latter of which usually resolves on removal of the causative insult.

Chronic pancreatitis can develop in the setting of chronic alcoholism, protein energy malnutrition (PEM), ductal obstruction, hyperparathyroidism, renal transplantation, and mucoviscidosis, but can also be of unknown etiology (i.e., idiopathic chronic pancreatitis). Chronic alcoholism is the most common cause of chronic pancreatitis in the western world.

The natural history of chronic pancreatitis is punctuated by recurrent episodes of painful acute pancreatic inflammation, the so-called relapsing or recurrent chronic pancreatitis. Possible complications that may develop include malabsorption; weight loss; diabetes mellitus; ascites and/or pleural effusion; narrowing of the common bile duct, duodenum, and/or colon; left-sided portal hypertension from thrombosis of the splenic, superior mesenteric, and/or portal veins; major arterial hemorrhage; and chronic pain.

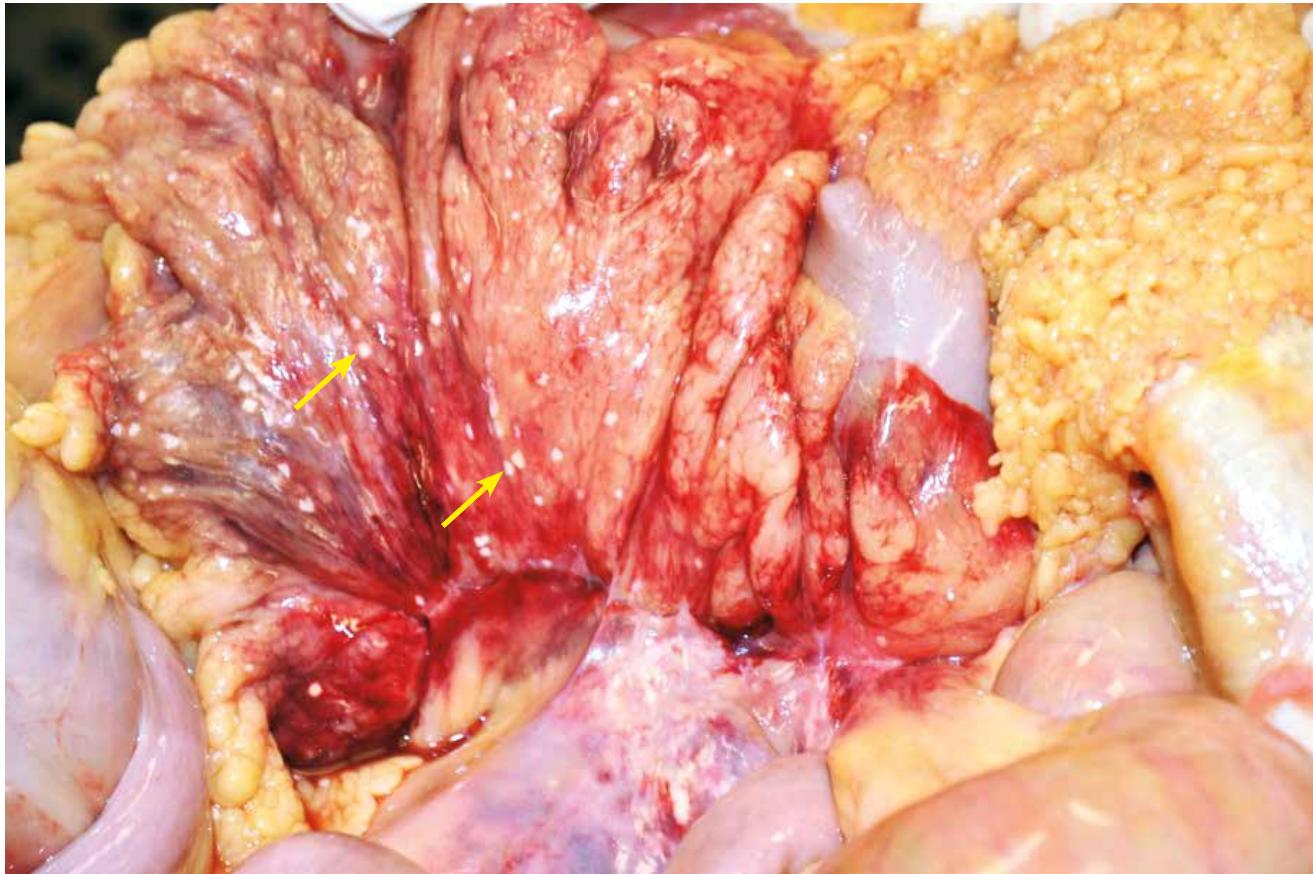


Image 10: Chalky spots of fat necrosis (saponification) (arrows) of the mesentery in a case of acute pancreatitis.



The pathological features of chronic pancreatitis and acute pancreatitis were discussed at the Second International Symposium on Pancreatitis at Marseilles (57). The inflammatory process of chronic pancreatitis is initially directed at the exocrine tissue, which is destroyed first and then followed by destruction of the islets of Langerhans. However, the functional reserve capacity of the pancreas is so great that clinically significant pancreatic insufficiency does not occur until more than 85% of functioning tissue is lost, and only then the clinical sequelae of malabsorption, steatorrhea, and insulin-dependent diabetes will ensue.

Pathologically, established chronic pancreatitis is defined by the combination of fibrosis, parenchymal atrophy, and ductal pathology (**Images 11 A to F**). In the early stages of the disease, the pancreas may be normal but will become firm later on. Its surface may be pink or grey-white and its lobulated appearance will disappear in the most severely affected areas, with a white appearance and little or no bleeding on sectioning of the tissue (58). The main pancreatic duct may be segmentally dilated or exhibit a spiral or corkscrew appearance along its entire length. Grossly evident atrophy of the pancreas occurs in the final stages of disease evolution when the gland is often noticeably shrunken and hardened.

Microscopically, precipitation of proteinaceous material within the lumina of the intercalated and canalicular ductules, from supersaturation of protein enzymes in the pancreatic juice of chronic alcoholics, is the earliest change that is evident. Mineralization of the precipitated proteinaceous material is facilitated by secretion of ionized calcium into the pancreatic juice to give rise to the characteristic “calcification” that develops on progression of the disease (**Image 11A**). Variable chronic inflammatory cell infiltration of the interstitium occurs in association with progressive, destructive loss of acinar tissue and the deposition/replacement by dense fibrous tissue near ducts and within and/or between lobules (**Images 11B to E**). In established disease, the parenchyma is wholly replaced by fibrous tissue punctuated by a few nests of acinar tissue and some resistant residual islet cells. It is unclear why the islet cells persist in this prolonged

inflammatory process and survive the longest. It has been postulated that their extremely rich blood supply makes them more resistant to ischemia (56). Despite their persistence, it must be noted that affected individuals will still develop diabetes mellitus despite the “normal” appearance of the islets with another postulate being that the surrounding fibrous tissue prevents entry of the blood sugar regulating hormones into the circulation by occluding small venules (56).

From an etiological perspective, chronic pancreatitis can be broadly categorized into that due to chronic alcoholism (aCP) and that due to obstruction of the pancreatic ductal system, the so-called obstructive chronic pancreatitis (oCP). These two broad categories of chronic exhibit distinct and differentiable pathological features (56).

In alcoholic chronic pancreatitis, a lobular distribution of lesions is evident with features of both obstruction from protein plugs and dilatation of the canalicular and intercalated ducts (56).

The precipitation of protein plugs in the ductal system of the pancreas of alcoholics is very likely a result of an increase in concentration of the protein content of pancreatic juice, since the pancreatic juice of alcoholic patients is supersaturated with enzyme protein (58, 59). A glycoprotein of 13 500 daltons was isolated from calculi in ten patients with chronic pancreatitis (59-61). The initial component of the protein plug is believed to be the constituent proteins in pure pancreatic juice but the isolated glycoprotein predominates later. Calcium carbonate (calcite) is progressively added to result in the characteristic calcifications seen histologically. Enhanced secretion of calcium ions into the pancreatic juice may facilitate the process (62). Alcohol may cause most of its damaging effects by creating multiple points of ductal obstruction from precipitation of these protein plugs (63). Small, rounded ductular cavities lined by cuboidal epithelium are commonly seen in association with the ductular obstruction and contain either pure pancreatic juice, semi-digested debris and necrotic material, or blood (64). Ductular proliferation proximal to the points of obstruction is thought to be responsible for the fore-

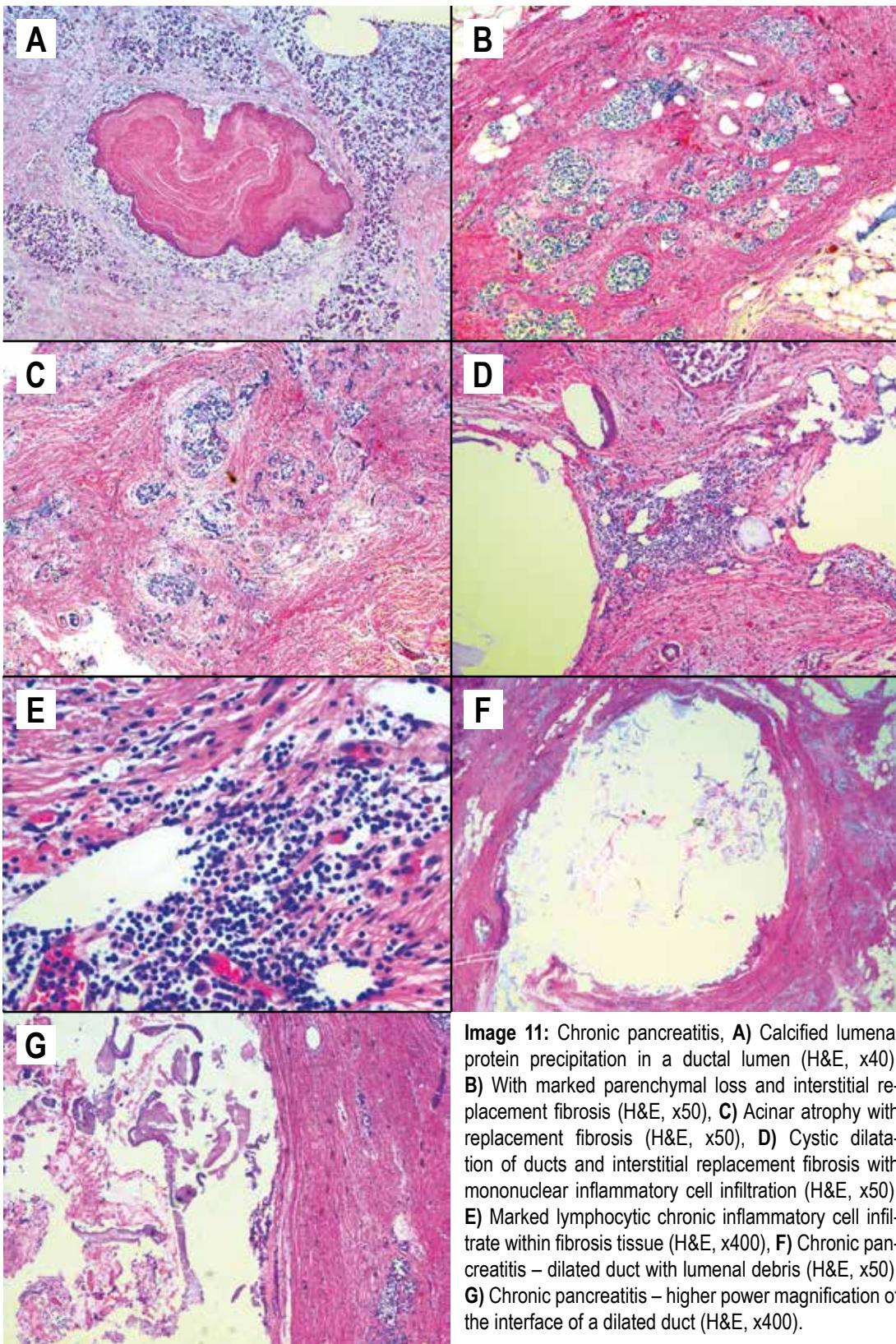


Image 11: Chronic pancreatitis, **A)** Calcified luminal protein precipitation in a ductal lumen (H&E, x40), **B)** With marked parenchymal loss and interstitial replacement fibrosis (H&E, x50), **C)** Acinar atrophy with replacement fibrosis (H&E, x50), **D)** Cystic dilatation of ducts and interstitial replacement fibrosis with mononuclear inflammatory cell infiltration (H&E, x50), **E)** Marked lymphocytic chronic inflammatory cell infiltrate within fibrosis tissue (H&E, x400), **F)** Chronic pancreatitis – dilated duct with luminal debris (H&E, x50), **G)** Chronic pancreatitis – higher power magnification of the interface of a dilated duct (H&E, x400).



going pathology, which constitutes one of the earliest responses to injury (65). The precipitated protein plugs result in ductular dilatation, which is followed by acinar atrophy. A variable inflammatory infiltrate may develop in the interstitium and considerable fibrous tissue is laid down near the ducts and within the lobules. Disappearance of parenchymal tissue occurs with associated progressive replacement by dense fibrous tissue, which often contains scanty inflammatory cell infiltrates (**Image 11E**). The ducts can be either widely dilated or normal. Dilatation of the ducts may be the consequence of occlusion of their lumina by protein plugs in the early stages of the disease, calculi in the late stage, or by traction of adjacent fibrous tissue bands on the outside of the duct walls to give rise to pseudosacculations. In the final stage of the disease, the pancreas is replaced by fibrous tissue with only a few nests of acinar cells and some resilient islet cells remaining. Again, it is unclear why the islets cells persist and survive the longest and it has been postulated that their extremely rich blood supply makes them more resistant to ischemia (56).

Nakamura and colleagues investigated and demonstrated the development, enlargement, and progression of intraluminal protein plugs in chronic pancreatitis with incorporation of calcium carbonate, desquamated epithelium, and intraductal debris by creating three-dimensional profiles of the pancreatic ducts (from the secondary branches through to the terminal acini) by examining serial sections of pancreatic biopsies from patients with chronic pancreatitis, duct obstruction secondary to a small tumor, and from a patient within normal pancreas (66). They showed the calculi were composed of various proteins with a so-called “stone protein” of around 13 000 daltons predominating. Phosphorous and magnesium accounted for less than 5% of their dry weight and sodium less than 0.5%. In cross-section, the calculi contained amorphous centers with progressive concentric layers of calcification being laid down from the outside inwards. All stages of evolution of pancreatic calculi were seen, ranging from the initial proteinaceous plugs to fully formed stones. The mature calculi varied considerably in size, shape, and weight.

In contrast, obstructive pancreatitis is rarely associated with intraductal precipitates with the small ducts often having a normal appearance but with more widespread damage of the exocrine component.

Many investigators stressed that alcoholic chronic pancreatitis was a pathologically distinct entity which can be differentiated from obstructive pancreatitis, with the cardinal features of differentiation being a lobular distribution of lesions, alterations of the intralobular ducts (i.e., dilatation and epithelial atrophy), frequent protein plugs within the ductal lumina, perineural inflammation, and nerve changes as occurs in alcoholic chronic pancreatitis (**Table 1**) (67-69).

The pathological changes of oCP are well described. Obstruction of the pancreatic ductal system can arise from multiple causes that include fibrosis of the ampulla of Vater, papillary inflammation, strictures of the main pancreatic duct (congenital or acquired), and tumors. The macroscopic features of oCP are similar to that of aCP but with markedly different microscopic features. The lesions of obstructive pancreatitis are diffuse and lack a lobular topography with no sparing of the exocrine component of the pancreas. The major ducts maintain a regularity of their caliber with no alternating segments of stenosis and dilatation, but being moderately dilated, with the smaller branches being of normal caliber. The ductal epithelium is intact with empty ductal lumina and rare protein plugs and calcifications (70).

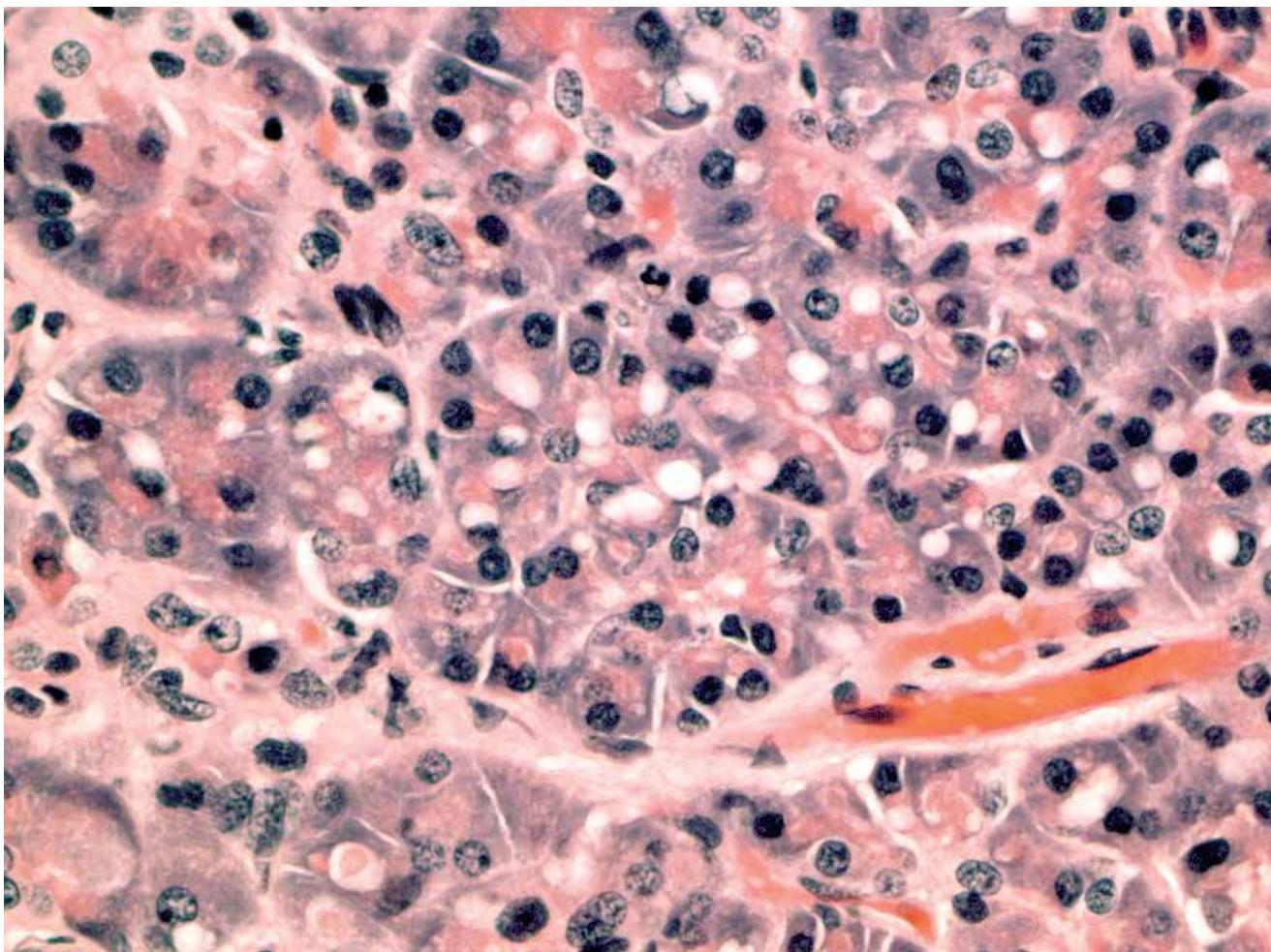
Pancreatic Changes in Hypothermia

Historically, a variety of changes in fatal hypothermia have been described in the medical literature between 1940 to present day and consist of acute inflammation, hemorrhages, and optically-clear cytoplasmic vacuolation of the pancreatic acinar cells (**Image 12**), with a variable reported frequency of between 10-73% (71). No explanations for the pathogenesis of these changes are known.

In 1943, Muller et al. first reported on numerous, fine, granular, non-fatty vacuoles of variable frequency in the protoplasm of pancreatic acinar cells (72, 73), and

Table 1: Comparison of Alcoholic Chronic Pancreatitis and Obstructive Chronic Pancreatitis

Feature	Alcoholic Chronic Pancreatitis	Obstructive Chronic Pancreatitis
Topography of lesions	Lobular distribution	Diffuse involvement (no sparing of exocrine tissue)
Duct morphology: Major ducts	Alternating segments of stenosis and dilatation	Moderately dilated but of regular caliber
Duct morphology: Intralobular ducts	Dilated with epithelial atrophy	Normal caliber. Intact epithelium
Protein plugs and calculi	Frequent luminal protein plugs	Empty lumina; rare protein plugs and calcification
Perineural inflammatory infiltration	Present	Absent


Image 12: Cytoplasmic vacuolation of pancreatic acinar cells (H&E, x400).



this finding was re-reported by Gillner and Waltz in 1971 who had also identified them in epithelial cells (74). However, it must be noted that Buchner, in another study, did not find any pathological changes in the pancreatic islands (75).

In their 2007 publication on their review of 143 cases of fatal hypothermia in which microscopic examination of the pancreas had occurred in 62 cases, Preuss et al. identified 24 cases (38.7%) with optically empty vacuoles of the adenoid cells (71). The vacuoles were located adjacent to the well-circumscribed nuclei, frequently in the basal parts of the cells. A control group of 25 non-hypothermia cases was also examined and no vacuoles were identified.

They concluded from the analysis that hemorrhage and inflammation of the pancreas cannot be regarded as reliable signs of death from hypothermia since bleeding was identified in both cohort and control groups. Only cytoplasmic vacuolation of pancreatic acinar cells appeared more frequently in hypothermia. Vacuulations were not found in either of the control groups, with or without a history of alcoholism. However, they were observed in connection with signs of chronic pancreatitis. Similar findings were described by Gillner and Waltz. Their pathogenesis is postulated to be along the lines of the general hypoxia akin to deaths that occur at high altitude (74). An alternative explanation that has been offered is that the vacuoles in the pancreatic acinar cells reflect impaired pancreatic secretion as a manifestation of the pre-stage of dyschylia, with the secretory pancreatic granules remaining in the acinar cells because of impaired exocytosis instead of being excreted into the pancreatic duct.

Gedigk's textbook of pathology in 1990 stated that every dysfunction of the metabolism of the adenoid cells from hypoxia, hypothermia, or toxic damage resulted in a decrease or loss of the permeability barrier of the cells with the loss of protection against auto digestion (76). The permeability barrier ensured that the enzymes did not infiltrate the cytoplasm of the acinar cells. He stated that enzymatic auto digestion of the acinar cells because of impaired permeability is the cause of acute pancreatitis. However, cytoplasmic

vacuolation of acinar cells was not described by him as a morphological sign of pancreatitis. Since subclinical acute pancreatitis was observed by other authors in fatalities with heavy shock or pronounced circulatory depression, they concluded that the changes in the acinar cells or pancreatic duct system are the result of hypoxia (77). As such, the cytoplasmic vacuoles of the pancreatic acinar cells are either vesicles filled with enzymes that could not be secreted because of impaired exocytosis or autophagic vacuoles on the base of an impaired permeability of the acinar cells, or fatty degeneration from hypoxia (76, 77).

Preuss et al. reported that microscopically observable, optically empty cytoplasmic vacuoles of the pancreatic acinar cells from impaired exocytosis have been known as a sign of chronic alcoholism for years and are associated with leukocytic infiltration and fibrosis (71). Since they identified optically empty vacuoles in 38.7% of their cases of hypothermia in the absence of other signs of chronic pancreatitis, the presence of the vacuoles was interpreted as an additional sign of hypothermia. However, the content of the vacuoles in hypothermia remains unanswered and further investigations are needed. They were certain that macroscopic or microscopic hemorrhage and inflammation can be ruled out as part of the diagnostic criteria for fatal hypothermia.

Cytoplasmic vacuolation of the cells of the anterior pituitary gland has also been described in hypothermia (78, 79).

Tumors of the Pancreas

Both benign and malignant tumors of the pancreas can develop in either the exocrine or endocrine components.

Adenocarcinomas of the pancreas are relatively infrequent in the practice of forensic pathology as most times the diagnosis is well known after it has been clinically established and result in a natural cause and manner of death. Most times, these cases do not come to the attention of forensic pathologists and, as such, malignant neoplasms of the pancreas do not usually

present for postmortem examination unless there is some peripheral medicolegal issue which has arisen related either to the diagnosis and/or treatment of the lesion. Therefore, the forensically relevant neoplastic lesions of the pancreas consist of physiologically active tumors of the endocrine portion of the gland, more so those that secrete insulin.

Endocrine tumors of the pancreas account for 1 to 2% of all pancreatic neoplasms (80).

They were formerly known as islet cell tumors but this term is only properly applied to tumors composed of cells normally present in the pancreatic islets (i.e., insulin, glucagon, somatostatin, and pancreatic poly-

peptide) and pancreatic endocrine tumor (PET) is the preferred more generic name (81, 82).

They may also be referred to as pancreatic neuroendocrine tumors (PanNET or PNET), which are neuroendocrine neoplasms arising from cells of the endocrine and nervous system within the pancreas (**Images 13 and 14**).

Functional tumors associated with secretion of a relevant hormone are classified according to the hormone produced (e.g., insulinoma, glucagonoma, somatostatinoma, or vipoma) and the related endocrine syndrome. This is also applicable to neoplasms associated with syndromes from hormones produced by

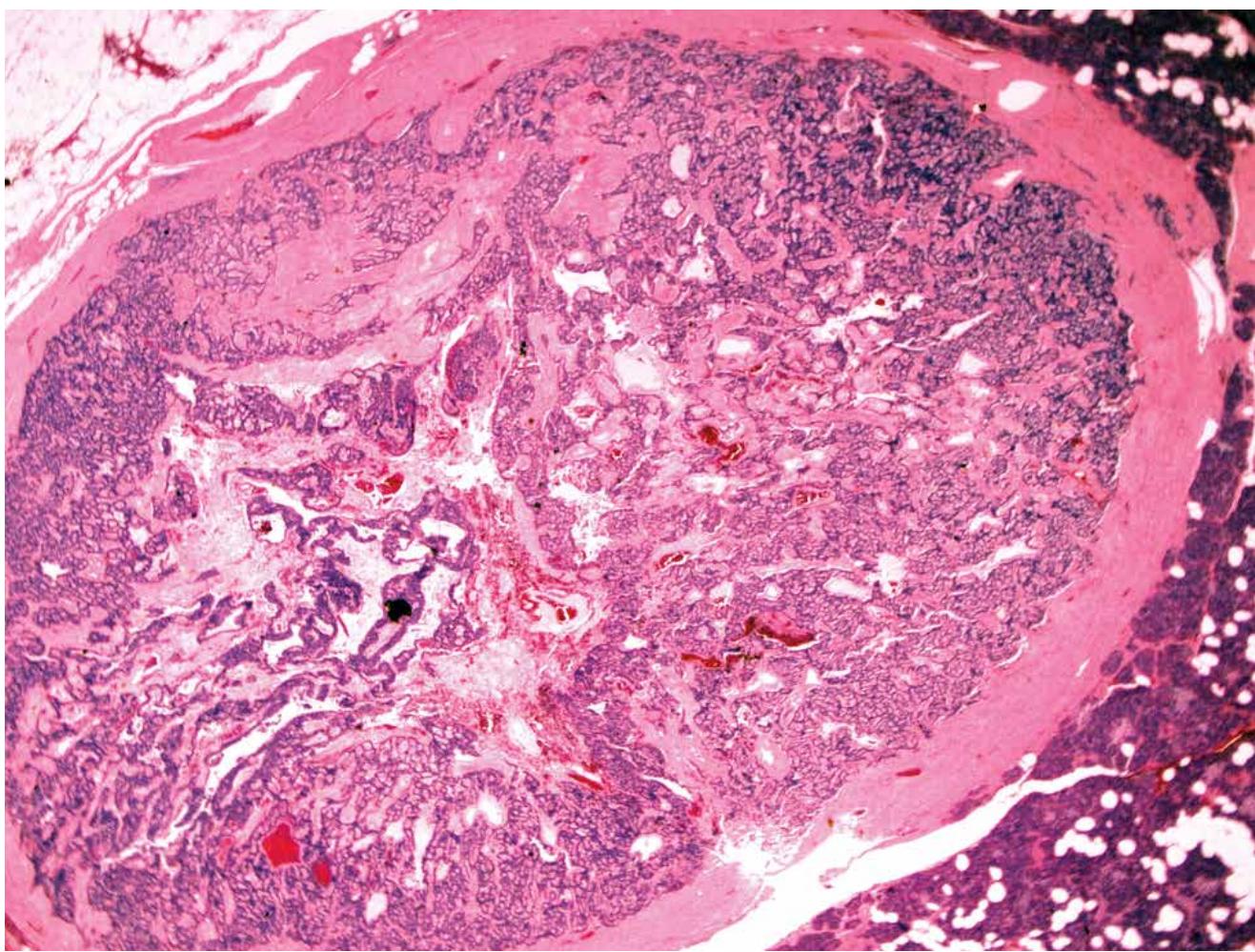


Image 13: Encapsulated pancreatic endocrine tumor (H&E, x50).

cells which are ectopic to the adult pancreas such as gastrin, adrenocorticotrophic hormone, serotonin, or growth hormone releasing factor. Pancreatic endocrine tumors not associated with distinct hormonal syndrome are otherwise classified as nonfunctioning. Sixty to eighty five percent of pancreatic endocrine tumors are functional as determined in a large series of surgically removed tumors, with insulinoma being the most frequent subtype, accounting for up to 70%, followed by gastrinomas (80, 82-84). Approximately 15 to 25% of all pancreatic endocrine tumors may be associated with multiple endocrine neoplasia type 1 (MEN-1).

The threshold diameter for grossly evident tumors is 0.5 cm and tumors below this size are considered microadenomas (85). The occurrence of multiple microadenomas of the pancreas may be seen in MEN-1 syndrome. Multiple endocrine neoplasia type 1 is an inherited predisposition to tumors of the anterior pituitary, parathyroid glands, pancreas, duodenum, and occasionally in the stomach, ileum, lung, and thymus (86-88). The *MEN 1* gene is a tumor suppressor gene that codes for a protein called menin (89).

The prevalence of pancreatic endocrine tumors is estimated to be less than one in 100 000 and the incidence rate is deemed to be substantially lower because of the inherently more favorable prognosis generally (90).

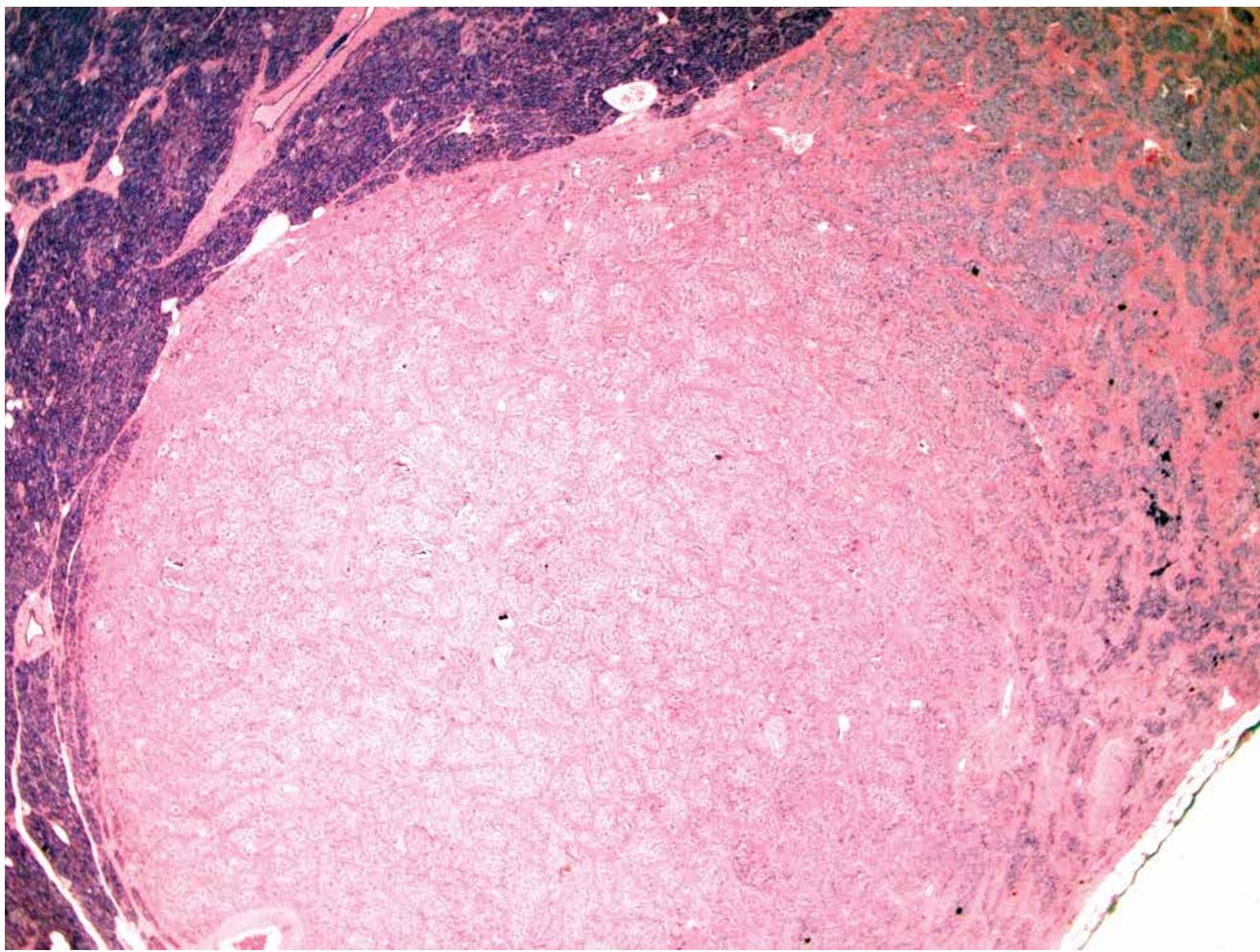


Image 14: Pancreatic endocrine tumor (H&E, x50).



Functional insulinomas will result in hyperinsulinemic hypoglycemia, which can prove to be fatal and needs to be differentiated from the exogenous administration of insulin. Classically, patients with functional insulinomas and hyperinsulinemic hypoglycemia will present with a history of mental confusion, weakness, fatigue, and seizures whilst fasting, and blood glucose concentrations below 50 mg% with immediate resolution of their symptoms following ingestion of glucose, which constitutes the so-called "Whipple triad" (91). Analysis of serum extracted from postmortem blood for insulin and C-peptide will reveal elevated concentrations of both insulin and C-peptide in an approximately 1:1 ratio, in contrast to exogenous administration of insulin in which the concentration of insulin will be many times greater than the concentration of C-peptide. Given that many tumors are microadenomas, it may be impossible to identify the location of the tumor in the pancreas, duodenum, or elsewhere even on diligent examination and serial sectioning. In the absence of a grossly or microscopically identifiable insulinoma, it is the ratio of insulin to C-peptide that will establish the postmortem diagnosis that a functional insulin-secreting endocrine neoplasm was responsible.

Functional gastrinomas result from the inappropriate secretion of gastrin and give rise to the clinical Zollinger-Ellison syndrome (ZES), which is characterized by gastric acid hypersecretion, intractable peptic ulceration, and occasionally severe diarrhea (92, 93). Zollinger-Ellison syndrome is sporadic in 60 to 75% of cases with the remainder being a manifestation of MEN-1 syndrome.

The clinical manifestation of glucagonoma syndrome results from the catabolic action of excessively elevated glucagon concentrations (94) and consists of weight loss, mild glucose intolerance, depression, normochromic normocytic anemia, a tendency to develop deep vein thrombosis, and a skin rash known as necrolytic migratory erythema (95). It has not been described in extra-pancreatic glucagon producing tumors.

The Verner-Morrison syndrome results from the excessive secretion of vasoactive intestinal polypeptide (VIP) by VIPomas and is defined by watery diarrhea, hypokalemia, and achlorhydria (WDHA) (96).

An additional, less well defined syndrome results from the widespread inhibitory effects of somatostatin when produced by a pancreatic endocrine tumor and consists of diabetes, cholecystolithiasis, steatorrhea, indigestion, hypochlorhydria, and occasional anemia (97, 98).

Other rare endocrine syndromes are infrequently observed with pancreatic endocrine tumors from ectopic hormone production by tumors of the pancreas and can be due to the production of adrenocorticotrophic hormone (ACTH) in Cushing syndrome, serotonin (a typical carcinoid syndrome), growth hormone releasing factor (acromegaly), and parathyroid hormone (PTH) in paraneoplastic hypercalcemia (99-104). Combinations of various hormonal syndromes or transitions have been described but are extremely rare.

Nonfunctional endocrine neoplasms of the pancreas tend to become clinically apparent from symptoms associated with their large size, invasion of adjacent organs, or the development of metastases. The relevant history will be of abdominal pain, jaundice, and weight loss. Infrequently, they may present as pancreatitis (105) or in association with hematologic abnormalities or eosinophilic infiltration of the skin (106, 107).

Pancreatic endocrine neoplasms are potentially malignant and the rate of malignancy varies amongst the different tumor types. Insulinomas have the lowest incidence of malignancy of only 5-15% (90, 108), whereas 60-85% of the other tumor types, inclusive of nonfunctioning tumors, are malignant (109).

In general, malignant metastasizing pancreatic endocrine tumors are slow-growing indolent neoplasms with survival from the time of diagnosis usually being in the range of two to ten years. Metastasizing gastrinomas arising in the pancreas carry a shorter survival compared to those arising in the duodenum (110, 111).

CONCLUSION

The spectrum of traumatic and natural disease pathology that can affect the adult pancreas is multiple and varied. The more commonly encountered entities have been presented from both pathological and pathophysiological perspectives. Acute pancreatitis has not been dealt with since it has been specifically addressed in a separate article in this issue (55). Although many of the conditions are extremely rare and may never be encountered in the professional lifetimes of an individual pathologist, forensic pathologists still need to be aware of them in case they are one day faced with these entities as possible diagnoses at autopsy because of clinical concerns raised in life or to explain unexpected biochemical results and unexpected deaths.

REFERENCES

- 1) Moore KL. The pancreas. In: Clinically-oriented anatomy. 3rd ed. Baltimore: Lippincott Williams & Wilkins; 1992. p. 187-9.
- 2) Craig MH, Talton DS, Hauser CJ, Poole GV. Pancreatic injuries from blunt trauma. *Am Surg*. 1995 Feb; 61(2):125-8. PMID: 7531962.
- 3) Bradley EL 3rd, Young PR Jr, Chang MC, et al. Diagnosis and initial management of blunt pancreatic trauma: guidelines from a multi-institutional review. *Ann Surg*. 1998 Jun; 227(6):861-9. PMID: 9637549. PMCID: PMC1191392. <https://doi.org/10.1097/00000658-199806000-00009>.
- 4) Cogbill TH, Moore EE, Feliciano DV, et al. Conservative management of duodenal trauma: a multicentric perspective. *J Trauma*. 1990 Dec; 30(12):1469-75. PMID: 2258957. <https://doi.org/10.1097/00005373-199012000-00005>.
- 5) Madiba TE, Mokoena TR. Favourable prognosis of the surgical drainage of gunshot, stab and blunt trauma of the pancreas. *Br J Surg*. 1995 Sep; 82(9):1236-9. PMID: 7552005. <https://doi.org/10.1002/bjs.1800820926>.
- 6) Rougé-Maillart C, Tracqui A, Tortel MC, et al. Fetal blunt pancreatic trauma secondary to assault and battery: a case report. *Int J Legal Med*. 2001 Dec; 115(3):162-4. PMID: 11775019. <https://doi.org/10.1007/s004140100235>.
- 7) Errouhani A, Ameur A, Chkoff R, et al. Les traumatismes duodéno-pancréatiques. *J Chir (Paris)*; 1997; 134:9-13. French.
- 8) Sim EH, Mandal AK, Schlater T, et al. Factors affecting the outcome in pancreatic trauma. *J Trauma*. 1984 Feb; 24(2):125-8. PMID: 6198528. <https://doi.org/10.1097/00005373-198402000-00006>.
- 9) Davis JJ, Cohn I Jr, Nance FC. Diagnosis and management of blunt abdominal trauma. *Ann Surg*. 1976 Jun; 183(6):672-8. PMID: 973754. PMCID: PMC1344272. <https://doi.org/10.1097/00000658-197606000-00009>.
- 10) Graham JM, Mattox KL, Jordan GL Jr. Traumatic injury is of the pancreas. *Am J Surg*. 1978 Dec; 136(6):744-8. PMID: 717659. [https://doi.org/10.1016/0002-9610\(78\)90349-5](https://doi.org/10.1016/0002-9610(78)90349-5).
- 11) Carrel T, Lerut J, Niederhauser U, et al. [Diagnosis and treatment of traumatic injuries of the duodenum and pancreas: 21 cases]. *J Chir (Paris)*. 1990 Oct; 127(10):438-44. PMID: 2262516.
- 12) Goins WA, Rodriguez A, Joshi M, Jacobs D. Intra-abdominal abscess after blunt abdominal trauma. *Ann Surg*. 1990 Jul; 212(1):60-5. PMID: 2363605. PMCID: PMC1358075. <https://doi.org/10.1097/00000658-199007000-00009>.
- 13) Wisner DH, Wold RL, Frey CF. Diagnosis and treatment of pancreatic injuries. An analysis of management principles. *Arch Surg*. 1990 Sep; 125(9):1109-13. PMID: 1698047. <https://doi.org/10.1001/archsurg.1990.01410210035004>.
- 14) Northrup WF 3rd, Simmons RL. Pancreatic trauma: a review. *Surgery*. 1972 Jan; 71(1):27-43. PMID: 4550235.
- 15) Karl HW, Chandler JG. Mortality and morbidity of pancreatic injury. *Am J Surg*. 1977 Nov; 134(5):549-54. PMID: 920878. [https://doi.org/10.1016/0002-9610\(77\)90431-7](https://doi.org/10.1016/0002-9610(77)90431-7).
- 16) Di Maio D, Di Maio V. Pancreas. In: Forensic pathology. 2nd ed. Boca Raton: CRC Press; 2001. p. 134-5.
- 17) Pena SDJ, Medovy H. Child abuse and traumatic pseudocyst of the pancreas. *J Pediatr*. 1973 Dec; 83(6):1026-8. PMID: 4757515. [https://doi.org/10.1016/s0022-3476\(73\)80542-6](https://doi.org/10.1016/s0022-3476(73)80542-6).
- 18) Patton JH Jr, Fabian TC. Complex pancreatic injuries. *Surg Clin North Am*. 1996 Aug; 76(4):783-95. PMID: 8782473. [https://doi.org/10.1016/s0039-6109\(05\)70480-1](https://doi.org/10.1016/s0039-6109(05)70480-1).
- 19) Ivatury RR, Nassoura ZE, Simon RJ, Rodriguez A. Complex duodenal injuries. *Surg Clin North Am*. 1996 Aug; 76(4):797-812. PMID: 8782474. [https://doi.org/10.1016/s0039-6109\(05\)70481-3](https://doi.org/10.1016/s0039-6109(05)70481-3).
- 20) Saukko P, Knight B. Knight's forensic pathology. 3rd ed. Boca Raton: CRC Press; c2004. Chapter 6, Chest and abdominal injuries; p. 222-34.
- 21) Jacombs AS, Wines M, Holland A, et al. Pancreatic trauma in children. *J Pediatr Surg*. 2004 Jan; 39(1):96-9. PMID: 14694281. <https://doi.org/10.1016/j.jpedsurg.2003.09.011>.
- 22) Barnes PM, Norton CM, Dunstan FD, et al. Abdominal injury due to child abuse. *Lancet*. 2005 Jul 16-22; 366(9481):234-5. PMID: 16023514. [https://doi.org/10.1016/s0140-6736\(05\)66913-9](https://doi.org/10.1016/s0140-6736(05)66913-9).
- 23) Gaines BA, Shultz BS, Morrison K, Ford HR. Duodenal injuries in children: beware of child abuse. *J Pediatr Surg*. 2004 Apr; 39(4):600-2. PMID: 15065036. <https://doi.org/10.1016/j.jpedsurg.2003.12.010>.
- 24) Callahan K., Knight LD. The pancreas in child abuse. *Acad Forensic Pathol*. 2018 Jun; 8(2):219-38. <https://doi.org/10.23907/2018.016>.
- 25) Mallick IH, Thoufeeq MH. Pancreatic trauma from a book. *JOP*. 2004 Jul; 5(4):217-9. PMID: 15254350.
- 26) Stalnaker RL, McElhaney JH, Roberts VL. Human torso response to blunt trauma. In: Human impact response: measurement and simulation. New York: Plenum Press; 1973. p. 182-99.
- 27) Cooper GJ, Taylor DE. Biophysics of impact injury to the chest and abdomen. *J R Army Med Corps*. 1989 Jun; 135(2):58-67. PMID: 2527980. <https://doi.org/10.1136/jramc-135-02-04>.
- 28) Lucas CE. Diagnosis and treatment of pancreatic and duodenal injury. *Surg Clin North Am*. 1977 Feb; 57(1):49-65. PMID: 854854. [https://doi.org/10.1016/s0039-6109\(16\)41133-3](https://doi.org/10.1016/s0039-6109(16)41133-3).
- 29) Akhrass R, Yafee MB, Brandt CP, et al. Pancreatic trauma: a ten-year multi-institutional experience. *Am Surg*. 1997 Jul; 63(7):598-604. PMID: 9202533.
- 30) McManus JFA. General pathology: the biological aspects of disease. Chicago: Year Book Medical Publishers; 1966. 739 p.
- 31) Robbins SL, Cotran RS. Pathologic basis of disease. 2nd ed. Philadelphia: W.B. Saunders; 1979. 1653 p.
- 32) Shimizu M, Hayashi T, Saitoh Y, et al. Postmortem autolysis in the pancreas: multivariate statistical study. The influence of clinicopathological conditions. *Pancreas*. 1990; 5(1):91-4. PMID: 2293713. <https://doi.org/10.1097/00006676-199001000-00013>.

- 33) Nevalainen TJ, Anttila J. Ultrastructural and functional changes in pancreatic acinar cells during autolysis. *Virchows Arch B Cell Pathol.* 1977 Aug 10; 24(3):197-207. PMID: 410152.
- 34) Boyer PD, Lardy H, Myrback K. The enzymes. 2nd ed. New York: London: Academic Press; 1960. p. 233-41.
- 35) Bessis M. Ciba Foundation Symposium - Cellular injury. London: Churchill Livingstone; c1964. Chapter 13, Studies on cell agony and death: an attempt at classification; p. 287-328.
- 36) Wehner F, Wehner HD, Subke J. Delimitation of the time of death by immunohistochemical detection of glucagon in pancreatic alpha-cells. *Forensic Sci Int.* 2001 Dec 27; 124(2-3):192-9. PMID: 11792511. [https://doi.org/10.1016/s0379-0738\(01\)00608-9](https://doi.org/10.1016/s0379-0738(01)00608-9).
- 37) Stefan Y, Orci L, Mulaisse-Lugae F, et al. Quantitation of endocrine cell content in the pancreas of nondiabetic and diabetic humans. *Diabetes.* 1982 Aug; 31(8 Pt 1):694-700. PMID: 6131002. <https://doi.org/10.2337/diab.31.8.694>.
- 38) Gepts W. Pathologic anatomy of the pancreas in juvenile diabetes mellitus. *Diabetes.* 1965 Oct; 14(10):619-33. PMID: 5318831. <https://doi.org/10.2337/diab.14.10.619>.
- 39) Foulis AK, Liddle CN, Farquharson MA, et al. The histopathology of the pancreas in type 1 (insulin-dependent) diabetes mellitus: a 25-year review of deaths in patients under 20 years of age in the United Kingdom. *Diabetologia.* 1986 May; 29(5):267-74. PMID: 3522324. <https://doi.org/10.1007/bf00452061>.
- 40) Gamble DR, Taylor KW, Cumming H. Coxsackie viruses and diabetes mellitus. *Br Med J.* 1973 Nov 3; 4(5887):260-2. PMID: 4753237. PMCID: PMC1587352. <https://doi.org/10.1136/bmj.4.5887.260>.
- 41) Yoon JW, Austin M, Onodera T, Notkins AL. Isolation of a virus from the pancreas of a child with diabetic ketoacidosis. *N Engl J Med.* 1979 May 24; 300(21):1173-9. PMID: 219345.
- 42) Bottazzo GF, Florin-Christensen A, Doniach D. Islet-cell antibodies in diabetes mellitus with autoimmune polyendocrine deficiencies. *Lancet.* 1974 Nov 30; 2(7892):1279-83. PMID: 4139522. [https://doi.org/10.1016/s0140-6736\(74\)90140-8](https://doi.org/10.1016/s0140-6736(74)90140-8).
- 43) MacCuish AC, Irvine WJ, Barnes EW, Duncan LJ. Antibodies to pancreatic islet cells in insulin-dependent diabetics with coexistent autoimmune disease. *Lancet.* 1974 Dec 28; 2(7896):1529-31. PMID: 4140978. [https://doi.org/10.1016/s0140-6736\(74\)90281-5](https://doi.org/10.1016/s0140-6736(74)90281-5).
- 44) MacCuish AC, Jordan J, Campbell CJ, et al. Cell-mediated immunity to human pancreas in diabetes mellitus. *Diabetes.* 1974 Aug; 23(8):693-7. PMID: 4478993. <https://doi.org/10.2337/diab.23.8.693>.
- 45) Foulis AK, Stewart JA. The pancreas in recent-onset type 1 (insulin-dependent) diabetes mellitus: insulin content of islets, insulitis and associated changes in the exocrine acinar tissue. *Diabetologia.* 1984 Jun; 26(6):456-61. PMID: 6381192. <https://doi.org/10.1007/bf00262221>.
- 46) Foulis AK, McGill M, Farquharson MA. Insulitis in type 1 (insulin-dependent) diabetes mellitus in man--macrophages, lymphocytes, and interferon-gamma containing cells. *J Pathol.* 1991 Oct; 165(2): 97-103. PMID: 1744803. <https://doi.org/10.1002/path.1711650203>.
- 47) Bottazzo GF, Dean BM, McNally JM, et al. In situ characterization of autoimmune phenomena and expression of HLA molecules in the pancreas in diabetic insulitis. *N Engl J Med.* 1985 Aug 8; 313(6):353-60. PMID: 3159965. <https://doi.org/10.1056/nejm198508083130604>.
- 48) Xin A, Mizukami H, Inaba W, et al. Pancreas atrophy and islet amyloid deposition in patients with elderly-onset type 2 diabetes. *J Clin Endocrinol Metab.* 2017 Sep 1; 102(9):3162-3171. PMID: 28505316. <https://doi.org/10.1210/jc.2016-3735>.
- 49) Lohr M, Kloppel G. Residual insulin positivity and pancreatic atrophy in relation to duration of chronic type 1 (insulin-dependent) diabetes mellitus and microangiopathy. *Diabetologia.* 1987 Oct; 30(10):757-62. PMID: 3322901. <https://doi.org/10.1007/bf00275740>.
- 50) Campbell-Thompson ML, Kaddis JS, Wasserfall C, et al. The influence of type 1 diabetes on pancreatic weight. *Diabetologia.* 2016 Jan; 59(1):217-21. PMID: 26358584. PMCID: PMC4670792. <https://doi.org/10.1007/s00125-015-3752-z>.
- 51) Kobayashi T, Aida K, Fukui T, et al. Pancreatic ductal hyperplasia/dysplasia with obstructive chronic pancreatitis: an association with reduced pancreatic weight in type 1 diabetes. *Diabetologia.* 2016 Apr; 59(4):865-7. PMID: 26820736. PMCID: PMC4779123. <https://doi.org/10.1007/s00125-016-3867-x>.
- 52) Alzaid A, Aideyan O, Nawaz S. The size of the pancreas in diabetes mellitus. *Diabet Med.* 1993 Oct; 10(8):759-63. PMID: 8261759. <https://doi.org/10.1111/j.1464-5491.1993.tb00160.x>.
- 53) Goda K, Sasaki E, Nagata K, et al. Pancreatic volume in type 1 and type 2 diabetes mellitus. *Acta Diabetol.* 2001; 38(3):145-9. PMID: 11827436. <https://doi.org/10.1007/s005920170012>.
- 54) Macauley M, Percival K, Thelwall PE, et al. Altered volume, morphology and composition of the pancreas in type 2 diabetes. *PLoS One.* 2015 May 7; 10(5):e0126825. PMID: 25950180. PMCID: PMC4423920. <https://doi.org/10.1371/journal.pone.0126825>.
- 55) Stoppacher R. Sudden death due to acute pancreatitis. *Acad Forensic Pathol.* 2018 Jun; 8(2):239-55. <https://doi.org/10.23907/2018.017>.
- 56) Singh SM, Reber HA. The pathology of chronic pancreatitis. *World J Surg.* 1990 Jan-Feb; 14(1):2-10. PMID: 2407035. <https://doi.org/10.1007/bf01670538>.
- 57) Gyr K, Singer M, Sarles H. Pancreatitis - concepts and classification. Amsterdam: Elsevier; 1984. 450 p.
- 58) Sarles H, Sahel J, Staub JL, et al. Chronic pancreatitis. In: The exocrine pancreas. Philadelphia: W.B. Saunders; 1979.
- 59) De Caro A, Lohse J, Sarles H. Characterization of a protein isolated from pancreatic calculi of men suffering from chronic calcifying pancreatitis. *Biochem Biophys Res Commun.* 1979 Apr 27; 87(4):1176-82. PMID: 111670. [https://doi.org/10.1016/s0006-291x\(79\)80031-5](https://doi.org/10.1016/s0006-291x(79)80031-5).
- 60) Sarles H, Sahel J. Pathology of chronic calcifying pancreatitis. *Am J Gastroenterol.* 1976 Aug; 66(2):117-39. PMID: 788498.
- 61) Lohse J, Verine HJ, Sarles H. Studies on pancreatic stones. I. In vitro dissolution. *Digestion.* 1981; 21(3):125-32. PMID: 7215715. <https://doi.org/10.1159/000198553>.
- 62) Sarles H. Chronic calcifying pancreatitis--chronic alcoholic pancreatitis. *Gastroenterology.* 1974 Apr; 66(4):604-16. PMID: 4595185.
- 63) Sarles H, Tiscornia, O, Palasciano G. Chronic alcoholism and canine exocrine pancreas secretion. A long-term follow-up study. *Gastroenterology.* 1977 Feb; 72(2):238-43. PMID: 556609.
- 64) Clain JE, Barbezat GO, Marks IN. Exocrine pancreatic enzyme and calcium secretion in health and pancreatitis. *Gut.* 1981 May; 22(5):355-8. PMID: 7250746. PMCID: PMC1419246. <https://doi.org/10.1136/gut.22.5.355>.
- 65) Kennedy RH, Bockman DE, Viscanga L, et al. Pancreatic extracellular matrix alteration in chronic pancreatitis. *Pancreas.* 1987; 2(1):61-72. PMID: 3575315. <https://doi.org/10.1097/00006676-198701000-00010>.
- 66) Nakamura K, Sarles H, Payan H. Three-dimensional reconstruction of the pancreatic ducts in chronic pancreatitis. *Gastroenterology.* 1972 May; 62(5):942-9. PMID: 5029079.
- 67) Payan H, Sarles H, Demirdjian M, et al. Study of the histological features of chronic pancreatitis by correspondence analysis. Identification of chronic calcifying pancreatitis as an entity. *Rev Eur Etud Clin Biol.* 1972 Aug-Sep; 17(7):663-70. PMID: 4650268.
- 68) Tasso F, Stemmelin N, Sarles H, Clop J. Comparative morphometric study of the human pancreas in its normal state and in primary chronic calcifying pancreatitis. *Biomedicine.* 1973 Mar; 18(2):134-44. PMID: 4354463.



- 69) Sahel J, Cros RC, Durbec JP, et al. Multicenter pathological study of chronic pancreatitis. Morphological regional variations and differences between chronic calcifying pancreatitis and obstructive pancreatitis. *Pancreas*. 1986; 1(6):471-7. PMID: 3562440. <https://doi.org/10.1097/00006676-198611000-00001>.
- 70) Reber HA. Chronic pancreatitis: etiology, pathology and diagnosis. In: Surgical diseases of the pancreas. Philadelphia: Lea and Febiger; 1987.
- 71) Preuss J, Lignitz E, Dettmeyer R, Madea B. Pancreatic changes in cases of death due to hypothermia. *Forensic Sci Int*. 2007 Mar 2; 166(2-3):194-8. PMID: 16829005. <https://doi.org/10.1016/j.forsciint.2006.05.034>.
- 72) Muller E, Rotter W, Carow G, Kloos KF. Über Untersuchungsergebnisse bei Todesfällen nach allgemeiner Unterkühlung des Menschen in Seenot. *Beitr Pathol Anat*. 1943; 108:552-89. German.
- 73) Muller E. [Pathology of general hypothermia in men]. *Acta Neuroveg (Wien)*. 1955; 11(1-4):146-68. PMID: 13258195. German.
- 74) Gillner E, Waltz H. Zur symptomatik des erfrierens. *Krim Forens Wiss*. 1971; 5:179-185. German.
- 75) Buchner F. Die pathologie der unterkühlung. *Klin Wochenschr*. 1943; 22:89-92.
- 76) Gedigk P. Pankreas, in: Eder, Gedigk (Eds.), Allgemeine pathologie und pathologische anatomie. Berlin: Springer;1990. p. 623-30. German.
- 77) Remmele W. Pathologie, vol. 3. Berlin: Springer; 1997.
- 78) Doberentz E, Preuss-Wössner J, Kuchelmeister K, Madea B. Histological examination of the pituitary glands in cases of fatal hypothermia. *Forensic Sci Int*. 2011 Apr 15; 207(1-3):46-9. PMID: 20864279. <https://doi.org/10.1016/j.forsciint.2010.08.022>.
- 79) Ishikawa T, Miyaishi S, Tachibana T, et al. Fatal hypothermia related vacuolation of hormone-producing cells in the anterior pituitary. *Leg Med (Tokyo)*. 2004 Jul; 6(3):157-63. PMID: 15231284. <https://doi.org/10.1016/j.legalmed.2004.05.004>.
- 80) Solcia E, Capella C, Kloppel G. Tumors of the pancreas. In: AFIP Atlas of tumor pathology. 3rd series, fascicle 20. Washington: Armed Forces Institute of pathology; 1997.
- 81) Heitz PU, Kasper M, Polak JM, Kloppel G. Pancreatic endocrine tumors: immunocytochemical analysis of 125 tumors. *Hum Pathol*. 1982 Mar; 13(3):263-71. PMID: 7076209. [https://doi.org/10.1016/s0046-8177\(82\)80183-4](https://doi.org/10.1016/s0046-8177(82)80183-4).
- 82) Kloppel G, Heitz PU. Pancreatic endocrine tumors. *Pathol Res Pract*. 1988 Apr; 183(2):155-68. PMID: 2898775. [https://doi.org/10.1016/s0344-0338\(88\)80043-8](https://doi.org/10.1016/s0344-0338(88)80043-8).
- 83) Kent RB 3rd, van Heerden JA, Weiland LH. Nonfunctioning islet cell tumors. *Ann Surg*. 1981 Feb; 193(2):185-90. PMID: 6258500. PMCID: PMC1345039. <https://doi.org/10.1097/00000658-198102000-00010>.
- 84) Broughan TA, Leslie JD, Soto JM, Hermann RE. Pancreatic islet cell tumors. *Surgery*. 1986 Jun; 99(6):671-8. PMID: 2424108.
- 85) Kloppel G, Willemer S, Stamm B, et al. Pancreatic lesions and hormonal profile of pancreatic tumors in multiple endocrine neoplasia type I. An immunocytochemical study of nine patients. *Cancer*. 1986 May 1; 57(9):1824-32. PMID: 2420439. [https://doi.org/10.1002/1097-0142\(19860501\)57:9%3C1824::aid-cncr2820570920%3E3.0.co;2-q](https://doi.org/10.1002/1097-0142(19860501)57:9%3C1824::aid-cncr2820570920%3E3.0.co;2-q).
- 86) Rosai J, Higa E, Davie J. Mediastinal endocrine neoplasm in patients with multiple endocrine adenomatosis. A previously unrecognized association. *Cancer*. 1972 Apr; 29(4):1075-83. PMID: 4401563. [https://doi.org/10.1002/1097-0142\(197204\)29:4%3C1075::aid-cncr2820290457%3E3.0.co;2-o](https://doi.org/10.1002/1097-0142(197204)29:4%3C1075::aid-cncr2820290457%3E3.0.co;2-o).
- 87) Duh QY, Hybarger CP, Geist R, et al. Carcinoids associated with multiple endocrine neoplasia syndromes. *Am J Surg*. 1987 Jul; 154(1): 142-8. PMID: 2886072. [https://doi.org/10.1016/0002-9610\(87\)90305-9](https://doi.org/10.1016/0002-9610(87)90305-9).
- 88) Solcia E, Capella C, Fiocca R, et al. Gastric argyrophil carcinoidosis in patients with Zollinger-Ellison syndrome due to type 1 multiple endocrine neoplasia. A newly recognized association. *Am J Surg Pathol*. 1990 Jun; 14(6):503-13. PMID: 1970928. <https://doi.org/10.1097/00000478-199006000-00001>.
- 89) Chandrasekharappa SC, Guru SC, Manickam P, et al. Positional cloning of the gene for multiple endocrine neoplasia-type 1. *Science*. 1997 Apr 18; 276(5311):404-7. PMID: 9103196. <https://doi.org/10.1126/science.276.5311.404>.
- 90) Moldrow RE, Connelly RR. Epidemiology of pancreatic cancer in Connecticut. *Gastroenterology*. 1968 Dec; 55(6):677-86. PMID: 4302500.
- 91) Field JB. Insulinoma. In: Endocrine tumors. Boston: Blackwell Scientific Publications; 1993. p. 497-530.
- 92) Jensen RT, Gardner JD. Gastrinoma. In: The pancreas: biology, pathobiology and disease. New York: Raven Press; 1993.
- 93) Zollinger RM. Gastrinoma: The Zollinger-Ellison syndrome. *Semin Oncol*. 1987 Sep; 14(3):247-52. PMID: 2888193.
- 94) Fujita J, Seino Y, Ishida H, et al. A functional study of a case of glucagonoma exhibiting typical glucagonoma syndrome. *Cancer*. 1986 Feb 15; 57(4):860-5. PMID: 2867823. [https://doi.org/10.1002/1097-0142\(19860215\)57:4%3C860::aid-cncr2820570429%3E3.0.co;2-u](https://doi.org/10.1002/1097-0142(19860215)57:4%3C860::aid-cncr2820570429%3E3.0.co;2-u).
- 95) Mallinson CN, Bloom SR, Warin AP, et al. A glucagonoma syndrome. *Lancet*. 1974 Jul 6; 2(7871):1-5. PMID: 4134714. [https://doi.org/10.1016/s0140-6736\(74\)91343-9](https://doi.org/10.1016/s0140-6736(74)91343-9).
- 96) Bloom SR, Polak JM, Pearse AG. Vasoactive intestinal peptide and watery-diarrhoea syndrome. *Lancet*. 1973 Jul 7; 2(7819):14-6. PMID: 4123289. [https://doi.org/10.1016/s0140-6736\(73\)91947-8](https://doi.org/10.1016/s0140-6736(73)91947-8).
- 97) Krejs GJ, Orci L, Conlon JM, et al. Somatostatinoma syndrome. Biochemical, morphologic and clinical features. *N Engl J Med*. 1979 Aug 9; 301(6):285-92. PMID: 377080. <https://doi.org/10.1056/nejm197908093010601>.
- 98) Sessa F, Arcidiaco M, Valenti L, et al. Metastatic psammomatous somatostatinoma of the pancreas causing severe ketoacidosis diabetes cured by surgery. *Endocr Pathol*. 1997 Winter; 8(4):327-333. PMID: 12114794. <https://doi.org/10.1007/bf02739935>.
- 99) Heitz PU, Kloppel G, Polak JM, Staub JJ. Ectopic hormone production by endocrine tumors: localization of hormones at the cellular level by immunocytochemistry. *Cancer*. 1981 Nov 1; 48(9):2029-37. PMID: 6271390. [https://doi.org/10.1002/1097-0142\(19811101\)48:9%3C2029::aid-cncr2820480920%3E3.0.co;2-n](https://doi.org/10.1002/1097-0142(19811101)48:9%3C2029::aid-cncr2820480920%3E3.0.co;2-n).
- 100) Melmed S, Yamashita S, Kovacs K, et al. Cushing's syndrome due to ectopic proopiomelanocortin gene expression by islet cell carcinoma of the pancreas. *Cancer*. 1987 Feb 15; 59(4):772-8. PMID: 3026608. [https://doi.org/10.1002/1097-0142\(19870215\)59:4%3C772::aid-cncr2820590418%3E3.0.co;2-h](https://doi.org/10.1002/1097-0142(19870215)59:4%3C772::aid-cncr2820590418%3E3.0.co;2-h).
- 101) Wilander E, El-Salhay M, Willen R, Grimelius L. Immunocytochemistry and electron microscopy of an argentaffin endocrine tumour of the pancreas. *Virchows Arch A Pathol Anat Histol*. 1981; 392(3):263-9. PMID: 6115499. <https://doi.org/10.1007/bf02155664>.
- 102) Sano T, Asa SL, Kovacs K. Growth hormone-releasing hormone-producing tumors: clinical, biochemical, and morphological manifestations. *Endocr Rev*. 1988 Aug; 9(3):357-73. PMID: 3145190. <https://doi.org/10.1210/edrv-9-3-357>.



- 103) Berger G, Trouillas J, Bloch B, et al. Multihormonal carcinoid tumor of the pancreas. Secreting growth hormone-releasing factor as a cause of acromegaly. *Cancer*. 1984 Nov 15;54(10):2097-108. PMID: 6435852. [https://doi.org/10.1002/1097-0142\(19841115\)54:10%3C2097::aid-cncr2820541009%3E3.0.co;2-x](https://doi.org/10.1002/1097-0142(19841115)54:10%3C2097::aid-cncr2820541009%3E3.0.co;2-x).
- 104) Bostwick DG, Quan R, Hoffman AR, et al. Growth-hormone-releasing factor immunoreactivity in human endocrine tumors. *Am J Pathol*. 1984 Nov; 117(2):167-70. PMID: 6093542. PMCID: PMC1900448.
- 105) Simpson WF, Adams DB, Metcalf JS, Anderson MC. Nonfunctioning pancreatic neuroendocrine tumors presenting as pancreatitis: report of four cases. *Pancreas*. 1988; 3(2):223-31. PMID: 3375232. <https://doi.org/10.1097/00006676-198804000-00019>.
- 106) Aabo K, Romond E, Dimitrov NV, et al. Pancreatic islet cell carcinoma associated with multiple hormone secretion and pancytopenia. Evidence of a serum factor suppressing hematopoiesis. *Cancer*. 1983 May 1; 51(9):1691-6. PMID: 6299505. [https://doi.org/10.1002/1097-0142\(19830501\)51:9%3C1691::aid-cncr2820510922%3E3.0.co;2-o](https://doi.org/10.1002/1097-0142(19830501)51:9%3C1691::aid-cncr2820510922%3E3.0.co;2-o).
- 107) Kniffin WD Jr, Spencer SK, Memoli VA, LeMarbre PJ. Metastatic islet cell amphicrine carcinoma of the pancreas. Association with an eosinophilic infiltration of the skin. *Cancer*. 1988 Nov 1; 62(9):1999-204. PMID: 2844387. [https://doi.org/10.1002/1097-0142\(19881101\)62:9%3C1999::aid-cncr2820620921%3E3.0.co;2-j](https://doi.org/10.1002/1097-0142(19881101)62:9%3C1999::aid-cncr2820620921%3E3.0.co;2-j).
- 108) Donow C, Pipeleers-Marichal M, Stamm B, et al. [The pathology of insulinoma and gastrinoma. The location, size, multicentricity, association with multiple endocrine type-I neoplasms and malignancy]. *Dtsch Med Wochenschr*. 1990 Sep 14; 115(37):1386-91. PMID: 1976084.
- 109) Kimura W, Kuroda A, Morioka Y. Clinical pathology of endocrine tumors of the pancreas. Analysis of autopsy cases. *Dig Dis Sci*. 1991 Jul; 36(7):933-42. PMID: 2070707. <https://doi.org/10.1007/bf01297144>.
- 110) Donow C, Pipeleers-Marichal MA, Schroder S, et al. Surgical pathology of gastrinoma. Site, size, multicentricity, association with multiple endocrine neoplasia type 1, and malignancy. *Cancer*. 1991 Sep 15; 68(6):1329-34. PMID: 1678681. [https://doi.org/10.1002/1097-0142\(19910915\)68:6%3C1329::aid-cncr2820680624%3E3.0.co;2-7](https://doi.org/10.1002/1097-0142(19910915)68:6%3C1329::aid-cncr2820680624%3E3.0.co;2-7).
- 111) Weber HC, Venzon DJ, Lin JT, et al. Determinants of metastatic rate and survival in patients with Zollinger-Ellison syndrome: a prospective long-term study. *Gastroenterology*. 1995 Jun; 108(6):1637-49. PMID: 7768367. [https://doi.org/10.1016/0016-5085\(95\)90124-8](https://doi.org/10.1016/0016-5085(95)90124-8).



The Pancreas in Child Abuse

Katherine Callahan, Laura D. Knight

ABSTRACT

The pancreas can be a critical indicator of inflicted injury in young children. Due to its retroperitoneal location and the amount of incision of the abdomen required to cause injury, the pancreas is unlikely to be significantly injured in minor trauma incidents. Typical blunt force injury mechanisms for the pancreas include motor vehicle collisions, inflicted injury from blows or kicks, and bicycle handlebar injuries with deep incision of the abdomen. The death of a toddler is described in which a pancreatic injury was a critical indicator of abusive injury rather than the claimed accidental fall or cardiopulmonary resuscitation-related trauma. Review of the medical literature regarding the epidemiology, etiology, and pathology of childhood pancreatic injuries is discussed. Pancreatic injury is a marker of severe blunt force trauma and should rouse a suspicion of nonaccidental trauma in young children. In the absence of a severe, high velocity or deep abdominal incision traumatic mechanism, such as motor vehicle collision or bicycle handlebar injury, pancreatic laceration specifically is a marker of inflicted injury in children under the age of five. *Acad Forensic Pathol.* 2018 8(2): 219-238

AUTHORS

Katherine Callahan MD, Washoe County Regional Medical Examiner's Office

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work.

Laura D. Knight MD, Washoe County Regional Medical Examiner's Office

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work.

CORRESPONDENCE

Katherine Callahan MD, 990 East Ninth St, Reno NV 89512, kscallahan@gmail.com

ETHICAL APPROVAL

As per Journal Policies, ethical approval was not required for this manuscript

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies conducted with animals or on living human subjects

STATEMENT OF INFORMED CONSENT

No identifiable personal data were presented in this manuscript

DISCLOSURES & DECLARATION OF CONFLICTS OF INTEREST

The authors, reviewers, editors, and publication staff do not report any relevant conflicts of interest

FINANCIAL DISCLOSURE

The authors have indicated that they do not have financial relationships to disclose that are relevant to this manuscript

KEYWORDS

Forensic pathology, Autopsy, Child abuse, Nonaccidental trauma, Pancreas, Intraabdominal injuries

INFORMATION

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

©2018 Academic Forensic Pathology International • (ISSN: 1925-3621) • <https://doi.org/10.23907/2018.016>

Submitted for consideration on 15 Mar 2018. Accepted for publication on 22 Apr 2018

CASE STUDY

A 2-year 8-month-old girl with no significant medical history was reportedly found unresponsive at the bottom of six concrete steps in the garage of her caretaker's residence. She was transported by ambulance to the nearest local hospital where death was pronounced shortly after arrival following unsuccessful resuscitative efforts.

Autopsy revealed multiple contusions of the face, scalp, chest, abdomen, back, arms, and legs. Contusions of the chest and abdomen are shown in **Image 1**. Internally, there were multiple liver lacerations (**Image 2**) involving the left lobe, caudate lobe, and right lobe, with 225 mL hemoperitoneum (**Image 3**). The right adrenal gland (**Image 4**) was transected and there was extensive right periadrenal and retroperitoneal hemorrhage. The head/neck of the pancreas had a contusion and a 1 cm superficial laceration (**Image 5**). Extensive hemorrhage was in the mediastinal connective tissue (seen in the right side of the mediastinum in **Image 6**) with extension of the hemorrhage into the hilar pleura of both lungs and along the carotid sheaths (**Image 7**) in the neck. The heart had a 0.5 cm transmural laceration of the right auricle and a laceration of the endocardial surface of the right atrium with 100 mL hemopericardium (seen within the intact pericardial sac in **Image 6**). The anterolateral aspect of the left third rib had a non-displaced fracture (**Image 8A**) with hemorrhage in the adjacent intercostal musculature and in the overlying serratus anterior muscle (**Image 8B**). There were no skull fractures or intracranial injuries. No natural diseases or congenital abnormalities were identified at autopsy. Toxicology testing was negative for drugs and alcohols.

Histologic examination of the right adrenal gland, pancreas, and thymus revealed extravasated erythrocytes with no significant neutrophilic or other inflammatory cell infiltrate, indicating acute perimortem injury (**Images 9 to 11**). No fibrosis, fibroblastic proliferation, or hemosiderin-laden macrophages were observed to suggest chronic or repetitive injury.

Several weeks after the toddler's death, the caretaker admitted to placing the decedent's body at the bottom

of the garage stairs in an attempt to stage the scene to appear consistent with a fall. He also admitted to striking her in the chest/abdomen multiple times with two closed fists. He subsequently pled guilty to the District Attorney's charges and was sentenced to life in prison. During the sentencing hearing, the forensic pathologist was called to testify. The direct examination focused on the extent of injuries and the pathologist's diagnosis of inflicted injury, while the cross-examination raised the issue of cardiopulmonary resuscitation- (CPR) related injuries.

DISCUSSION

Pancreatic injuries are seen fairly uncommonly in pediatric autopsies. Since the pancreas has a retroperitoneal location, it is often spared during more minor abdominal trauma events (1). Injuries of the gland are rare, accounting for less than 2% of all abdominal injuries in children (2). However, pancreatic injuries may be underestimated, particularly in more minor trauma episodes not resulting in death due to the clinical difficulty of diagnosis and/or the presence of other distracting intraabdominal injuries. Pancreatic injuries include peripancreatic hemorrhage/hematoma, pancreatic contusion, pancreatic laceration, pancreatic transection (i.e., full thickness laceration), and associated ductal injuries. These injuries are most commonly due to blunt force trauma in children, while penetrating trauma (such as gunshot or stab injury) is seen more frequently in adults. Due to the close anatomic proximity, injuries of the liver, spleen, stomach, small bowel (especially duodenum), and adrenal glands may accompany pancreatic injury.

The unique anatomical features of children make them more susceptible to blunt abdominal injuries. A less muscular and thinner anterior abdominal wall and less intraabdominal adipose tissue provide less cushioning and resistance to a blow to the abdomen, compared to adults. In a direct, deep impact of the pediatric abdomen, the pancreas is compressed between the force on the abdominal wall and the unyielding spinal column, resulting in laceration, transection, and/or hemorrhage (**Figure 1**) (1, 3). Aside from an inflicted blow to the abdomen, other etiologies of such direct, deep impacts



Image 1A: Contusions of the anterior chest and abdomen.

with significant pancreatic injury are most commonly motor vehicle collisions and bicycle handlebar injuries (1, 4-6). A retrospective study by Jacombs et al. of all children under 16 years of age with pancreatic trauma admitted to a major children's hospital in New South Wales demonstrated that the majority of blunt force pancreatic injuries were due to motor vehicle collisions, with the majority of injuries being contusions or lacerations without duct injury or tissue loss

(7). Transection of the pancreas was reported in 20% of the 65 cases of pancreatic injuries, and the transection cases included both survivors and nonsurvivors (7). Nonaccidental injury (i.e., inflicted trauma) was the etiology in ten of the 65 cases (15%), with six survivors and four deceased. Other individually rarer etiologies included falls and accidents associated with bicycles, horses, skateboards, and go-karts (7). Bicycle handlebar-related accidents tend to produce



Image 1B: Contusions of the lateral left chest and abdomen.

isolated but severe pancreatic injury (6). The discrete, focused impact of a handlebar end is not dissimilar to an inflicted blow. In other less focused blunt force impacts, the force is dispersed over a broader body surface area, compared with the concentrated force of an assailant's fist or foot in abusive injury (8). A high incidence of hollow-organ injuries (i.e., stomach, small bowel, and duodenal perforations) has been reported in pediatric nonaccidental trauma cases, for similar reasons, with 50% of the abdominally injured patients having hollow viscus injuries in one study, as compared to less than 10% of adults with blunt abdominal trauma (8). This difference is likely attributable both to the concentrated application of force in abusive injury and the anatomical vulnerability of children, as previously discussed.

Falls are the most common explanation provided by caregivers for blunt abdominal injuries in an attempt to conceal the true nature of inflicted injuries (9). A 2016 study reviewed blunt abdominal trauma cases in children admitted to two level one trauma centers, comparing the patterns of injuries seen in nonaccidental trauma to those seen after a fall-related incident (9). Nonaccidental trauma was the most common cause of blunt abdominal trauma for patients under five years old (9). In the study group of patients younger than five years, the mortality rate for nonaccidental blunt abdominal trauma was 17.46%, while there were no deaths in children who sustained abdominal injuries in falls (9). Nonaccidental trauma also produced more severe injuries in general, with higher injury severity scores. In this same study group of patients under age five, the incidence of pancreatic injuries was



Image 1C: Contusions of the lateral right chest and abdomen.

significantly higher in nonaccidental trauma (25.4% of cases, n = 16) compared with falls (5.7% of cases, n = 2), with an associated risk ratio of 4.44 (9). The magnitude of this risk ratio weighs pancreatic blunt injury heavily toward nonaccidental etiology; however, a limitation of the study is that it did not stratify different types of pancreatic injury to distinguish the more severe and likely more specific pancreatic laceration from other less-severe injuries such as pancreatic contusion. The authors indicate the presence of pancreatic injury (or hollow viscus injury) should provoke clinical suspicion of nonaccidental trauma (9).

Cardiopulmonary resuscitation is often performed on children who have sustained blunt abdominal trauma, in particular those who die from their injuries. Cardiopulmonary resuscitation is also a common mechanism

postulated as an explanation for inflicted abdominal injuries. The potential exists for injuries to occur during CPR and it is important to recognize and classify these injuries appropriately. A retrospective study of all children under the age of 14 who died in Melbourne, Australia from 1994 to 1996 was undertaken to determine the incidence, type, and pattern of injury related to resuscitation attempts in children who die (10). Children who had recognized trauma prior to resuscitation were excluded from the study. Injuries detected in the resuscitated group included: superficial cutaneous bruises/abrasions, airway injury, lip injury, pulmonary contusion, splenic hematoma, and dental injury. Most injuries in the resuscitated group were minor in nature and no intraabdominal injuries were reported (10). Similarly, Price et al. reported no intraabdominal injuries in 324 natural pediatric deaths,

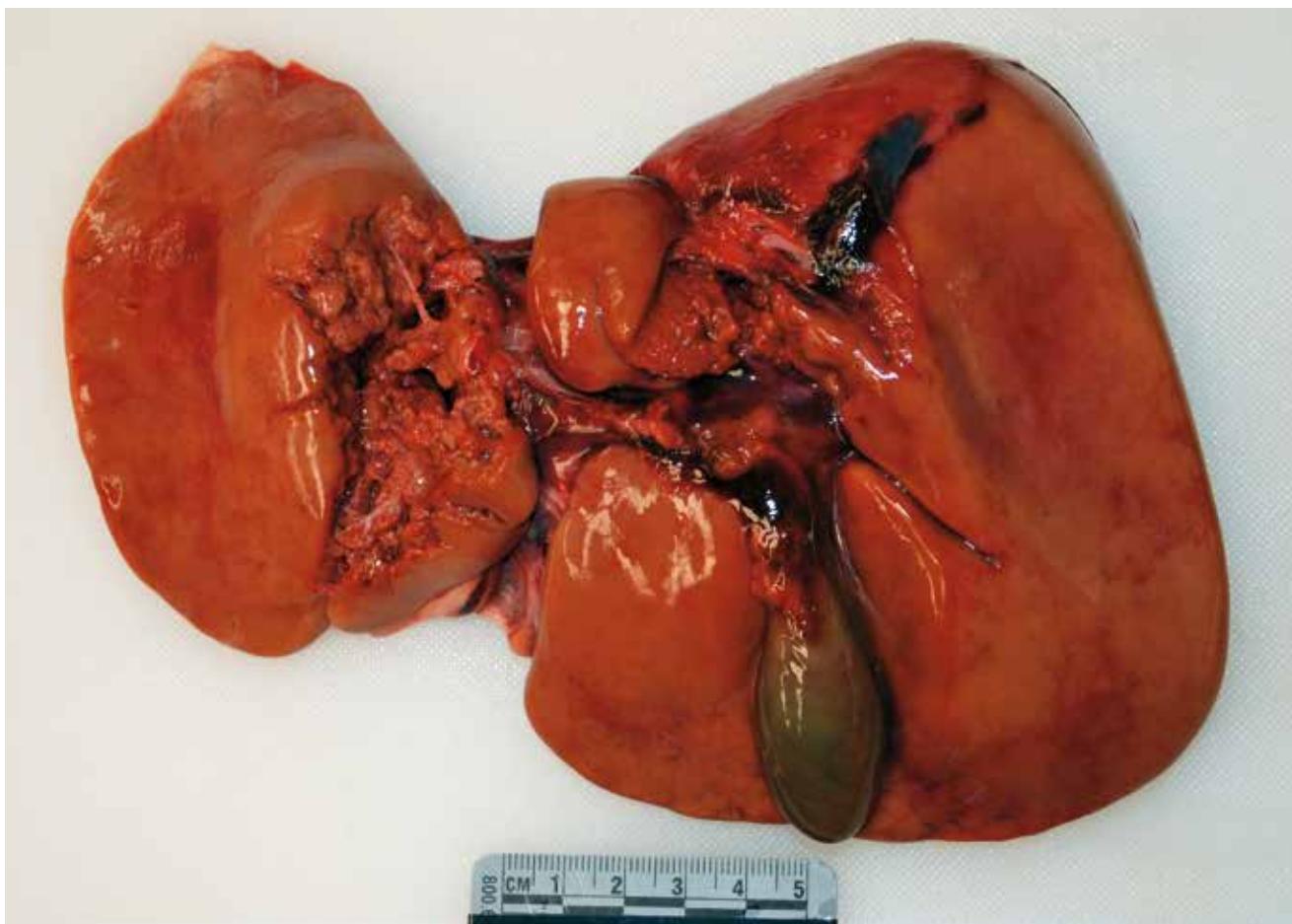


Image 2A: Lacerations of the posterior surface of the liver.

all of which received CPR (11). In 1984, Waldman et al. reported an 8-year-old girl who underwent CPR with interposed abdominal compressions (IAC-CPR) and ultimately died of a ruptured cerebellar arteriovenous malformation (12). At autopsy she was found to have a 2.5 cm liver laceration; intraluminal blood in the stomach, duodenum, and proximal jejunum; hemorrhage in the parenchyma of the pancreas; and 150 mL hemoperitoneum. Alternative techniques to standard CPR, including IAC-CPR, generally require additional training, personnel, and equipment. To date, no adjunct has been shown to be universally superior to standard manual CPR for prehospital basic life support (13). Overall, the likelihood of CPR-related abdominal injuries in children is very low and pancreatic laceration has never been reported in association with CPR to our knowledge. However, if intraabdominal injuries are identified at the time of au-

topsy, questions regarding alternative CPR techniques may be warranted.

Inflicted abdominal blunt injuries, in general, have significantly higher mortality than do accidental injuries, with reported mortality rates up to 50% (14-18). Delay in seeking medical treatment (due to an attempt to conceal the abuse) undoubtedly contributes to this higher mortality rate (18). Factors that may contribute to the mortality rate in pancreatic injuries specifically include associated complications (such as pancreatitis, peritonitis, bile leak, etc.), delay in presentation, nonspecific presentation leading to delayed diagnosis, and the difficulty of diagnosis.

In the clinical setting, pancreatic injury is rare and difficult to diagnose, being subtle and often overlooked when there is multi-organ trauma involving liver,



Image 2B: Lacerations of the anterior surface of the liver.

spleen, and/or kidney (19). Diagnosis may be delayed, as radiologic imaging findings are of post-traumatic pancreatitis, with edema and blood infiltration manifesting as pancreatic enlargement and peripancreatic fluid, which may take hours to develop (19). Computed tomography (CT) scanning is the preferred clinical modality for assessing pancreatic injury. The CT scan may appear normal in the first 12 hours following pancreatic trauma (19). The portions of a lacerated or transected pancreas may remain in close apposition and be difficult to detect on CT. When they occur, lacerations or transections tend to occur at the junction of the body and tail due to shearing injuries and compression against the spine (19). However, this may also depend on the direction of the force or blow. Ductal injuries may also be difficult to detect

on CT scanning, and raise the risk of complications (19). Endoscopic retrograde cholangiopancreatography (ERCP) is increasingly being used to evaluate for ductal injuries, allowing for non-operative treatment if no ductal injury is identified, or more prompt operative treatment if a ductal injury is present. Endoscopic retrograde cholangiopancreatography is also clinically useful in managing the late complications of pancreatic injury by drainage of pseudocysts or fistulas (19). Of note, however, is the risk of ERCP-associated acute pancreatitis (20). A systematic review and meta-analysis of complications of ERCP in pediatric patients reported a complication rate of 6%, with post-ERCP pancreatitis representing the bulk of complications, and bleeding and infections associated with ERCP being less common (21). However,

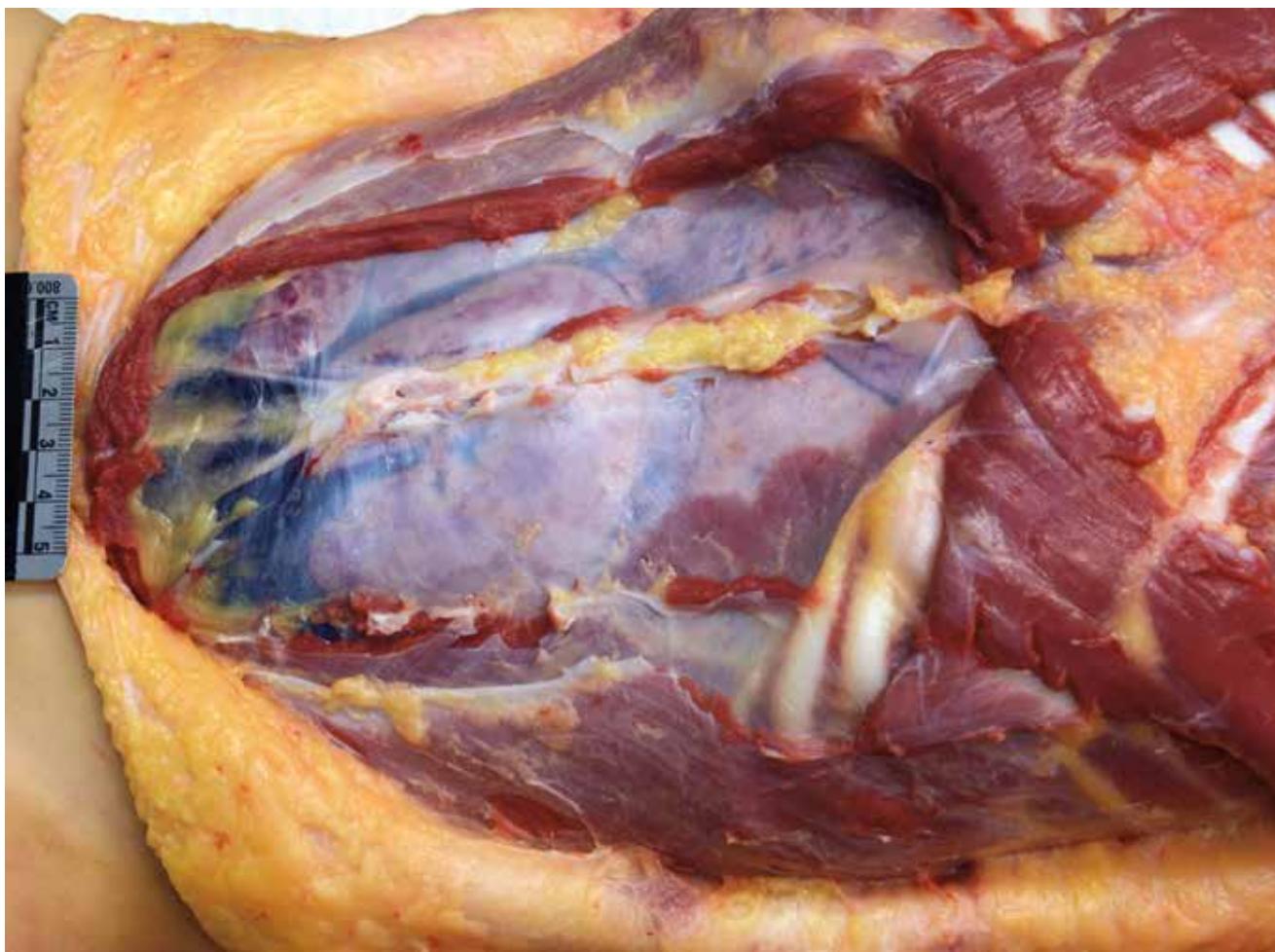


Image 3: Reflection of the rectus abdominis with hemoperitoneum visible through the intact peritoneal lining.

these patients represent a variety of disease states and ERCP intervention types, and the inclusion of chronic pancreaticobiliary disease cases likely increases the pooled complication rate. It is important for the forensic pathologist evaluating the pancreas following ERCP to consider whether an iatrogenic component plays a role in pathologic findings such as pancreatitis or perforation; the clinical history is critical to obtain in previously hospitalized patients. Magnetic resonance cholangiopancreatography (MRCP) provides a non-invasive alternative for evaluation of injury to the ductal components of the pancreas (19), but may provide less precise anatomical delineation.

Regarding laboratory testing and diagnosis of pancreatic injuries, amylase sensitivity and specificity are low (6), but serial levels in the clinical setting may aid in diagnosis (7). In the study by Jacombs et al. previously described, the amylase level was elevated in about half of those tested at the time of presentation with such an injury, increasing to 63% after admission with serial testing (7). A Clinical Report from the American Academy of Pediatrics on the evaluation of suspected child abuse recommends that clinical screening laboratory tests include liver and pancreatic enzyme concentrations in all children presenting with serious trauma, even if they are not exhibiting acute



Image 4: Transection and periadrenal hemorrhage of right adrenal gland (on left) and unremarkable left adrenal gland (on right).

abdominal symptoms, as abdominal trauma may be masked or overlooked in the setting of other injuries (22). Postmortem testing for lipase and/or amylase is subject to issues of false elevation due to postmortem pancreatic autolysis, hemolyzed serum specimens (which clinical laboratories may reject), and difficult interpretation due to lack of specificity (particularly for amylase). Another article in this issue, by Brown and Prahlow, addresses the utility of postmortem pancreatic enzyme testing (23).

At autopsy, recognition of pancreatic trauma in the infant or child is relatively straightforward, though caution should be taken regarding the postmortem interval and autolytic postmortem changes that can produce a dark discoloration mimicking hemorrhage. If a laceration is present, its size should be measured and documented, along with its location (i.e., head, body, or tail of pancreas), whether full-thickness (i.e., transection), and whether major ductal structures appear to be involved. Photographs of all injuries should be taken *in situ*, *ex situ*, and following sectioning. Histologic examination of sites of peripancreatic hemorrhage, pancreatic contusion, or pancreatic laceration can aid in demonstrating true hemorrhage, acute in-

flammation of vital reaction, or evidence of acute injury superimposed on older injury. Acute pancreatitis may accompany blunt injury of the pancreas if there is a survival period following the trauma incident. Histologic elements of tissue repair, including fibroblast proliferation, fibrosis and scar formation, increased vascularity, and hemosiderin-laden macrophages are reported as histologic evidence of older trauma (24). Iron and trichrome stains may be utilized to highlight hemosiderin deposition and fibrosis, respectively (24), though all of these findings should generally be visible on hematoxylin and eosin stained slides. In a report of a series of four cases of repetitive blunt abdominal trauma, Dye et al. described toddlers aged one to two years with acute abdominal trauma as the cause of death, with histologic findings supporting prior episode(s) of trauma. Three of the four cases demonstrated evidence of older pancreatic injury (with acute pancreatic injury superimposed); histologic findings of older injury (e.g., fibrosis, reactive fibroblast proliferation, and/or hemosiderin-laden macrophages in the pancreas) were unexplained by any natural disease process and were also absent in age-matched atraumatic controls (24).



Image 5: Pancreas with contusion and laceration of the surface of the head/neck.

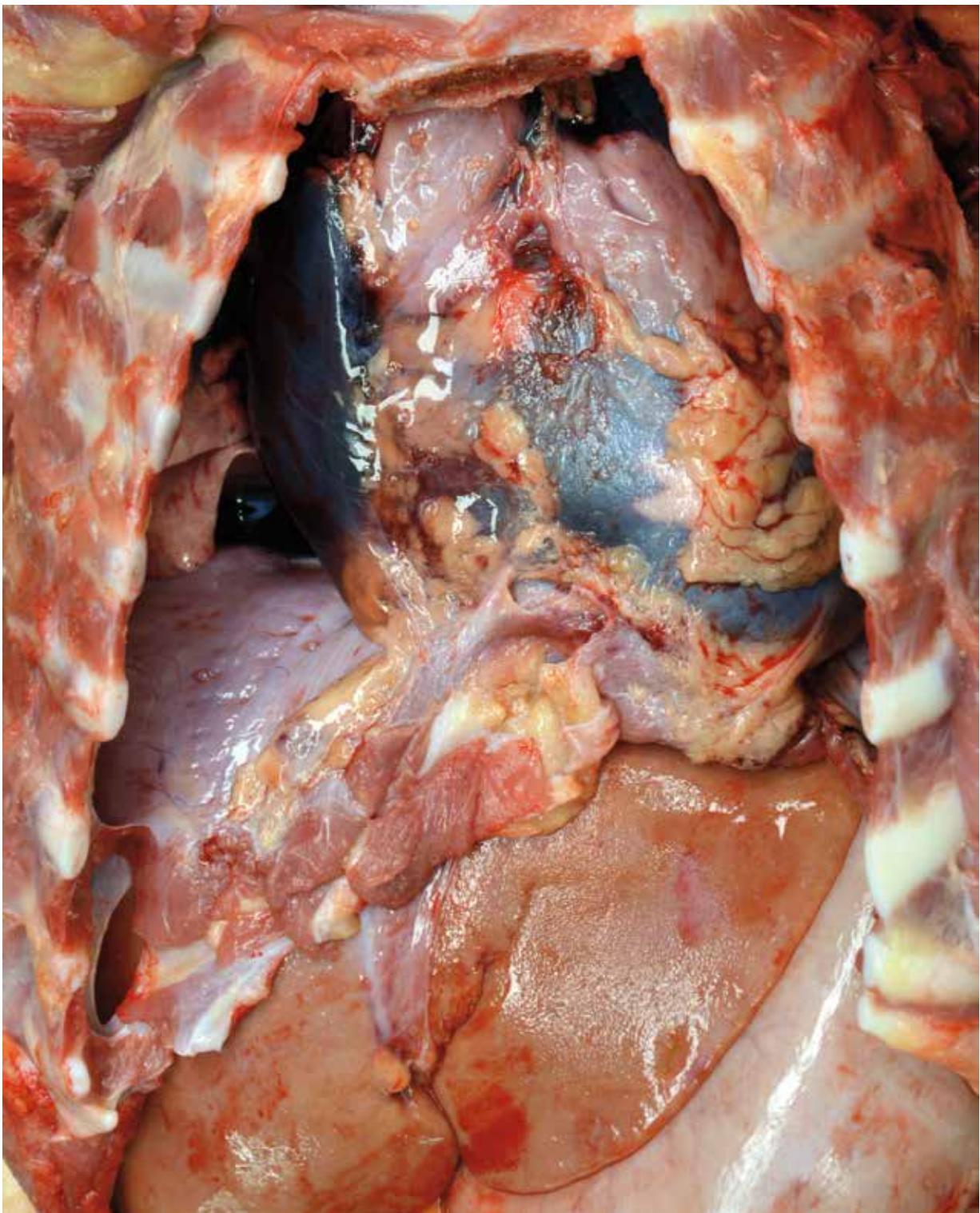


Image 6: Hemopericardium visible through the intact pericardial sac and extensive hemorrhage within the mediastinal connective tissue to the right of the pericardial sac.

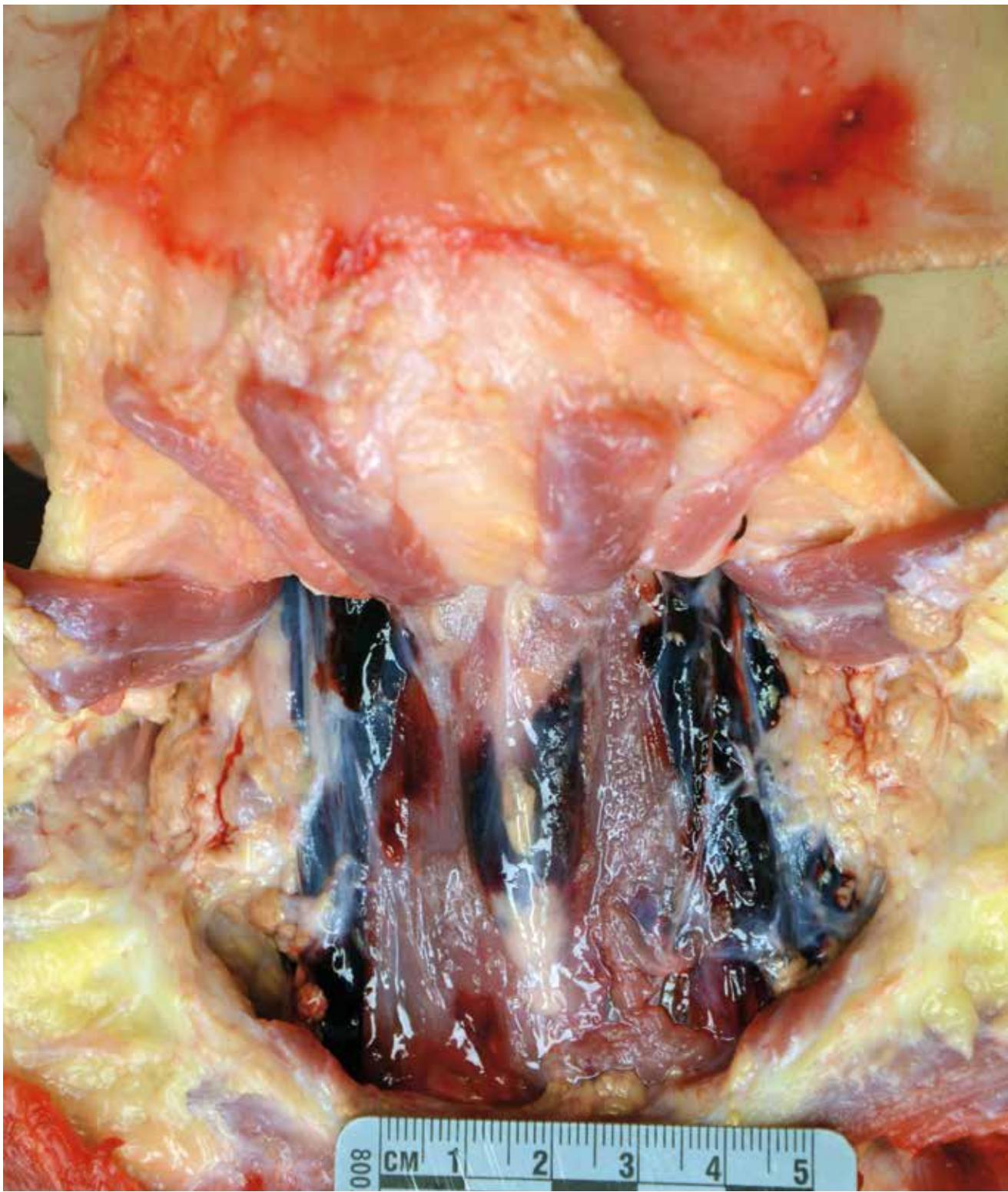


Image 7: Hemorrhage tracking along carotid sheaths of the neck.

Other signs of older trauma to the pancreas could include fistula formation or pseudocyst. Pseudocysts developed in just under one-third of pediatric pancreatic blunt force trauma survivors in the study by Ja-combs et al. in New South Wales, and were the most common complication following pancreatic injury (7). Other complications of pancreatic trauma include pancreatitis and intraabdominal abscess (19). Chronic

pancreatitis may develop following pancreatic trauma, including inflicted trauma. In a case series of 49 childhood pancreatitis cases, one third of cases caused by trauma were due to child abuse (25). The differential diagnosis for etiologies of relapsing acute or chronic pancreatitis in childhood includes congenital anomalies (pancreas divisum, choledochal cysts), diabetes (with associated hypertriglyceridemia), cystic



Image 8A: Non-displaced fracture of the anterolateral left third rib.

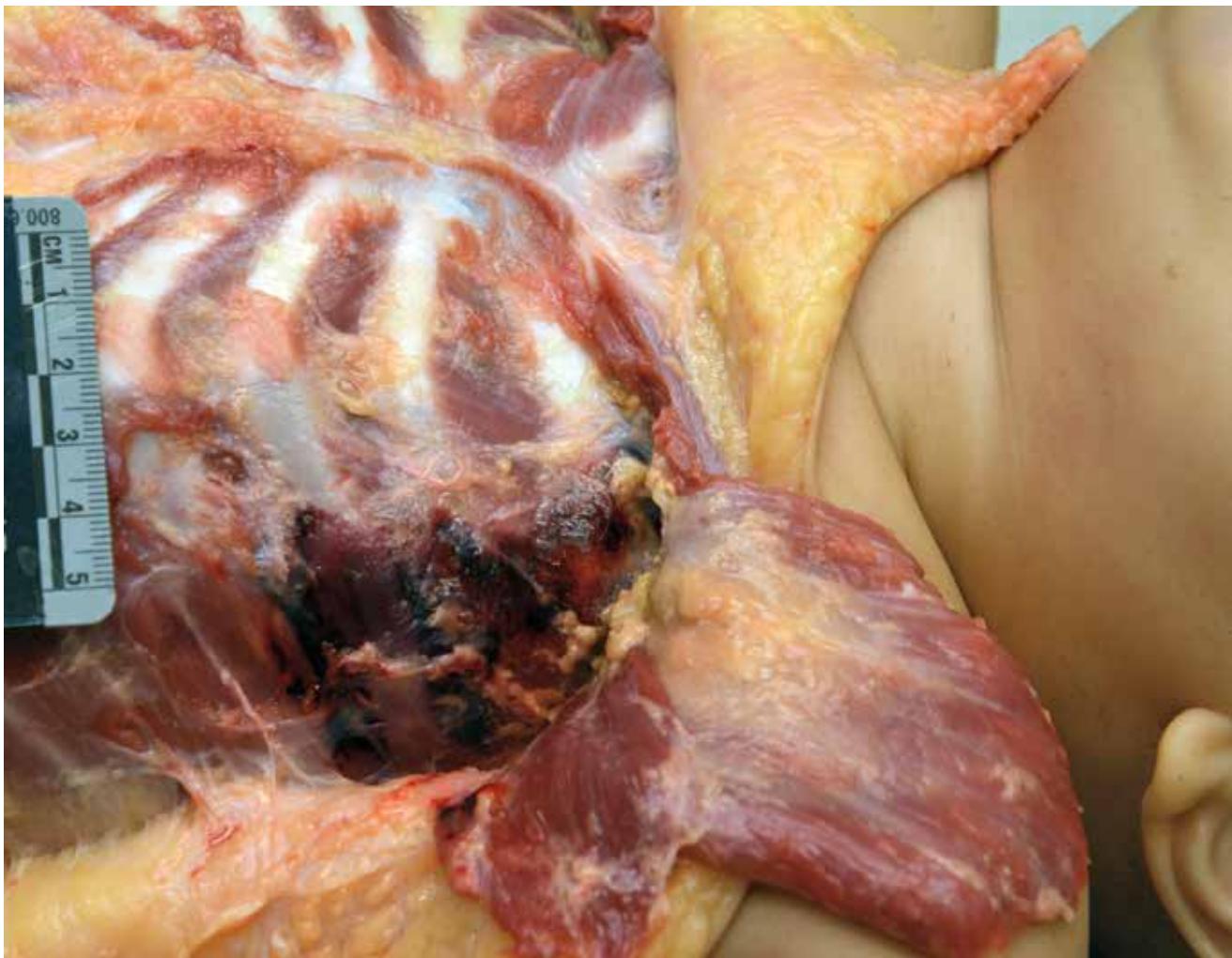


Image 8B: Hemorrhage of the left serratus anterior muscle.

fibrosis, hereditary pancreatitis, drugs, infection (such as mumps), and inflicted trauma (26).

CONCLUSION

Pancreatic injury is a marker of severe blunt trauma in children and should raise suspicion of nonaccidental trauma. In the absence of a history that is compatible with direct, deep incursion of the abdomen and/or high velocity impact (such as motor vehicle collision,

handlebar injury, etc.), inflicted injury is likely. Pancreatic laceration has not been reported in association with CPR in young children, to our knowledge, and falls are far less likely to produce serious pancreatic injuries in young children compared to nonaccidental trauma. Histologic examination of pancreatic injury is useful in suspected child abuse cases, as it may document acute as well as older injury to establish the often repetitive nature of abusive injury.

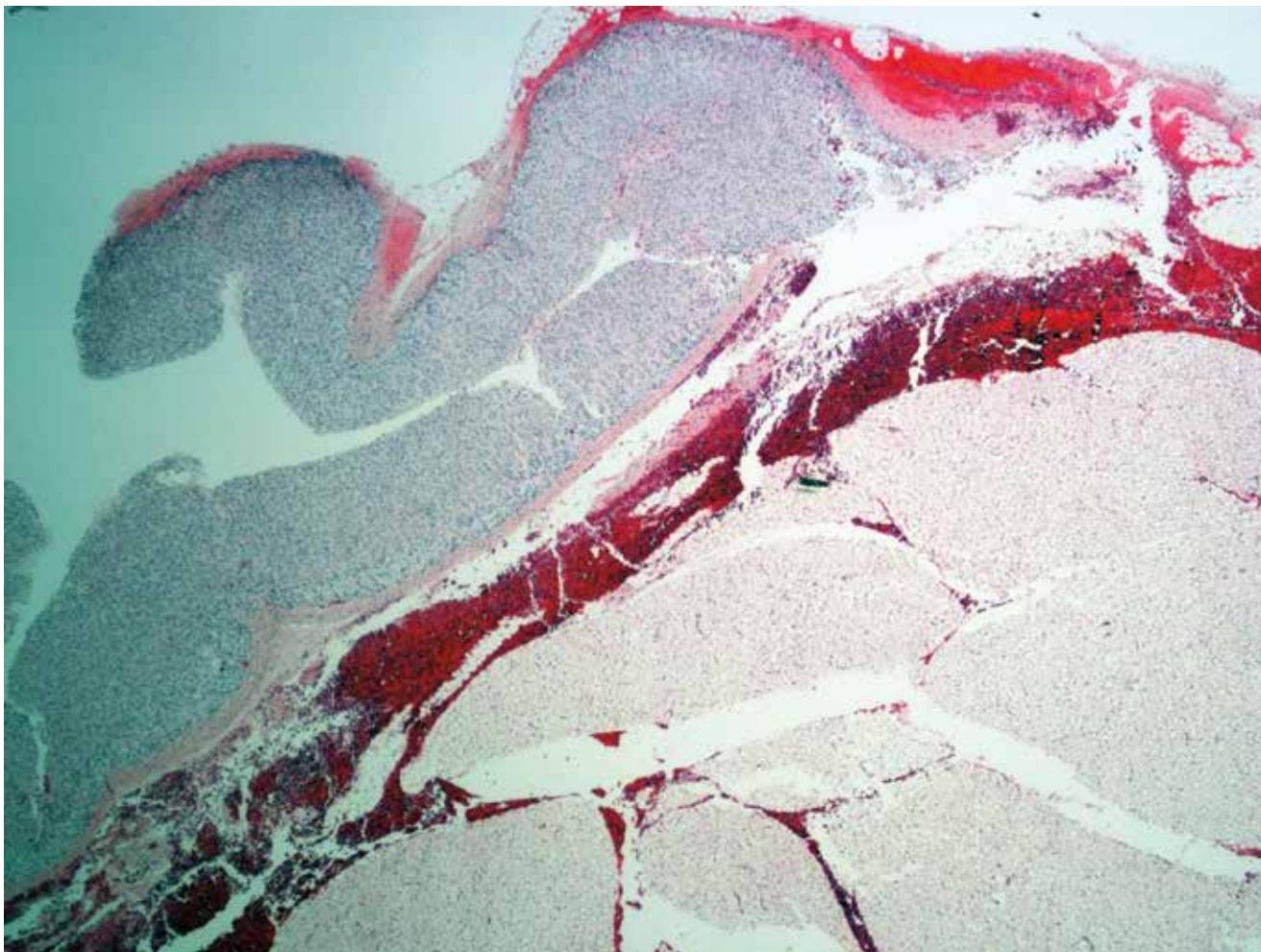


Image 9A: Histology of the right adrenal gland in **Image 4** showed disruption of the cortical parenchyma and fibrous capsule, and extravasated erythrocytes within the adjacent fibroadipose tissue (H&E, x20).

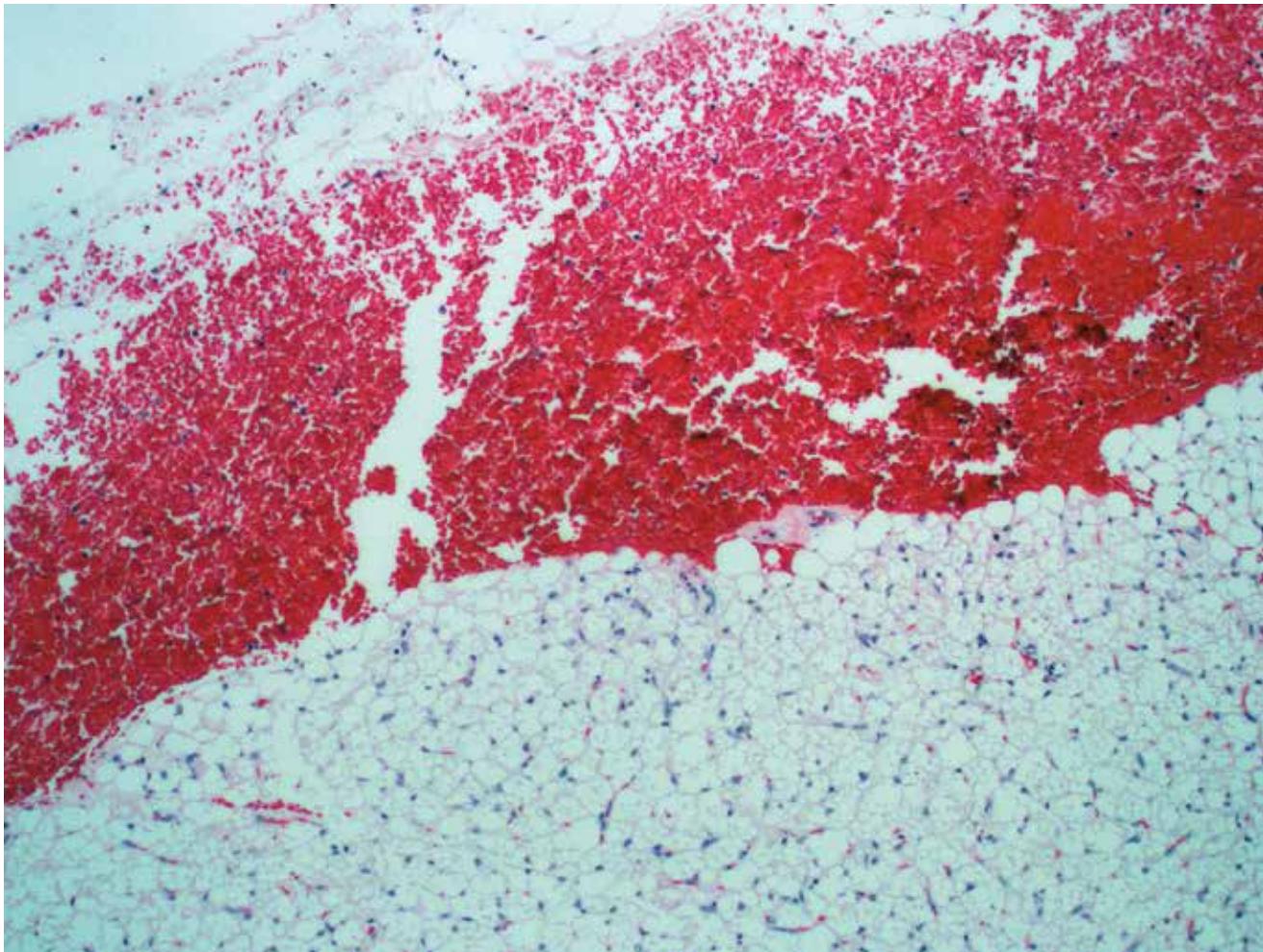


Image 9B: Histology of the periadrenal fibroadipose tissue in **Image 9A** at higher power showed extravasated erythrocytes with no significant neutrophilic or other inflammatory cell infiltrate (H&E, x100).

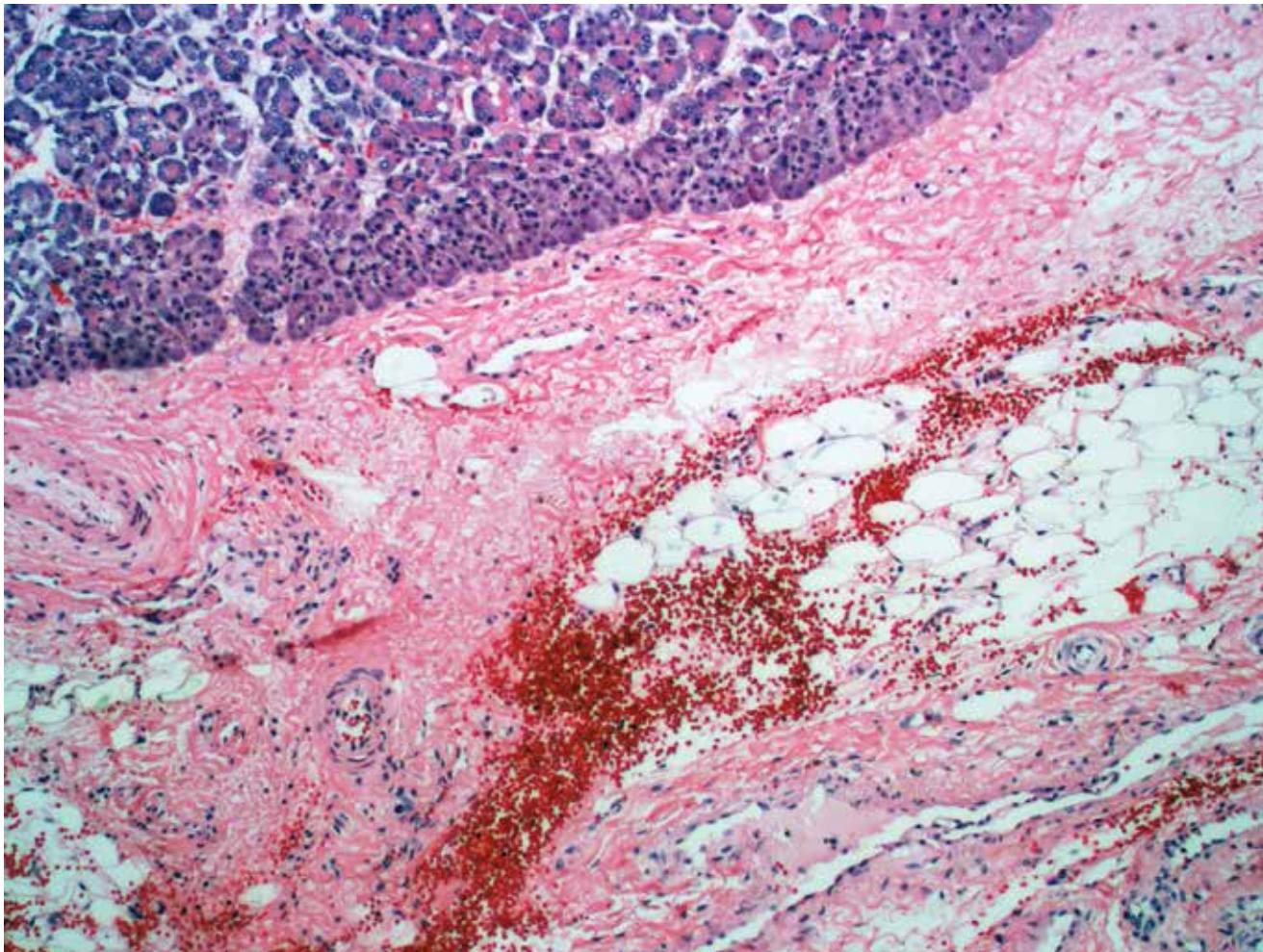


Image 10: Histology of the head/neck of the pancreas in **Image 5** showed extravasated erythrocytes within the peripancreatic connective tissue with no significant neutrophilic or other inflammatory cell infiltrate (H&E, x100).

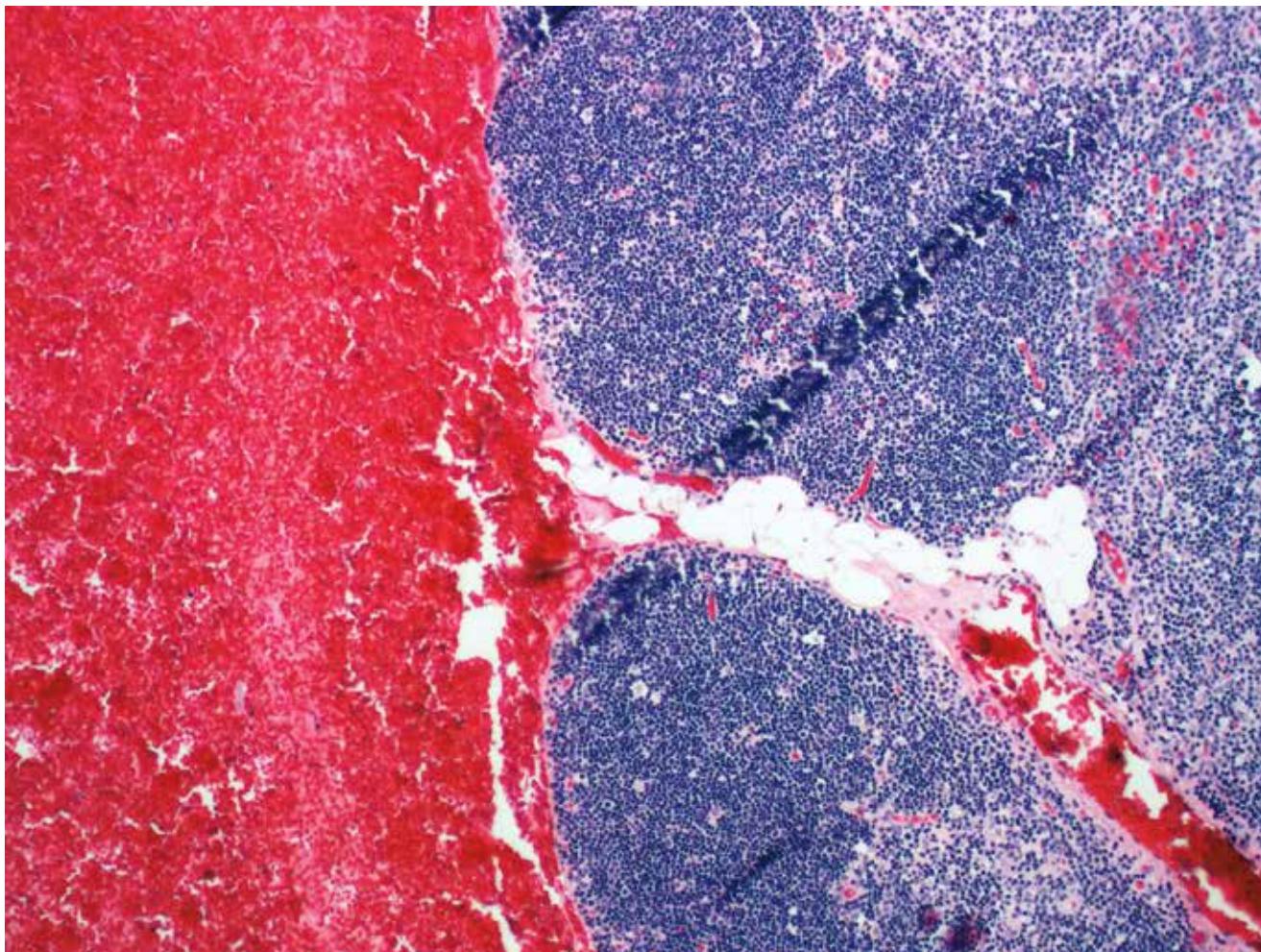


Image 11: Histology of the thymus showed extravasated erythrocytes within the interstitial connective tissue with no significant neutrophilic or other inflammatory cell infiltrate (H&E, x100).

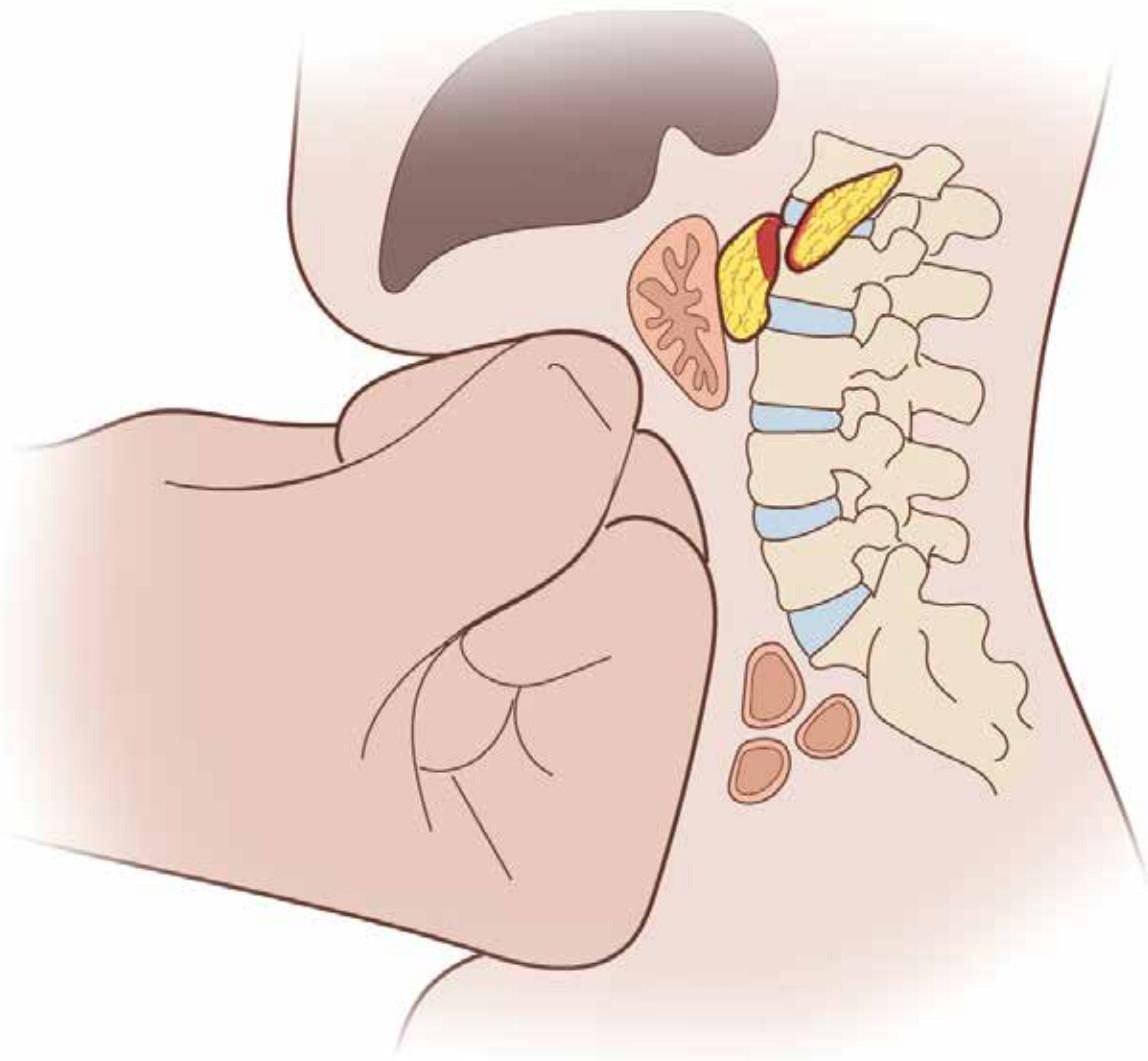


Figure 1: With a direct blow, the pancreas is compressed between the force applied to the abdominal wall and the underlying spinal column. Created under contract by professional medical illustrator Diana Kryski.

REFERENCES

- 1) Hong MJ, Porter LM, Esernio-Jenssen DD, et al. Pancreatic laceration in a pediatric patient: an unexpected diagnosis. *Case Rep Pediatr.* 2017; 2017:2681835. PMID: 29230341. PMCID: PMC5688251. <https://doi.org/10.1155/2017/2681835>.
- 2) Almaramhy HH, Guraya SY. Computed tomography for pancreatic injuries in pediatric blunt abdominal trauma. *World J Gastrointest Surg.* 2012 Jul 27; 4(7):166-70. PMID: 22905284. PMCID: PMC3420983. <https://doi.org/10.4240/wjgs.v4.i7.166>.
- 3) Dolinak D, Matsches E, Lew E. Forensic pathology principles and practice. Burlington (MA): Elsevier Academic Press; 2005. 616 p.
- 4) Milroy CM. Forensic pathology of infancy and childhood. New York: Springer Science+Business Media; c2014. Chapter 13, Blunt abdominal and thoracic injuries in children; p. 291-325.
- 5) Lam JPH, Eunson GJ, Munro FD, Orr JD. Delayed presentation of handlebar injuries in children. *BMJ.* 2001 May 26; 322(7297): 1288-9. PMID: 11375234. PMCID: PMC1120385. <https://doi.org/10.1136/bmj.322.7297.1288>.
- 6) Arkovitz MS, Johnson N, Garcia VF. Pancreatic trauma in children: mechanisms of injury. *J Trauma.* 1997 Jan; 42(1):49-53. PMID: 9003257. <https://doi.org/10.1097/000005373-199701000-00009>.
- 7) Jacobson ASW, Wines M, Holland A, et al. Pancreatic trauma in children. *J Pediatr Surg.* 2004 Jan; 39(1):96-9. PMID: 14694381. <https://doi.org/10.1016/j.jpedsurg.2003.09.011>.
- 8) Roaten JB, Partrick DA, Bensard DD, et al. Visceral injuries in nonaccidental trauma: spectrum of injury and outcomes. *Am J Surg.* 2005 Dec; 190(6):827-9. PMID: 16307928. <https://doi.org/10.1016/j.amjsurg.2005.05.049>.
- 9) Carter KW, Moulton SL. Pediatric abdominal injury patterns caused by "falls": a comparison between nonaccidental and accidental trauma. *J Pediatr Surg.* 2016; 51(2):326-328. PMID: 26850907. <https://doi.org/10.1016/j.jpedsurg.2015.10.056>.
- 10) Ryan MP, Young SJ, Wells DL. Do resuscitation attempts in children who die, cause injury? *Emerg Med J.* 2003 Jan; 20(1):10-2. PMID: 12533359. PMCID: PMC1725991. <https://doi.org/10.1136/emj.20.1.10>.
- 11) Price EA, Rush LR, Perper JA, Bell MD. Cardiopulmonary resuscitation-related injuries and homicidal blunt abdominal trauma in children. *Am J Forensic Med Pathol.* 2000 Dec; 21(4):307-10. PMID: 11111786. <https://doi.org/10.1097/00000433-200012000-00001>.
- 12) Waldman PJ, Walters BL, Grunau CF. Pancreatic injury associated with interposed abdominal compressions in pediatric cardiopulmonary resuscitation. *Am J Emerg Med.* 1984 Nov; 2(6):510-2. PMID: 6397200. [https://doi.org/10.1016/0735-6757\(84\)90076-7](https://doi.org/10.1016/0735-6757(84)90076-7).
- 13) Guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care. Part 6: advanced cardiovascular life support: section 4: devices to assist circulation. The American Heart Association in collaboration with the International Liaison Committee on Resuscitation. *Circulation.* 2000 Aug 22; 102(8 Suppl):I105-11. PMID: 10966668. https://doi.org/10.1161/01.cir.102.suppl_1.i-105.
- 14) Kepron C, Walker A, Milroy CM. Are there hallmarks of child abuse? II. Non-osseous injuries. *Acad Forensic Pathol.* 2016 Dec; 6(4): 591-607. <https://doi.org/10.23907/2016.057>.
- 15) Trokel M, DiScala C, Terrin NC, Sege RD. Blunt abdominal injury in the young pediatric patient: child abuse and patient outcomes. *Child Maltreat.* 2004 Feb; 9(1):111-7. PMID: 14871002. <https://doi.org/10.1177/1077559503260310>.
- 16) Cameron CM, Lazortiz S, Calhoun AD. Blunt abdominal injury: simultaneously occurring liver and pancreatic injury in child abuse. *Pediatr Emerg Care.* 1997 Oct; 13(5):334-6. PMID: 9368247. <https://doi.org/10.1097/00006565-199710000-00009>.
- 17) Maguire SA, Uphadyaya M, Evans A, et al. A systematic review of abusive visceral injuries in childhood—their range and recognition. *Child Abuse Negl.* 2013 Jul; 37(7):430-45. PMID: 23306146. <https://doi.org/10.1016/j.chab.2012.10.009>.
- 18) Cooper A, Floyd T, Barlow B, et al. Major blunt abdominal trauma due to child abuse. *J Trauma.* 1988 Oct; 28(10):1483-7. PMID: 3172310. <https://doi.org/10.1097/00005373-198810000-00015>.
- 19) Debi U, Kaur R, Prasad KK, et al. Pancreatic trauma: a concise review. *World J Gastroenterol.* 2013 Dec 21; 19(47):9003-11. PMID: 24379625. PMCID: PMC3870553. <https://doi.org/10.3748/wjg.v19.i47.9003>.
- 20) Stoppacher R. Sudden death due to acute pancreatitis. *Acad Forensic Pathol.* 2018 Jun; 8(2):239-55. <https://doi.org/10.23907/2018.017>.
- 21) Usatin D, Fernandes M, Allen IE, et al. Complications of endoscopic retrograde cholangiopancreatography in pediatric patients; a systematic literature review and meta-analysis. *J Pediatr.* 2016 Dec; 179: 160-165.e3. PMID: 27663215. PMCID: PMC5123955. <https://doi.org/10.1016/j.jpeds.2016.08.046>.
- 22) Christian, Committee on Child Abuse and Neglect. The evaluation of suspected child physical abuse. *Pediatrics.* 2015 Sep; 136(3):583. PMID: 26398954. <https://doi.org/10.1542/peds.2015-2010>.
- 23) Brown T, Prahlow J. Postmortem serum amylase and lipase analysis in the diagnosis of acute pancreatitis. *Acad Forensic Pathol.* 2018 Jun; 8(2):311-23. <https://doi.org/10.23907/2018.020>.
- 24) Dye DW, Peretti FJ, Kokes CP. Histologic evidence of repetitive blunt force abdominal trauma in four pediatric fatalities. *J Forensic Sci.* 2008 Nov; 53(6):1430-3. PMID: 18808370. <https://doi.org/10.1111/j.1556-4029.2008.00883.x>.
- 25) Ziegler DW, Long JA, Philippart AI, Klein MD. Pancreatitis in childhood. Experience with 49 patients. *Ann Surg.* 1988 Mar; 207(3): 257-61. PMID: 3345113. PMCID: PMC1493389.
- 26) Forbes A, Leung JW, Cotton PB. Relapsing acute and chronic pancreatitis. *Arch Dis Child.* 1984 Oct; 59(10):927-34. PMID: 6497429. PMCID: PMC1628872. <https://doi.org/10.1136/adc.59.10.927>.



Sudden Death Due to Acute Pancreatitis

Robert Stoppacher

ABSTRACT

Acute pancreatitis can present as sudden, expected death and, therefore, fall under the jurisdiction of the medical examiner/coroner (ME/C). Although its etiologies are varied, alcohol abuse, trauma, and drugs are important to consider in the forensic setting. It is therefore important for the forensic pathologist to have an understanding of these and other etiologies, to have a functional knowledge of the pancreatic anatomy and physiology, and to be able to diagnose acute pancreatitis and distinguish it from postmortem artifact. This review will highlight the forensic aspects of acute pancreatitis, with particular focus on acute hemorrhagic pancreatitis. This will include an overview of the developmental anatomy and normal physiology of the pancreas, the various causes of pancreatitis that may result in deaths coming to the attention of the ME/C, the underlying pathophysiology of the disease, the postmortem diagnosis of acute pancreatitis, and ancillary studies that support the diagnosis. *Acad Forensic Pathol.* 2018 8(2): 239-255

AUTHOR

Robert Stoppacher MD, Onondaga County Medical Examiner's Office

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work.

CORRESPONDENCE

Robert Stoppacher MD, 100 Elizabeth Blackwell Street Syracuse NY 13210, RobertStoppacher@ongov.net

ETHICAL APPROVAL

As per Journal Policies, ethical approval was not required for this manuscript

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies conducted with animals or on living human subjects

STATEMENT OF INFORMED CONSENT

No identifiable personal data were presented in this manuscript

DISCLOSURES & DECLARATION OF CONFLICTS OF INTEREST

The author, reviewers, editors, and publication staff do not report any relevant conflicts of interest

FINANCIAL DISCLOSURE

The author has indicated that he does not have financial relationships to disclose that are relevant to this manuscript

KEYWORDS

Forensic pathology, Pancreatitis, Hemorrhagic pancreatitis, Trauma, Alcohol

INFORMATION

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

©2018 Academic Forensic Pathology International • (ISSN: 1925-3621) • <https://doi.org/10.23907/2018.017>

Submitted for consideration on 22 Feb 2018. Accepted for publication on 22 Apr 2018



INTRODUCTION

The pancreas plays critical roles in digestion, glucose metabolism, and the maintenance of homeostasis. Perhaps, this is why the famous Austrian surgeon, Theodor Billroth, is credited with stating, “*God put the pancreas in the back because he did not want surgeons messing with it*” (1). In the United States, approximately 210 000 patients are admitted to a hospital annually for treatment of acute pancreatitis (2, 3). Much less commonly, acute pancreatitis will present as sudden, expected death and will be investigated by the medical examiner/coroner (ME/C). In this setting, it is relatively rare, accounting for less than 1% of deaths (4-7). This review will highlight the forensic aspects of sudden death from acute pancreatitis, with particular focus on acute hemorrhagic pancreatitis. Specifically, it will include pancreatic anatomy and physiology, common etiologies of acute pancreatitis, and the postmortem diagnosis of acute pancreatitis.

DISCUSSION

Anatomy/Physiology

In order to best understand the pathophysiology of acute pancreatitis, it is important to have a functional understanding of the pancreatic anatomy. Embryologically, the pancreas originates from the duodenum as dorsal and ventral pancreatic buds between the fourth and fifth weeks of gestation (8). The ventral bud rotates to become the uncinate process and main pancreatic duct (of Wirsung) and is closely related to the bile duct and common bile duct. The dorsal bud becomes the body and tail of the gland and in some instances retains the accessory pancreatic duct (of Santorini), which may have a separate entrance in the duodenum (9). As will be discussed, the relationship between the pancreatic ducts and common bile duct can have an impact on the development of gallstone pancreatitis.

The pancreas is a retroperitoneal organ located at the level of the first and second lumbar vertebrae (10). This is important to keep in mind in the setting of trauma with injury to these structures, and the potential effects on the pancreas. Additionally, there are

significant vascular structures in close proximity to the posterior aspect of the head and neck of the gland including the aorta, superior mesenteric artery, splenic artery, and junction of the superior mesenteric and splenic veins (portal vein) (8, 10).

Physiologically, the pancreas consists of both endocrine (islets of Langerhans) and exocrine components (acini). Approximately 10% of the gland is made up of islets that secrete three major hormones: insulin, glucagon, and somatostatin (11). The remaining 90% of the gland consists of the exocrine components that produce digestive enzymes estimated at 1500 – 2500 mL per day (10). These are packaged into zymogens as proenzymes where their release is facilitated through the actions of trypsin (12). The release and actions of these enzymes play important roles in both postmortem autolysis and in the pathophysiology of pancreatitis and the resultant alterations in homeostasis.

Epidemiology

Acute pancreatitis is an inflammatory disease that results in a spectrum of mortality related to the severity of disease. Mild acute pancreatitis, also known as edematous pancreatitis, tends to be self-limiting and has a mortality of less than 1% (13, 14), while severe acute pancreatitis, or hemorrhagic pancreatitis, is associated with mortality rates ranging from 10-30% (15-18). Typically, deaths resulting from acute pancreatitis would not fall under the jurisdiction of the ME/C; however, acute pancreatitis can be a cause of sudden unexpected death and can be seen in the forensic setting. Although the incidence of fatal acute pancreatitis in the ME/C setting is not known, the reported incidence of acute pancreatitis first diagnosed at autopsy ranges between 30-42% (19-21). In a forensic autopsy-based study, Tsokos and Braun researched acute pancreatitis deaths at the Institute of Legal Medicine in Hamburg, Germany between 2000 and 2004 (4). During that time, 6178 autopsy examinations were performed and 27 cases of fatal acute pancreatitis were identified, resulting in a 0.44% frequency of the disease. Other forensic and autopsy studies have reported a frequency of fatal acute pancreatitis between 0.2% and 0.8% (5-7).



Pathophysiology

The majority of cases of acute pancreatitis are caused by biliary disease (gallstone pancreatitis) or alcohol use/abuse. Together, these two etiologies account for approximately 75% of the cases of acute pancreatitis seen clinically in the United States; with 40% attributed to biliary disease and 35% attributed to alcohol use/abuse (22, 23). In gallstone pancreatitis, a stone becomes lodged in the bile duct or sphincter of Oddi. It is proposed that this results in injury to the exocrine acinar cells through increased pancreatic duct pressures (12, 24). Therefore, variations in the bile duct/pancreatic duct anatomy can potentially be a factor in the development or severity of gallstone pancreatitis. In the forensic setting, however, acute pancreatitis is most commonly seen in the context of alcoholism, either alone or superimposed on chronic pancreatitis (4, 25, 26). In part, this is due to the inherent selection bias of alcohol-related deaths frequently falling under ME/C jurisdiction. Alcohol (ethanol) causes pancreatitis through a group of related mechanisms. First, it leads to intracellular accumulation of digestive enzymes and there premature activation and release. It also increases the permeability of pancreatic ductules, which allows enzymes to reach the acinar cells, and

it increases the protein content of digestive enzymes and decreases the bicarbonate levels and trypsin inhibitor concentrations, thereby promoting protein plugs that block duct outflow (12, 27, 28).

There are a wide variety of less common causes, as seen in **Table 1** (29–32). Specific to the ME/C, pancreatitis should be considered in a delayed sudden death after abdominal trauma or after injury to the upper lumbar vertebrae. In jurisdictions that use “therapeutic complications” as a manner of death, pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP) and related to medications may fall under ME/C jurisdiction. More rarely, pancreatitis from a toxin (e.g., scorpion or snake) can occur. Another etiology that is more specific to forensic practice is hypothermia, in which hemorrhagic pancreatitis has been described (33). However, in a review of studies on pancreatic changes in hypothermia, the presence of hemorrhagic pancreatitis was not consistently seen and varied from 0–67% (34).

Independent of etiology, the common pathway of acute pancreatitis is injury to the acinar cells. Once these cells are injured, a host of changes occurs that result in the effective autodigestion of the parenchy-

Table 1: Causes of Acute Pancreatitis

More Common	Choledocholithiasis Alcoholism Post endoscopic retrograde cholangiopancreatography Drugs Abdominal trauma
Less Common	Malignancy/tumor Hypertriglyceridemia Hyperparathyroidism Hypercalcemia Viral infection (e.g., mumps, Coxsackie B, Hantavirus) Developmental abnormalities (e.g., pancreas divisum, annular pancreas) Toxins (e.g., scorpion or snake bite)

ma. These include fusion of lysosomal and zymogen granules with resultant activation of trypsinogen to trypsin, activation of the zymogen cascade, and initiation of the inflammatory cell response (12). As the inflammatory response grows, it can become systemic and affect the cardiovascular, respiratory, and renal systems (35, 36). This can result in systemic inflammatory response syndrome (SIRS), shock, diffuse intravascular coagulopathy (DIC), and electrolyte abnormalities (30).

Autopsy Pathology

The gross appearance of acute pancreatitis can vary greatly from mild hyperemia of portions of the gland to frank hemorrhagic necrosis that extends to the ad-

jacent tissue and beyond. Some examples are shown in **Images 1 to 6**. As is the case with many aspects of forensic pathology, it is important for the autopsy pathologist to differentiate genuine disease from postmortem artifact. This is especially true in the pancreas, where the native enzymes and proteins produce rapid autolytic changes. As the cells break down in the postmortem state, digestive enzymes/chemicals that are typically contained in cells and ducts act on the parenchyma to produce degeneration and chemical necrosis. This process is not unlike the pathophysiology of acute pancreatitis where, despite the etiology, the acinar cells become injured and release their contents into the surrounding tissue, which results in additional injury. Given these similarities, it should not be surprising that postmortem autolysis and antemortem

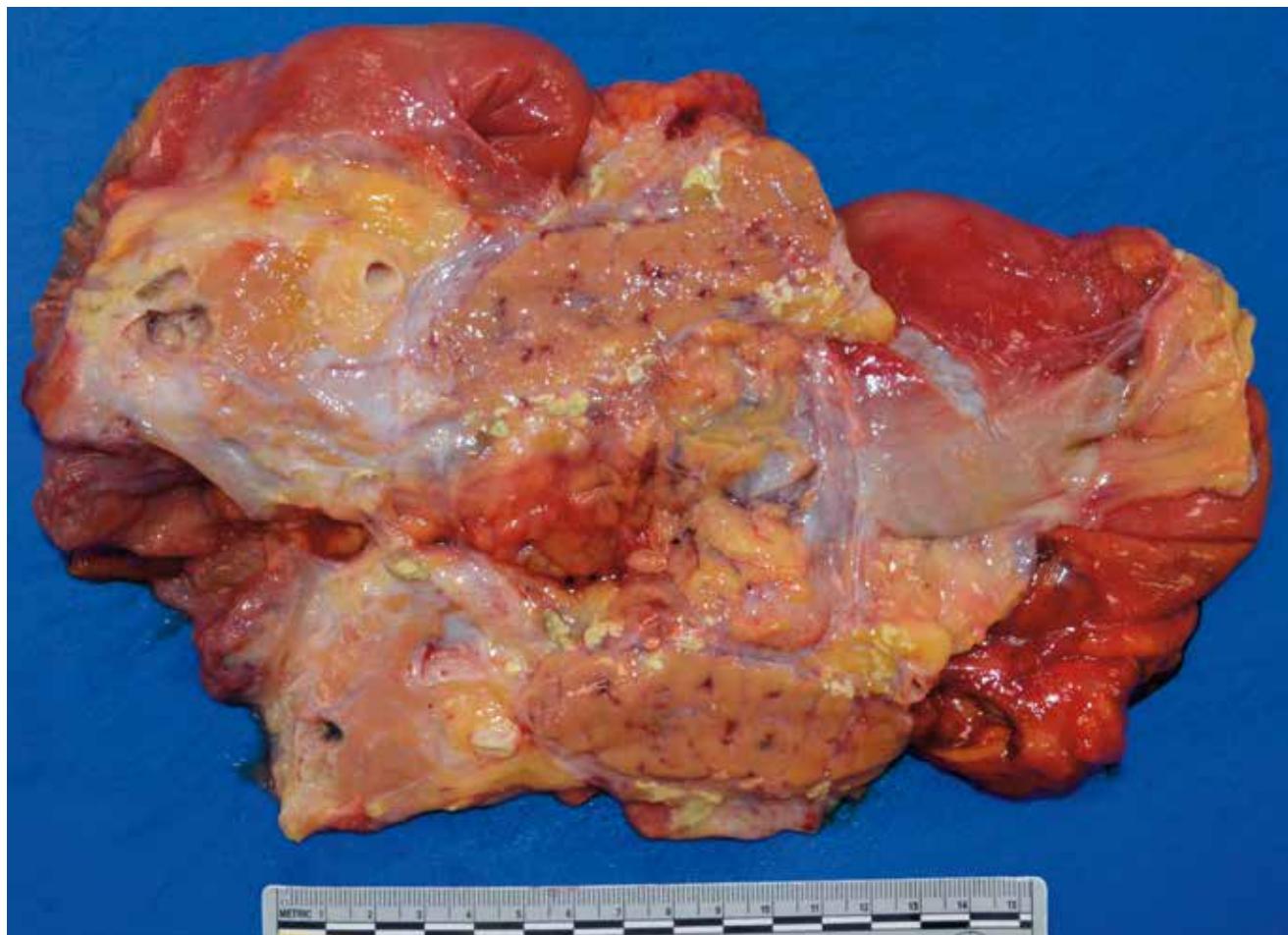


Image 1: Gross appearance of acute pancreatitis with fat necrosis in fileted pancreas.

pancreatitis might appear similar in the gross state. The only way to definitively confirm the presence of pancreatitis is to examine the tissue microscopically and identify the acute inflammatory cell infiltrate necessary to make such a diagnosis (**Images 7 and 8**). The acute inflammation is often best seen in the interstitial tissue, which is somewhat spared from the chemical breakdown (**Image 9**). Other features reported to be helpful in distinguishing pancreatitis from autolysis are fat necrosis and calcium deposition (37); however, fat necrosis without inflammation is frequently seen in postmortem autolysis. It is also important to consider the overall state of decomposition of the body, the po-

sitioning of the body, and the distribution of change in the pancreas, as more advanced decomposition, prone positioning, and diffuse interstitial hyperemia/hemorrhage, are more likely to be associated with postmortem autolysis.

Although acute pancreatitis without hemorrhage is capable of causing death, hemorrhagic pancreatitis is more commonly reported in autopsy-based studies involving sudden death (4, 6, 7, 25). It is likely that the combination of DIC and local auto-digestion result in the hemorrhage seen in pancreatitis (**Images 10 to 12**). In an experimental study, Bakarev proposed that



Image 2: Gross appearance of pancreas with fat necrosis (chalky, yellow discoloration).

pancreatic fat necrosis and hemorrhagic necrosis were separate morphological and functional entities (38). The study showed that common bile duct ligation alone produces findings of fat necrosis, while common bile duct ligation in addition to injection of phospholipid A2 produces hemorrhagic necrosis, and with injection of trypsin, produces massive hemorrhage. If hemorrhagic pancreatitis results in significant retroperitoneal bleeding, it is possible that the overlying posterior peritoneal lining can be disrupted and intra-peritoneal hemorrhage (hemoperitoneum) can occur. This is most commonly reported in association with rupture of pancreatic pseudocysts (39, 40), but there are also case reports describing acute intra-peritoneal hemorrhage in the setting of acute hemorrhagic pancreatitis (41-44) and a single report of this in the forensic literature (45). In this report, five cases of acute hemorrhagic pancreatitis were described, all of which had associated hemorrhage in the peritoneal cavity and destruction of the elastic tissue of the vessels. From a pathophysiologic perspective, this

can occur if there is hemorrhage in the retroperitoneal tissue that produces sufficient pressure to disrupt the posterior peritoneal lining, similar to intra-peritoneal hemorrhage from a ruptured abdominal aortic aneurysm. In the forensic setting, it is important to consider this as an alternative to trauma when there is pancreatic hemorrhage with or without retroperitoneal or intra-peritoneal hemorrhage.

Ancillary Testing

Clinically, acute pancreatitis is broadly classified as either mild or severe. Based on the Atlanta classification, severe acute pancreatitis is marked by either evidence of organ failure (systolic blood pressure below 90 mmHg, arterial partial pressure of oxygen 60 mmHg or lower, serum creatinine level of 2 mg/dL or higher, or gastro-intestinal bleeding greater than 500 mL in 24 hours), local complications (necrosis, abscess, or pseudocyst), Ranson score of 3 or higher, or acute physiologic assessment and chronic

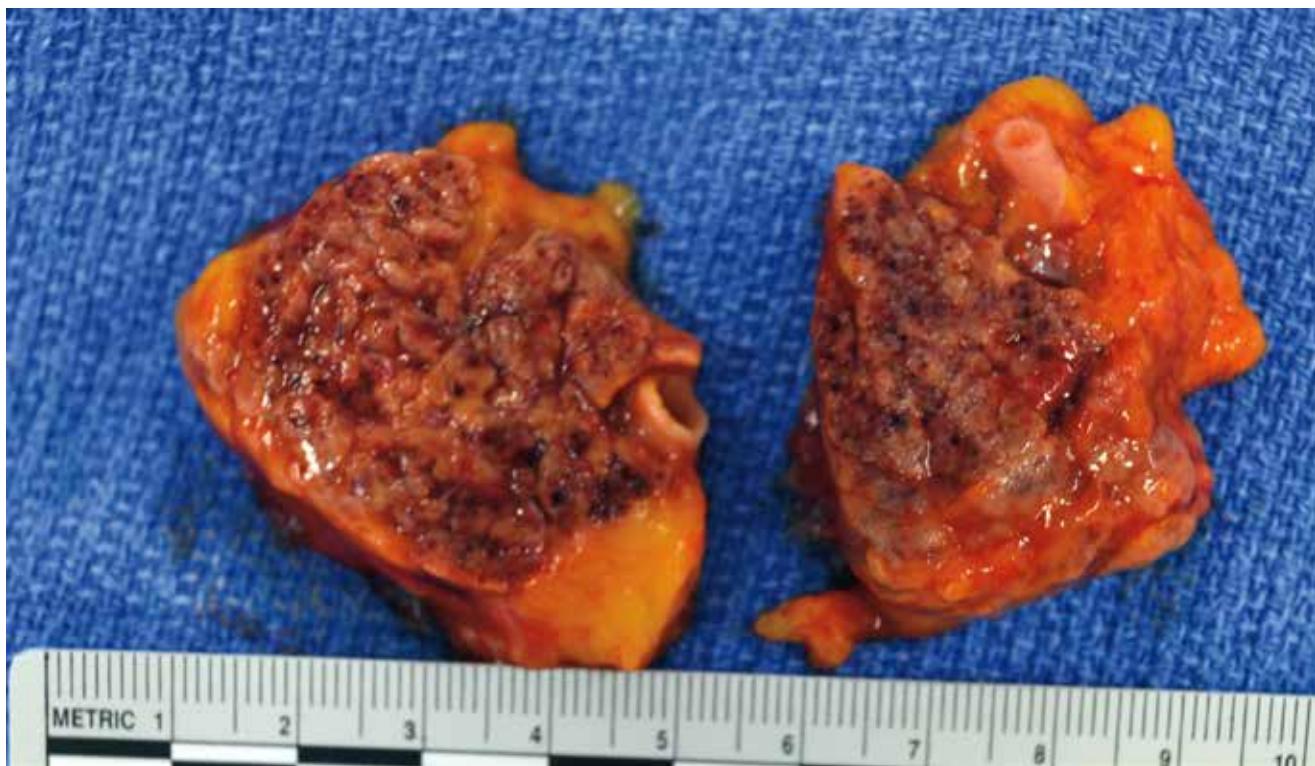


Image 3: Gross appearance of acute hemorrhagic pancreatitis (mild).

health evaluation (APACHE) score of 8 or higher (35). In addition to these criteria, there are a number of scoring systems used clinically to guide therapy and predict outcomes in acute pancreatitis (**Table 2**) (32, 35, 46). Most of these involve clinical assessment and laboratory data that are not able to be measured in the postmortem state. Despite this, there are ancillary tests that can be performed after death that may help to confirm the postmortem diagnosis of acute pancreatitis. Specifically, vitreous testing can reveal elevated glucose concentrations (greater than 200 µg/dL) as well as increased vitreous urea nitrogen (VUN) and

creatinine concentrations, indicative of hyperglycemia and renal failure, respectively. In addition, testing of postmortem serum amylase and lipase may also be useful, although results must be interpreted with caution depending on the postmortem interval and lack of specificity of low level elevations (47). Imaging studies such as computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound (US) are frequently used to assess pancreatitis in the clinical setting (32). With the increasing use of CT scans in the postmortem setting, this will become a useful adjunct to making the diagnosis of acute pancreatitis. How-

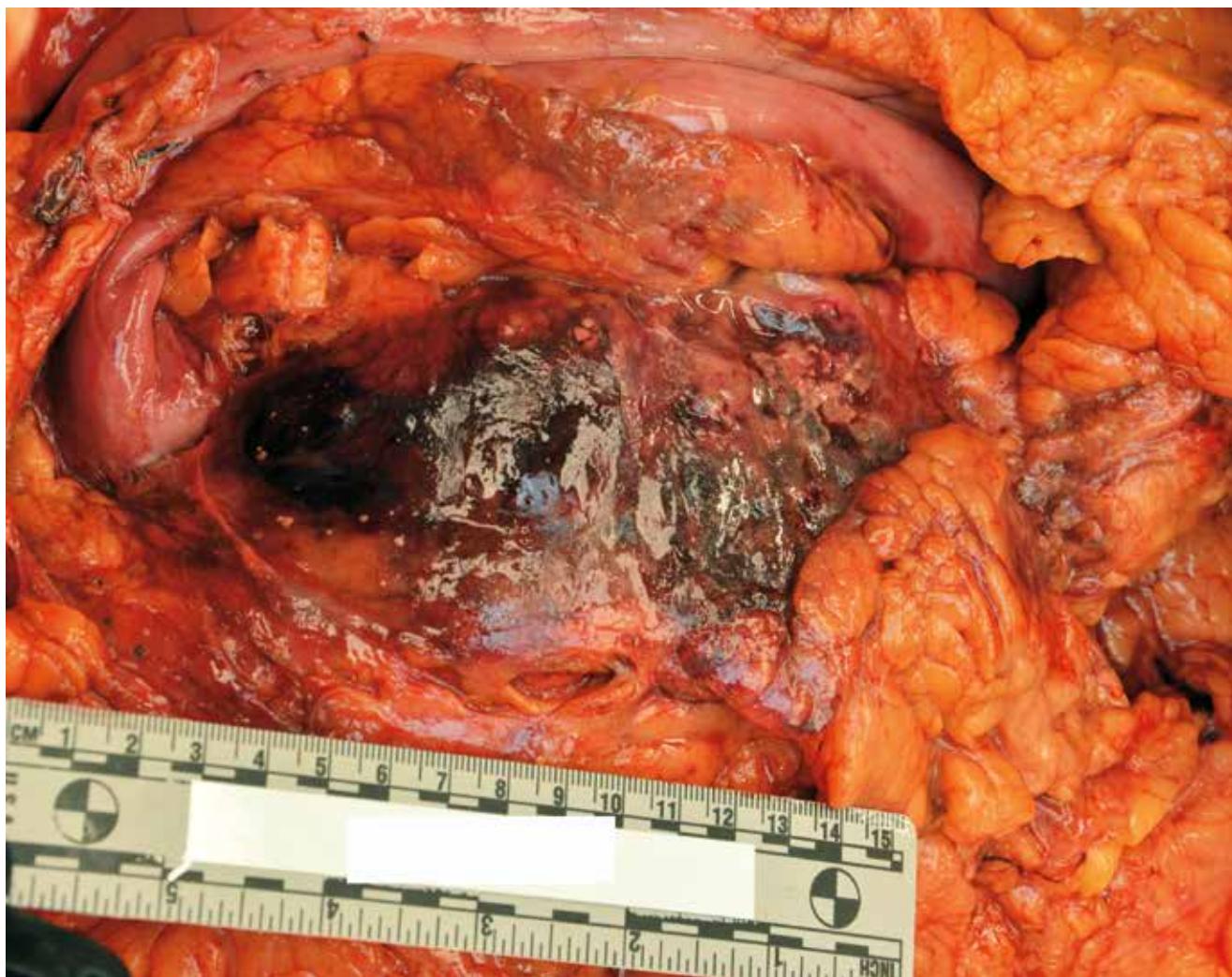


Image 4: *In situ* appearance of acute hemorrhagic pancreatitis with retroperitoneal hemorrhage. (Image courtesy of Washoe County Regional Medical Examiner's Office).



Image 5: Gross appearance of acute hemorrhagic pancreatitis after evisceration of tissue block. (Image courtesy of Washoe County Regional Medical Examiner's Office).

ever, as newer modalities such as postmortem CT angiography become more common, the importance of artifacts relative to the pancreas must be considered (48).

CONCLUSION

Although infrequent in the forensic setting, acute pancreatitis should be considered in sudden, unexpected deaths, particularly in those related to alcohol abuse and in delayed deaths after abdominal trauma. In this

setting, hemorrhagic pancreatitis is more common, and can be associated with frank intra-peritoneal hemorrhage. The gross findings of acute pancreatitis may overlap with those of postmortem autolysis, and therefore microscopic evidence of acute inflammation must be present to confirm the diagnosis. Ancillary studies, including vitreous testing and postmortem serum amylase and lipase testing, may be performed to support the diagnosis and explain the underlying pathophysiology. Where available, postmortem CT imaging may also serve as a useful adjuvant.



Image 6: Gross appearance of acute hemorrhagic pancreatitis in sectioned pancreas. (Image courtesy of Washoe County Regional Medical Examiner's Office).

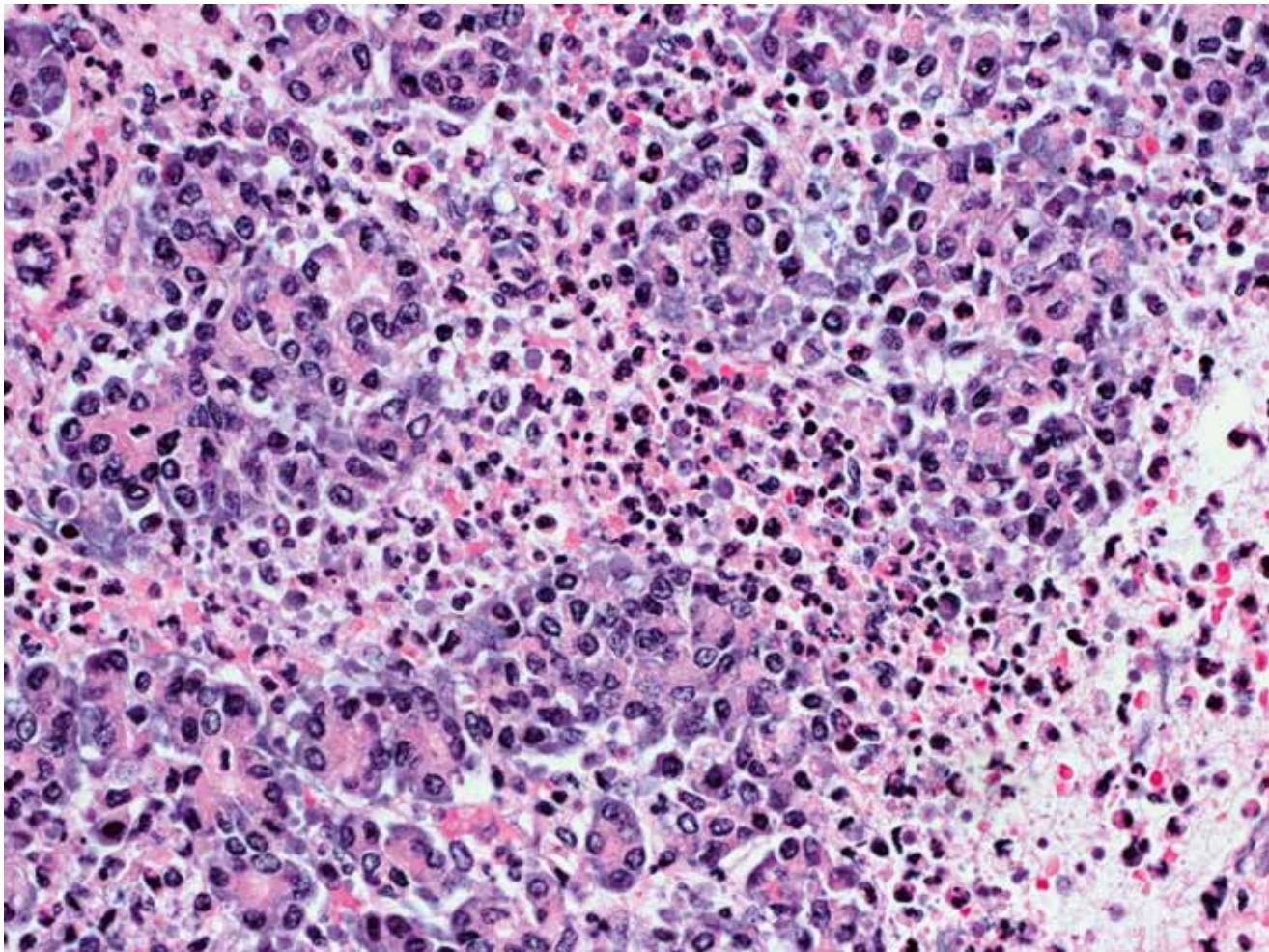


Image 7: Acute inflammation of pancreatic acinar cells (H&E, x400).

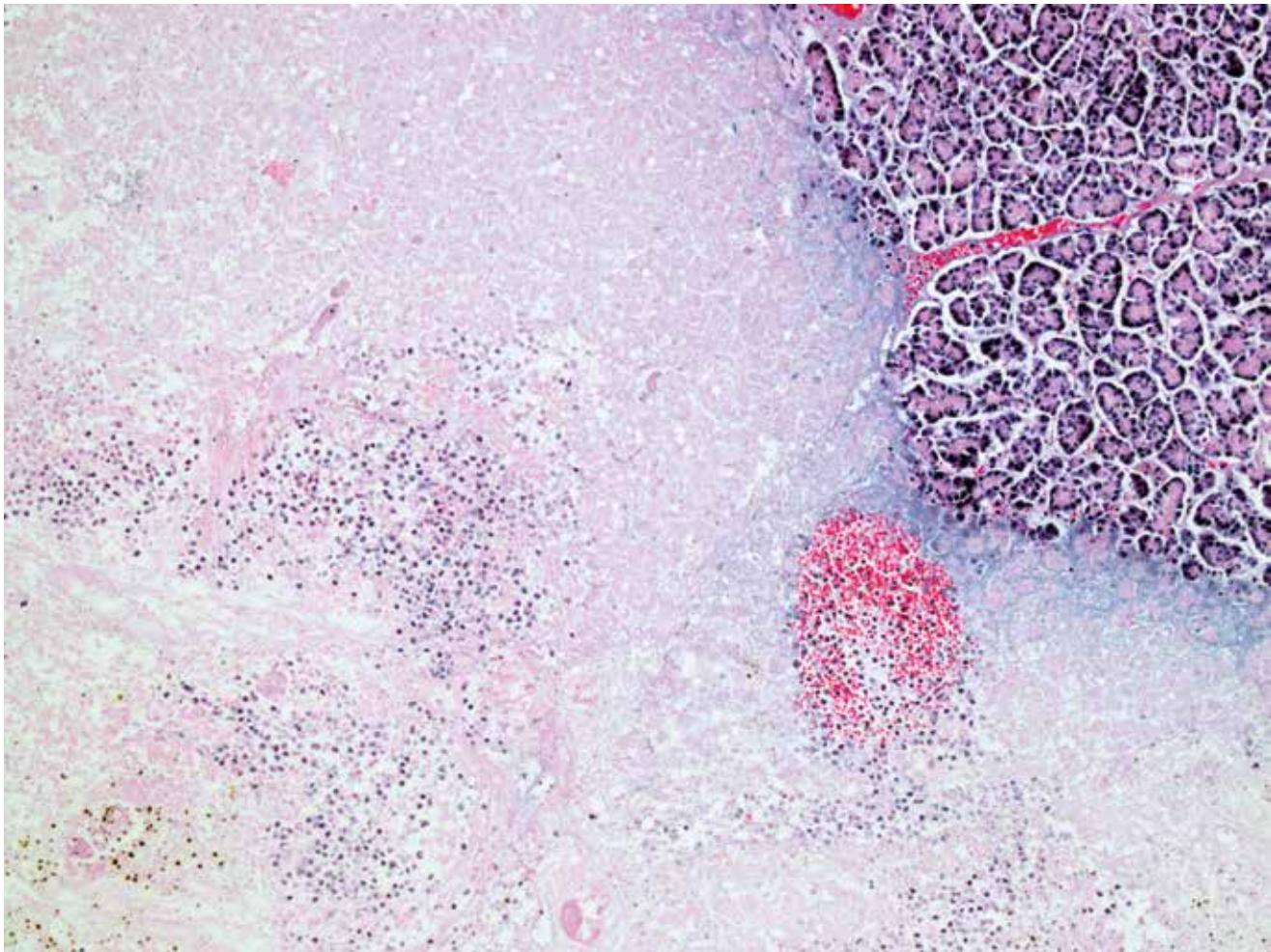


Image 8: Pancreatic necrosis and inflammation adjacent to normal pancreatic tissue (H&E, x200).

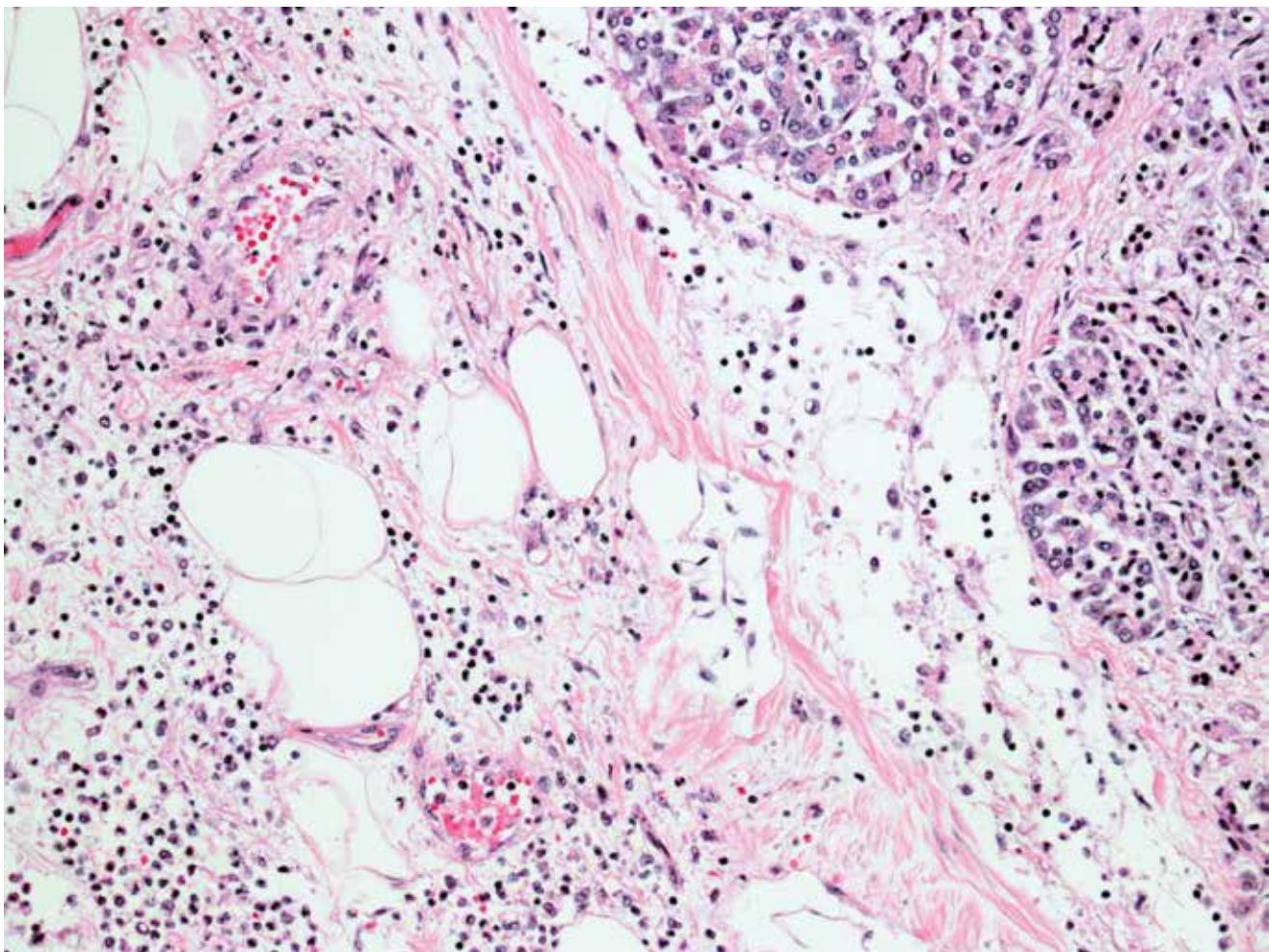


Image 9: Pancreas with interstitial edema and acute inflammation (H&E, x200).

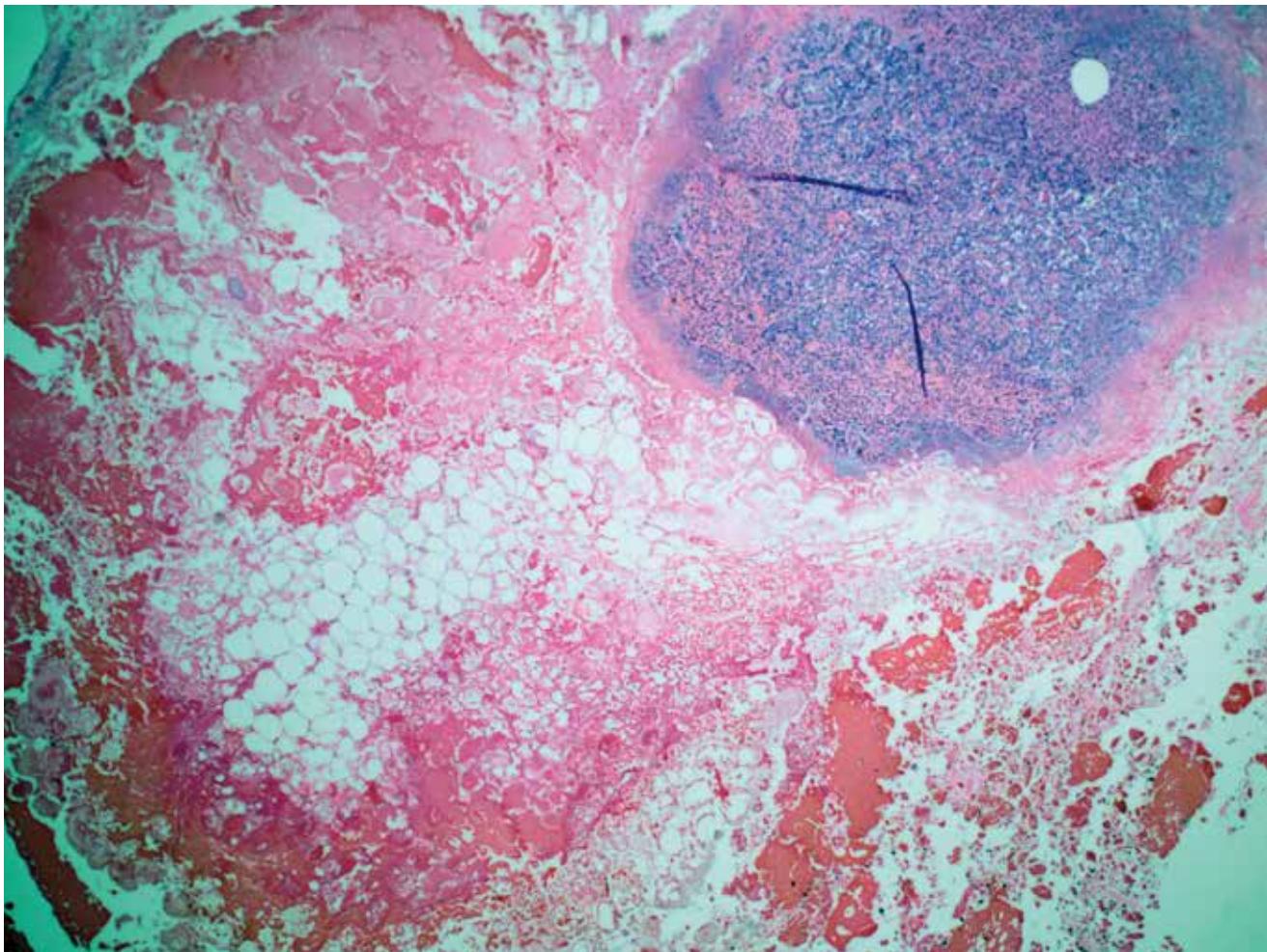


Image 10: Interstitial hemorrhage in acute hemorrhagic pancreatitis (H&E, x40).

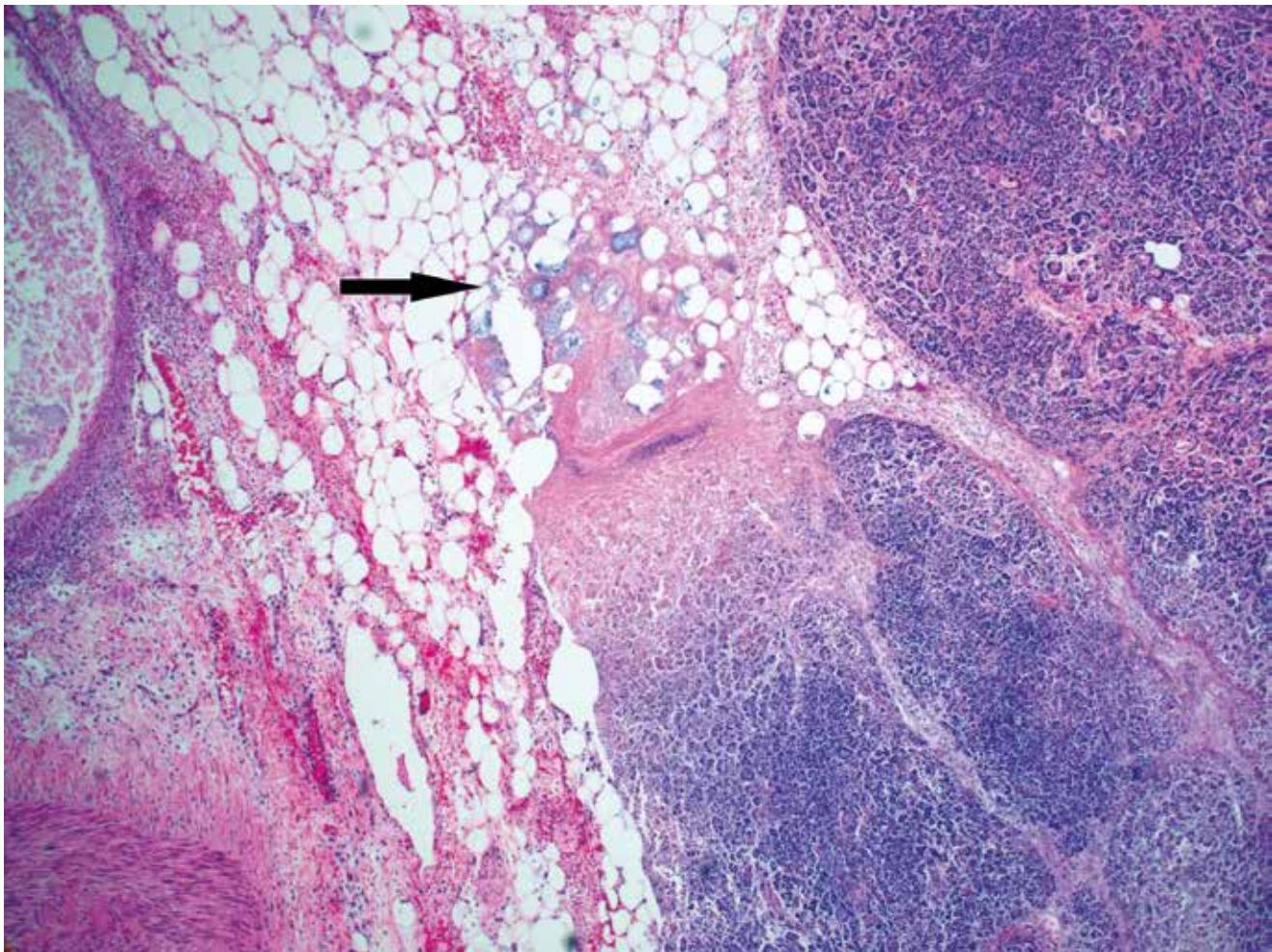


Image 11: Hemorrhage and fat necrosis (arrow) in acute hemorrhagic pancreatitis (H&E, x40).

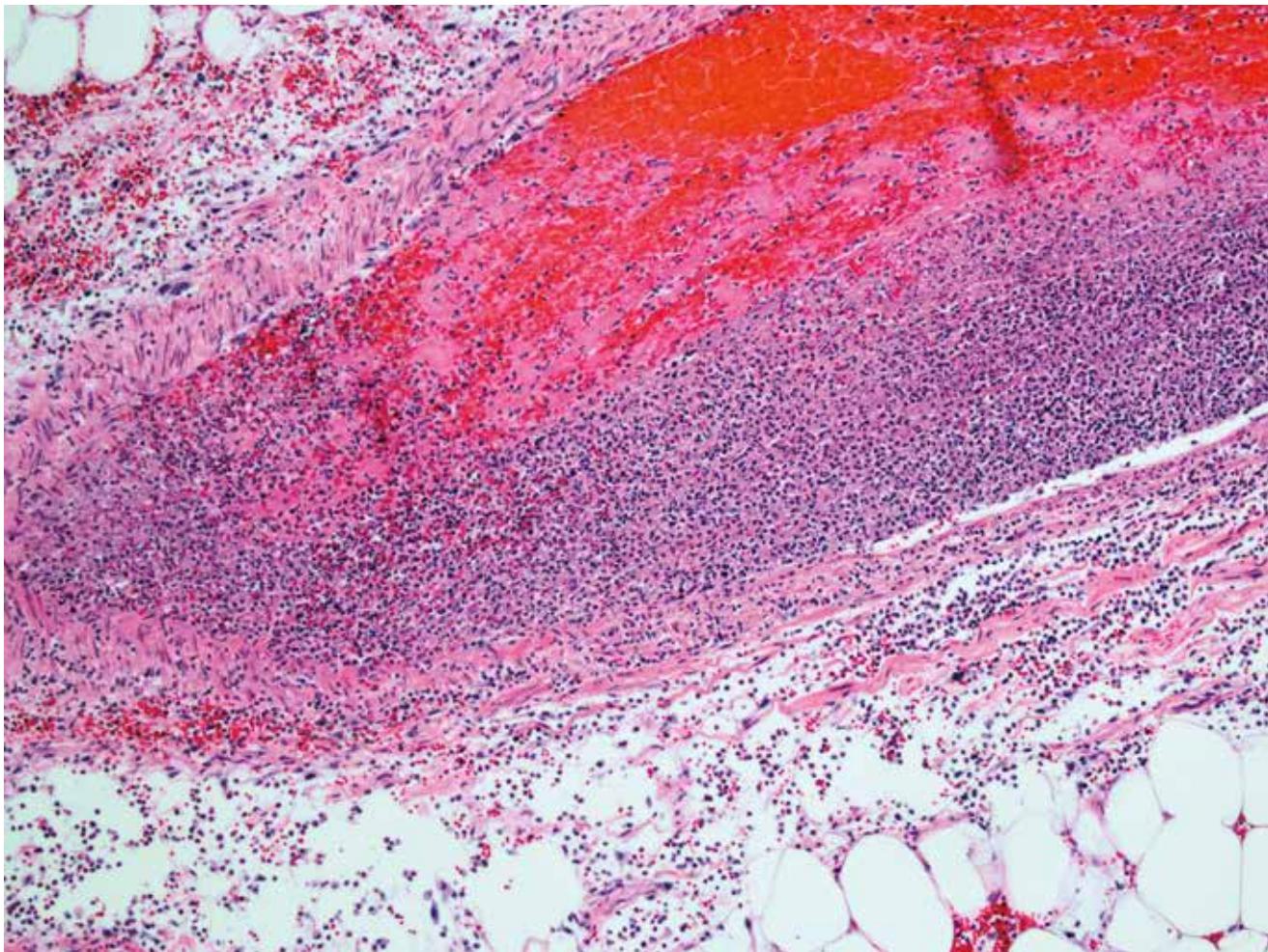


Image 12: Acute inflammation of vessel with thrombosis in acute hemorrhagic pancreatitis (H&E, x100). (Image courtesy of Washoe County Regional Medical Examiner's Office).

**Table 2:** Clinical Scoring Systems Used in Acute Pancreatitis

Ranson's Criteria	
At admission/diagnosis	Age > 55 White blood cell count > 16 000 per mm ³ Blood glucose > 200 mg/dL Serum lactate dehydrogenase (LDH) > 350 IU/L Serum aspartate aminotransferase (AST) > 250 IU/L
During initial 24 hours	Hematocrit decrease > 10% Blood urea nitrogen (BUN) increase > 5 mg/dL Serum calcium < 8 mg/dL Base deficit > 4 mmol/L PaO_2 < 60 mmHg
Bedside Index of Severity in Acute Pancreatitis (BISAP)	
Blood urea nitrogen (BUN) > 25 mg/dL	
Abnormal mental status with Glasgow coma scale < 15	
Evidence of systemic inflammatory response syndrome (SIRS)	
Age > 60	
Pleural effusion	

REFERENCES

- 1) Schein M. Aphorisms & quotations for the surgeon. Shrewsbury (UK): TFM Publishing; 2004. 276 p.
- 2) Russo MW, Wei JT, Thiny MT, et al. Digestive and liver diseases statistics. 2004. *Gastroenterology*. 2004 May; 126(5):1448-53. PMID: 15131804. <https://doi.org/10.1053/j.gastro.2004.01.025>.
- 3) Swaropp VS, Chari ST, Clain JE. Severe acute pancreatitis. *JAMA*. 2004 Jun 16; 291(23):2865-8. PMID: 15199038. <https://doi.org/10.1001/jama.291.23.2865>.
- 4) Tsokos M, Braun C. Acute pancreatitis presenting as sudden, unexpected death: an autopsy-based study of 27 cases. *Am J Forensic Med Pathol*. 2007 Sep;28(3):267-70. PMID: 17721182. <https://doi.org/10.1097/paf.0b013e3181425615>.
- 5) DiMaio VJ, DiMaio DJ. Natural death as viewed by the medical examiner: a review of 1000 consecutive autopsies of individuals dying of natural disease. *J Forensic Sci*. 1991 Jan; 36(1):17-24. PMID: 2007867. <https://doi.org/10.1520/JFS13000J>.
- 6) Shetty BS, Boloor A, Menezes RG, et al. Postmortem diagnosis of acute haemorrhagic pancreatitis. *J Forensic Leg Med*. 2010 Aug; 17(6):316-20. PMID: 20650420. <https://doi.org/10.1016/j.jflm.2010.04.013>.
- 7) Renner IG, Savage WT 3rd, Pantoja JL, Renner VJ. Death due to acute pancreatitis. A retrospective analysis of 405 autopsy cases. *Dig Dis Sci*. 1985 Oct; 30(10):1005-18. PMID: 3896700. <https://doi.org/10.1007/bf01308298>.
- 8) Klimstra DS. Pancreas. In: Sternberg SS. Histology for pathologists. 2nd ed. Philadelphia: Lippencott-Raven; 1997. 1216 p.
- 9) Sadler TW. Langman's Medical Embryology. 6th ed. Baltimore: Williams and Wilkins, 1990. 411 p.
- 10) Fischer JE, Bower RH, Bell RH. Liver, biliary, and pancreatic function. In: Davis JH. Clinical Surgery: Vol. 1. St. Louis: Mosby, 1987.
- 11) Guyton AC. Textbook of medical physiology. 8th ed. Philadelphia: W.B. Saunders; 1991.1056 p.
- 12) Medscape [Internet]. New York: Medscape, LLC; c1994-2018. Acute pancreatitis; [cited 2018 Feb 13]. Available from: <https://emedicine.medscape.com/article/181364>.
- 13) Russo MW, Wei JT, Thiny, MT, et al. Digestive and liver disease statistics. 2004. *Gastroenterology*. 2004 May; 126(5):1448-53. PMID: 15131804. <https://doi.org/10.1053/j.gastro.2004.01.025>.
- 14) Triester SL, Kowdley KV. Prognostic factors in acute pancreatitis. *J Clin Gastroenterol*. 2002 Feb; 34(2):167-76. PMID: 11782614. <https://doi.org/10.1097/00004836-200202000-00014>.
- 15) Devenis C, Johnson CD, Bassi C, et al. Diagnosis, objective assessment of severity, and management of acute pancreatitis. Santorini Consensus Conference. *Int J Pancreatol*. 1999 Jun; 25(3):195-210. PMID: 10453421.
- 16) Mayerle J, Hlouschek, V, Lerch MM. Current management of acute pancreatitis. *Nat Clin Pract Gastroenterol Hepatol*. 2005 Oct; 2(10):473-83. PMID: 16224479. <https://doi.org/10.1038/ncpgasthep0293>.



- 17) Carnovale A, Rabitti PG, Manes G, et al. Mortality in acute pancreatitis; is it an early or a late event? *JOP*. 2005 Sep 10; 6(5):438-44. PMID: 16186665.
- 18) Cavallini G, Frulloni L, Bassi C, et al. Prospective multicenter survey on acute pancreatitis in Italy (ProInf-AISP): results on 1005 patients. *Dig Liver Dis*. 2004 Mar; 36(3):205-11. PMID: 15046191. <https://doi.org/10.1016/j.dld.2003.11.027>.
- 19) Corfield AP, Cooper MJ, Williamson RC. Acute pancreatitis: a lethal disease of increasing incidence. *Gut*. 1985 Jul;26(7):724-9. PMID: 4018637. <https://doi.org/10.1136/gut.26.7.724>.
- 20) Lankisch PG, Schirren CA, Kunze E. Undetected fatal acute pancreatitis: why is the disease so frequently overlooked? *Am J Gastroenterol*. 1991 Mar; 86(3):322-6. PMID: 1705388.
- 21) Wilson C, Imrie CW. Deaths from acute pancreatitis: why do we miss the diagnosis so frequently? *Int J Pancreatol*. 1988 May; 3(4): 273-81. PMID: 2455008. <https://doi.org/10.1007/BF02788456>.
- 22) Whitcomb DC, Yadav D, Adam S, et al. Multicenter approach to recurrent acute and chronic pancreatitis in the United States: the North American Pancreatitis Study 2 (NAPS2). *Pancreatology*. 2008; 8(4-5):520-31. PMID: 18765957. PMCID: PMC2790781. <https://doi.org/10.1159/000152001>.
- 23) Banks PA. Epidemiology, natural history, and predictors of disease outcome in acute and chronic pancreatitis. *Gastrointest Endosc*. 2002 Dec; 56(6 Suppl):S226-30. PMID: 12447272. [https://doi.org/10.1016/s0016-5107\(02\)70016-3](https://doi.org/10.1016/s0016-5107(02)70016-3).
- 24) Suda K, Miyano T. Bile pancreatitis. *Arch Pathol Lab Med*. 1985; 109(5); 433-6. PMID: 3838657.
- 25) Turner AR, Dener C. Diagnostic dilemma of sudden deaths due to acute hemorrhagic pancreatitis. *J Forensic Sci*. 2007 Jan;52(1):180-2. PMID: 17209933. <https://doi.org/10.1111/j.1556-4029.2006.00316>.
- 26) Srettabunjong S, Limgitupasun W. Severe acute hemorrhagic pancreatitis secondary to cholelithiasis as a rare cause of sudden unexpected death in medico-legal case: a case report. *Medicine (Baltimore)*. 2016 Aug;95(34):e4680. PMID: 27559973. PMCID: PMC400340. <https://doi.org/10.1097/MD.00000000000004680>.
- 27) Lerch MM Albrecht E, Ruthenburger M, et al. Pathophysiology of alcohol-induced pancreatitis. *Pancreas*. 2003 Nov; 27(4):291-6. PMID: 14576489. <https://doi.org/10.1097/00006676-200311000-00003>.
- 28) Yadav D, Papachristou GI, Whitcomb DC. Alcohol-associated pancreatitis. *Gastroenterol Clin North Am*. 2007 Jun; 36(2):219-38, vii. PMID: 17533076. <https://doi.org/10.1016/j.gtc.2007.03.005>.
- 29) Quinlan JD. Acute pancreatitis. *Am Fam Physician*. 2014 Nov 1; 90(9):632-9. PMID: 25368923.
- 30) Gill JR. Pancreatitis: a forensic perspective. *Acad Forensic Pathol*. 2016; 6(2):237-48. <https://doi.org/10.23907/2016.025>.
- 31) Kilt TP, Kilt C, Erarsian S. A rare cause of acute pancreatitis: Hantavirus infection. *Acta Gastroenterol Belg*. 2017 Jan-Mar; 80(1): 59-61. PMID: 29364099.
- 32) Carroll JK, Herrick B, Gipson T, Lee SP. Acute pancreatitis: diagnosis, prognosis, and treatment. *Am Fam Physician*. 2007 May 15; 75(10):1513-20. PMID: 17555143.
- 33) DiMaio DJ, DiMaio VJM. *Forensic pathology*. Boca Raton: CRC Press, 1993. 528 p.
- 34) Madea B, Tsokos M, Preuss J. *Forensic pathology reviews*. Vol 5. Totowa (NJ): Humana Press, c2008. Chapter 1, Deaths due to hypothermia; p. 3-24.
- 35) Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis-2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013 Jan;62(1):102-11. PMID: 23100216. <https://doi.org/10.1136/gutjnl-2012-302779>.
- 36) Steer ML, Garg P, Saluja AK. Pathogenic mechanisms of acute pancreatitis. *Curr Opin Gastroenterol*. 2012 Sep; 28(5):507-15. PMID: 22885948. PMCID: PMC3682674.
- 37) Ye GH, Zhang YG, Yu LS, et al. [Acute necrotizing pancreatitis and postmortem autolysis of pancreas]. *Fa Yi Xue Za Zhi*. 2008 Apr; 24(2):94-6, 101. PMID: 18605036.
- 38) Bakarev MA, Vasilev AV, Protsenko SI. Pancreatic fat necrosis and hemorrhagic necrosis as separate morphologic and functional entities. *Bull Exp Biol Med*. 2013 Apr; 154(6):805-9. PMID: 23658929. <https://doi.org/10.1007/s10517-013-2061-0>.
- 39) Kelly SB, Gauhar T, Pollard R. Massive intraperitoneal hemorrhage from a pancreatic pseudocyst. *Am J Gastroenterol*. 1999 Dec; 94(12):3638-41. PMID: 10606335. [https://doi.org/10.1016/s0002-9270\(99\)00515-8](https://doi.org/10.1016/s0002-9270(99)00515-8).
- 40) Fiai G, Andreu-Sandberg A, LaPinta M, et al. Potentially fatal bleeding in acute pancreatitis: pathophysiology, prevention, and treatment. *Pancreas*. 2003 Jan; 26(1):8-14. PMID: 12499910. <https://doi.org/10.1097/00006676-200301000-00002>.
- 41) Querido S, Carvalho I, Moleiro F, Póvoa P. Fatal acute necrohemorrhagic pancreatitis with massive intraperitoneal and retroperitoneal bleeding: a rare cause of exsanguination. *BMJ Case Rep*. 2016 Jan 20; 2016. pii: bcr2015213732. PMID: 26791128. PMCID: PMC4735153. <https://doi.org/10.1136/bcr-2015-213732>.
- 42) Washiro M, Kusashio K, Yasutomi J, et al. A case of acute pancreatitis with spontaneous massive bleeding into peritoneal cavity. *Nihon Rinsho Geka Gakkai Zasshi*. 2007; 68(12):3083-6. <https://doi.org/10.3919/jjsa.68.3083>.
- 43) Puolakkain P, Lempinin M, Schroder T. Fatal pancreatitis: a study of 64 cases. *Acta Chir Scand*. 1986 May; 152:379-83. PMID: 3739548.
- 44) Frey CF. Hemorrhagic pancreatitis. *Am J Surg*. 1979 May;137(5): 616-23. PMID: 453456. [https://doi.org/10.1016/0002-9610\(79\)90034-5](https://doi.org/10.1016/0002-9610(79)90034-5).
- 45) Murty OP, Agarwal A, Krishnan R. Sudden death due to acute pancreatitis: autopsy observations. *J Forensic Med Toxicol*. 2008; 25(2):47-53.
- 46) Chatzicostas C, Roussomoustakaki M, Viachonikolos IG, et al. Comparison of Ranson, APACHE II, and APACHE III scoring systems in acute pancreatitis. *Pancreas*. 2002 Nov; 25(4):331-5. PMID: 12409825. <https://doi.org/10.1097/00006676-200211000-00002>.
- 47) Brown TJ, Prahlaw J. Postmortem serum amylase and lipase analysis in the diagnosis of acute pancreatitis. *Acad Forensic Pathol*. 2018 Jun; 8(2):311-23. <https://doi.org/10.23907/2018.020>.
- 48) Bruguer C, Grabherr S. *Atlas of postmortem angiography*. Lausanne (Switzerland): Springer International Publishing, 2016. Chapter 19, Radiologic artefacts of postmortem computed tomography angiography; p. 231-50.



Differential Diagnosis of Hepatic Necrosis Encountered at Autopsy

Daniel C. Butler, David N. Lewin, Nicholas I. Batalis

ABSTRACT

The liver is subject to a variety of extrinsic and intrinsic insults that manifest with both specific and nonspecific patterns of necrosis. In the autopsy setting, these patterns are often encountered as incidental findings or even causes of death. There are several etiologies of hepatic necrosis, including toxins, drug injuries, viral infections, ischemic injuries, and metabolic disease, all of which possess overlapping gross and histologic presentations. Nonetheless, patterned necrosis in the context of clinical and demographic history allows for the forensic pathologist to develop a differential diagnosis, which may then be pruned into a specific or likely cause. The aim of the following review is to elucidate these patterns in the context of the liver diseases from which they arise with the goal developing a differential diagnosis and ultimate determination of etiology. *Acad Forensic Pathol.* 2018 8(2): 256-295

AUTHORS

Daniel C. Butler MD, Medical University of South Carolina - Department of Pathology and Laboratory Medicine

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work.

David N. Lewin MD, Medical University of South Carolina - Department of Pathology and Laboratory Medicine

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work.

Nicholas I. Batalis MD, Medical University of South Carolina - Department of Pathology and Laboratory Medicine

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work.

CORRESPONDENCE

Daniel C. Butler MD, 96 Jonathan Lucas St, Charleston SC 29425-2503, butlerdc@musc.edu

ETHICAL APPROVAL

As per Journal Policies, ethical approval was not required for this manuscript

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies conducted with animals or on living human subjects

STATEMENT OF INFORMED CONSENT

No identifiable personal data were presented in this manuscript

DISCLOSURES & DECLARATION OF CONFLICTS OF INTEREST

Nicholas I. Batalis is the Associate Editor-in-Chief of Academic Forensic Pathology: The Official Publication of the National Association of Medical Examiners. The authors, reviewers, and publication staff do not report any other relevant conflicts of interest

FINANCIAL DISCLOSURE

The authors have indicated that they do not have financial relationships to disclose that are relevant to this manuscript

KEYWORDS

Forensic pathology, Liver necrosis, Acute liver failure, Hepatitis

INFORMATION

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

©2018 Academic Forensic Pathology International • (ISSN: 1925-3621) • <https://doi.org/10.23907/2018.018>

Submitted for consideration on 9 Mar 2018. Accepted for publication on 13 Apr 2018



INTRODUCTION

The liver is subject to a variety of insults that induce acute and chronic changes. Acute hepatitis lasts less than six months but may progress to chronic hepatitis with repeated insults or unresolved injury. In its most severe form, hepatic injury evolves into acute liver failure (ALF) or acute-on-chronic liver failure (ACLF), two conditions with a high mortality rate secondary to a rapid decline in liver function. In all of these conditions, necrosis is a common feature, arising from multiple etiologies that manifest with both specific and nonspecific histologic patterns. The following review will discuss these etiologies and associated patterns in the context of the liver diseases from which they arise with the goal of aiding forensic pathologists in developing a differential diagnosis and identifying specific causes of hepatic necrosis encountered at autopsy.

DISCUSSION

Apoptosis and Necrosis

Apoptosis and necrosis are the two central modes of cell death in the liver. Apoptosis is a regulated process that may either be physiologic or pathologic. In the former, apoptosis culls aged cells, functions in embryologic development, and is vital to adulthood remodeling (e.g., follicular atresia following ovulation). Necrosis, on the other hand, is abrupt cell death that is almost always pathologic. In the liver, necrosis is often a response to extrinsic insults such as medication/medication metabolites, toxins, infection, ischemia, and trauma. Though rare, intrinsic autoimmune injury is also a source of hepatic injury (1).

Morphologically, apoptosis displays cellular condensation, nuclear condensation (pyknosis), nuclear fragmentation (karyorrhexis), and cytoplasmic blebbing. Eventually, chromatin and organelles are packaged into vesicles, forming so-called apoptotic, acidophil, or Councilman bodies (**Image 1**), that are easily phagocytosed by Kupffer cells with little to no inflammatory activation. By contrast, necrosis features cellular swelling with cytoplasmic blebs that lyse the cell,

spilling intracellular contents into the surrounding environment, and ultimately eliciting an inflammatory response. This characteristic swelling and consequent karyolysis is referred to as oncotic necrosis (2).

Livers with diffuse necrosis show characteristic gross pathologic findings. Early, the liver may be edematous with foci of necrosis presenting as pale, tan-yellow punctate lesions, while more extensive involvement leads to loss of the liver parenchyma with large patches of necrosis and wrinkling of the capsule (**Images 2A and 2B**) (3).

Liver Anatomy

The degree and pattern of necrosis can be useful in determining the etiology and is often described in reference to the anatomy of the hepatic lobule and acinus. The hepatic acinus partitions liver lobules into zones according to their proximity to afferent arterioles. Zone 1 (perilobular) is most proximal to the hepatic arterioles, zone 2 is between the central vein and hepatic arterioles (midlobular), and zone 3 is adjacent to the central vein (centrilobular) (**Image 3**). Injury following these acinar patterns is referred to as zonal necrosis. Bridging necrosis describes cell death that links vasculature, whether the portal veins (portal-portal), the central veins (central-central), or portal and central veins (central-portal) (**Image 4**). When cell-death diffusely involves some hepatic lobules, it is referred to as submassive necrosis (**Image 5**), whereas diffuse involvement of all hepatic lobules is termed massive necrosis (**Image 6**) (3).

Acute and Chronic Hepatitis

Focal/multi-focal necrosis, sometimes called patchy necrosis, does not follow a zonal pattern, but rather involves random, individual clusters of hepatocytes (**Image 7**). This pattern is typical of acute hepatitis, falling under the umbrella of “lobular disarray,” which also includes ballooning degeneration of hepatocytes, lobular and sinusoidal inflammation, Kupffer cell hyperplasia, increased apoptotic bodies, and cholestasis. If this process lasts longer than six months, it is deemed chronic, and often presents with progressive

fibrosis (3). In some processes, including chronic hepatitis, there is focal necrosis of hepatocytes at the limiting plate between the portal tract connective tissue and start of hepatic parenchyma with an associated lymphocytic infiltrate (**Image 8**). This process is commonly called piecemeal necrosis, though updates in terminology have renamed it interface hepatitis and troxis necrosis, the latter originating from the Greek term for “nibbling” (4).

Acute Liver Failure

Acute and chronic hepatitis may progress to ALF and ACLF. Acute liver failure is characterized by a dramatic decline in hepatic function in a patient without

prior liver disease. Three categories of ALF are subdivided based on the time between onset of encephalopathy and first appearance of jaundice: hyperacute (0-1 week), acute (1-4 weeks), and subacute (4-12 weeks) (5). These subclassifications not only aid in prognosis (hyperacute presentations are favorable to acute and subacute presentations), but are also suggestive of etiology and histopathologic findings.

The incidence of ALF is rare, particularly in the developed world. In the United States, population based studies estimated 5.5 cases per million (6). There are multiple potential etiologies, particularly those involving drug injury and infection, though in many cases the cause is unknown (7). Awareness and inter-

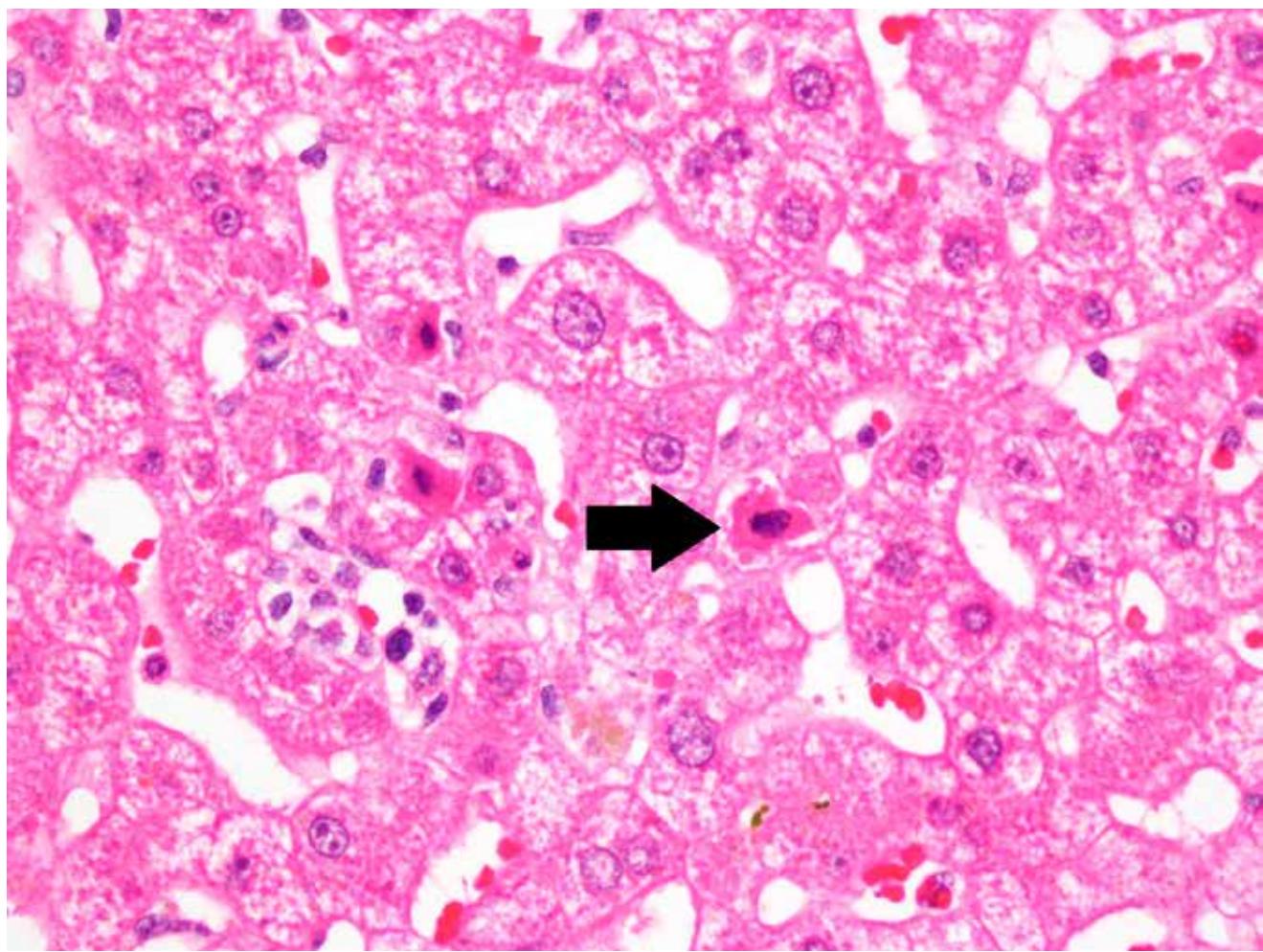


Image 1: Section of liver showing several hypereosinophilic, apoptotic hepatocytes (arrow) (H&E, x400).

ventions, including emergency liver transplant, have greatly improved overall survival to greater than 65% (8, 9), though 45% of adults and 56% of children may recover without the need of liver transplantation (7).

Acute-On-Chronic Liver Failure

Acute liver failure is distinguished from ACLF by the presence of preexisting liver disease and usually involves an acute decompensation of cirrhosis that manifests clinically with acute encephalopathy, ascites, gastrointestinal hemorrhage, or bacterial peritonitis (10). The mortality rate is high in ACLF and correlates with the number of extra-hepatic organ

failures. In a large prospective study, the 28-day mortality increased from 32% in patients with two organ failures to 78.6% in patients with three organ failures or more. In this study, ACLF was most common in young patients with active alcoholism and frequently involved extra-hepatic kidney failure. In more than 40% of cases, a precipitating event that initiated acute decompensation was not identified. In those where a precipitating event was identified, infection was the most common source (11). Other precipitants include acute alcoholic hepatitis after binge-drinking, drug injury, hepatic ischemia secondary to hypotension, and acute viral infection (12).

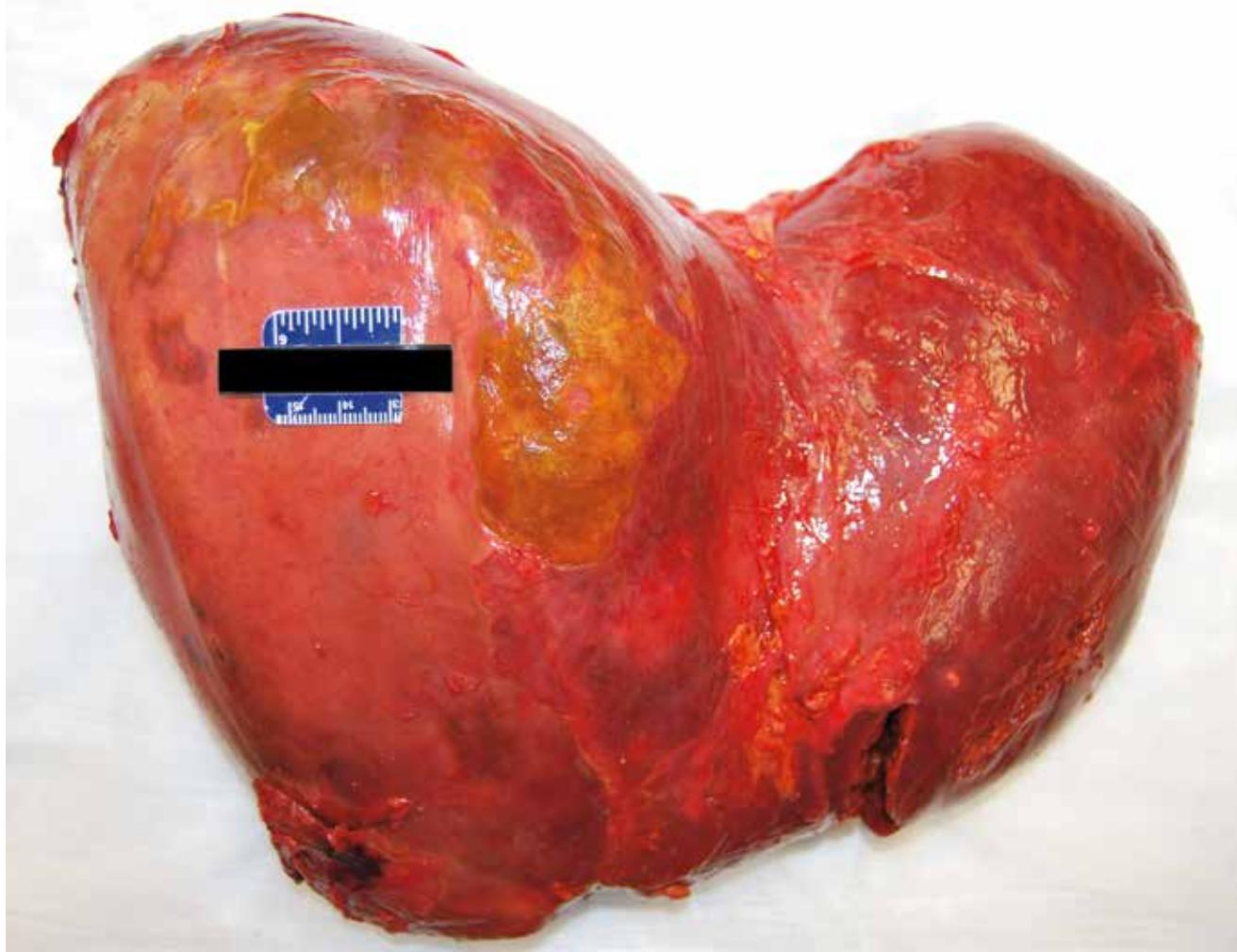


Image 2A: Anterior surface of a liver with massive hepatic necrosis associated with acute pancreatitis showing wrinkling along with patchy areas of red and yellow-orange discoloration.

Hepatic Injury and Necrosis

Alcohol

Alcoholic liver disease exists on a spectrum from early steatosis to acute hepatitis, fibrosis, and cirrhosis. Steatosis generally begins in zone 3 and extends toward the portal triads in more severe cases. Lipid deposition begins with small droplets (microvesicular), but with time accumulates into larger droplets (macrovesicular) that distend the hepatocyte membrane and displace the nucleus (13).

Chronic ethanolism induces the cytochrome P450 pathway, leading to an increase in reactive oxygen species that both signals lipid peroxidation and the formation of acetaldehyde protein adducts that directly damage mitochondria. Intrahepatic glutathione, which normally reduces these reactive oxygen species, is consequently depleted, predisposing hepatocytes to oxidative injury. Prolonged oxidative stress and adduct formation incite hepatocellular injury, with derangement of the microtubulin network and accumulation of eosinophilic, intracytoplasmic cytokeratins (Mallory bodies) (**Image 9**). As membrane stability declines, ballooning degeneration and

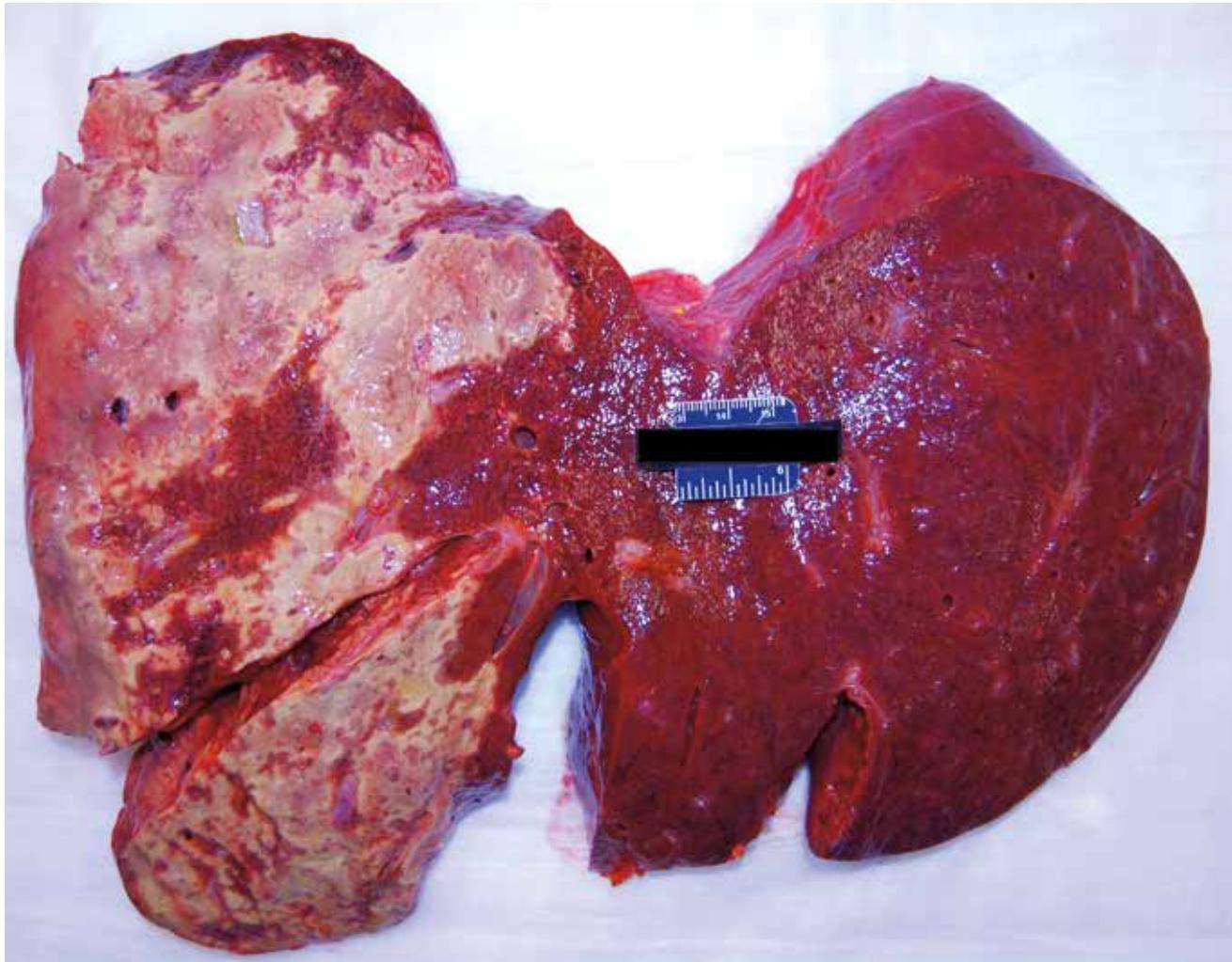


Image 2B: Cross-section of a liver with massive hepatic necrosis associated with acute pancreatitis showing widespread necrosis in the left side of the liver.

eventual oncotic necrosis occurs (**Image 10**). Mallory bodies themselves are immunogenic actors that signal downstream activation of tumor necrosis factor (TNF)-alpha, activating cell-death and neutrophil recruitment (14, 15).

Chronic alcohol abuse not only produces cytotoxic reactive oxygen species and acetaldehyde adducts, but also leads to bacterial overgrowth in the gastrointestinal tract, increased gut permeability, and the transfer of bacteria to the liver (16, 17). This combination activates innate immunity, particularly Kupffer cells, and promotes the inflammatory response that characterizes alcoholic hepatitis.

Acute hepatitis is a feared complication of alcoholic liver disease that occurs in 35% to 40% of patients (18). The mortality rate is 6.8% (19), but increases with age, female sex, and concomitant viral hepatitis C infection (20). Acute alcoholic hepatitis involves an acute lobular infiltrate against a background of steatosis. Portal inflammation is typically inconspicuous but may show small collections of lymphocytes. A dense portal infiltrate should raise suspicion of chronic hepatitis, particularly hepatitis B and C infection. Because cytochrome P450 enzymes are focused in centrilobular hepatocytes, necrosis generally begins in zone 3, heralded by ballooning degeneration that devolves into karyolysis. Neutrophils satellite these ballooning hepatocytes and Mallory bodies. In active

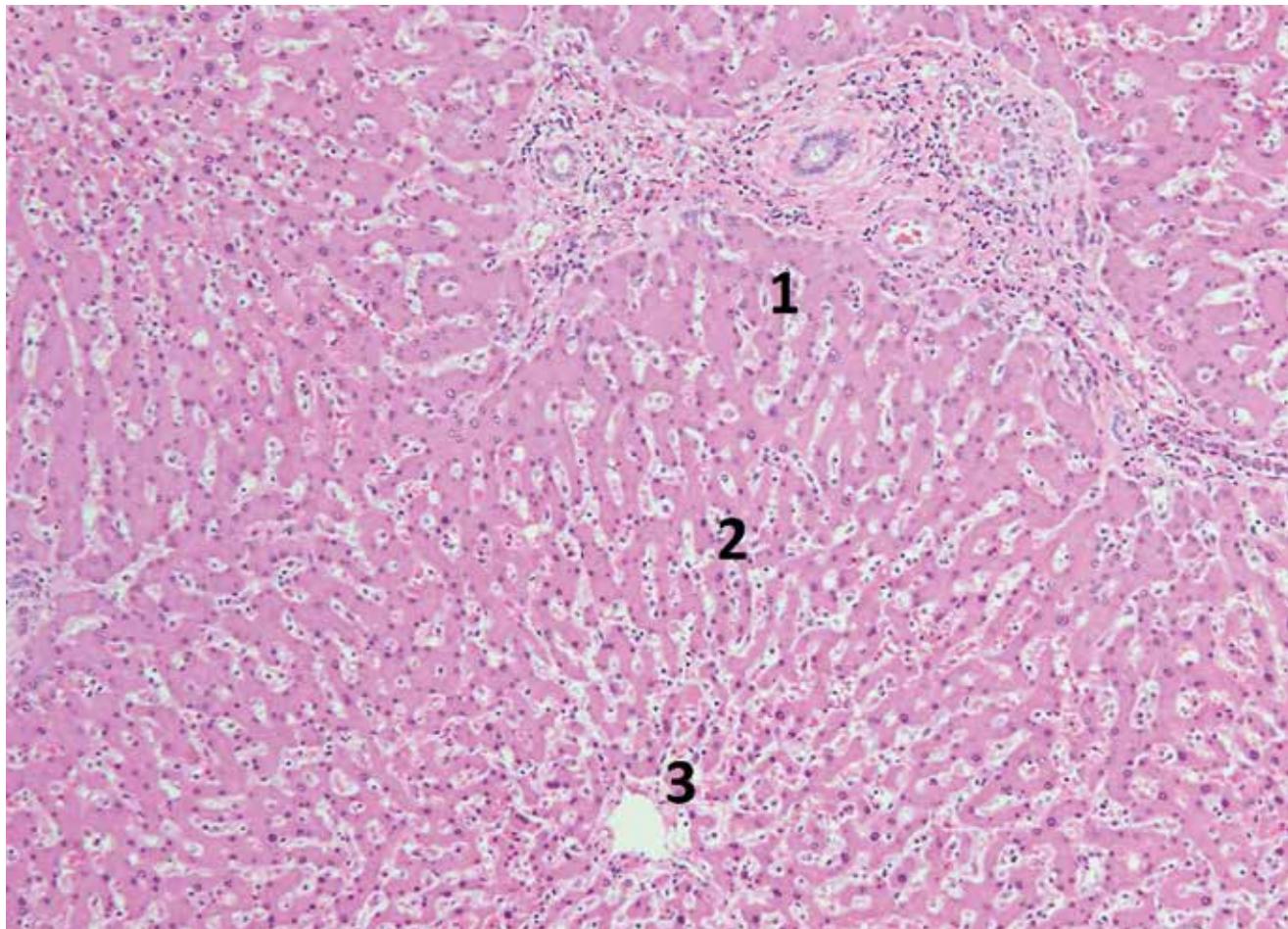


Image 3: Normal liver lobule showing zones with zone 1 nearest the portal triad and zone 3 nearest the central vein (H&E, x100).

and ongoing injury, apoptotic bodies are present that have not yet been phagocytosed by Kupffer cells. Additional histologic features include glycogenated hepatocytes, megamitochondria, cholestasis, and portal ductular reactions (21, 22). Grossly, alcoholic livers are enlarged and fatty secondary to steatosis (**Image 11**), but, with prolonged injury and fibrotic change, shrink and become multi-nodular (i.e., cirrhosis) (**Image 12**).

Hepatic necrosis and inflammation are potent activators of perisinusoidal stellate cells, which initiate fibrogenesis. Fibrosis begins in zone 3, webbing outward in a perisinusoidal pattern that produces the classic “chicken wire” appearance. In later stages, centrilobular fibrosis extends to the portal triads, creating

central-portal and portal-portal fibrotic crosslinks. Regenerative parenchyma encircled by fibrous septae creates the micronodular appearance seen in cirrhotic livers (13). Active alcoholism in a patient with otherwise compensated cirrhosis may superimpose an acute hepatitis, leading to rapid decline and ACLF (12). In these cases, the degree of bridging necrosis, along with other histologic features such as apoptosis, Mallory bodies, and eosinophilic degeneration of hepatocytes, has been associated with poor prognosis (23).

Drug Induced Liver Injury

There are two mechanisms of adverse drug reactions that broadly delineate histopathological findings: in-

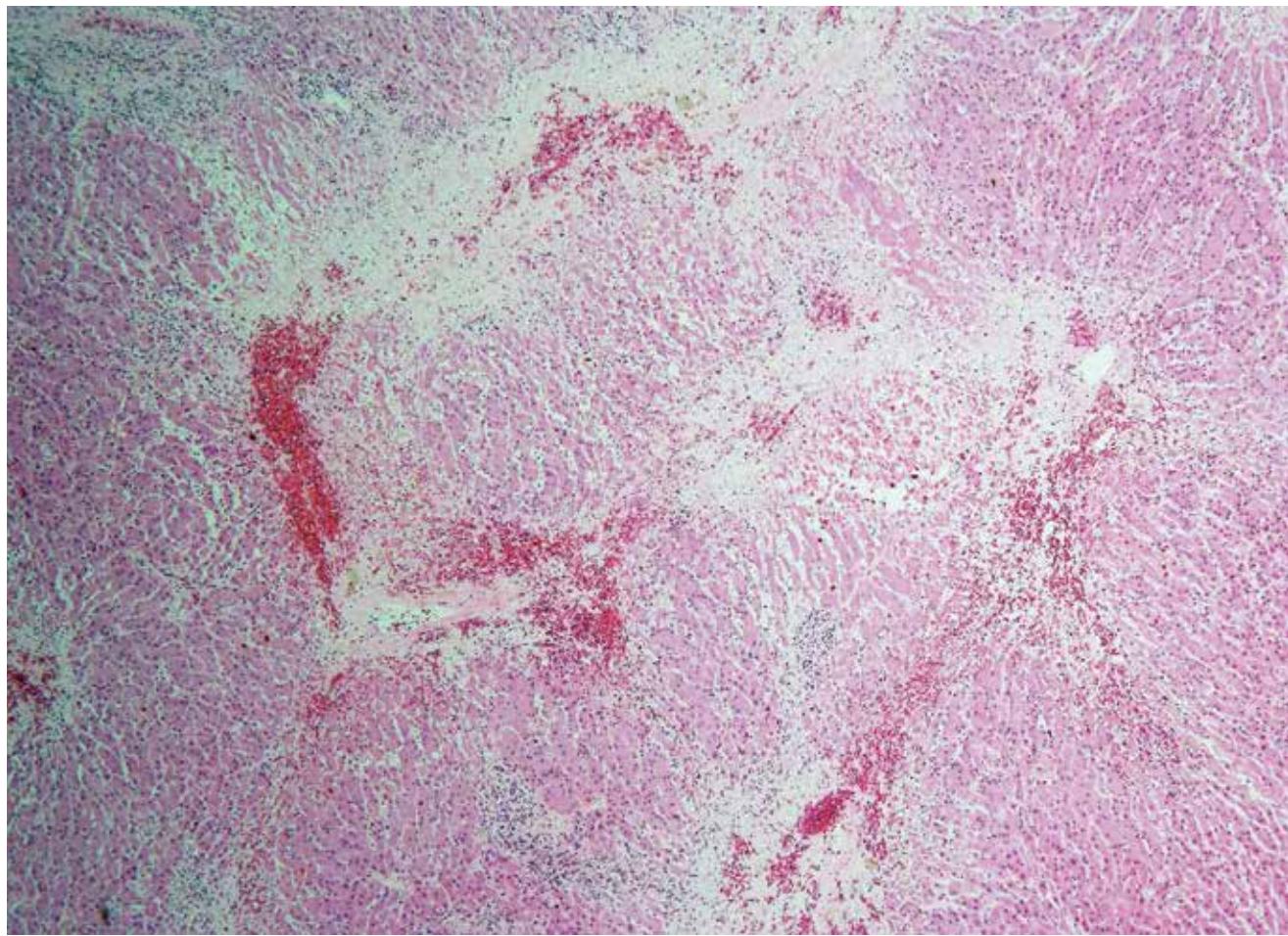


Image 4: Bridging necrosis in a liver due to the toxic effects of ethanol and oxycodone (H&E, x40).

trinistic and idiosyncratic. An intrinsic reaction results in predictable dose-dependent injury secondary to the drug itself or a byproduct of the drug. By contrast, idiosyncratic drug reactions are less predictable and likely driven by an immunogenic response to drug metabolites. The timeline between ingestion of a drug and an idiosyncratic reaction is likewise unpredictable, occurring anywhere between a couple of days and up to a year from first administration (24).

Intrinsic Injury

Acetaminophen is the most common cause of both intrinsic hepatotoxicity and ALF in Europe and the

United States (9, 25, 26). Acetaminophen is sold as an over-the-counter analgesic or in combination with other drugs, such as anticholinergics and opioids. In a study using data collected from the ALF study group between 1998 and 2012, over half of acetaminophen-related ALF was due to acetaminophen-opioid mixtures. These patients were older (mean age 39 years), with increased comorbidities, and more likely to unintentionally overdose (27). Other population studies have shown that unintentional acetaminophen is responsible for 25% of ALF in pediatric patients (6).

Under recommended doses (3-4 g/day), acetaminophen is generally a safe and effective analgesic. The

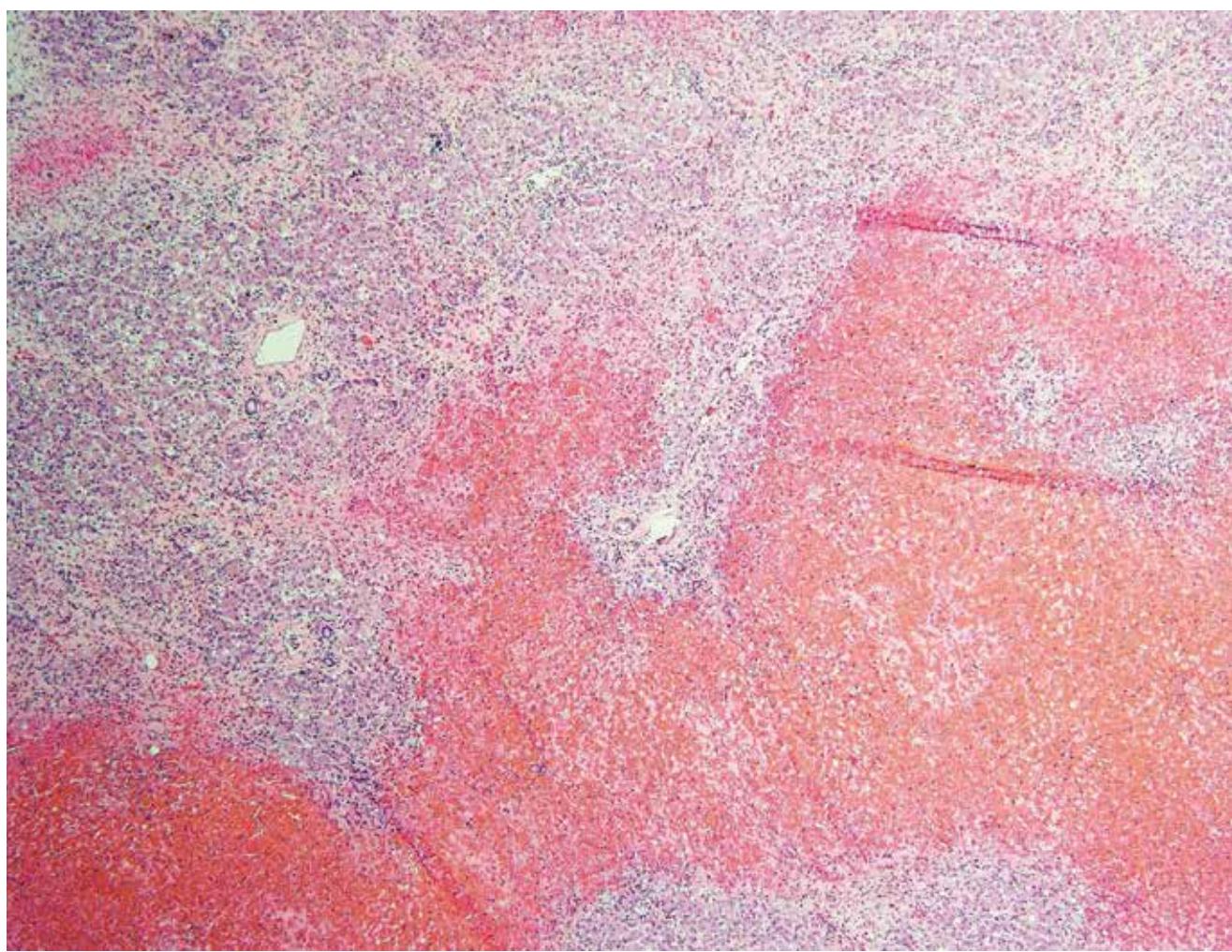


Image 5: Submassive necrosis in an individual with hepatic veno-occlusive disease (H&E, x40).

majority of acetaminophen is conjugated with sulfate and glucuronide and safely excreted in the urine. The remainder is oxidized through the cytochrome P450 pathway, producing the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI) as a byproduct, which is detoxified by glutathione. Toxic concentrations of acetaminophen saturate sulfate and glucuronide conjugation and thereby shunt the reaction toward the cytochrome P450 pathway, producing excess NAPQI while at the same time depleting glutathione stores. NAPQI is then free to trigger widespread mitochondrial dysfunction and ultimately hepatic necrosis (28).

Cytochrome P450 enzymes are located in centrilobular hepatocytes, which explains the characteristic pattern of zone 3 coagulative necrosis seen in acetaminophen toxicity (**Images 13 and 14**). In contrast to alcoholic hepatitis, there is generally sparse inflammation, though an increase in Kupffer cells/macrophages may be identified secondary to damage-associated molecular patterns (DAMPs) released from necrotic hepatocytes (28, 29). Other agents, such as halothane and carbon tetrachloride, also induce zone 3 necrosis with little inflammation (29).

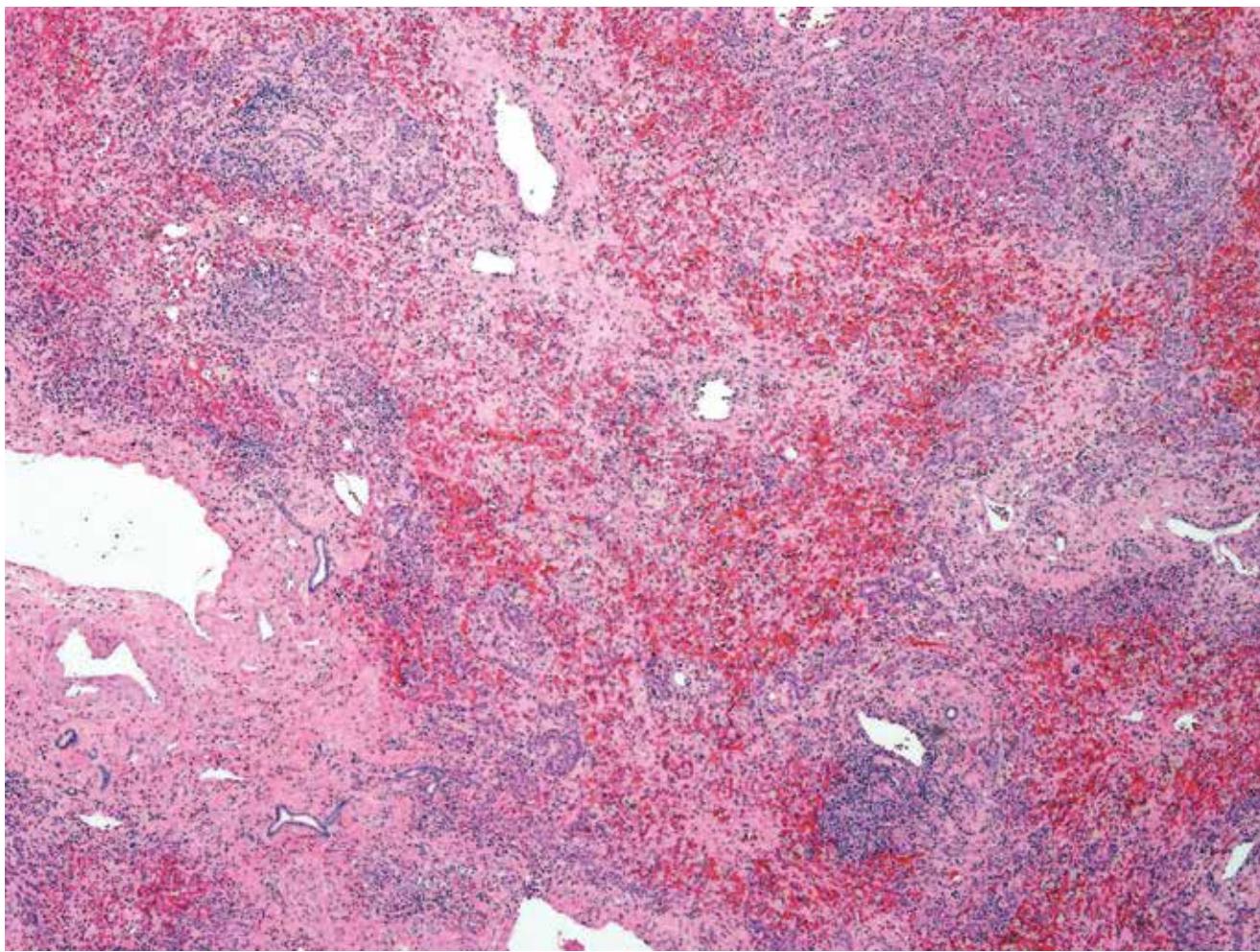


Image 6: Massive necrosis in an individual fulminant hepatic failure of unknown etiology (H&E, x40).

Idiosyncratic Injury

Idiosyncratic hepatotoxicity accounts for up to 11% of ALF in adult patients (7). There are a great variety of prescription and non-prescription agents responsible for idiosyncratic reactions. A US prospective study found that nearly half of the drugs implicated in liver injury were antimicrobials (e.g., sulfonamides, ketoconazole), followed by central nervous system agents (e.g., monoamine oxidase inhibitors, phenytoin, valproate). Herbal and dietary supplements accounted for 9% of reactions, most commonly linked to products promoting weight loss and muscle growth (30). Idiosyncratic reactions follow a subacute clinical course

and affect older populations, particularly those 60 years and older (7, 31). Typically, the prognosis of idiosyncratic ALF without transplant is poor compared to intrinsic injury (9, 32).

Just as there are a wide variety of agents responsible for idiosyncratic injury, there are a number of associated histologic patterns. None of these patterns are pathognomonic, and all may mimic other liver disease processes, which makes determining a specific etiology difficult. Often, microscopy illustrates the extent of injury rather than the precise etiology. Hepatocellular injury may begin as acute hepatitis with patchy necrosis or interface hepatitis and develop into liver

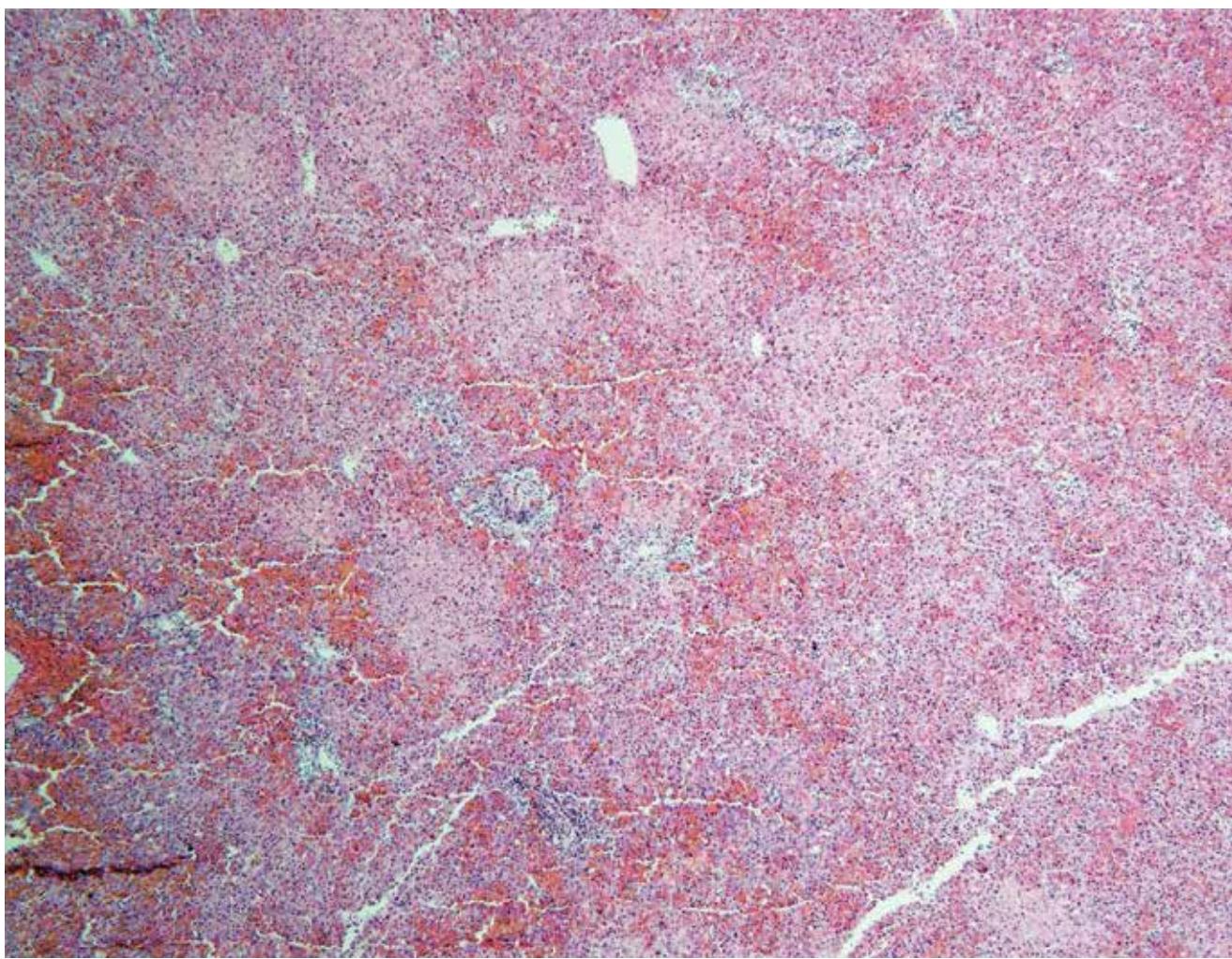


Image 7: Patchy areas of necrosis and hemorrhage in an infant with disseminated herpes simplex virus type 1 (H&E, x40).

failure once necrosis becomes confluent (i.e., massive/submassive necrosis) (**Image 15**) (33). In contrast to intrinsic injury, idiosyncratic reactions show marked portal inflammation. Lymphocytes are typically present; however, there may also be eosinophils and granulomas, which suggest a more favorable prognosis (33, 34). Isoniazid, monoamine oxidase inhibitors, anti-convulsants, and antimicrobials typically follow this pattern. Amiodarone hepatotoxicity mimics alcoholic hepatitis, presenting as a steatohepatitis with marked Mallory bodies and neutrophil satellitosis (29).

Injuries that follow a subacute clinical course may feature submassive necrosis, which includes segments

of regenerative nodules scattered throughout zones of confluent necrosis (**Image 16**). Regenerative hyperplasia is caused by hepatic progenitor cell activation once 50% of hepatocytes have been lost (35). These nodules may be confused with cirrhotic nodules and a Masson trichrome stain may help distinguish the two — the dense type one collagen of cirrhotic nodules stains a bright blue whereas the early regenerative nodules stain a light, grey-blue due to the mixture of collagen and ground substance (28). Other features associated with hepatic necrosis due to idiopathic drug reactions are hepatocyte rosette formation, lobular disarray, and hemorrhage, which represent severe parenchymal injury (33).

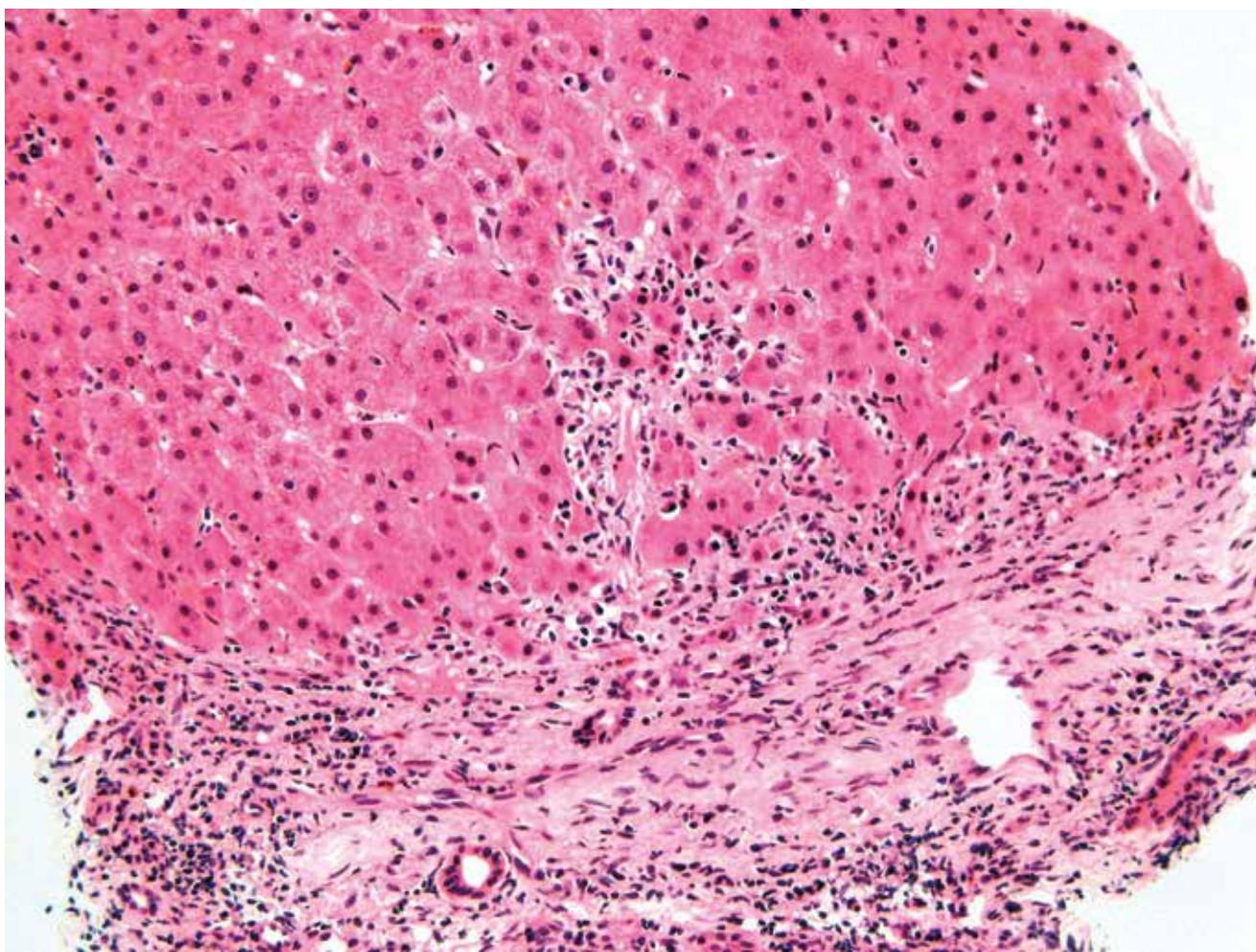


Image 8: Microscopic section showing a lymphocytic portal infiltrate extending into the surrounding parenchyma, also known as piece-meal necrosis, troxis necrosis, or interface hepatitis (H&E, x200).

Viral Infection

Hepatotrophic Viruses

Globally, hepatotrophic viral infections are the most common etiology of hepatitis and ALF, particularly infections involving hepatitis A, E, and B (25). Hepatitis A (HAV) follows fecal-oral transmission, generally arising from contaminated food and water supplies. Improved sanitation and vaccination have dramatically decreased its incidence; however, outbreaks have occurred in low-endemic regions involving intravenous drug users and human immunodeficiency virus (HIV) positive men who have sex with men (36). Globally, the World Health Organization has estimated 1.5 million cases of HAV infection occur each year.

Children under the age of six years generally remain asymptomatic while older children and adults have a 70% risk of developing acute liver dysfunction (37). Although HAV is a common cause of acute hepatitis (38), progression to ALF is rare, accounting for approximately 3-4% of cases in the United States between 1998 and 2007 (7, 9).

Similar to HAV, hepatitis E (HEV) infection occurs through fecal-oral transmission. In 2015, an estimated 44 000 deaths occurred due to HEV, accounting for 3.3% of viral hepatitis mortality (39). In the United States, ALF due to HEV is negligible (7, 9), though there are reports suggesting a small proportion of HEV hepatitis may be misdiagnosed as drug-induced liver injury (40). Hepatitis E is a common cause of both

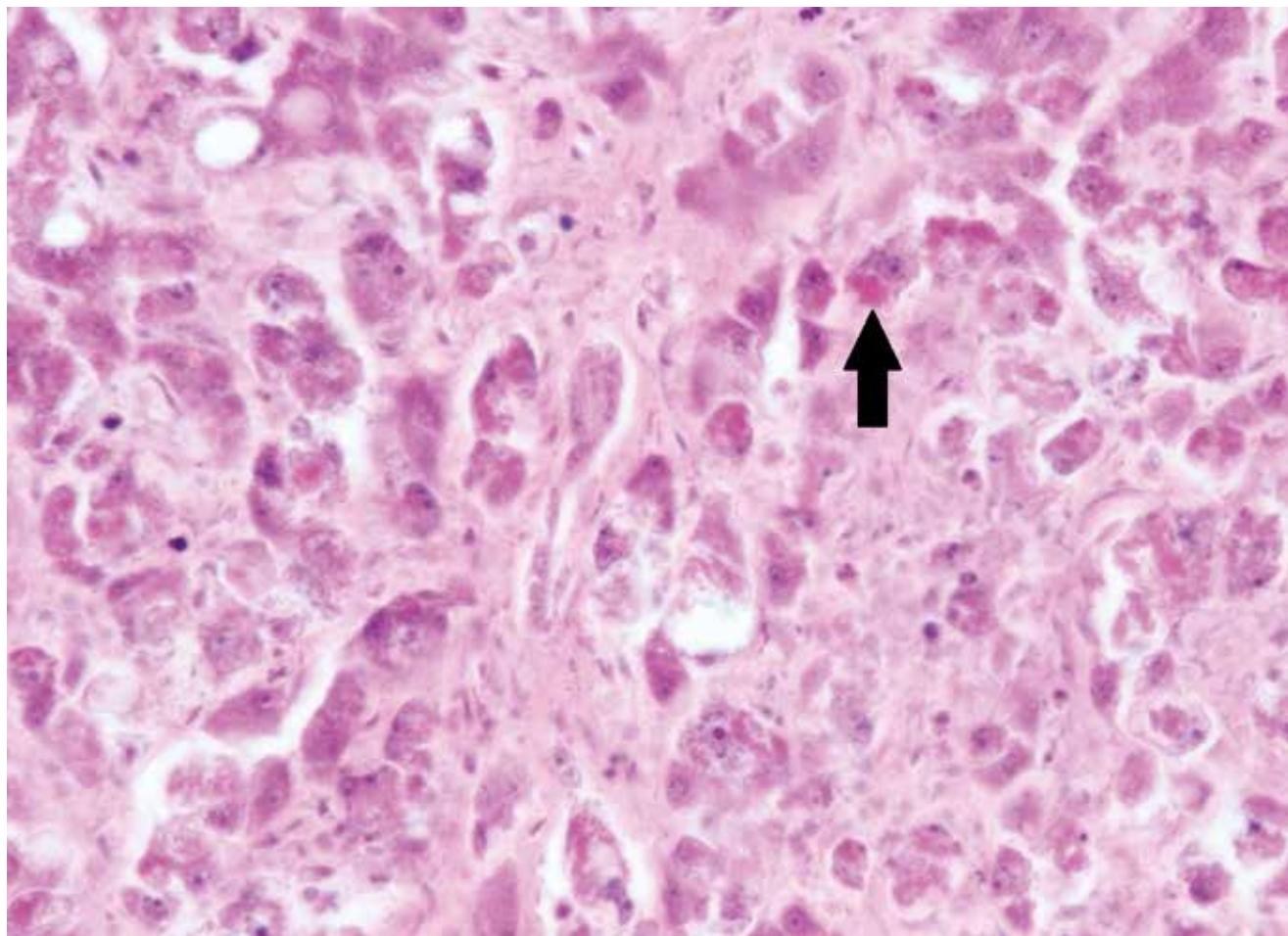


Image 9: Section from an individual with alcoholic hepatitis showing prominent Mallory bodies (arrow) (H&E, x400).

acute hepatitis and ACLF. Though ALF is a feared complication in pregnant women, there is a higher risk of infection in males (38).

While HAV and HEV do not progress to chronic hepatitis, hepatitis B (HBV) produces both acute and chronic hepatic infection. In 2010, approximately 248 million individuals were chronically infected with HBV, mostly focused in sub-Saharan and Western Pacific regions (41). In the United States, HBV infections have significantly decreased due to vaccination efforts beginning in the 1990s. Nonetheless, between 2011 and 2012 there were an estimated 847 000 individuals with chronic infection (particularly involving non-Hispanic Asians) and, in 2015, 21 900 cases of acute hepatitis (42, 43). Hepatitis B is responsible for

7% of cases in the United States (7) and may cause ACLF due to either HBV reactivation or acute HBV hepatitis in a compensated, cirrhotic liver (12). Coinfection with hepatitis D (HDV), an HBV dependent virus, may also potentiate acute hepatitis and possibly ALF or ACLF. Hepatitis C (HCV) is a common source of chronic hepatitis, leading to cirrhosis in 20% of cases (3). Though an uncommon cause of ALF, decompensation secondary to an acute insult may result in ACLF; however, progression is less common than ACLF due to alcoholic cirrhosis (11).

Because HAV, HEV, and HBV share common histologic features, diagnosis often relies on serologic markers. Nonetheless, early viral hepatitis presents with lobular disarray and focal/multifocal necrosis

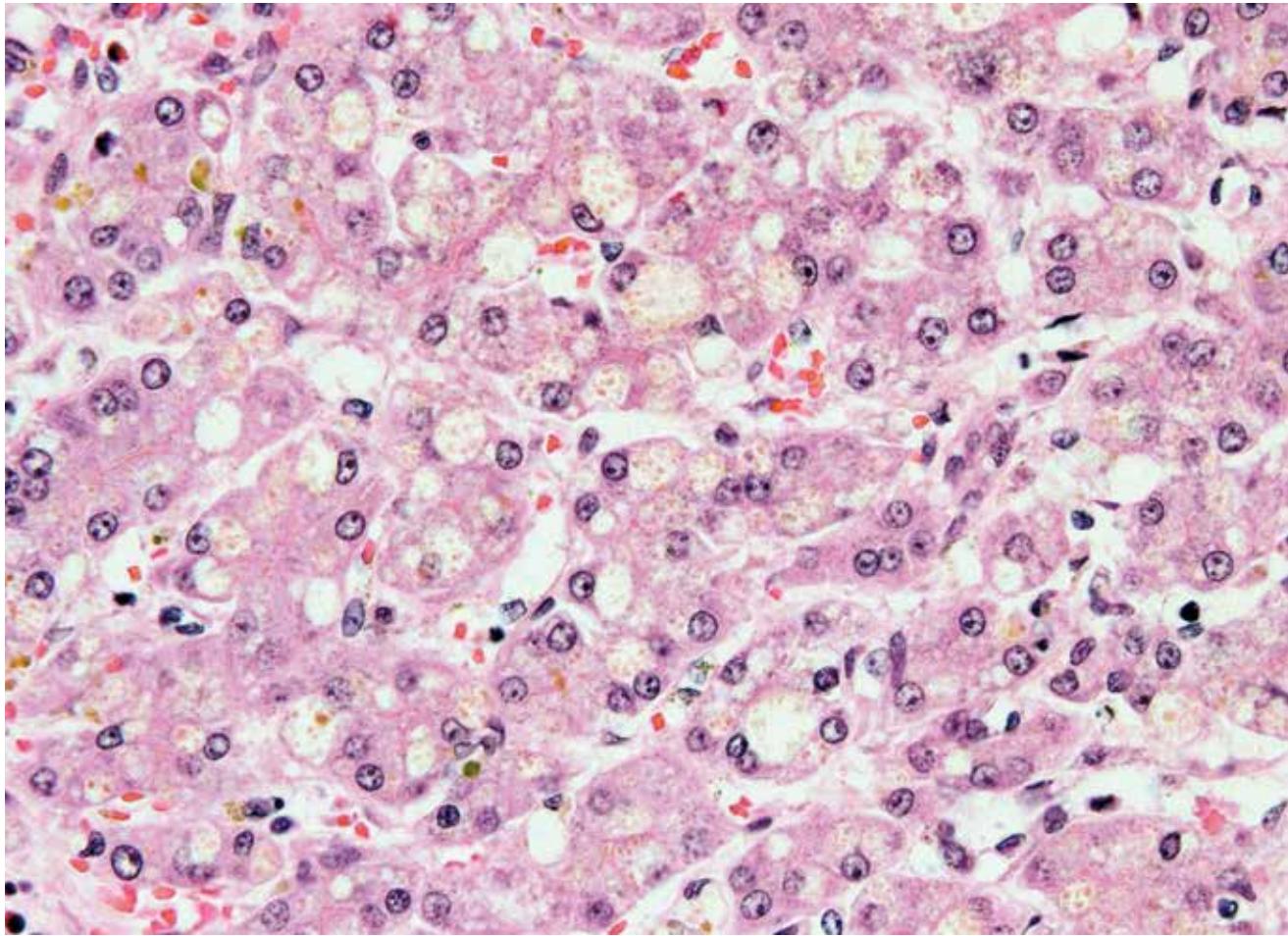


Image 10: Marked ballooning degeneration of hepatocytes (H&E, x400).

surrounded by a lymphocytic infiltrate (spotty necrosis). In many cases, necrosis does not become diffuse and the parenchymal architecture is not altered. However, in ALF, focal necrosis evolves into submassive and massive necrosis (28). In some studies, HEV is shown to generate more severe confluent necro-

sis with neutrophil infiltration in the sinusoids (44). Portal inflammation may be more prominent in HAV, with a lymphocytic infiltrate spilling beyond the portal connective tissue and into the hepatic parenchyma. Hepatitis B infected hepatocytes expressing surface antigen contain nuclear, ground-glass inclusions sur-

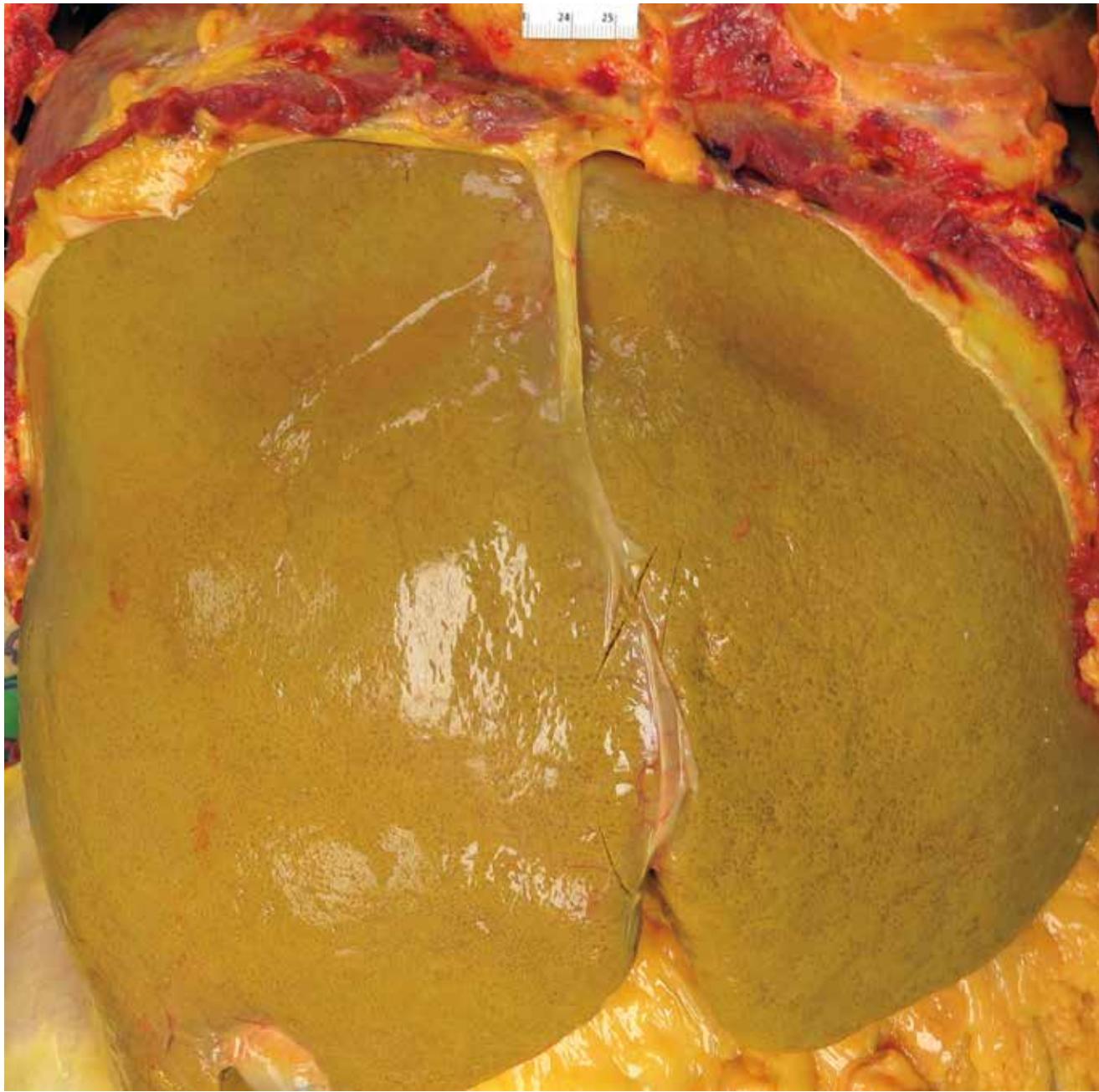


Image 11: Gross photograph of an enlarged, fatty liver in an individual with alcoholic hepatitis.

rounded by a halo (**Image 17**). Acute HCV infection shows mild portal and lobular inflammation with a lymphocytic infiltrate and negligible interface hepatitis. The degree of ballooning degeneration is also less compared to the other hepatotrophic viruses (45).

Non-Hepatotrophic Viruses

Though rare, non-hepatotrophic viruses such as herpes virus (HSV), adenovirus, Epstein-Barr virus (EBV), and cytomegalovirus (CMV) generate hepatitis and even ALF, predominantly in newborns, pregnant women, and the immunosuppressed.

In a study examining non-acetaminophen-related pediatric ALF, 25.2% of children 0-6 months of age tested positive for HSV with a mortality rate of 60% within the first 21 days of the study period (46). Herpes simplex virus hepatitis often does not present with classic mucocutaneous lesions, so antemortem suspicion for disseminated infection may be low. As a result, diagnosis is made at autopsy in more than half of cases. Immunosuppression, whether from recent transplantation or coinfection with HIV, and pregnancy in the third trimester are significant risk factors for disseminated herpes; however, up to 24% of affected patients may be immunocompetent (47). Epstein-Barr



Image 12: Gross photograph of a cirrhotic liver.

virus, CMV, and adenovirus affect similar patient populations, though to a lesser degree than HSV (38, 46, 48).

Grossly, non-hepatotrophic hepatitis shows punctate discoloration that correlates histologically with circumscribed areas of patchy necrosis and associated nuclear fragments (“dirty necrosis”). Necrosis may diffusely involve the hepatic parenchyma, particularly in neonates (**Image 18**). In HSV, the nuclei of infected hepatocytes are enlarged and distorted by eosinophilic, ground-glass nuclear inclusions (Cowdry body inclusions). Cowdry A bodies represent early infection and present with small, central nuclear inclusions separated from the nuclear membrane by a halo (**Image**

19). Cowdry B inclusions are larger inclusions that eccentrically push nuclear material to the border of the nuclear membrane and are associated with late stage infection (28, 45). Cytomegalovirus and adenovirus also express cytopathic effect, but their inclusions are often more basophilic and surrounded by a halo (“owl’s eye” inclusions). In addition, basophilic granules are found in the cytoplasm of CMV infected hepatocytes, sometimes surrounded by neutrophilic microabscesses. In adenovirus, inclusions are more often located in hepatocytes peripheral to the areas of necrosis (**Image 20**) (45, 49). Compared to the other viruses, EBV shows less necrosis and more lymphocytic inflammation that fills the sinusoids and portal tracts (50). As shown, when non-hepatotrophic viral infection is



Image 13: Gross image demonstrating profound centrilobular necrosis.

suspected, immunohistochemical stains for a number of viruses are available and useful in confirming the precise viral agent. Though rare in the United States, hepatocellular injury resulting from dengue virus and the yellow fever virus has been reported, characteristically showing zone 2 necrosis (28).

Autoimmune

Autoimmune hepatitis (AIH) is a chronic liver disease of unknown etiology. Classically, AIH affects young white females who present with vague symptoms of endocrine dysfunction, hepatitis, elevated IgG, and auto-antibodies (51); however, there has been recent expansion of this phenotype to include both genders, all ages, and multiple ethnic groups (52). Autoim-

mune hepatitis is most common in northern Europe, accounting for an annual incidence of 1.9 per 100 000 (3), and rare in the United States (53). A combination of genetic predisposition and environmental insult likely triggers AIH. In one study, nearly 10% of AIH were induced by drugs. Within this cohort, nitrofurantoin, commonly used to treat urinary tract infections, and minocycline, commonly used to treat acne, were responsible for over 90% of cases (54).

Autoimmune hepatitis may be asymptomatic or range in presentation from acute hepatitis to ALF and ACLF. Acute and fulminant AIH occurs in 25% to 75% (52) and 5% (7) of patients, respectively (**Image 21**). At presentation, previously asymptomatic patients may already have cirrhosis from chronic, subclinical in-

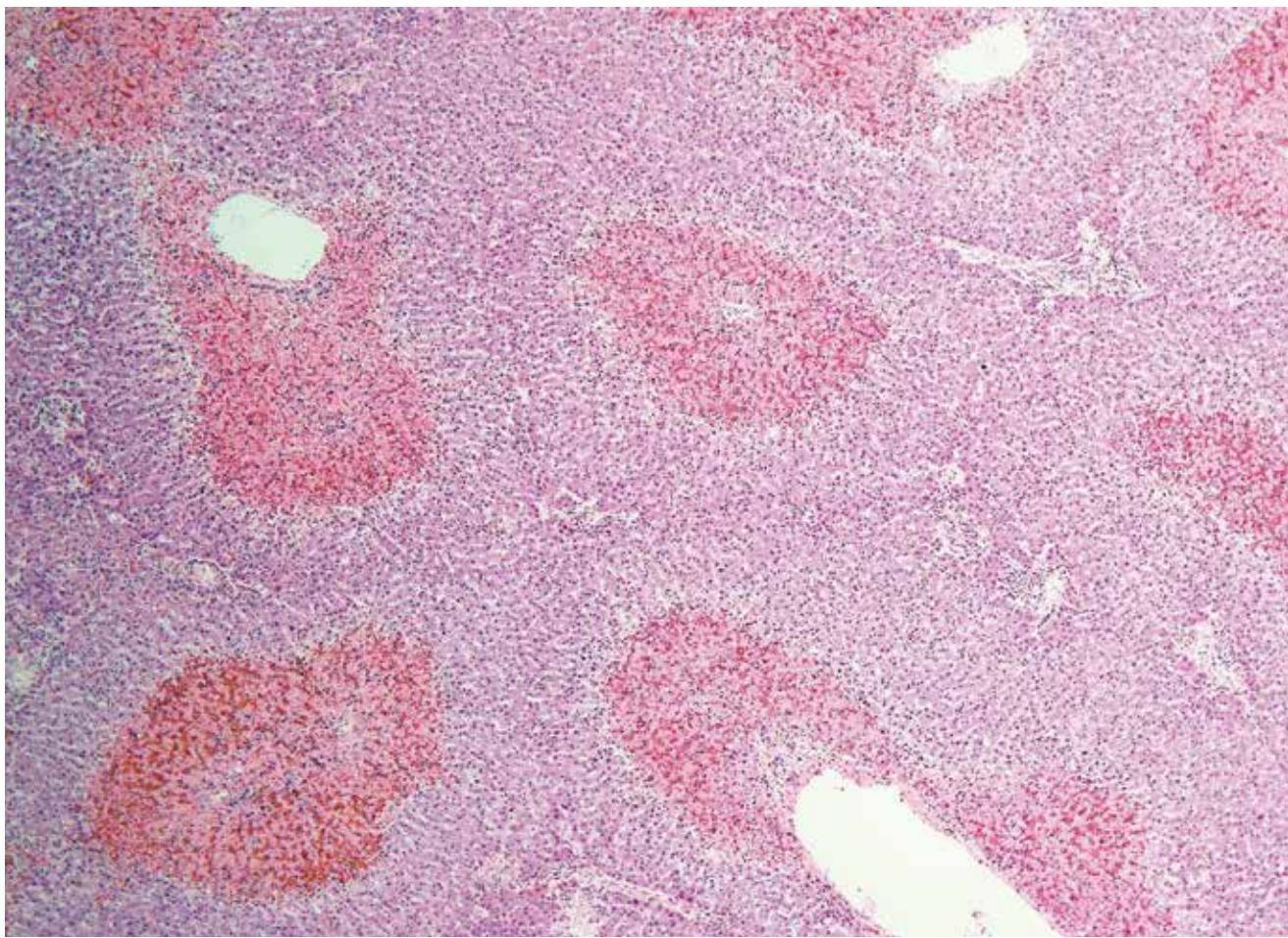


Image 14A: Microscopic section showing prominent centrilobular necrosis (H&E, x40).

jury (55, 56). In these instances, acute exacerbation, whether from a *de novo* flair of autoimmune injury or superimposed viral infection, may lead to ACLF.

As a chronic hepatitis, AIH presents with interface necrosis (84 to 98% of cases) and varying degrees of background fibrosis. The associated inflammatory infiltrate typically consists of plasma cells, but may also contain lymphocytes and histiocytes (57). Lymphocytes entrapped in the cytoplasm of hepatocytes (emperipoleisis) are found in up to 78% of cases (**Image 22**) (58). Emperipoleisis is associated with more severe necroinflammatory disease and may serve a role in the pathogenesis of AIH through the initial induction of hepatocyte apoptosis (59). The hepatic lob-

ules may also be affected by a mononuclear infiltrate with associated lobular disarray. Hepatocyte rosetting, in which regenerative hepatocytes are arranged in a circular formation with a central lumen, is a common feature of AIH. Lobular necrosis ranges in severity, from focal necrosis up to bridging necrosis in 40% of cases (58). Confluent necrosis carries a 1.9-fold risk of progression to cirrhosis (55). Centrilobular necroinflammation has been described in acute and fulminant cases of AIH, making it difficult to distinguish from drug-induced injury and acute viral hepatitis. While not pathognomonic, the combined features of lobular necroinflammation involving zone 3 with a plasmacytic infiltrate, emperipoleisis, and hepatocyte rosetting supports the diagnosis of AIH (60).

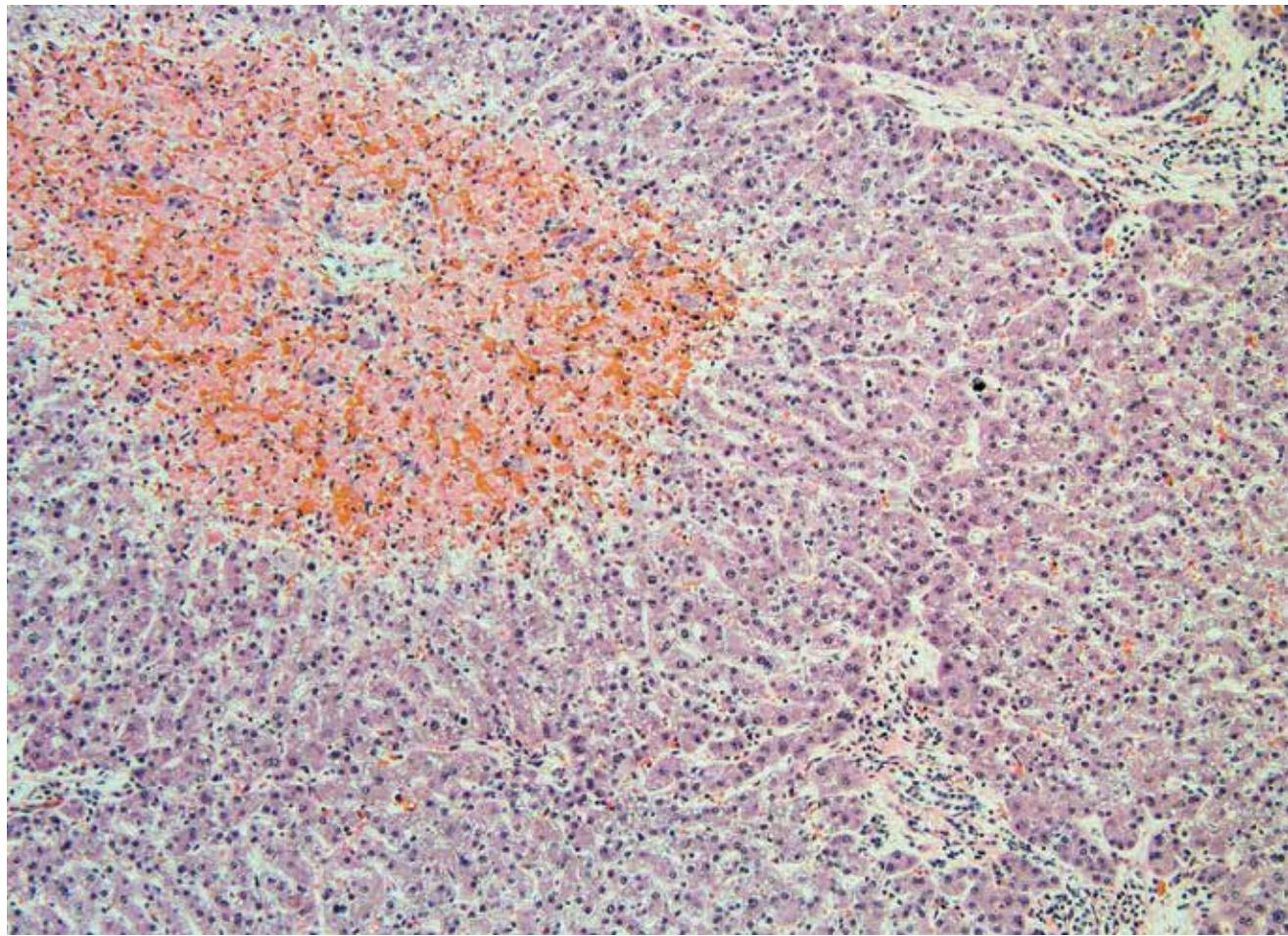


Image 14B: Microscopic section showing prominent centrilobular necrosis (H&E, x100)



Image 15: Cross section of a liver with acute liver failure and submassive necrosis due to herbal medications and ethanol.

Ischemia

Because circulatory failure is common prior to death, hepatic necrosis associated with cardiac shock is a typical finding at autopsy. Low cardiac output results in increased central venous pressure that back flows

into the hepatic vein. Clinically, right-sided heart failure, including causes such as left-sided heart failure, pulmonary hypertension, constrictive pericarditis, and tricuspid regurgitation, leads to passive hepatic congestion, perisinusoidal edema, and ischemic necrosis of hepatocytes (61). Though rare, Budd-Chiari



Image 16: Gross photograph of a liver with acute liver failure with regenerative nodules due to isoniazid.

syndrome, in which the hepatic vein becomes thrombosed, produces the same effect (62). Gross findings classically include hepatomegaly with purple discoloration secondary to congestion (**Image 23**). The cut surface shows a classic nutmeg appearance due to alternating necrosis and hemorrhage. Histologically, there is prominent central vein congestion, sinusoidal edema, and zone 3 necrosis (**Image 24**). In severe cases, necrosis is diffuse with a central-central bridging pattern. Long standing heart failure may result in fibrotic changes within the central vein wall with fibrosis webbing throughout the sinusoids in a pattern similar to alcoholic liver disease (63).

Major hepatic trauma is commonly encountered in the autopsy setting and may present with hepatic necrosis, presumably secondary to ischemia (**Image 25**). Angioembolization is an initial approach to achieving hemostasis in high-grade liver injuries, though there are many associated complications, including abscess formation, bile leak, and major hepatic necrosis. In a retrospective study of 538 patients with hepatic trauma receiving angioembolization, up 42% of complications were due to major hepatic necrosis, most commonly occurring in patients with penetrating injury. Additionally, gel-foam embolization of either the proper hepatic artery or multiple sites was more

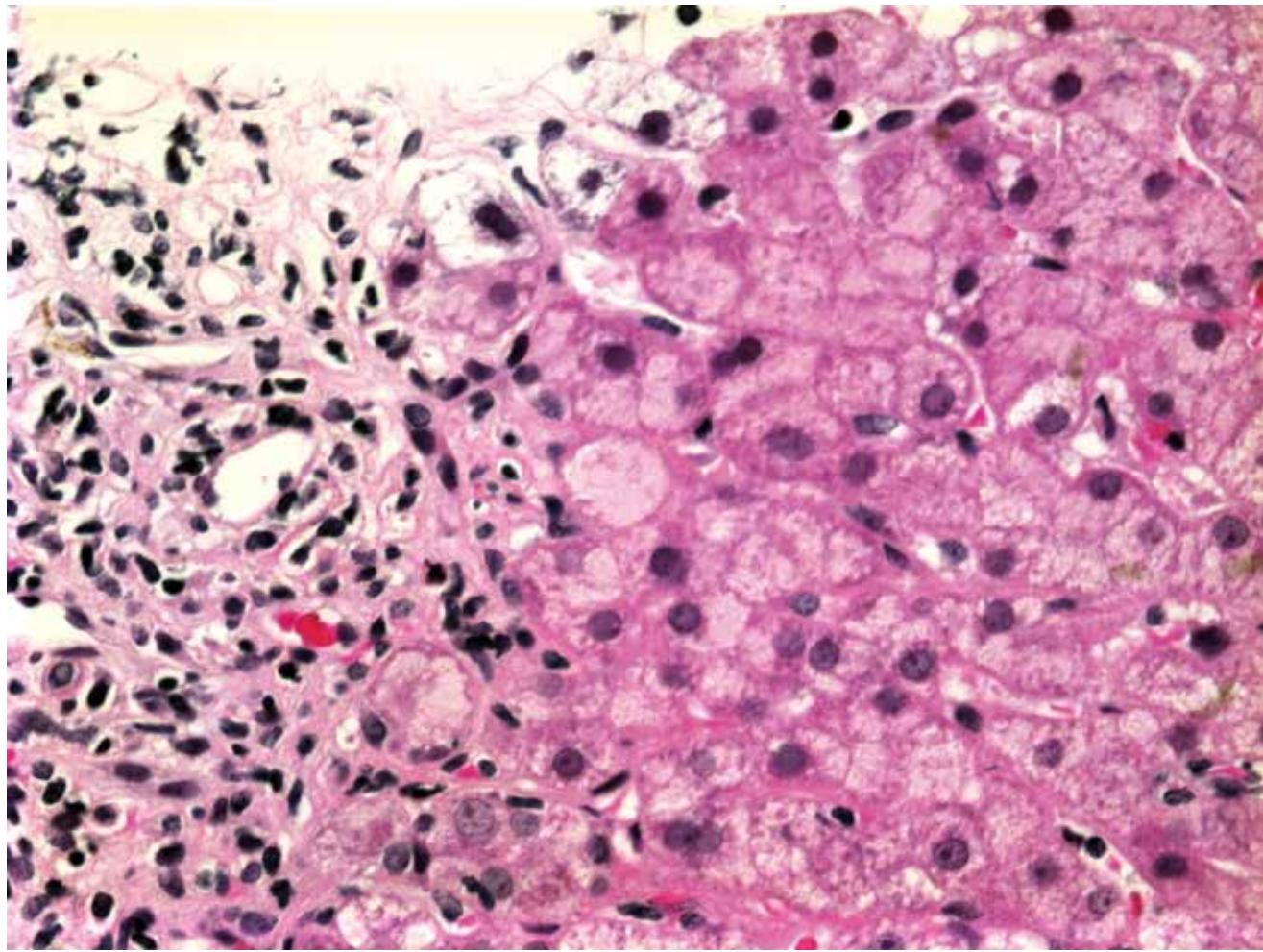


Image 17: Microscopic section showing a lymphocytic portal infiltrate with adjacent ground glass hepatocytes, characteristic of hepatitis B infection (H&E, x400).

likely to potentiate necrosis secondary to diffuse hepatic ischemia (64).

Metabolic

Nonalcoholic fatty liver disease (NAFLD) is a common etiology of chronic liver disease that may rarely be a cause of hepatic necrosis and ALF. It is defined by

steatosis without alcohol abuse, adverse drug reaction, or viral infection (65). Globally, NAFLD affects 6.3% to 33% (median 20%) of individuals (66). Obesity and type two diabetes mellitus are recognized risk factors. In the United States, Hispanic Americans are at increased risk, followed by Caucasians and African Americans (67). Histologically, steatohepatitis is identical to alcoholic hepatitis, making clinical history paramount.

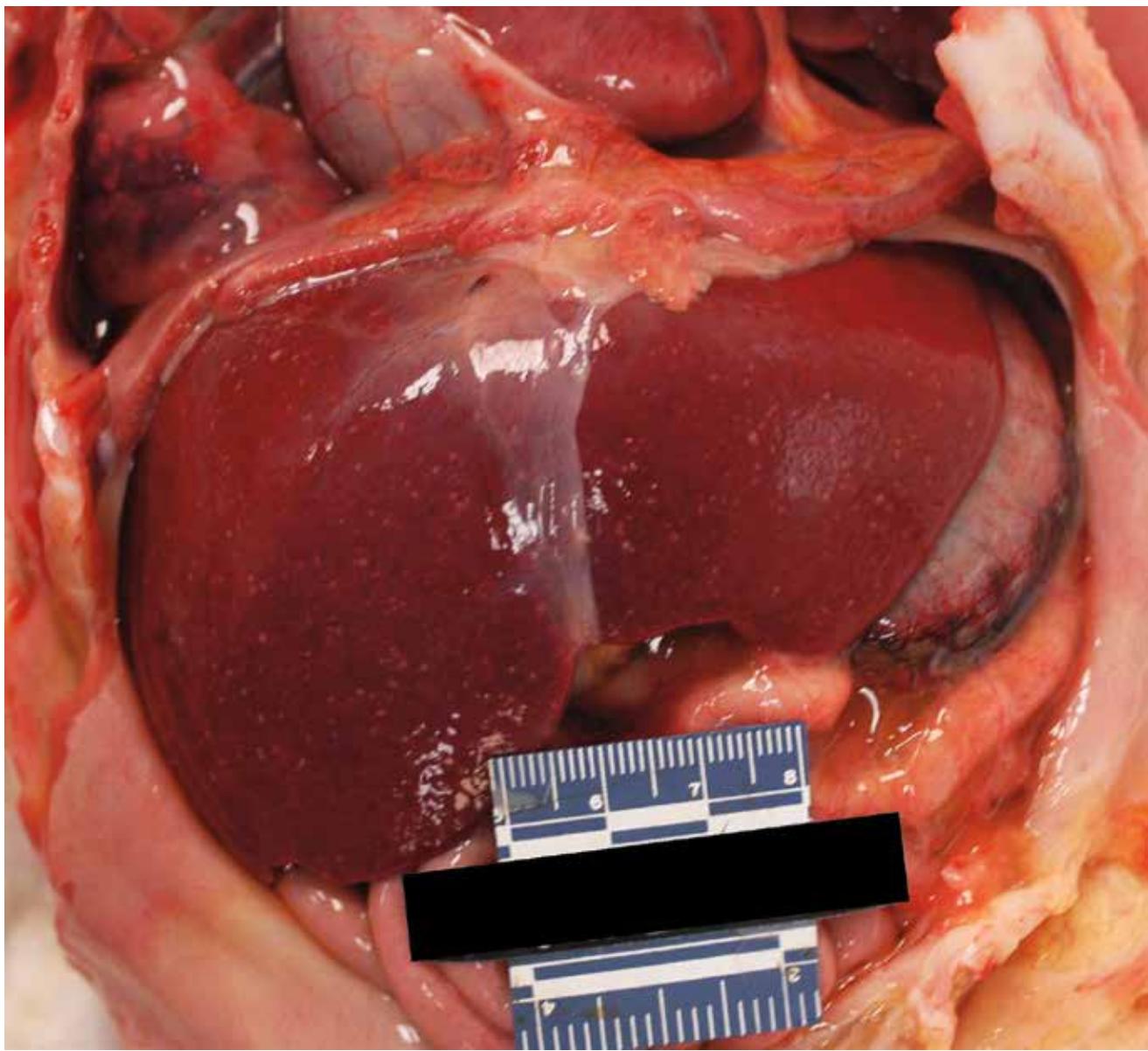


Image 18A: *In situ* gross photograph of neonate who died from unsuspected disseminated herpes infection. Note the pale speckling of the parenchyma.

Wilson disease is an autosomal recessive disorder resulting in impaired copper excretion that accumulates in tissues and organs, particularly the liver. Copper promotes the generation of free radicals that induces a steatohepatitis similar to NAFLD (68). In up to 2% of cases, Wilson disease may progress to ALF (7). In suspected cases, special stains, including rhodanine and orcein, may highlight copper deposits in hepatocytes (68).

Other metabolic causes of hepatic injury include hemochromatosis and galactosemias, which are prominently seen in pediatric populations (7, 48).

Artifact

One finding encountered frequently by the forensic pathologist that may mimic massive hepatic necrosis is autolysis. Both processes may lead to large areas

of non-viable hepatocytes that at first glance may be difficult to distinguish. However, autolysis tends to cause a complete “white out” of the hepatic parenchyma with loss of architecture, dropout of the nuclei, and absence of other pathologic features (**Image 26**). This is in contrast to actual necrosis in which the cells tend to be better preserved and sections may show additional pathologic features (**Image 27**). Autolysis should be suspected in cases with widespread microscopic changes in the liver, and likely other organs, without a history compelling for liver failure, in individuals with extended postmortem intervals or obesity, and deaths occurring in warm environments or with inadequate refrigeration after death.

CONCLUSION

Due to the number of potential causes, hepatic necrosis is frequently encountered at autopsy and may

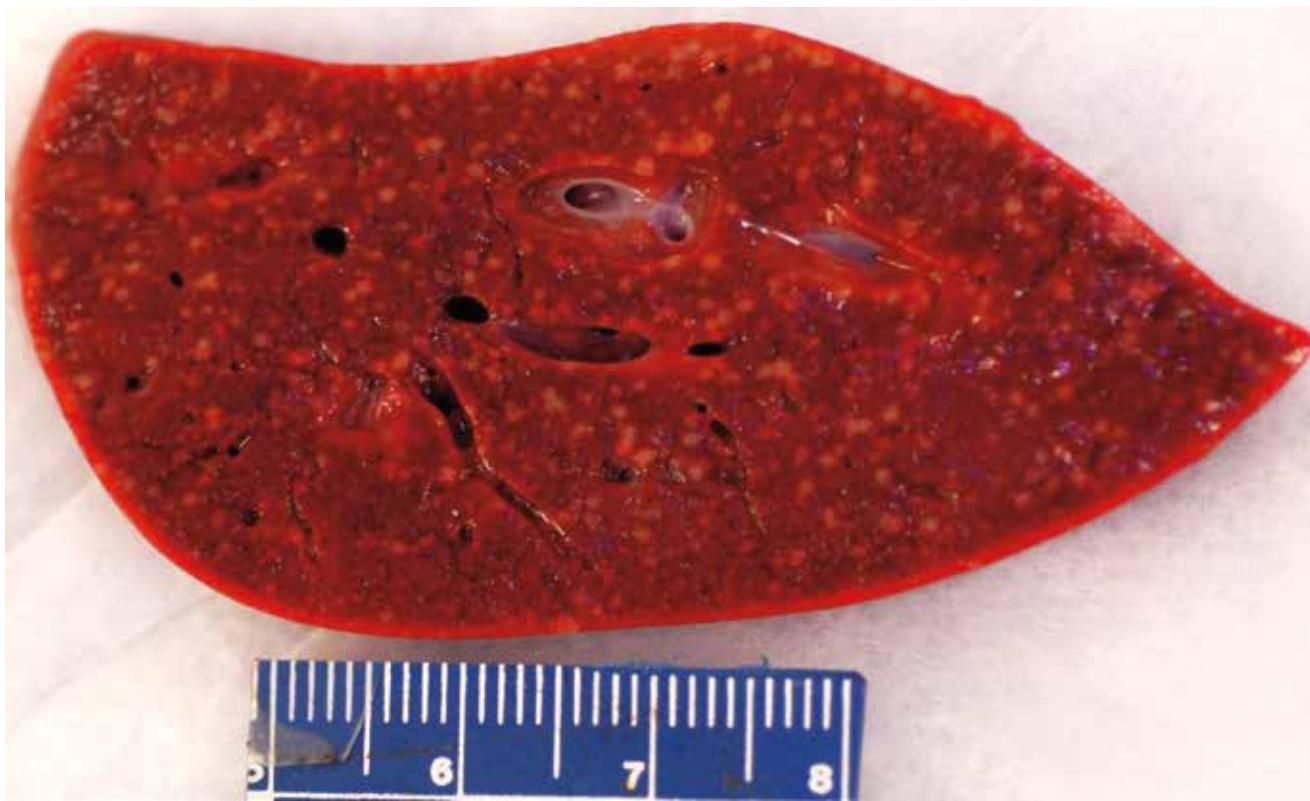


Image 18B: Cross-section gross photograph of neonate who died from unsuspected disseminated herpes infection. Note the pale speckling of the parenchyma.

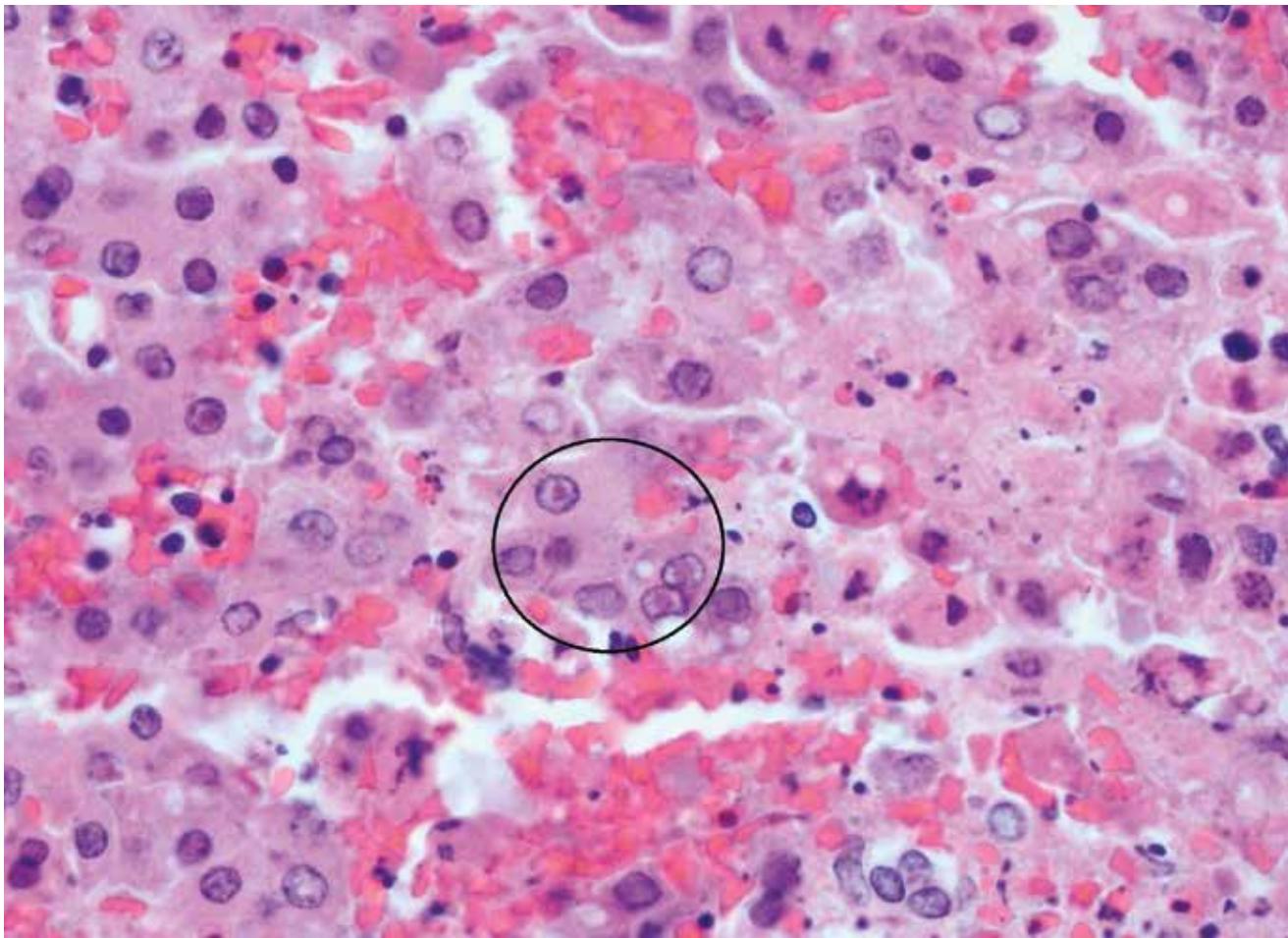


Image 19A: High power section showing necrosis, hemorrhage, and hepatocytes with Cowdry type A inclusions (circle) (H&E, x400).

present with diverse gross and histologic features in individuals of varying demographics. While many of the diseases presented have “classical” pathologic findings, in practice there is significant overlap of gross and microscopic features, making it a challenge to identify a precise etiology. **Table 1** provides a sum-

mary of some of the more common causes of hepatic necrosis. Ultimately, placing gross and histologic features in the context of clinical and social history is required to develop an appropriate differential diagnosis and cause of death.

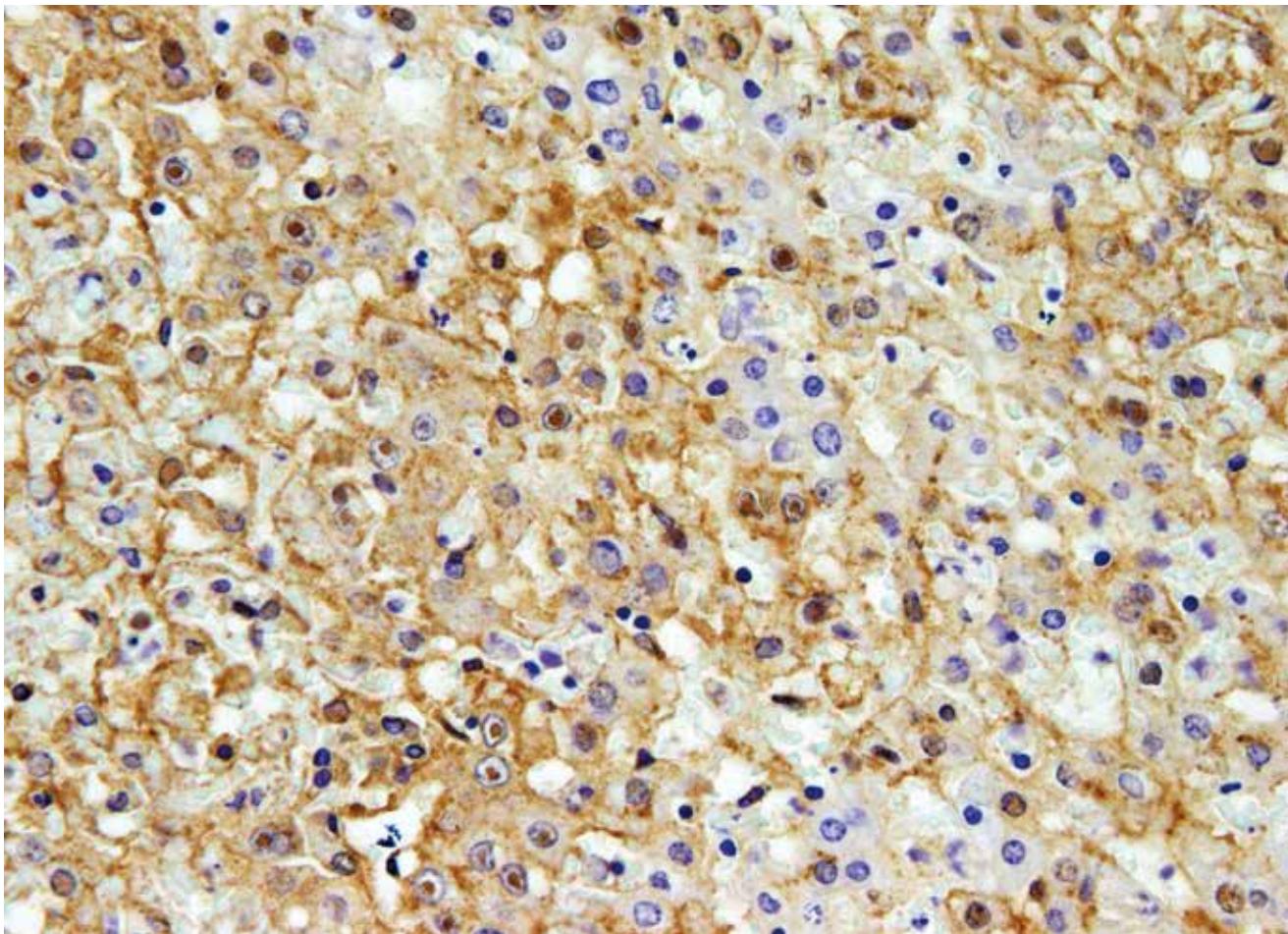


Image 19B: Herpes simplex virus type 1 immunohistochemical stain of same specimen (magnification x400).

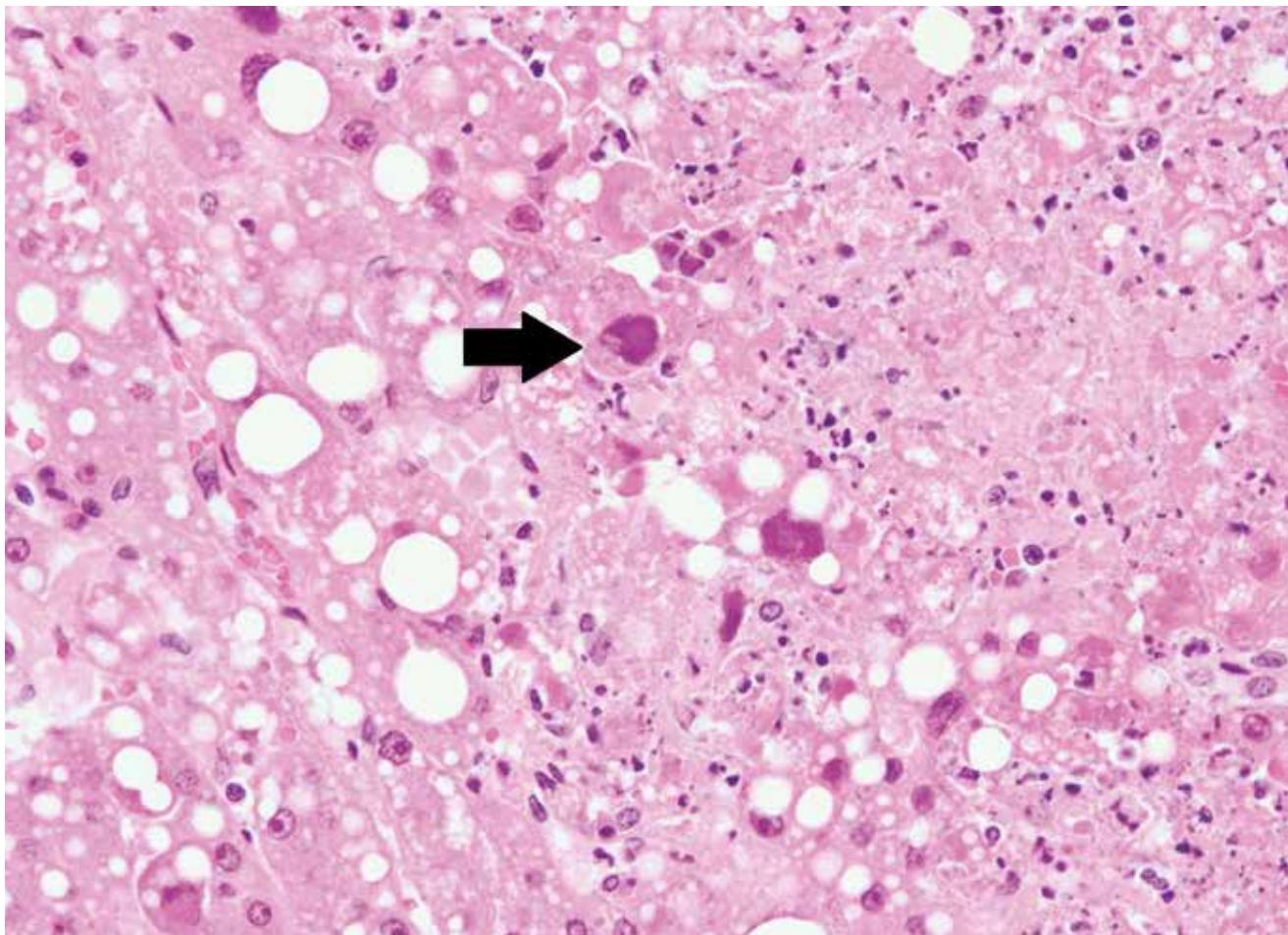


Image 20A: High power of an adult with disseminated adenovirus infection showing large, irregular, basophilic inclusions (arrow) adjacent to an area of necrosis (H&E, x400).

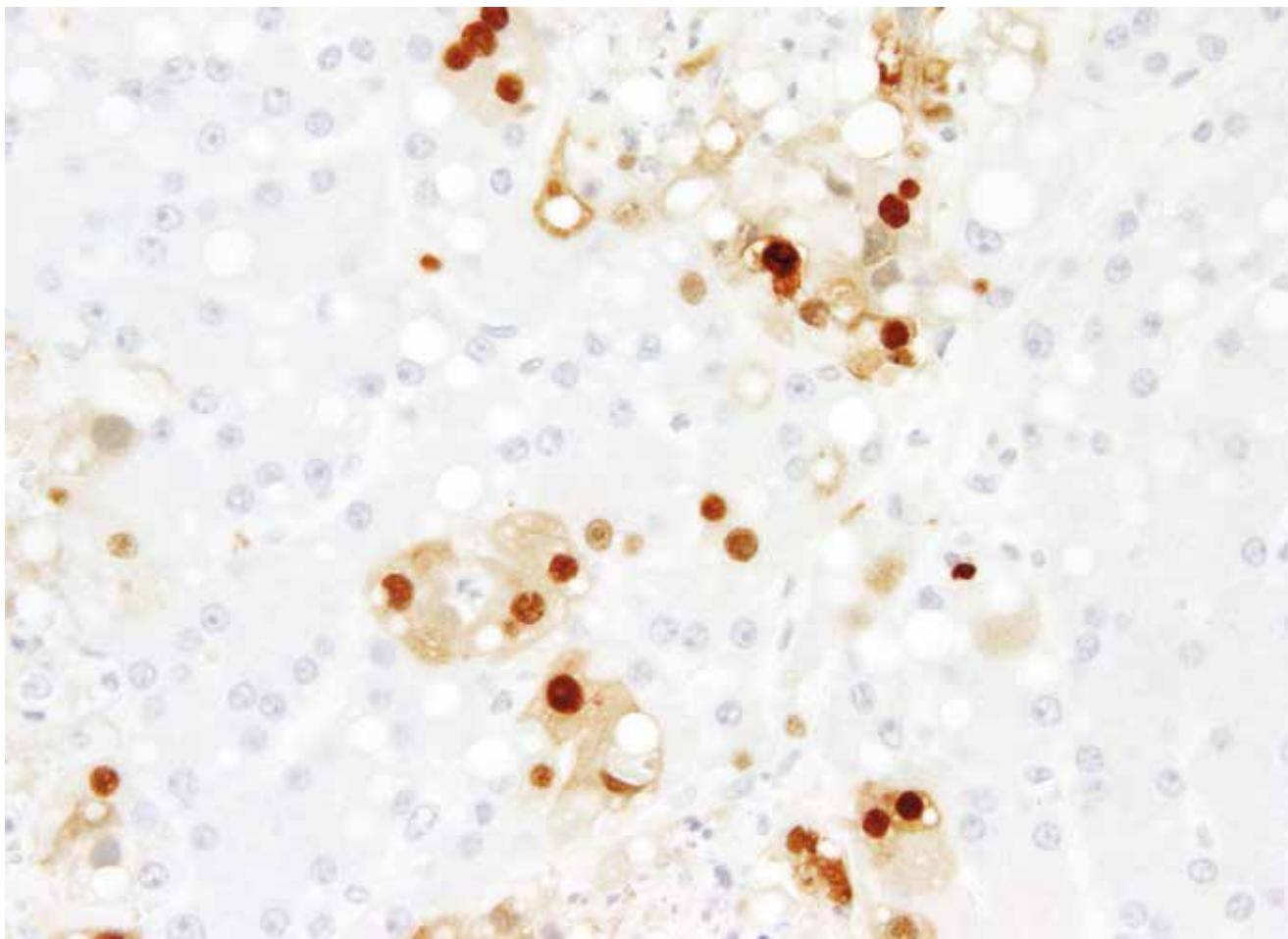


Image 20B: Adenovirus immunostain of same specimen (magnification x400).



Image 21: Cross-section of a liver with fulminant liver failure due to autoimmune hepatitis. The parenchyma has a yellow-orange discoloration and was markedly softened.

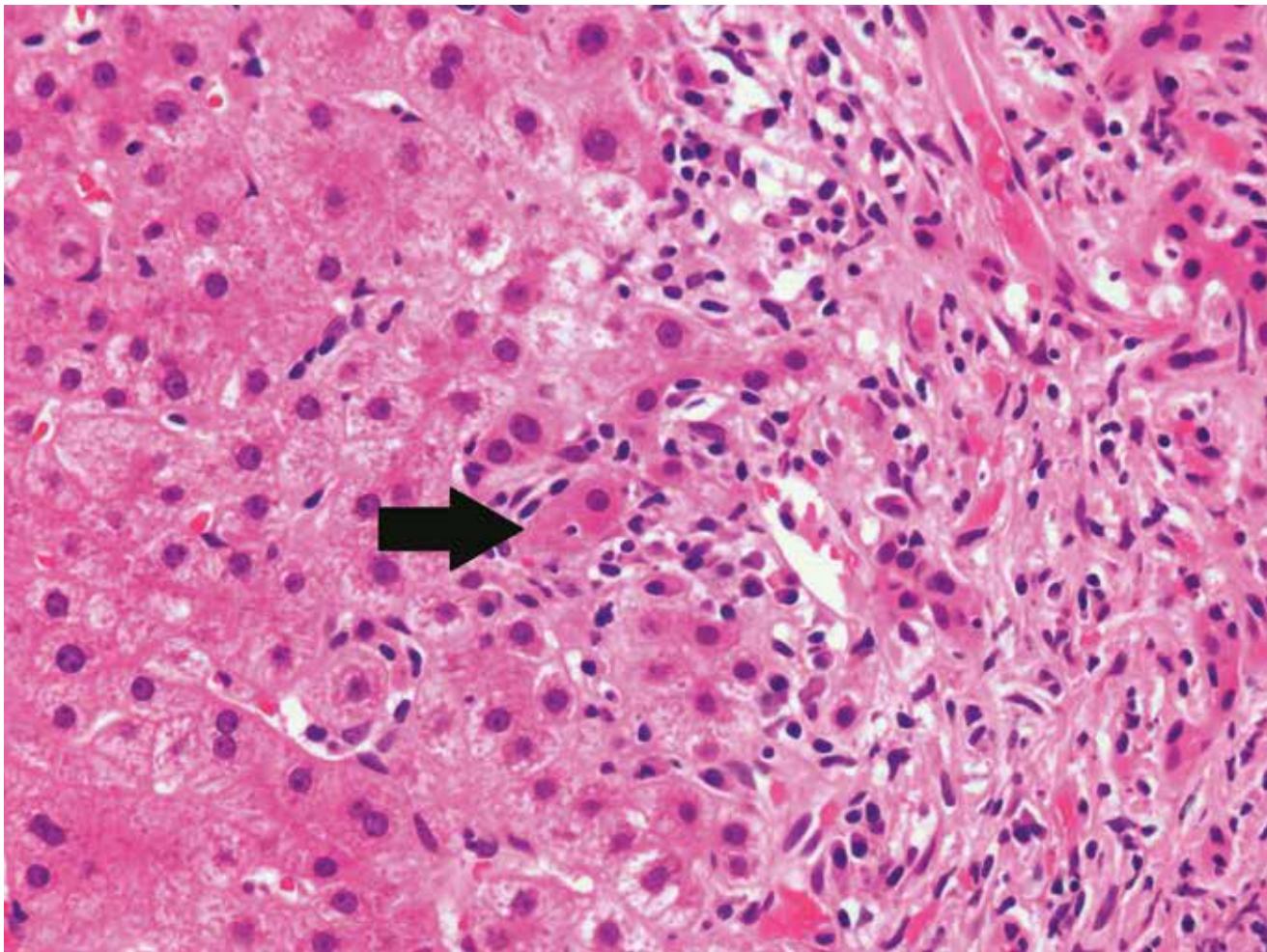


Image 22: Photomicrograph of a lymphocyte entrapped within a hepatocyte, known as emperipoleisis (arrow) (H&E, x200).



Image 23: Gross photograph of a liver with ischemic necrosis. Note the thrombus adjacent to the ruler.

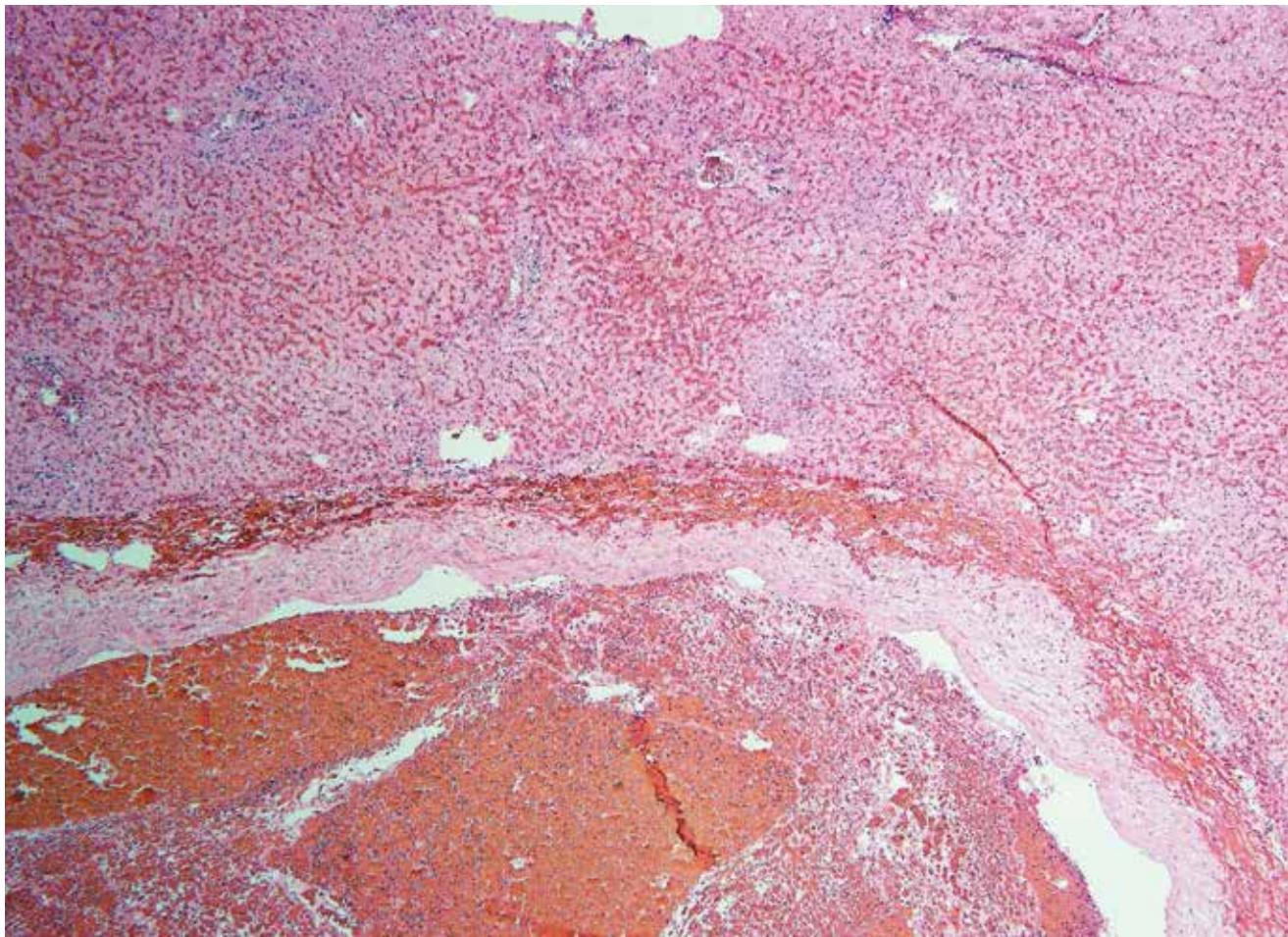


Image 24A: Microscopic section of ischemic hepatitis showing thrombus within a large blood vessel and associated sinusoidal congestion (H&E, x40).

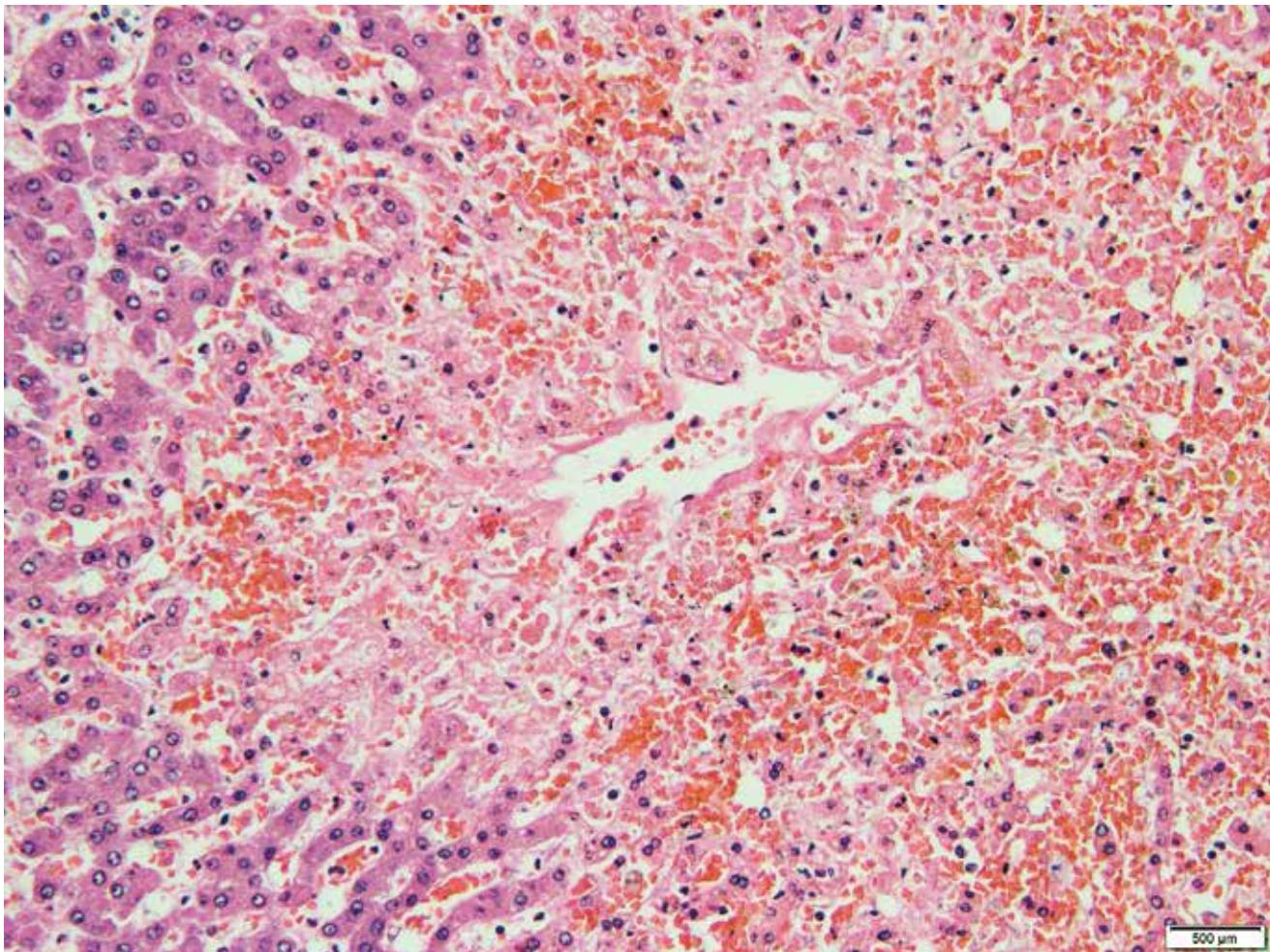


Image 24B: Microscopic section of ischemic hepatitis showing early centrilobular necrosis (H&E, x200).

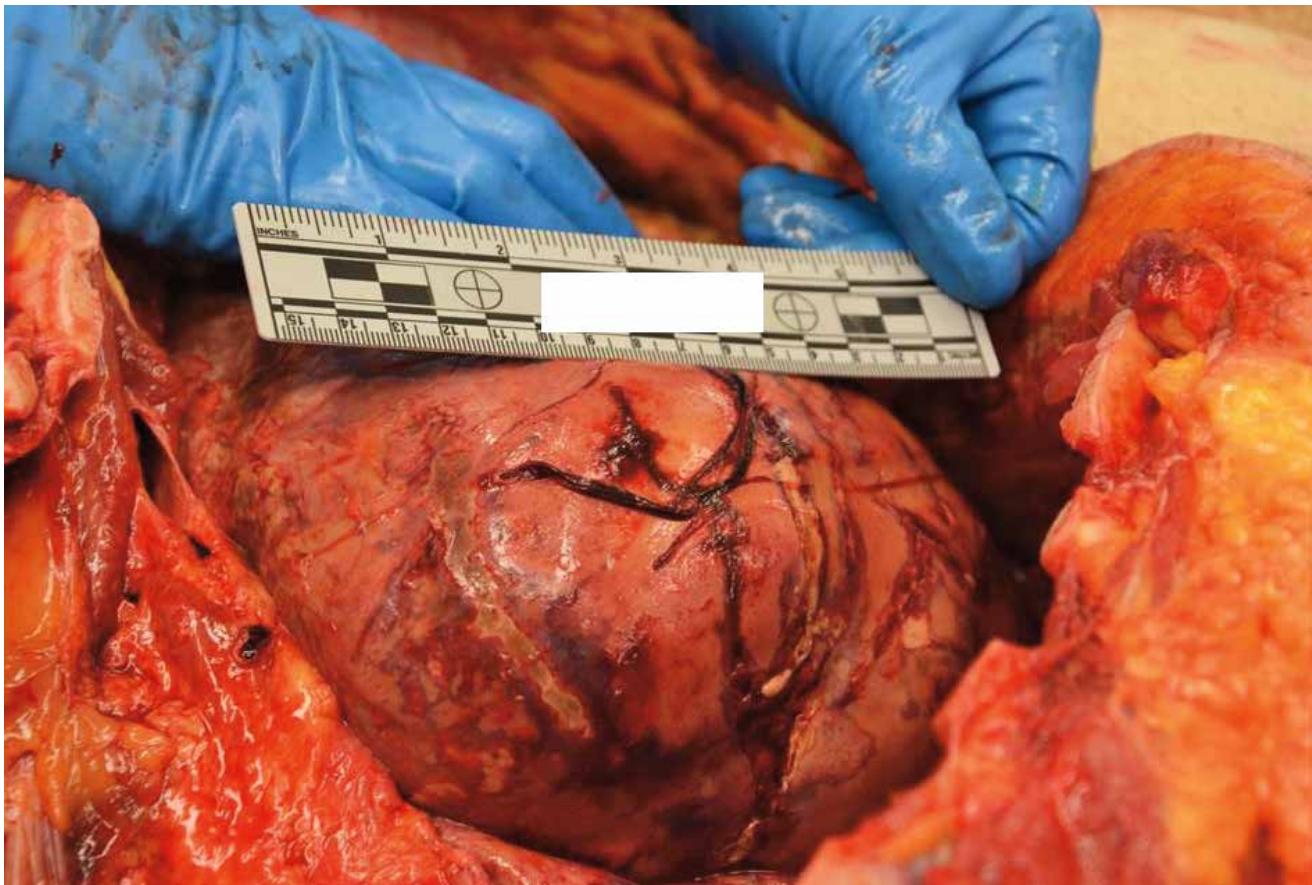


Image 25A: Gross photograph of traumatic herniation of right hepatic lobe through a diaphragmatic laceration. (Photo courtesy of Washoe County Regional Medical Examiner's Office).

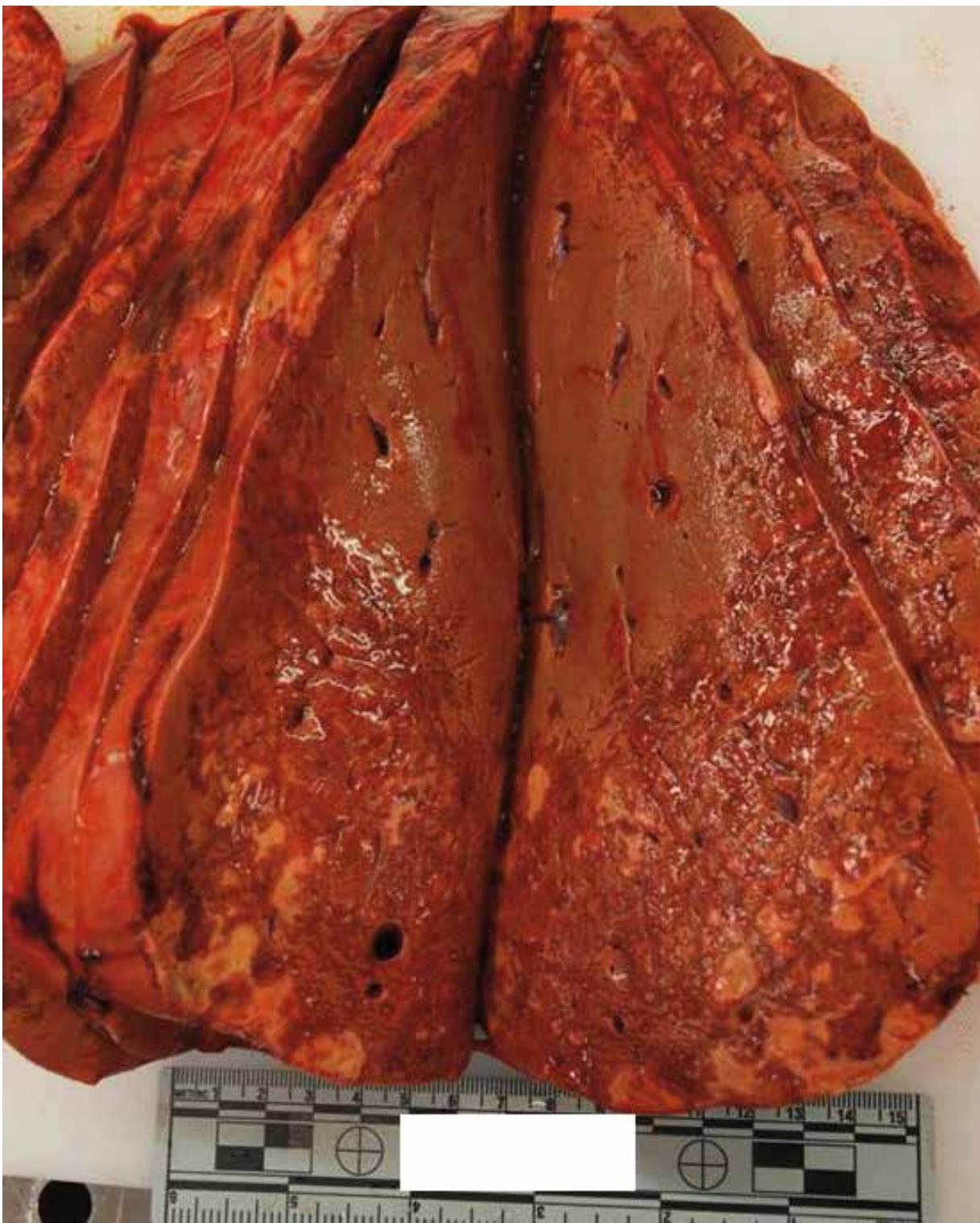


Image 25B: Serial sections displaying approximately 50% parenchymal necrosis. (Photo courtesy of Washoe County Regional Medical Examiner's Office).

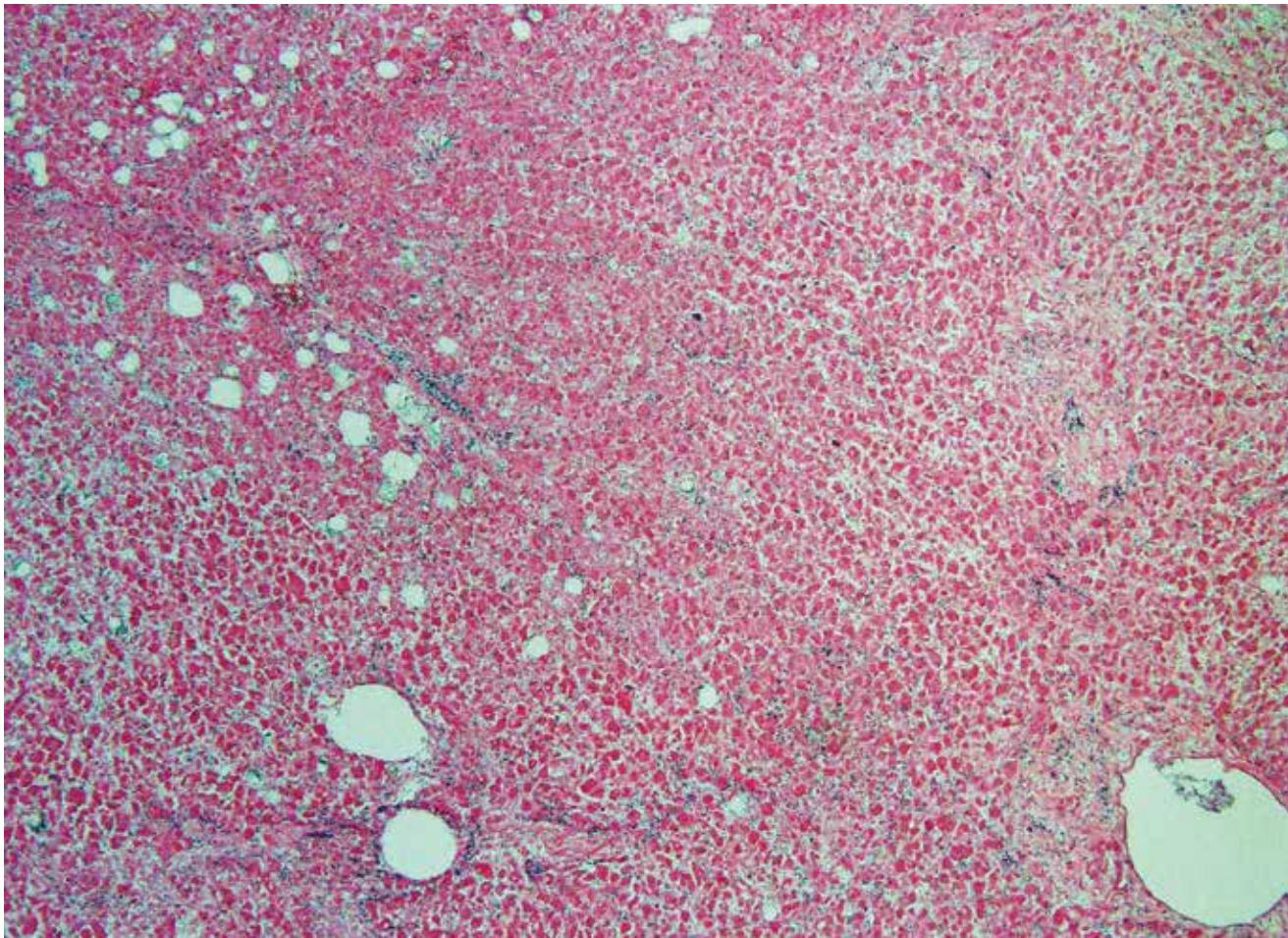


Image 26A: Microscopic section of a liver with marked autolysis showing widespread loss of architecture and tissue breakdown (H&E, x40).

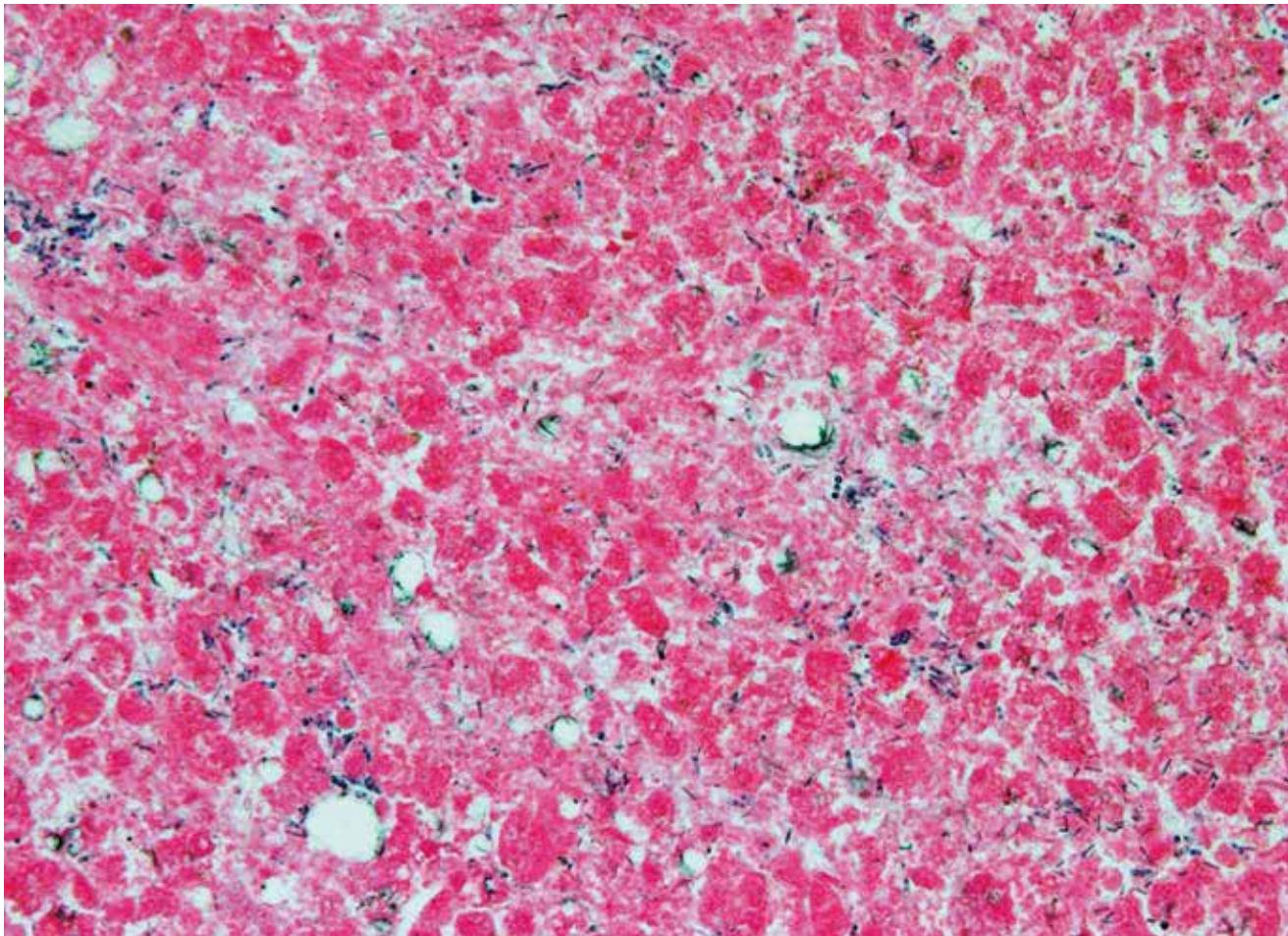


Image 26B: Microscopic section of a liver with marked autolysis showing total dropout of the nuclei, loss of normal hepatocyte structure, and scattered growth of microorganisms in the absence of inflammation (H&E, x400).

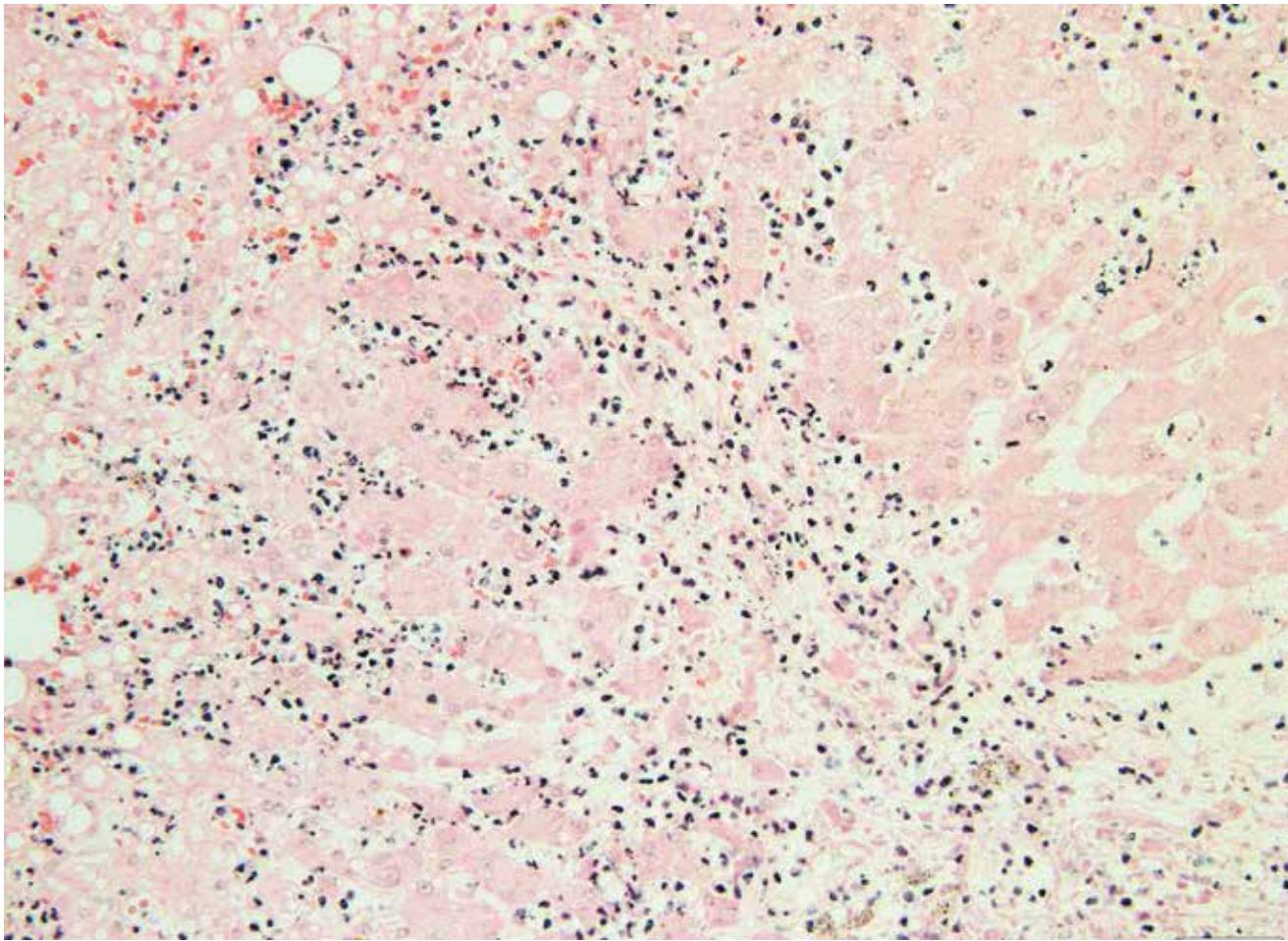


Image 27: Microscopic section of a liver with massive necrosis showing relative preservation of the hepatocyte nuclei and a brisk acute inflammatory infiltrate (H&E, x400)

Table 1: Causes of Hepatic Necrosis with Associated Demographics, Pathological Features, and Ancillary Studies Available to Aid in Diagnosis.

Category	Age	Clinical Presentation	Gross Features	Microscopic Features	Ancillary Studies
Alcohol	Adulthood	Variable, may result in ALF or ACLF	Enlarged, fatty liver or cirrhosis	Steatosis, lobular inflammation, Mallory bodies	
Intrinsic drug (acetaminophen, halothane, carbon tetrachloride)	Varies	ALF	Centrilobular necrosis	Zone 3 necrosis without significant inflammation	Toxicology
Idiosyncratic drug (numerous including antimicrobial, herbal, and CNS agents)	Varies; typically adulthood	Subacute liver failure	Varies; possible submassive necrosis and regenerative nodules	Varies	Toxicology
Hepatotrophic viruses	Varies, typically adulthood	Varies, including ALF and ACLF	Varies	Portal lymphocytic infiltrate	Serology, PCR, IHC stains
Non-hepatotrophic viruses	Varies	ALF	Punctate pale lesions throughout parenchyma	Patchy necrosis, viral inclusions	Serology, PCR, IHC stains
Autoimmune	Young adults	Varies, including ALF and ACLF; also endocrine dysfunction, elevated IgG, autoantibodies	Varies	Zone 3 necrosis, plasma cell infiltrate, resetting, and emperipoleisis	
Ischemia	Varies, typically adulthood	Circulatory collapse, blood loss, CHF	Varies, purple discoloration to passive congestion	Varies, typically Zone 3 necrosis	
Metabolic	Childhood	Varies	Varies	Varies	Special stains

ALF - Acute liver failure

ACLF - Acute-on-chronic liver failure

CNS - Central nervous system

PCR - Polymerase chain reaction

IHC - Immunohistochemical

CHF - Congestive heart failure

REFERENCES

- Guicciardi ME, Gores GJ. Apoptosis: a mechanism of acute and chronic liver injury. *Gut*. 2005 Jul; 54(7):1024-33. PMID: 15951554. PMCID: PMC1774601. <https://doi.org/10.1136/gut.2004.053850>.
- Guicciardi ME, Malhi H, Mott JL, Gores GJ. Apoptosis and necrosis in the liver. *Compr Physiol*. 2013 Apr; 3(2):977-1010. PMID: 23720337. PMCID: PMC3867948. <https://doi.org/10.1002/cphy.c120020>.
- Theise ND. Robbins basic pathology. 9th ed. Philadelphia: Saunders/Elsevier; c2013. Chapter 15, Liver, gallbladder, and biliary tract; p.603-44.
- Wang MX, Morgan T, Lungo W, et al. "Piecemeal" necrosis: renamed troxis necrosis. *Exp Mol Pathol*. 2001 Oct; 71(2):137-46. PMID: 11599920. <https://doi.org/10.1006/exmp.2001.2397>.
- O'Grady JG, Schalm SW, Williams R. Acute liver failure: redefining the syndromes. *Lancet*. 1993 Jul 31; 342(8866):273-5. PMID: 8101303. [https://doi.org/10.1016/0140-6736\(93\)91818-7](https://doi.org/10.1016/0140-6736(93)91818-7).
- Bower WA, Johns M, Margolis HS, et al. Population-based surveillance for acute liver failure. *Am J Gastroenterol*. 2007 Nov; 102(11):2459-63. PMID: 17608778. <https://doi.org/10.1111/j.1572-0241.2007.01388.x>.
- Lee WM, Squires RH Jr, Nyberg SL, et al. Acute liver failure: summary of a workshop. *Hepatology*. 2008 Apr; 47(4):1401-15. PMID: 18318440. PMCID: PMC3381946. <https://doi.org/10.1002/hep.22177>.
- Bernal W, Hyrylainen A, Gera A, et al. Lessons from look-back in acute liver failure? A single centre experience of 3300 patients. *J Hepatol*. 2013 Jul; 59(1):74-80. PMID: 23439263. <https://doi.org/10.1016/j.jhep.2013.02.010>.
- Ostapowicz G, Fontana RJ, Schiødt FV, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med*. 2002 Dec 17; 137(12):947-54. PMID: 12484709. <https://doi.org/10.7326/0003-4819-137-12-200212170-00007>.
- Moreau R, Jalan R, Arroyo V. Acute-on-chronic liver failure: recent concepts. *J Clin Exp Hepatol*. 2015 Mar; 5(1):81-5. PMID: 25941435. PMCID: PMC4415197. <https://doi.org/10.1016/j.jceh.2014.09.003>.



- 11) Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology*. 2013 Jun; 144(7):1426-37. PMID: 23474284. <https://doi.org/10.1053/j.gastro.2013.02.042>.
- 12) Bernal W, Jalan R, Quaglia A, et al. Acute-on-chronic liver failure. *Lancet*. 2015 Oct 17; 386(10003):1576-87. PMID: 26423181. [https://doi.org/10.1016/s0140-6736\(15\)00309-8](https://doi.org/10.1016/s0140-6736(15)00309-8).
- 13) Theise ND. Histopathology of alcoholic liver disease. *Clin Liver Dis*. 2013 Apr 24; 2(2):64-7. <https://doi.org/10.1002/cld.172>.
- 14) Crawford JM. Histologic findings in alcoholic liver disease. *Clin Liver Dis*. 2012 Nov; 16(4):699-716. PMID: 23101978. <https://doi.org/10.1016/j.cld.2012.08.004>.
- 15) Caulin C, Ware CF, Magin TM, Oshima RG. Keratin-dependent, epithelial resistance to tumor necrosis factor-induced apoptosis. *J Cell Biol*. 2000 Apr 3; 149(1):17-22. PMID: 10747083. PMCID: PMC2175089. <https://doi.org/10.1083/jcb.149.1.17>.
- 16) Gao B, Bataller R. Alcoholic liver disease: pathogenesis and new therapeutic targets. *Gastroenterology*. 2011 Nov; 141(5):1572-85. PMID: 21920463. PMCID: PMC3214974. <https://doi.org/10.1053/j.gastro.2011.09.002>.
- 17) Yan AW, Fouts DE, Brandl J, et al. Enteric dysbiosis associated with a mouse model of alcoholic liver disease. *Hepatology*. 2011 Jan; 53(1):96-105. PMID: 21254165. PMCID: PMC3059122. <https://doi.org/10.1002/hep.24018>.
- 18) Lucey MR, Mathurin P, Morgan TR. Alcoholic hepatitis. *N Engl J Med*. 2009 Jun 25; 360(26):2758-69. PMID: 19553649. <https://doi.org/10.1056/NEJMra0805786>.
- 19) Liangpunsakul S. Clinical characteristics and mortality of hospitalized alcoholic hepatitis patients in the United States. *J Clin Gastroenterol*. 2011 Sep; 45(8):714-9. PMID: 21085006. PMCID: 3135756. <https://doi.org/10.1097/mcg.0b013e3181fdef1d>.
- 20) Singal AK, Kuo YF, Anand BS. Hepatitis C virus infection in alcoholic hepatitis: prevalence patterns and impact on in-hospital mortality. *Eur J Gastroenterol Hepatol*. 2012 Oct; 24(10):1178-84. PMID: 22735607. <https://doi.org/10.1097/meg.0b013e328355cce0>.
- 21) Celli R, Zhang X. Pathology of alcoholic liver disease. *J Clin Transl Hepatol*. 2014 Jun; 2(2):103-9. PMID: 26357621. PMCID: PMC4521259. <https://doi.org/10.14218/JCTH.2014.00010>.
- 22) Sakhija P. Pathology of alcoholic liver disease, can it be differentiated from nonalcoholic steatohepatitis? *World J Gastroenterol*. 2014 Nov 28; 20(44):16474-9. PMID: 25469015. PMCID: PMC4248190. <https://doi.org/10.3748/wjg.v20.i44.16474>.
- 23) Rastogi A, Kumar A, Sakhija P, et al. Liver histology as predictor of outcome in patients with acute-on-chronic liver failure (ACLF). *Virchows Arch*. 2011 Aug; 459(2):121-7. PMID: 21744153. <https://doi.org/10.1007/s00428-011-1115-9>.
- 24) Hussaini SH, Farrington EA. Idiosyncratic drug-induced liver injury: an update on the 2007 overview. *Expert Opin Drug Saf*. 2014 Jan; 13(1):67-81. PMID: 24073714. <https://doi.org/10.1517/14740338.2013.828032>.
- 25) Bernal W, Auzinger G, Dhawan A, Wenden J. Acute liver failure. *Lancet*. 2010 Jul 17; 376(9736):190-201. PMID: 20638564. [https://doi.org/10.1016/s0140-6736\(10\)60274-7](https://doi.org/10.1016/s0140-6736(10)60274-7).
- 26) Larson AM, Polson J, Fontana RJ, et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. *Hepatology*. 2005 Dec; 42(6):1364-72. PMID: 16317692. <https://doi.org/10.1002/hep.20948>.
- 27) Serper M, Wolf MS, Parikh NA, et al. Risk factors, clinical presentation, and outcomes in overdose with acetaminophen alone or with combination products: results from the acute liver failure study group. *J Clin Gastroenterol*. 2016 Jan; 50(1):85-91. PMID: 26166142. PMCID: PMC5528869. <https://doi.org/10.1097/mcg.0000000000000378>.
- 28) Lefkowitch JH. The pathology of acute liver failure. *Adv Anat Pathol*. 2016 May; 23(3):144-58. PMID: 27058243. <https://doi.org/10.1097/pap.0000000000000112>.
- 29) Ramachandran R, Kakar S. Histological patterns in drug-induced liver disease. *J Clin Pathol*. 2009 Jun; 62(6):481-92. PMID: 19474352. <https://doi.org/10.1136/jcp.2008.058248>.
- 30) Chalasani N, Fontana RJ, Bonkovsky HL, et al. Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. *Gastroenterology*. 2008 Dec; 135(6):1924-34, 1934.e1-4. PMID: 18955056. PMCID: PMC3654244. <https://doi.org/10.1053/j.gastro.2008.09.011>.
- 31) Wei G, Bergquist A, Broomé U, et al. Acute liver failure in Sweden: etiology and outcome. *J Intern Med*. 2007 Sep; 262(3):393-401. PMID: 17697161. <https://doi.org/10.1111/j.1365-2796.2007.01818.x>.
- 32) Björnsson E. Drug-induced liver injury: Hy's rule revisited. *Clin Pharmacol Ther*. 2006 Jun; 79(6):521-8. PMID: 16765139. <https://doi.org/10.1016/j.cpt.2006.02.012>.
- 33) Kleiner DE, Chalasani NP, Lee WM, et al. Hepatic histological findings in suspected drug-induced liver injury: systematic evaluation and clinical associations. *Hepatology*. 2014 Feb; 59(2):661-70. PMID: 24037963. PMCID: PMC3946736. <https://doi.org/10.1002/hep.26709>.
- 34) Björnsson E, Kalaitzakis E, Olsson R. The impact of eosinophilia and hepatic necrosis on prognosis in patients with drug-induced liver injury. *Aliment Pharmacol Ther*. 2007 Jun 15; 25(12):1411-21. PMID: 17539980. <https://doi.org/10.1111/j.1365-2036.2007.03330.x>.
- 35) Katoonizadeh A, Nevens F, Verslype C, et al. Liver regeneration in acute severe liver impairment: a clinicopathological correlation study. *Liver Int*. 2006 Dec; 26(10):1225-33. PMID: 17105588. <https://doi.org/10.1111/j.1478-3231.2006.01377.x>.
- 36) Lin KY, Chen GJ, Lee YL, et al. Hepatitis A virus infection and hepatitis A vaccination in human immunodeficiency virus-positive patients: a review. *World J Gastroenterol*. 2017 May 28; 23(20):3589-3606. PMID: 28611512. PMCID: PMC5449416. <https://doi.org/10.3748/wjg.v23.i20.3589>.
- 37) Hepatitis A vaccines. *Wkly Epidemiol Rec*. 2000 Feb 4; 75(5):38-44. PMID: 10693358.
- 38) Gupta E, Ballani N, Kumar M, Sarin SK. Role of non-hepatotropic viruses in acute sporadic viral hepatitis and acute-on-chronic liver failure in adults. *Indian J Gastroenterol*. 2015 Nov; 34(6):448-52. PMID: 26589230. <https://doi.org/10.1007/s12664-015-0613-0>.
- 39) World Health Organization [Internet]. Geneva: World Health Organization; c2018. Hepatitis E; [updated 2017 Jul 7; cited 2018 Feb 22]. Available from: <http://www.who.int/mediacentre/factsheets/fs280/en/>.
- 40) Davern TJ, Chalasani N, Fontana RJ, et al. Acute hepatitis E infection accounts for some cases of suspected drug-induced liver injury. *Gastroenterology*. 2011 Nov; 141(5):1665-72.e1-9. PMID: 2185518. PMCID: PMC3654540. <https://doi.org/10.1053/j.gastro.2011.07.051>.
- 41) Schweitzer A, Horn J, Mikolajczyk RT, et al. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. *Lancet*. 2015 Oct 17; 386(10003):1546-55. PMID: 26231459. [https://doi.org/10.1016/s0140-6736\(15\)61412-x](https://doi.org/10.1016/s0140-6736(15)61412-x).

- 42) Roberts H, Kruszon-Moran D, Ly KN, et al. Prevalence of chronic hepatitis B virus (HBV) infection in U.S. households: National Health and Nutrition Examination Survey (NHANES), 1988-2012. *Hepatology*. 2016 Feb; 63(2):388-97. PMID: 26251317. <https://doi.org/10.1002/hep.28109>.
- 43) Viral hepatitis surveillance: United States, 2015 [Internet]. Atlanta: Centers for Disease Control and Prevention; [cited 2018 Feb 22]. 73 p. Available from: <https://www.cdc.gov/hepatitis/statistics/2015surveillance/pdfs/2015hepsurveillancerpt.pdf>.
- 44) Peron JM, Danjoux M, Kamar N, et al. Liver histology in patients with sporadic acute hepatitis E: a study of 11 patients from South-West France. *Virchows Arch.* 2007 Apr; 450(4):405-10. PMID: 1733266. <https://doi.org/10.1007/s00428-007-0382-y>.
- 45) Alves VAF. Acute Viral Hepatitis- Beyond A, B and C [Internet]. Evans (GA): United States & Canadian Academy of Pathology; 2017 [cited 2018 Feb 22]. Available from: https://handouts.uscap.org/AN2017/2017_CM10_alves_0101.pdf.
- 46) Schwarz KB, Dell Olio D, Lobrutto SJ, et al. Analysis of viral testing in nonacetaminophen pediatric acute liver failure. *J Pediatr Gastroenterol Nutr.* 2014 Nov; 59(5):616-23. PMID: 25340974. PMCID: PMC4305349. <https://doi.org/10.1097/mpg.0000000000000512>.
- 47) Norvell JP, Blei AT, Jovanovic BD, Levitsky J. Herpes simplex virus hepatitis: an analysis of the published literature and institutional cases. *Liver Transpl.* 2007 Oct; 13(10):1428-34. PMID: 17902129. <https://doi.org/10.1002/lt.21250>.
- 48) Sundaram SS, Alonso EM, Narkewicz MR, et al. Characterization and outcomes of young infants with acute liver failure. *J Pediatr.* 2011 Nov; 159(5):813-818.e1. PMID: 21521221. PMCID: 3177978. <https://doi.org/10.1016/j.jpeds.2011.04.016>.
- 49) Ronan BA, Agarwal N, Carey EJ, et al. Fulminant hepatitis due to human adenovirus. *Infection.* 2014 Feb; 42(1):105-11. PMID: 23979854. <https://doi.org/10.1007/s15010-013-0527-7>.
- 50) Mellinger JL, Rossaro L, Naugler WE, et al. Epstein-Barr virus (EBV) related acute liver failure: a case series from the US Acute Liver Failure Study Group. *Dig Dis Sci.* 2014 Jul; 59(7):1630-7. PMID: 24464209. PMCID: PMC4250929. <https://doi.org/10.1007/s10620-014-3029-2>.
- 51) Manns MP, Lohse AW, Vergani D. Autoimmune hepatitis--update 2015. *J Hepatol.* 2015 Apr; 62(1 Suppl):S100-11. PMID: 25920079. <https://doi.org/10.1016/j.jhep.2015.03.005>.
- 52) Czaja AJ. Diagnosis and management of autoimmune hepatitis: current status and future directions. *Gut Liver.* 2016 Mar; 10(2):177-203. PMID: 26934884. PMCID: PMC4780448. <https://doi.org/10.5009/gnl15352>.
- 53) Francque S, Vonghia L, Ramon A, Michielsen P. Epidemiology and treatment of autoimmune hepatitis. *Hepat Med.* 2012 Mar 16; 4:1-10. PMID: 24367228. PMCID: PMC3846915. <https://doi.org/10.2147/hmer.s16321>.
- 54) Björnsson E, Talwalkar J, Treeparsertsuk S, et al. Drug-induced autoimmune hepatitis: clinical characteristics and prognosis. *Hepatology.* 2010 Jun; 51(6):2040-8. PMID: 20512992. <https://doi.org/10.1002/hep.23588>.
- 55) Roberts SK, Therneau TM, Czaja AJ. Prognosis of histological cirrhosis in type 1 autoimmune hepatitis. *Gastroenterology.* 1996 Mar; 110(3):848-57. PMID: 8608895 <https://doi.org/10.1053/gast.1996.v110.pm8608895>.
- 56) Czaja AJ. Acute and acute severe (fulminant) autoimmune hepatitis. *Dig Dis Sci.* 2013 Apr; 58(4):897-914. PMID: 23090425. <https://doi.org/10.1007/s10620-012-2445-4>.
- 57) Tiniakos DG, Brain JG, Bury YA. Role of histopathology in autoimmune hepatitis. *Dig Dis.* 2015; 33 Suppl 2:53-64. PMID: 26642062. <https://doi.org/10.1159/000440747>.
- 58) de Boer YS, van Nieuwkerk CM, Witte BI, et al. Assessment of the histopathological key features in autoimmune hepatitis. *Histopathology.* 2015 Feb; 66(3):351-62. PMID: 25257662. <https://doi.org/10.1111/his.12558>.
- 59) Miao Q, Bian Z, Tang R, et al. Emperipoleisis mediated by CD8 T cells is a characteristic histopathologic feature of autoimmune hepatitis. *Clin Rev Allergy Immunol.* 2015 Jun; 48(2-3):226-35. PMID: 25051956. <https://doi.org/10.1007/s12016-014-8432-0>.
- 60) Nguyen Canh H, Harada K, Ouchi H, et al. Acute presentation of autoimmune hepatitis: a multicentre study with detailed histological evaluation in a large cohort of patients. *J Clin Pathol.* 2017 Nov; 70(11):961-969. PMID: 28428284. <https://doi.org/10.1136/jclinpath-2016-204271>.
- 61) Alvarez AM, Mukherjee D. Liver abnormalities in cardiac diseases and heart failure. *Int J Angiol.* 2011 Sep; 20(3):135-42. PMID: 22942628. PMCID: PMC3331650. <https://doi.org/10.1055/s-0031-1284434>.
- 62) O'Grady JG. Budd-chiari syndrome and acute liver failure: a complex condition requiring a rapid response. *Liver Transpl.* 2017 Feb; 23(2):133-134. PMID: 28006871. PMCID: 28006871. <https://doi.org/10.1002/lt.24695>.
- 63) Lefkowitch JH, Mendez L. Morphologic features of hepatic injury in cardiac disease and shock. *J Hepatol.* 1986; 2(3):313-27. PMID: 3722787. [https://doi.org/10.1016/s0168-8278\(86\)80043-5](https://doi.org/10.1016/s0168-8278(86)80043-5).
- 64) Dabbs DN, Stein DM, Scalea TM. Major hepatic necrosis: a common complication after angiembolization for treatment of high-grade liver injuries. *J Trauma.* 2009 Mar; 66(3):621-7; discussion 627-9. PMID: 19276729. <https://doi.org/10.1097/ta.0b013e31819919f2>.
- 65) Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. *Gastroenterology.* 2012 Jun; 142(7):1592-609. PMID: 22656328. <https://doi.org/10.1053/j.gastro.2012.04.001>.
- 66) Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther.* 2011 Aug; 34(3):274-85. PMID: 21623852. <https://doi.org/10.1111/j.1365-2036.2011.04724.x>.
- 67) Fazel Y, Koenig AB, Sayiner M, et al. Epidemiology and natural history of non-alcoholic fatty liver disease. *Metabolism.* 2016 Aug; 65(8):1017-25.
- 68) Pronicki M. Wilson disease - liver pathology. *Handb Clin Neurol.* 2017; 142:71-75. PMID: 28433112. <https://doi.org/10.1016/b978-0-444-63625-6.00007-0>.



Fatty Liver and the Forensic Pathologist

Christopher M. Milroy

ABSTRACT

Fatty liver is a common finding in clinical practice and at autopsy. It is most commonly seen associated with alcohol abuse and in non-alcoholic fatty liver disease (NAFLD). It may also be seen in many other conditions in both adults and children. It is now recognized that NAFLD, like alcoholic liver disease, may lead to end stage liver disease. Nonalcoholic fatty liver disease is associated with increased mortality from other disorders, particularly cardiovascular diseases. Fatty liver may be seen in many conditions that concern autopsy pathologists, including drug toxicity, anorexia, hepatic ischemia, and heatstroke. In infants, steatosis is common in sudden unexpected deaths. Fatty liver has been associated with sudden death and this review examines the pathology and role of fatty liver in sudden death.

Acad Forensic Pathol. 2018 8(2): 296-310

AUTHOR

Christopher M. Milroy MBChB MD LLB BA LLM FRCPath FFFLM FRCPC DMJ, The Ottawa Hospital - Anatomical Pathology

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work.

CORRESPONDENCE

Christopher M. Milroy MD, 501 Smyth Road, Ottawa ON Canada K1H 8L6, c.milroy@btopenworld.com

ETHICAL APPROVAL

As per Journal Policies, ethical approval was not required for this manuscript

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies conducted with animals or on living human subjects

STATEMENT OF INFORMED CONSENT

No identifiable personal data were presented in this manuscript

DISCLOSURES & DECLARATION OF CONFLICTS OF INTEREST

Christopher M. Milroy is the Editor-In-Chief of Academic Forensic Pathology: The Official Publication of the National Association of Medical Examiners. The author, reviewers, editors, and publication staff do not report any other relevant conflicts of interest

FINANCIAL DISCLOSURE

The author has indicated that he does not have financial relationships to disclose that are relevant to this manuscript

KEYWORDS

Forensic pathology, Fatty, Steatosis, Liver, NAFLD, Alcohol

INFORMATION

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

©2018 Academic Forensic Pathology International • (ISSN: 1925-3621) • <https://doi.org/10.23907/2018.019>

Submitted for consideration on 19 Mar 2018. Accepted for publication on 23 Apr 2018

INTRODUCTION

Fatty liver is common and can occur in many conditions in both adults and children (1). It is frequently found at autopsy, especially if microscopy is conducted. Fatty liver can be considered as a marker of other disorders and has been used as a cause of death in the past. While fatty liver is important in the pediatric age group, this paper concentrates on fatty liver in adults at autopsy and discusses its role in causing sudden death.

DISCUSSION

Histopathology of Fatty Liver

Fatty liver, also known as steatosis, occurs in two main patterns, macrovesicular steatosis, the most common pattern, and microvesicular steatosis (2). The two main patterns often overlap. Macrovesicular steatosis is identified by a single fat vacuole, with the nucleus displaced to the edge (**Image 1**), while microvesicular steatosis has multiple small cytoplasmic vacuoles with a typically centrally placed nucleus (**Image 2**). Macrovesicular steatosis can be seen in a wide range of insults to the liver including alcohol, diabetes mellitus and metabolic syndrome, obesity, malnutrition,

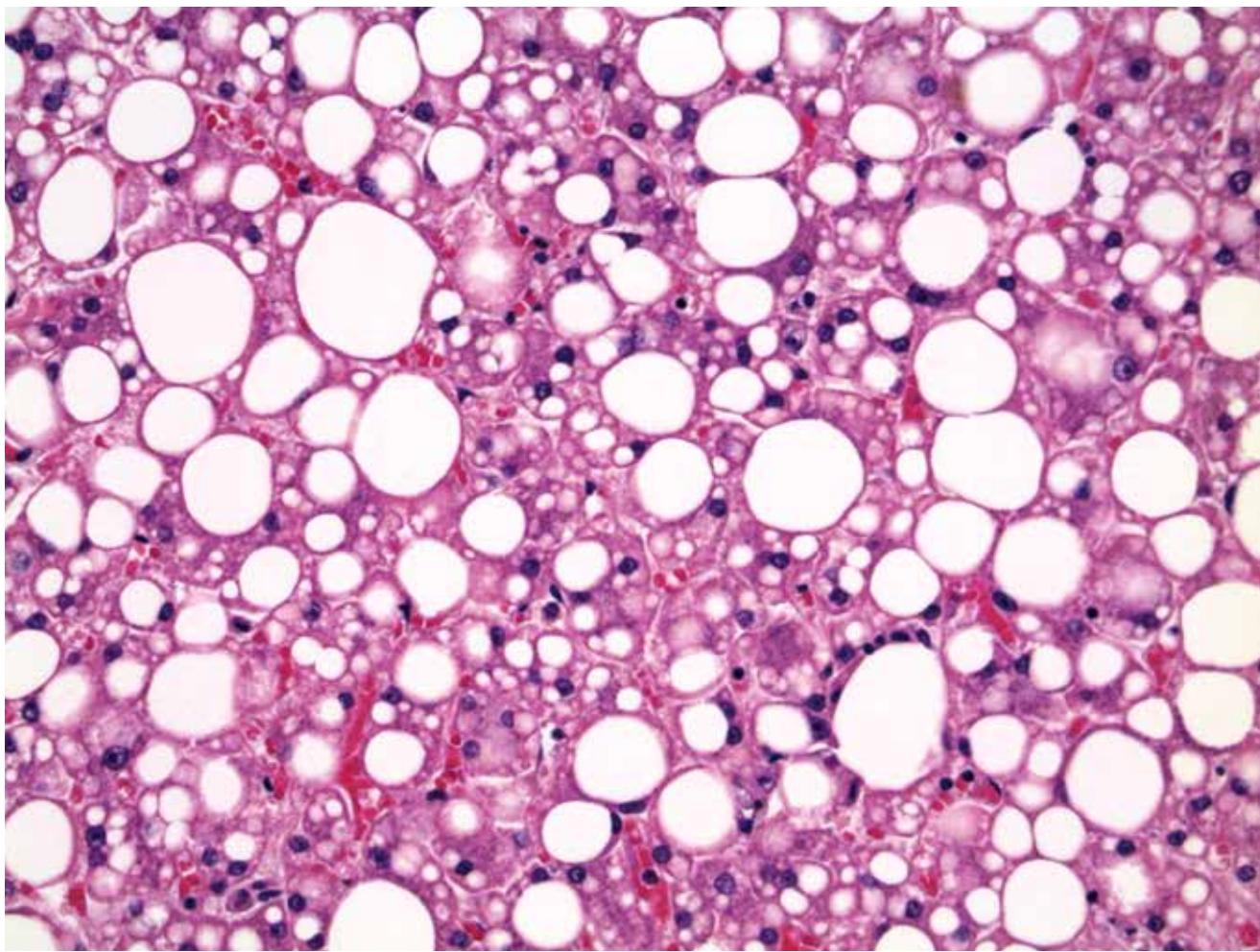


Image 1: Predominantly macrovesicular steatosis (H&E, x 200).

various metabolic disorders, drugs and toxins, and viral hepatitis. Microvesicular steatosis can be seen in a number of conditions such as acute fatty liver of pregnancy, Reyes syndrome, inherited disorders of fatty acid metabolism, infection, and drug toxicity, including salicylate, valproate, and tetracycline (1). Conditions associated with macrovesicular and microvesicular steatosis are listed in **Table 1**.

Steatohepatitis

Steatohepatitis, also known as steatonecrosis, refers to the pattern of cell injury in fatty liver disease. The mechanisms of injury overlap (3), and the morphology is similar between alcoholic and nonalcoholic

etiologies, such that the diagnosis of alcoholic steatohepatitis cannot be made on histology alone (4). Furthermore, alcoholic liver disease may exist with other comorbidities including NAFLD and hepatitis C infection (5).

Alcoholic Liver Disease

Alcoholic steatosis is seen in up to 90% of patients presenting for treatment of chronic alcoholism (6). Fatty change is mainly seen in the perivenular zone, but as the fatty change progresses it can be seen in all zones. Abstinence of alcohol results in fat disappearing in two to four weeks. Lipogranulomata may be seen at this stage, otherwise inflammation is absent in simple steatosis (1).

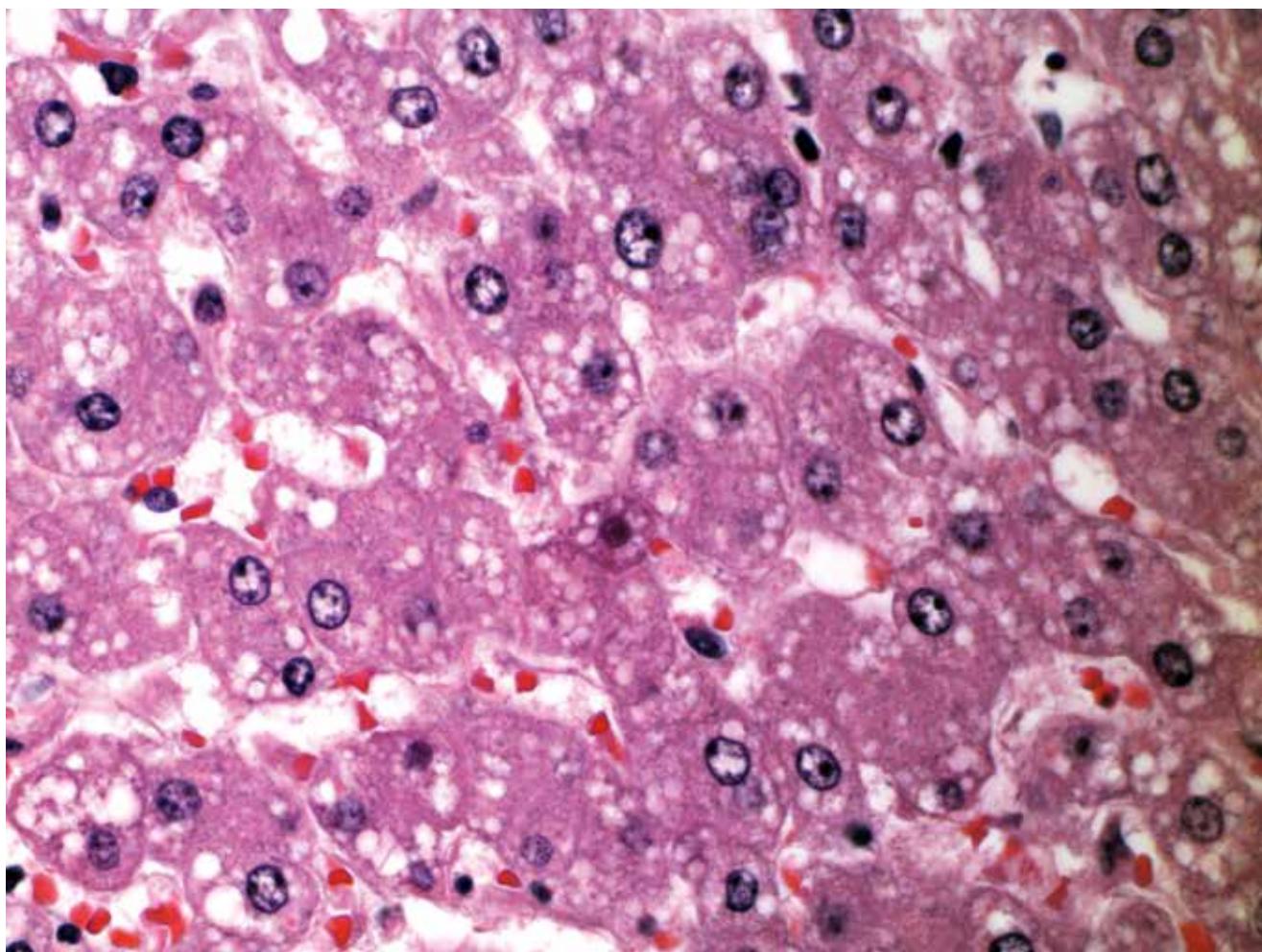


Image 2: Microvesicular steatosis (H&E, x 400).



Alcoholic foamy degeneration is a term used to describe microvesicular change seen with alcohol use (7). It is not associated with inflammation and Mallory-Denk bodies are usually absent. The condition subsides with abstinence.

Alcoholic hepatitis, also called alcoholic steatonecrosis, is characterized by steatosis, liver cell necrosis, and neutrophil inflammation (**Image 3**) (2, 5). In one study, it was present in 17 out of 100 liver biopsies in patients presenting for treatment of alcoholism (8). Sclerosing hyaline necrosis occurs when there is extensive perivenular hepatocyte necrosis with fibrosis (9). This may result in portal hypertension without cirrhosis. Venous lesions seen in alcoholic liver disease include lymphocytic phlebitis, phlebosclerosis, and veno-occlusive disease (10, 11). Phlebosclerosis, compression of hepatic vein radicles by perivenular fibrosis, is a universal finding in alcoholic hepatitis and cirrhosis, whereas veno-occlusive lesions, intimal

proliferation, and fibrosis were seen in 25% of biopsies and lymphocytic phlebitis, a predominantly lymphocytic inflammatory infiltrate in the hepatic vein branches, in 4%.

Perivenular fibrosis is defined as fibrosis surrounding two-thirds of a terminal hepatic venule, with the fibrosis measuring over 4 µm (**Image 4**). Fibrosis is a marker for more progressive disease if alcohol consumption continues (**Image 5**). In males drinking 40-80 grams of alcohol a day, nearly 40% had perivenular fibrosis.

Perivenular fibrosis is believed to be the precursor of cirrhosis (12, 13); however, only 20% of heavy drinkers develop cirrhosis (1). Cirrhosis is most typically micronodular, with nodules less than 3 mm. Macro-nodular cirrhosis may develop especially following abstinence, when regeneration of nodules takes place (14).

Table 1: Causes of Liver Steatosis

Macrovesicular Steatosis	Microvesicular Steatosis
Alcoholic fatty liver	Alcoholic foamy degeneration
Nonalcoholic fatty liver	Reyes syndrome
Obesity	Drugs
Diabetes mellitus	Acute fatty liver of pregnancy
Viral hepatitis	Inherited disorders of fatty acid metabolism
Drugs	Inherited urea cycle disorders
Total parenteral nutrition	Wolman disease
Malnutrition	Mitochondrial cytopathies
Wilson disease	Infection
Polycystic ovarian syndrome	Cholesterol ester storage disease
Mandibuloacral dysplasia	
Familial partial lipodystrophies	
Acquired lipodystrophies	
Hepatic ischemia	

Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease (NAFLD) is a term used for a range of changes seen in the liver and encompasses various terms including nonalcoholic steatohepatitis (NASH) and non-NASH fatty liver (NNFL), which is a term used to describe fatty liver disease that carries a better prognosis than NASH and typically presents with steatosis but with minimal, if any, inflammation or fibrosis (15).

Steatosis is defined as abnormal when exceeding 5% in microscopic sections (16). Nonalcoholic steatohepatitis involves inflammation, ballooned hepatocytes, and evidence of cell death; fibrosis may be present. Nonalcoholic steatohepatitis may progress to cirrhosis, typically in people who are over 60 years of age, are obese, and have diabetes. This cirrhosis is sometimes referred to as cryptogenic cirrhosis, though it has been questioned whether cirrhosis related to NASH is the same entity (17).

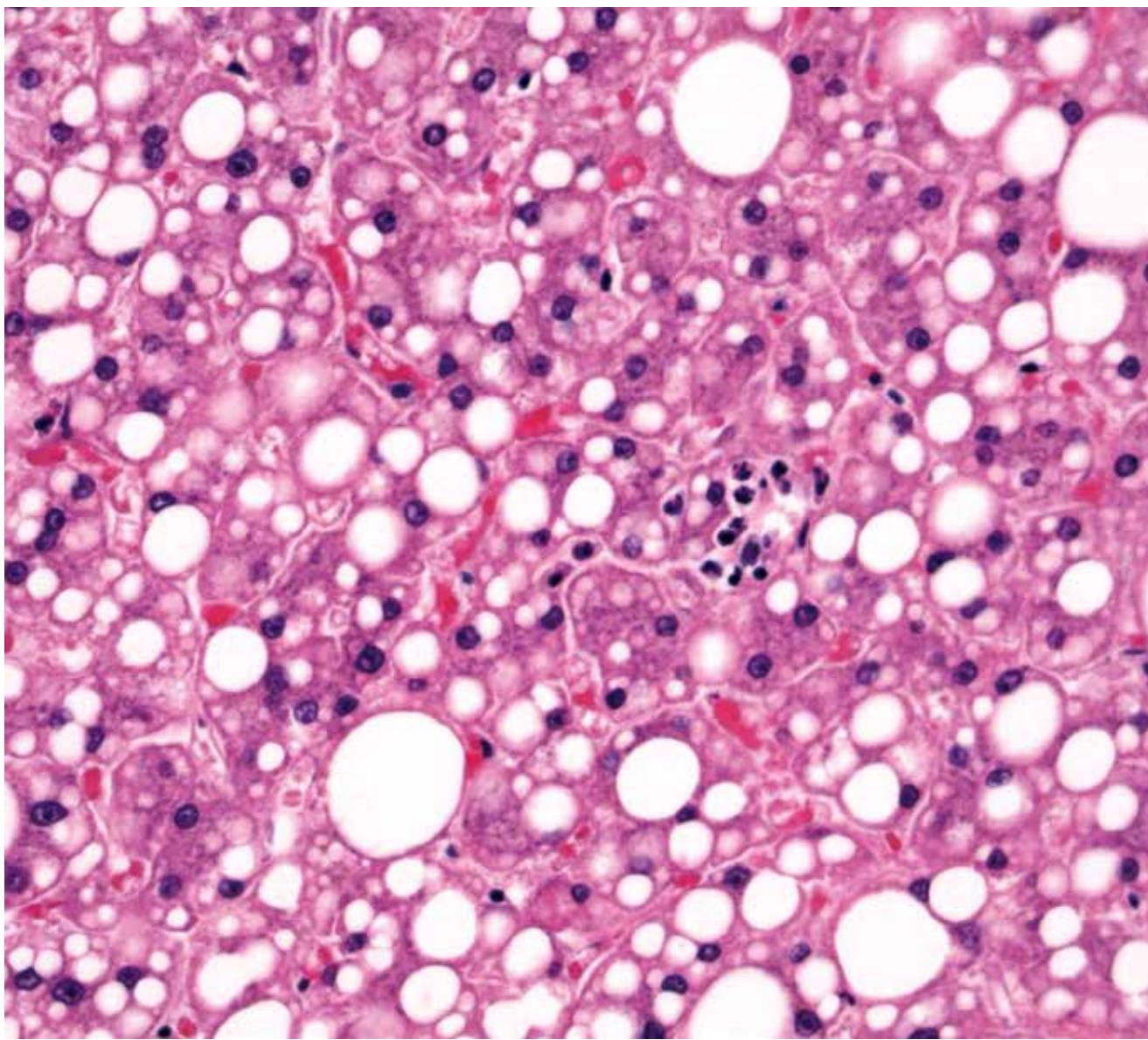


Image 3: Steatohepatitis (H&E, x 200).

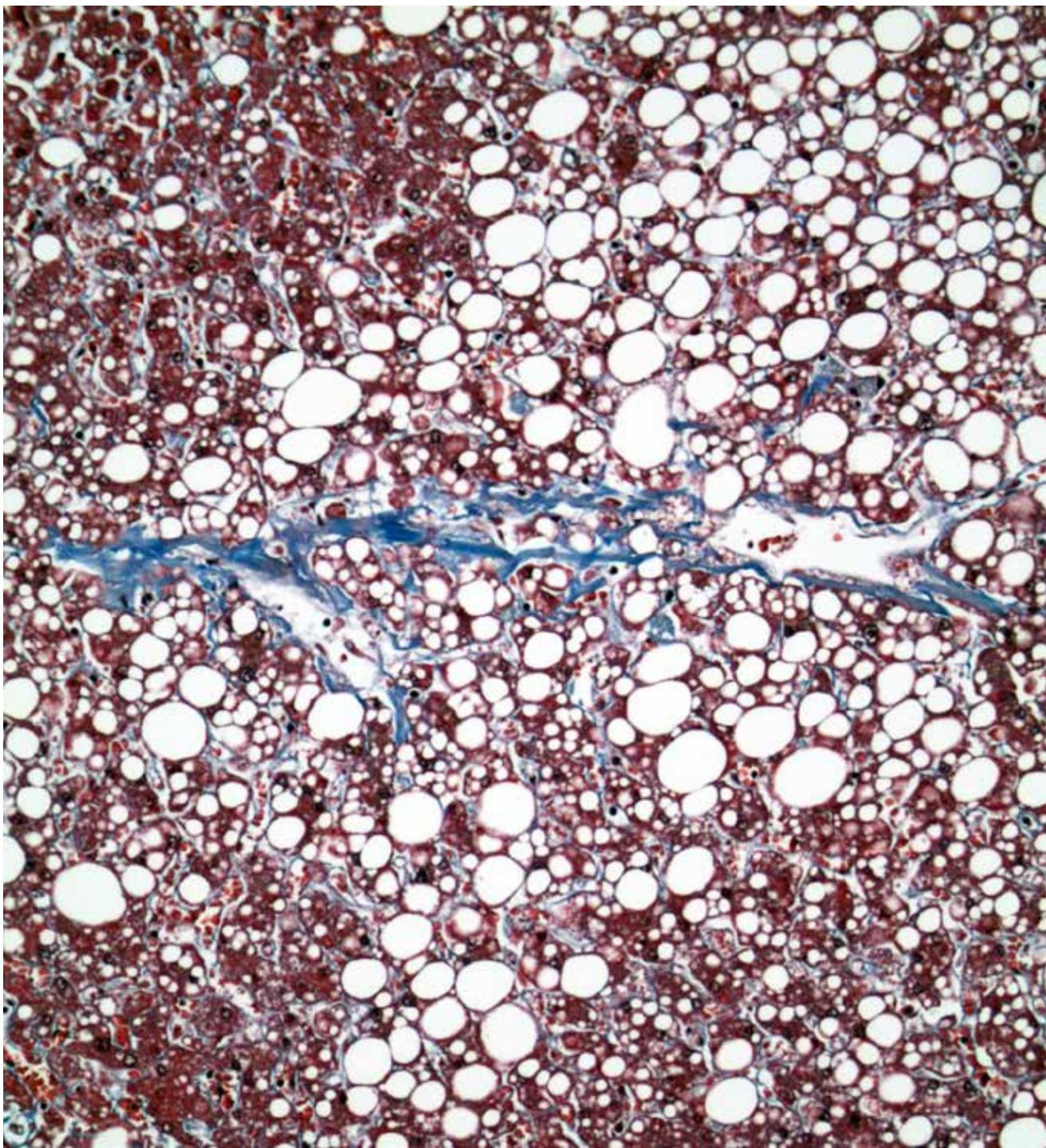


Image 4: Perivenular fibrosis (Masson trichrome, x100).

For a diagnosis of NASH, alcohol consumption should be less than 20 grams per day (18). Although significant ethanol consumption is an exclusionary criterion for the diagnosis of NASH, patients classified as having NASH were found to have had a significant lifetime exposure to alcohol (19). As there is overlap between NASH and alcoholic steatohepatitis (ASH) histologically, with the exception of an increased incidence of glycogenated nuclei (**Image 6**) in NASH (20), it can be impossible to tell the two disorders apart, especially in a medicolegal investigation when medical and social history may be limited.

Non-NASH-fatty liver (NNFL) is a term used for fatty liver without significant fibrosis or inflammation. It is

more stable than NASH, though progress to NASH may occur.

The frequency of NAFLD has been reported to be high in the general population (21). While a wide range of conditions may be associated with NAFLD, diabetes mellitus, obesity, and hyperlipidemia are the commonest associations (22). Nonalcoholic fatty liver disease may have a worldwide prevalence of 25%, and as high as 38% depending on criteria and region studied. In obese patients undergoing bariatric surgery, typically with a body mass index (BMI) over 35 kg/m², the prevalence of steatosis was 85-90%, with the prevalence of NASH of 25-20%, and unexpected cirrhosis of 1-2% (23).

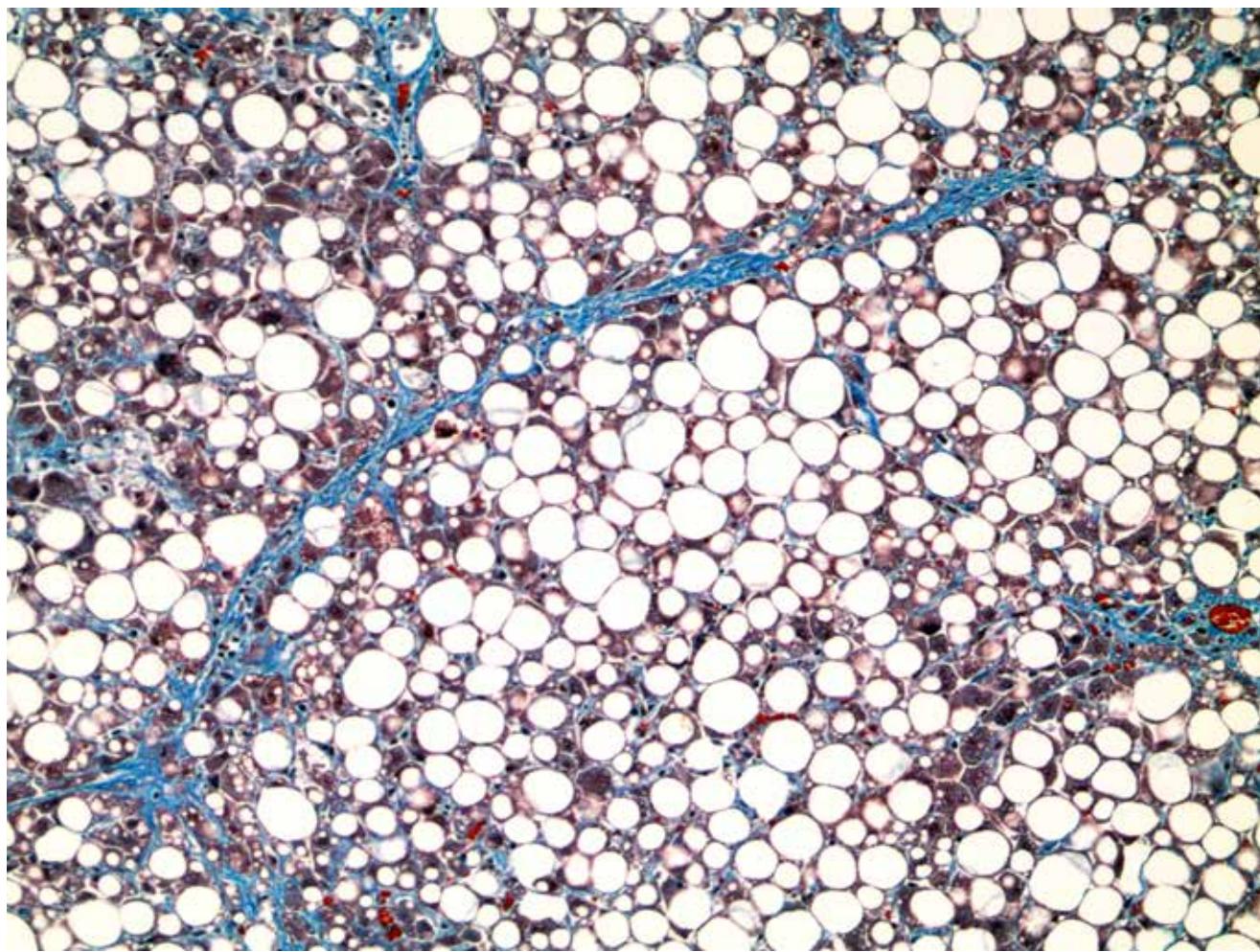


Image 5: Fibrosis with fatty change (Masson trichrome, x100).

Histological features of NASH include macrovesicular and microvesicular steatosis with portal and/or lobular inflammation (1). Fibrosis is present, typically in zone 3, around the peri-central veins. The hepatocytes may contain Mallory-Denk bodies (Mallory hyaline) and there may be lipogranulomas and glycogenated nuclei. The disease may progress to cirrhosis. Scoring systems for severity of NAFLD have been devised (24).

The risk of NAFLD is increased in obesity, which carries a 4.6-fold increase over nonobese people, as assessed by ultrasound (25). However, people with a normal BMI may still have fatty liver (26, 27). These patients tend to have visceral adiposity along with hy-

perinsulinemia and poor physical conditioning. Diabetes mellitus increases the risk of fatty liver and also increases the risk of cirrhosis (28). Patients with NASH cirrhosis are at risk of developing hepatocellular carcinoma (HCC) (29). Hepatocellular carcinoma has been associated with NNFL, suggesting steatosis alone is a risk factor for the development of HCC (30, 31).

Nonalcoholic fatty liver disease may coexist with other liver disorders. Patients with hepatitis C infection (HCV) have a poorer response to interferon therapy if they have steatosis, obesity, and hyperinsulinism and probably the combination accelerates progression (32). Steatosis also affects progression of primary biliary cholangitis (33).

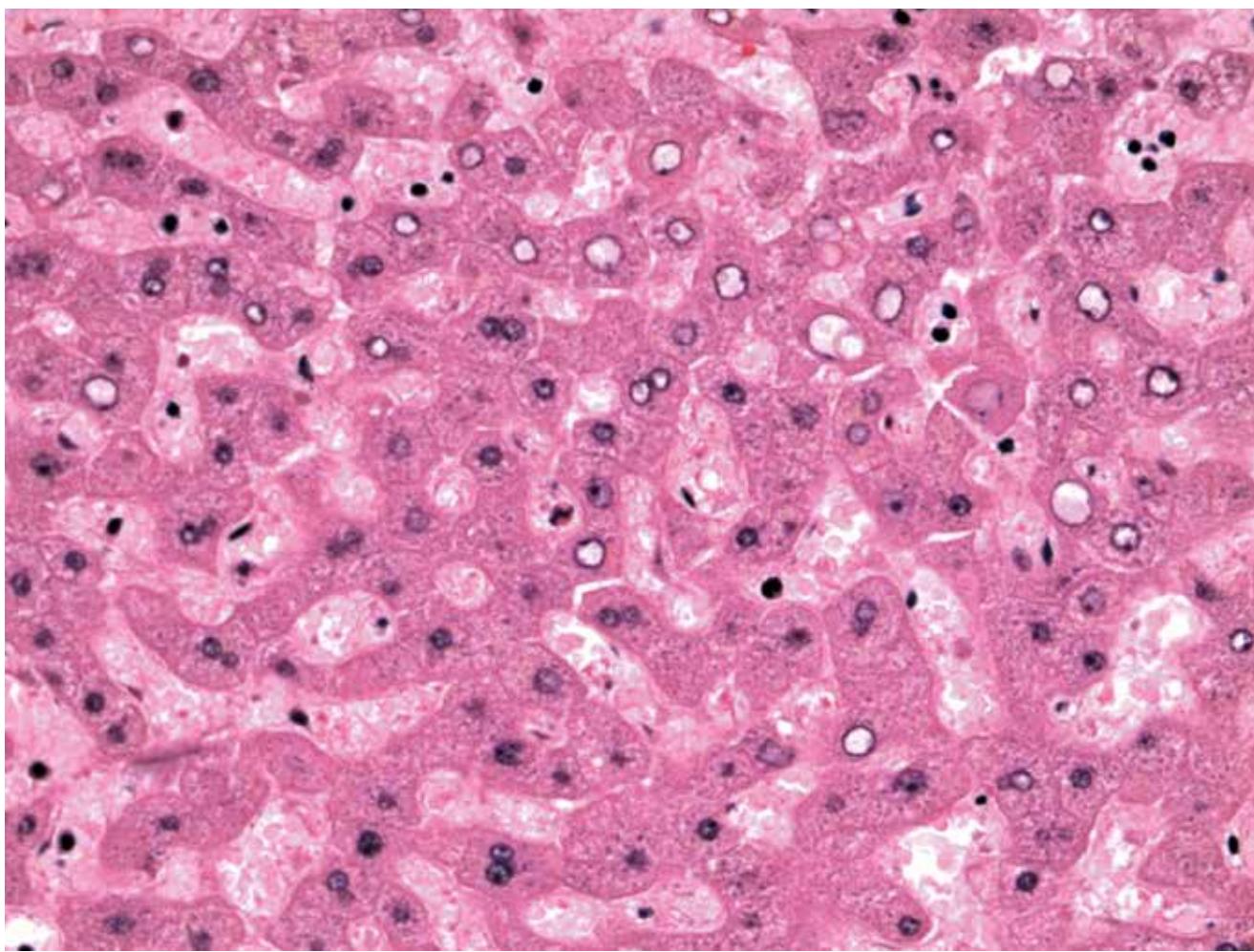


Image 6: Glycogenated nuclei (H&E, x200).



There are genetic, gender, and familial variations in NAFLD, which is more common among certain ethnic groups (34-36). Men have a higher rate of NAFLD than women. In the US, Latinos have a higher rate and African Americans a lower rate, when compared to rates of obesity in the population. There are differences in the distribution of body fat in these groups and in lipoprotein metabolism (37-39). First degree relatives have higher rates of NASH and genetic studies have linked NAFLD to certain genes including for patatin-like phospholipase 3 (*PNPLA3*), which may have a role in transferring fatty acids between lipids (40-43). Another is transmembrane 6 superfamily member 2 (*TM6SF2*), which is a regulator of hepatic lipid droplet content. These two genes are related to disease severity and related morbidities including vascular disease.

Clinical Features of Nonalcoholic Fatty Liver Disease

Patients with NAFLD are typically asymptomatic (44). They may have a history of fatigue and right upper quadrant pain. They often have obstructive sleep apnea and women may have polycystic ovaries. Neurological deficits have been reported occasionally, believed to be related to lipotoxicity. On external examination, there may be acanthosis nigra, palmar erythema, and spider angioma (spider nevi) (15). Biochemical abnormalities include elevated liver enzymes, iron, uric acid, and immunoglobulin A (15). Antinuclear antibodies may be positive. There is hepatomegaly.

Other Causes of Fatty Liver

Fatty liver is found in many conditions other than ALD and NAFLD. Macrovesicular and microvesicular steatosis can be seen with drug toxicity (Image 7), including nifedipine, diltiazem, tamoxifen, estrogen, and corticosteroids (1, 15). Solvents and petrochemicals can also cause fatty liver. Hepatitis C, B, and D infection may cause steatosis, as may disorders of lipoprotein and nutritional disorders, including anorexia nervosa and total parenteral nutrition, bypass surgery for obesity and small bowel resection, hepatic ischemia and systemic disorders such as cachexia,

heat stroke, cystic fibrosis, and inflammatory bowel disease (Image 8).

Mortality and Nonalcoholic Fatty Liver Disease

Patients diagnosed with NAFLD have a mortality of 10-12% over a 10 to 15 year period (45-49). Fibrosis is a predictor of mortality (50). The main causes of death are reported to be coronary artery disease, extrahepatic malignancies, and cirrhosis of the liver. One long-term study indicated that deaths from cirrhosis exceeded cardiac causes (47).

Fatty Liver at Autopsy

There have been few systematic studies of fatty liver at autopsy. A study of 207 obese patients was compared with 207 control patients examined at autopsy at the Western General Hospital in Toronto, Canada between 1960 and 1987 (51). Sixty-three patients had a history of alcohol use and were excluded from further analysis, leaving 351 in the analysis. Fatty liver was present in both groups, though more prevalent in the obese patients, and with greater severity than in controls. Steatohepatitis was seen in 22 of the 351 cases, including 18.5% of obese patients and only 2.7% of nonobese patients. Weight loss before death was also associated with steatosis. Fibrosis was seen more frequently in obese patients and was associated with diabetes mellitus.

An autopsy study from Northwestern Greece revealed frequent steatosis and steatohepatitis (52). The authors examined 498 medicolegal cases with a mean age of 64.51 years. The most common causes of death were ischemic heart disease (47.59%), traffic accidents (13.45%), and pulmonary embolism (8.23%). Other causes of death were each less than 5%. Of the 498 cases, 28.9% of cases had normal livers, steatosis was present in 31.3%, and steatohepatitis in 39.8% (52).

An autopsy study of livers in people dying of diabetic ketoacidosis with no prior history of diabetes mellitus revealed significant steatosis and steatohepatitis (53). The BMIs of these people were typically within the normal (nonobese) range.

Is Fatty Liver a Cause of Death?

Fatty liver has been reported as a cause of sudden death (54). In a study of alcohol-related deaths from Baltimore examined between 1957 and 1966, fatty liver and cirrhosis were noted to have increased as a cause of death (55). The authors noted that several hypotheses had been suggested for the proximate cause of death, including fatty emboli to the lungs and

the brain, hypoglycemia secondary to alcoholism, and alcoholic cardiomyopathy. They noted that a cardiac arrhythmia has been suspected as the mechanism of death, a cause they noted would be impossible to determine from postmortem examination.

Clark, in a review of 500 alcohol deaths from Glasgow, Scotland, classified 51 deaths as being “obscure,” with 32 cases having fatty liver (56). Both the

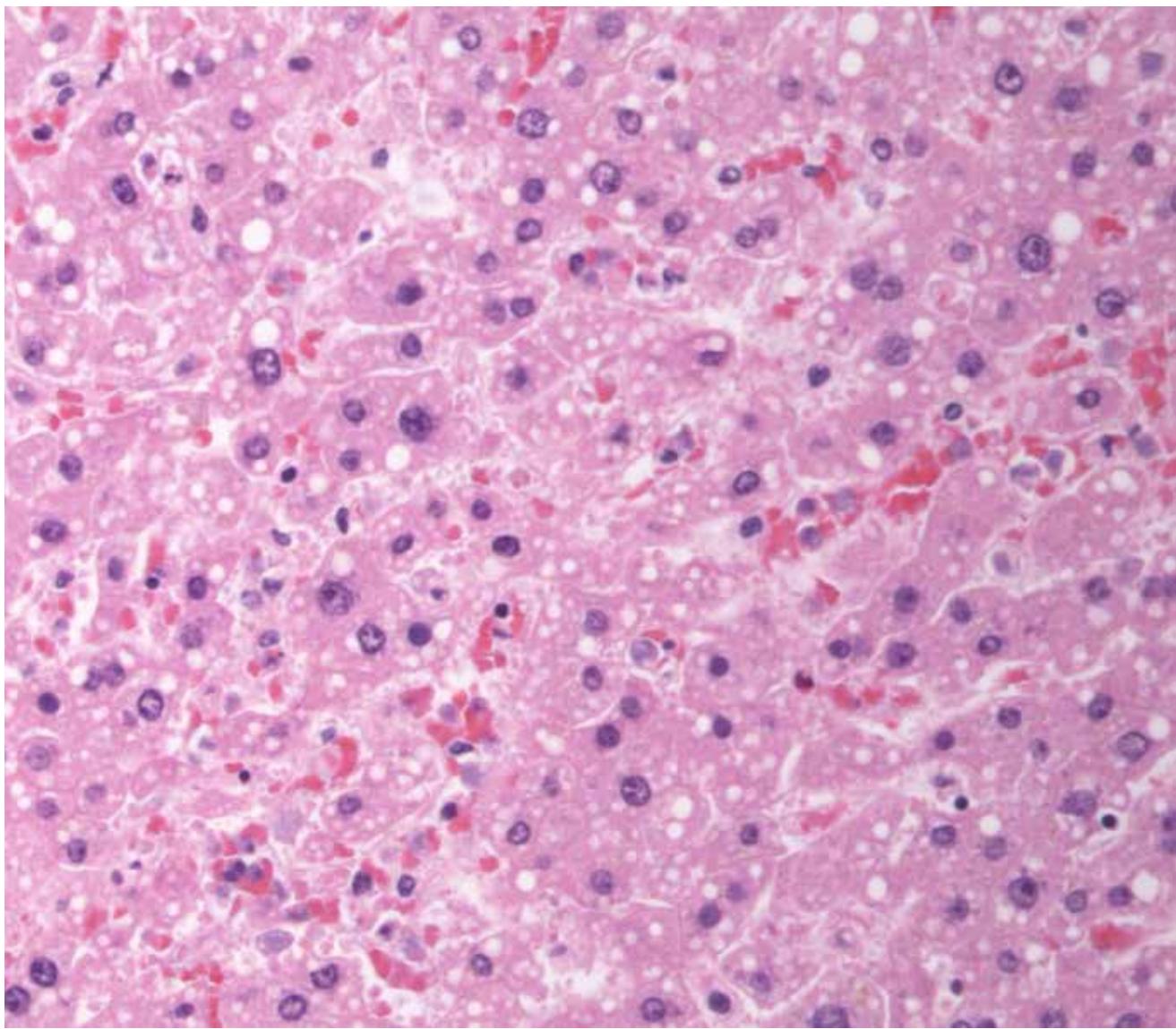


Image 7: Steatosis in colchicine toxicity (H&E, x200).

papers from Baltimore and Glasgow were published before alcoholic ketoacidosis was reported in post-mortem cases (57). This condition certainly provides an explanation for some deaths in cases of fatty liver. Another mechanism now recognized to be associated with alcoholics is cardiac arrhythmias associated with cirrhosis and alcoholic liver disease more severe than simple steatosis.

Nonalcoholic fatty liver disease has been associated with cardiac arrhythmias (58-61), the most common of which is atrial fibrillation. There is less data on ventricular arrhythmias. A small study of patients with NAFLD revealed they had evidence of autonomic dysfunction, and another study of diabetics revealed

that those with more severe NAFLD had prolonged QTc intervals on electrocardiogram examination (58). Thus, there are potential mechanisms for sudden death in patients with NAFLD, though further work is required to determine if this is so and what the risks are. Nonalcoholic fatty liver disease can be considered a multisystem disease (62).

Fatty Liver in the Pediatric Age Group

Fatty liver is not uncommon in the pediatric age group. An autopsy study in 2006 suggested an prevalence of around 10% (63), and the prevalence in a Japanese population was found to be 2.4% in another study (64). Nonalcoholic fatty liver disease in the pe-

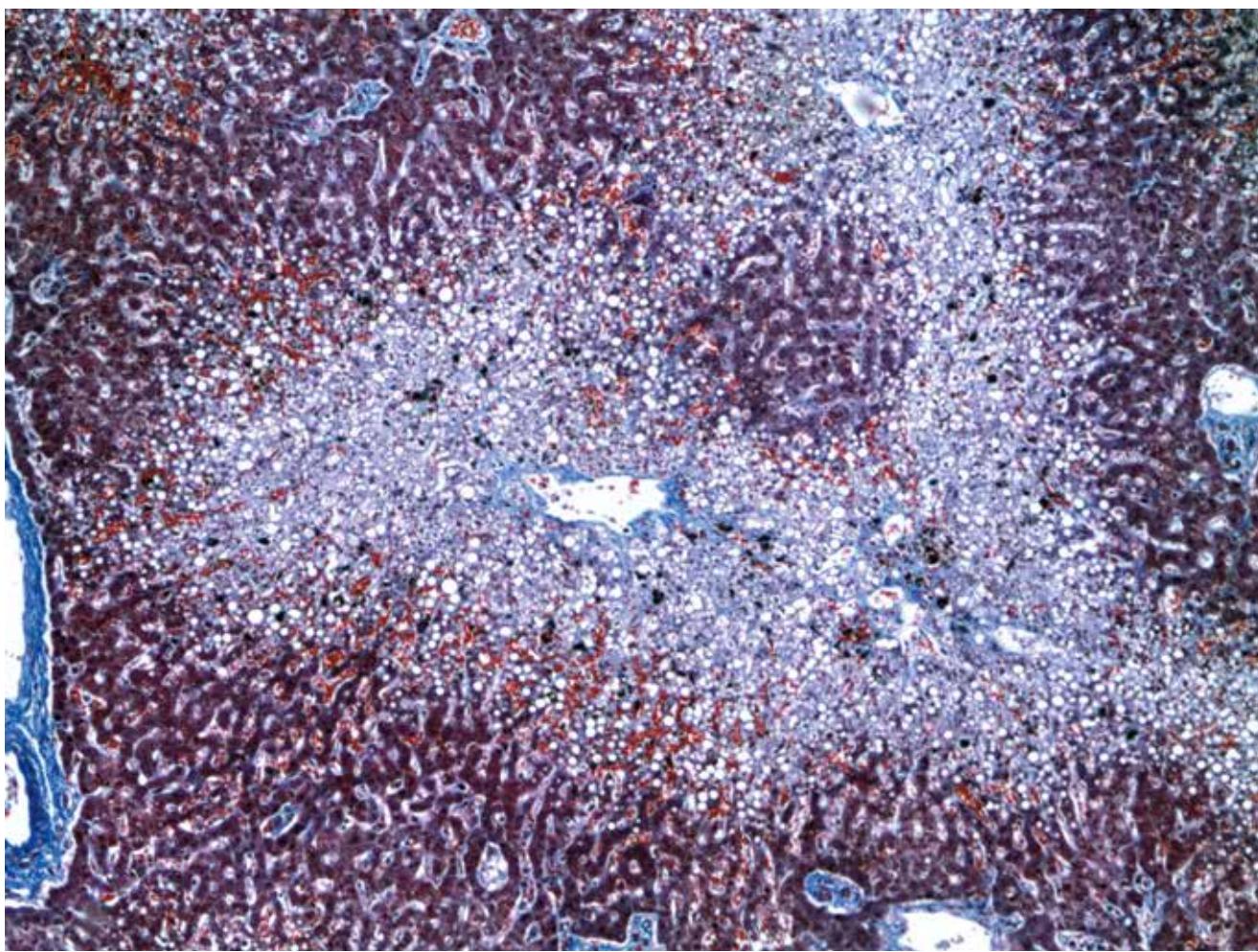


Image 8A: Steatosis in anorexia nervosa (Masson trichrome, x40).

diatric age group is associated with greater severity of steatosis, less lobular inflammation, and portal fibrosis and inflammation without perivenular fibrosis (65). Nonalcoholic fatty liver disease in children may progress to end stage liver disease (66).

Steatosis may be seen in metabolic disorders such as medium chain fatty acid disorders (67). Reyes syndrome and metabolic disorders should be excluded; however, steatosis has been reported to be common in sudden unexpected infant deaths and is not diagnostic of a metabolic disorder or Reyes syndrome (68, 69).

CONCLUSION

Fatty liver is common at autopsy in all age groups. In adults, it is most commonly seen in alcoholic and nonalcoholic fatty liver disease. The most common pattern is macrovesicular steatosis. As the disease progresses, fibrosis increases and cirrhosis may result. The pathologic features of these conditions typically overlap and histology alone is insufficient to distinguish them; history and other investigative findings may aid in diagnostic discernment. Fatty liver disease may be seen with some drugs and in some metabolic disorders. Microvesicular steatosis may be seen, including acute fatty liver of pregnancy and some drug toxicities.

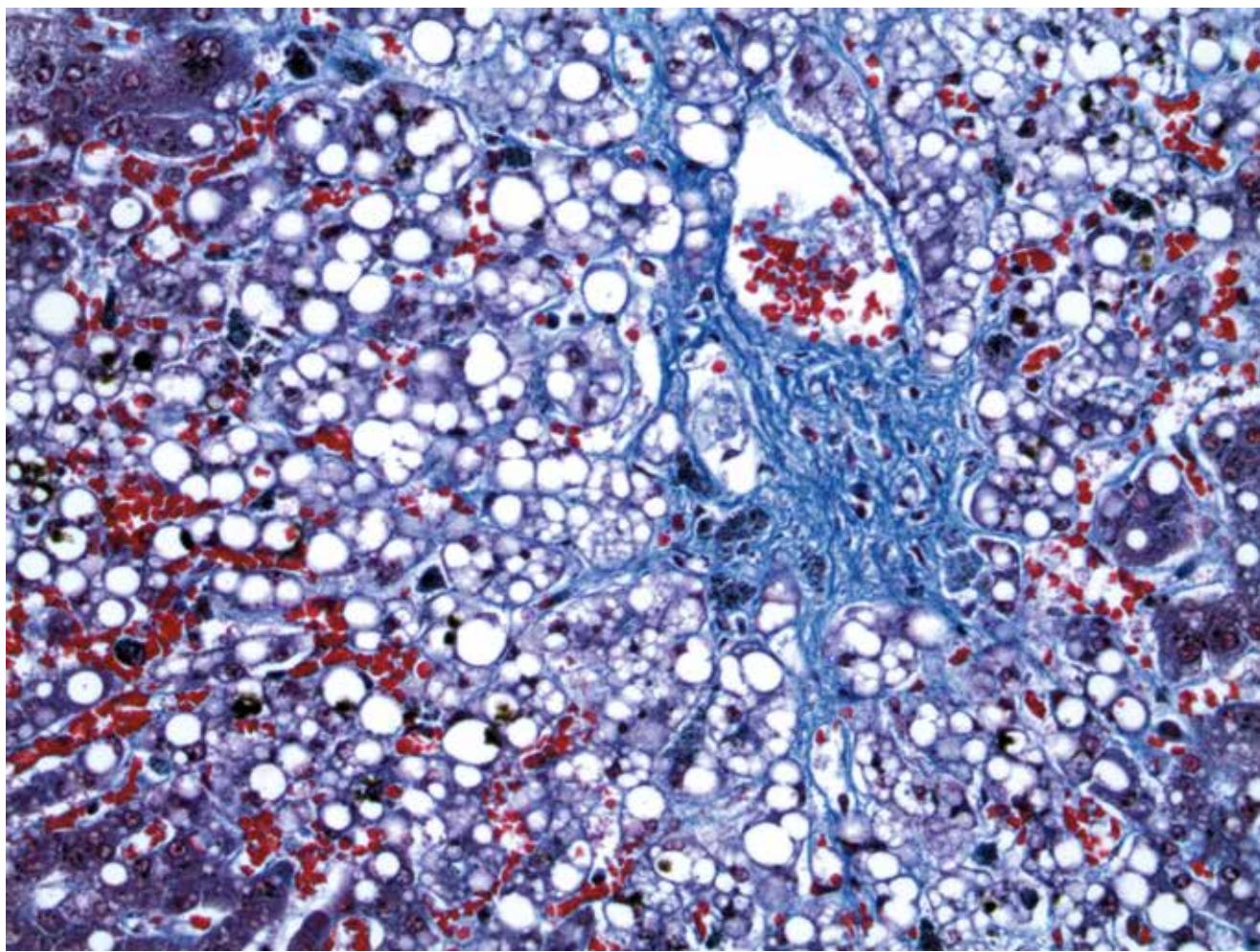


Image 8B: Steatosis in anorexia nervosa (Masson trichrome, x100).



Fatty liver is not an adequate stand alone cause of death. The presence of fatty liver at autopsy should not be considered as alcohol-related unless there is a clear history of alcohol use. Fatty liver is an indication of an underlying disorder, which may be the cause of death. The presence of fatty liver disease should prompt a search for an underlying cause of death such as alcoholic or diabetic ketoacidosis. While fatty liver as a cause of death has been challenged, there is now some evidence to support alcoholic and nonalcoholic fatty liver disease being related to cardiac arrhythmias and thus to sudden death.

REFERENCES

- 1) Tiniakos DG, Anstee QM, Burt AD. MacSween's pathology of the liver. 7th ed. Philadelphia: Elsevier; c2018. Chapter 5, Fatty liver disease; p. 308-71.
- 2) MacSween RN, Burt AD. Histologic spectrum of alcoholic liver disease. *Semin Liver Dis.* 1986 Aug; 6(3):221-32. PMID: 3022386. <https://doi.org/10.1055/s-2008-1040605>.
- 3) Syn WK, Teaberry V, Choi SS, Diehl AM. Similarities and differences in the pathogenesis of alcoholic and nonalcoholic steatohepatitis. *Semin Liver Dis.* 2009 May; 29(2):200-10. PMID: 19387919. PMCID: PMC3644873. <https://doi.org/10.1055/s-0029-1214375>.
- 4) Tannapfel A, Denk H, Dienes HP, et al. Histopathological diagnosis of non-alcoholic and alcoholic fatty liver disease. *Virchows Arch.* 2011 May; 458(5):511-23. PMID: 21442288. <https://doi.org/10.1007/s00428-011-1066-1>.
- 5) Yip WW, Burt AD. Alcoholic liver disease. *Semin Diagn Pathol.* 2006 Aug-Nov; 23(3-4):149-60. PMID: 17355088. <https://doi.org/10.1053/j.semdp.2006.11.002>.
- 6) Edmondson HA, Peters RL, Frankel HH, Borowsky S. The early stage of liver injury in the alcoholic. *Medicine (Baltimore).* 1967 Mar; 46(2):119-29. PMID: 6027458. <https://doi.org/10.1097/00005792-196703000-00006>.
- 7) Uchida T, Kao H, Quispe-Sjogren M, Peters RL. Alcoholic foamy degeneration--a pattern of acute alcoholic injury of the liver. *Gastroenterology.* 1983 Apr; 84(4):683-92. PMID: 6825980.
- 8) Bhathal PS, Wilkinson P, Clifton S, et al. The spectrum of liver diseases in alcoholism. *Aust N Z J Med.* 1975 Feb; 5(1):49-57. PMID: 1057913. <https://doi.org/10.1111/j.1445-5994.1975.tb03255.x>.
- 9) Edmondson HA, Peters RL, Reynolds TB, Kuzma OT. Sclerosing hyaline necrosis of the liver in the chronic alcoholic. A recognizable clinical syndrome. *Ann Intern Med.* 1963 Nov; 59:646-73. PMID: 14082718. <https://doi.org/10.7326/0003-4819-59-5-646>.
- 10) Goodman ZD, Ishak KG. Occlusive venous lesions in alcoholic liver disease. A study of 200 cases. *Gastroenterology.* 1982 Oct; 83(4):786-96. PMID: 7106509.
- 11) Burt AD, MacSween RN. Hepatic vein lesions in alcoholic liver disease: retrospective biopsy and necropsy study. *J Clin Pathol.* 1986 Jan; 39(1):63-7. PMID: 3950032. PMCID: PMC499614. <https://doi.org/10.1136/jcp.39.1.63>.
- 12) Nakano M, Worner TM, Lieber CS. Perivenular fibrosis in alcoholic liver injury: ultrastructure and histologic progression. *Gastroenterology.* 1982 Oct; 83(4):777-85. PMID: 7106508.
- 13) Worner TM, Lieber CS. Perivenular fibrosis as precursor lesion of cirrhosis. *JAMA.* 1985 Aug 2; 254(5):627-30. PMID: 4009897. <https://doi.org/10.1001/jama.254.5.627>.
- 14) Fauerholdt L, Schlichting P, Christensen E, et al. Conversion of micronodular cirrhosis into macronodular cirrhosis. *Hepatology.* 1983 Nov-Dec; 3(6):928-31. PMID: 6629323. <https://doi.org/10.1002/hep.1840030607>.
- 15) Argo CK, Henry ZH, Caldwell SH. Schiff's diseases of the liver. 12th ed. Hoboken (NJ): John Wiley and Sons; c2018. Chapter 32, Nonalcoholic fatty liver disease; p. 867-910.
- 16) Brunt EM. Pathology of nonalcoholic fatty liver disease. *Nat Rev Gastroenterol Hepatol.* 2010 Apr; 7(4):195-203. PMID: 20195271. <https://doi.org/10.1038/nrgastro.2010.21>.
- 17) Thuluvath PJ, Kantsevoy S, Thuluvath AJ, Savva Y. Is cryptogenic cirrhosis different from NASH cirrhosis? *J Hepatol.* 2018 Mar; 68(3):519-525. PMID: 29162389. <https://doi.org/10.1016/j.jhep.2017.11.018>.
- 18) Becker U, Deis A, Sørensen TI, et al. Prediction of risk of liver disease by alcohol intake, sex, and age: a prospective population study. *Hepatology.* 1996 May; 23(5):1025-9. PMID: 8621128. <https://doi.org/10.1053/jhep.1996.v23.pm0008621128>.
- 19) Hayashi PH, Harrison SA, Torgerson S, et al. Cognitive lifetime drinking history in nonalcoholic fatty liver disease: some cases may be alcohol related. *Am J Gastroenterol.* 2004 Jan; 99(1):76-81. PMID: 14687145. <https://doi.org/10.1046/j.1572-0241.2003.04013.x>.
- 20) Pinto HC, Baptista A, Camilo ME, et al. Nonalcoholic steatohepatitis. Clinicopathological comparison with alcoholic hepatitis in ambulatory and hospitalized patients. *Dig Dis Sci.* 1996 Jan; 41(1):172-9. PMID: 8565753. <https://doi.org/10.1007/bf02208601>.
- 21) Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology.* 2016 Jul; 64(1):73-84. PMID: 27607365. <https://doi.org/10.1002/hep.28431>.
- 22) Angulo P, Keach JC, Batts KP, Lindor KD. Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis. *Hepatology.* 1999 Dec; 30(6):1356-62. PMID: 10573511. <https://doi.org/10.1002/hep.510300604>.
- 23) Machado M, Marques-Vidal P, Cortez-Pinto H. Hepatic histology in obese patients undergoing bariatric surgery. *J Hepatol.* 2006 Oct; 45(4):600-6. PMID: 16899321. <https://doi.org/10.1016/j.jhep.2006.06.013>.
- 24) Kleiner DE, Brunt EM, Van Natta M, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology.* 2005 Jun; 41(6):1313-21. PMID: 15915461. <https://doi.org/10.1002/hep.20701>.
- 25) Bellentani S, Saccoccia G, Masutti F, et al. Prevalence of and risk factors for hepatic steatosis in Northern Italy. *Ann Intern Med.* 2000 Jan 18; 132(2):112-7. PMID: 10644271. <https://doi.org/10.7326/0003-4819-132-2-200001180-00004>.
- 26) Park SH, Kim BI, Yun JW, et al. Insulin resistance and C-reactive protein as independent risk factors for non-alcoholic fatty liver disease in non-obese Asian men. *J Gastroenterol Hepatol.* 2004 Jun; 19(6):694-8. PMID: 15151626. <https://doi.org/10.1111/j.1440-1746.2004.03362.x>.
- 27) Omagari K, Kadokawa Y, Masuda J, et al. Fatty Liver in non-alcoholic non-overweight Japanese adults: incidence and clinical characteristics. *J Gastroenterol Hepatol.* 2002 Oct; 17(10):1098-105. PMID: 12201871. <https://doi.org/10.1046/j.1440-1746.2002.02846.x>.

- 28) Silverman JF, O'Brien KF, Long S, et al. Liver pathology in morbidly obese patients with and without diabetes. *Am J Gastroenterol.* 1990 Oct; 85(10):1349-55. PMID: 2220728.
- 29) Younossi ZM, Oktay M, Henry L, et al. Association of nonalcoholic fatty liver disease (NAFLD) with hepatocellular carcinoma (HCC) in the United States from 2004 to 2009. *Hepatology.* 2015 Dec; 62(6):1723-30. PMID: 26274335. <https://doi.org/10.1002/hep.28123>.
- 30) Ertle J, Dechêne A, Sowa JP, et al. Non-alcoholic fatty liver disease progresses to hepatocellular carcinoma in the absence of apparent cirrhosis. *Int J Cancer.* 2011 May 15; 128(10):2436-43. PMID: 2112845. <https://doi.org/10.1002/ijc.25797>.
- 31) Baffy G, Brunt EM, Caldwell SH. Hepatocellular carcinoma in non-alcoholic fatty liver disease: an emerging menace. *J Hepatol.* 2012 Jun; 56(6):1384-91. PMID: 22326465. <https://doi.org/10.1016/j.jhep.2011.10.027>.
- 32) Solis-Herruzo JA, Pérez-Carreras M, Rivas E, et al. Factors associated with the presence of nonalcoholic steatohepatitis in patients with chronic hepatitis C. *Am J Gastroenterol.* 2005 May; 100(5):1091-8. PMID: 15842583. <https://doi.org/10.1111/j.1572-0241.2005.41059.x>.
- 33) Sorrentino P, Terracciano L, D'Angelo S, et al. Oxidative stress and steatosis are cofactors of liver injury in primary biliary cirrhosis. *J Gastroenterol.* 2010 Oct; 45(10):1053-62. PMID: 20393861. <https://doi.org/10.1007/s00535-010-0249-x>.
- 34) Weston SR, Leyden W, Murphy R, et al. Racial and ethnic distribution of nonalcoholic fatty liver in persons with newly diagnosed chronic liver disease. *Hepatology.* 2005 Feb; 41(2):372-9. PMID: 15723436. <https://doi.org/10.1002/hep.20554>.
- 35) Browning JD, Szczepaniak LS, Dobbins R, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology.* 2004 Dec; 40(6):1387-95. PMID: 15565570. <https://doi.org/10.1002/hep.20466>.
- 36) Schwimmer JB, McGreal N, Deutsch R, et al. Influence of gender, race, and ethnicity on suspected fatty liver in obese adolescents. *Pediatrics.* 2005 May; 115(5):e561-5. PMID: 15867021. <https://doi.org/10.1542/peds.2004-1832>.
- 37) Lear SA, Humphries KH, Kohli S, Birmingham CL. The use of BMI and waist circumference as surrogates of body fat differs by ethnicity. *Obesity (Silver Spring).* 2007 Nov; 15(11):2817-24. PMID: 18070773. <https://doi.org/10.1038/oby.2007.334>.
- 38) Wang J, Thornton JC, Russell M, et al. Asians have lower body mass index (BMI) but higher percent body fat than do whites: comparisons of anthropometric measurements. *Am J Clin Nutr.* 1994 Jul; 60(1):23-8. PMID: 8017333. <https://doi.org/10.1093/ajcn/60.1.23>.
- 39) Heo M, Faith MS, Pietrobelli A, Heymsfield SB. Percentage of body fat cutoffs by sex, age, and race-ethnicity in the US adult population from NHANES 1999–2004. *Am J Clin Nutr.* 2012 Mar; 95(3):594-602. PMID: 22301924. <https://doi.org/10.3945/ajcn.111.025171>.
- 40) Anstee QM, Day CP. The genetics of NAFLD. *Nat Rev Gastroenterol Hepatol.* 2013 Nov; 10(11):645-55. PMID: 24061205. <https://doi.org/10.1038/nrgastro.2013.182>.
- 41) Rinella ME, Sanyal AJ. NAFLD in 2014: genetics, diagnostics and therapeutic advances in NAFLD. *Nat Rev Gastroenterol Hepatol.* 2015 Feb; 12(2):65-6. PMID: 25560844. PMCID: PMC4984668. <https://doi.org/10.1038/nrgastro.2014.232>.
- 42) Anstee QM, Day CP. The genetics of nonalcoholic fatty liver disease: spotlight on PNPLA3 and TM6SF2. *Semin Liver Dis.* 2015 Aug; 35(3):270-90. PMID: 26378644. <https://doi.org/10.1055/s-0035-1562947>.
- 43) Dongiovanni P, Valenti L. Genetics of nonalcoholic fatty liver disease. *Metabolism.* 2016 Aug; 65(8):1026-37. PMID: 26409295. <https://doi.org/10.1016/j.metabol.2015.08.018>.
- 44) Reid AE. Nonalcoholic steatohepatitis. *Gastroenterology.* 2001 Sep; 121(3):710-23. PMID: 11522755. <https://doi.org/10.1053/gast.2001.27126>.
- 45) Adams LA, Lymp JF, Sauver JS, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology.* 2005 Jul; 129(1):113-21. PMID: 16012941. <https://doi.org/10.1053/j.gastro.2005.04.014>.
- 46) Ekstedt M, Franzén LE, Mathiesen UL, et al. Long-term follow-up of patients with NAFLD and elevated liver enzymes. *Hepatology.* 2006 Oct; 44(4):865-73. PMID: 17006923. <https://doi.org/10.1002/hep.21327>.
- 47) Ong JP, Pitts A, Younossi ZM. Increased overall mortality and liver-related mortality in non-alcoholic fatty liver disease. *J Hepatol.* 2008 Oct; 49(4):608-12. PMID: 18682312. <https://doi.org/10.1016/j.jhep.2008.06.018>.
- 48) Younossi ZM, Stepanova M, Rafiq N, et al. Pathologic criteria for nonalcoholic steatohepatitis: interprotocol agreement and ability to predict liver-related mortality. *Hepatology.* 2011 Jun; 53(6):1874-82. PMID: 21360720. <https://doi.org/10.1002/hep.24268>.
- 49) Stepanova M, Rafiq N, Makhlof H, et al. Predictors of all-cause mortality and liver-related mortality in patients with non-alcoholic fatty liver disease (NAFLD). *Dig Dis Sci.* 2013 Oct; 58(10):3017-23. PMID: 23775317. <https://doi.org/10.1007/s10620-013-2743-5>.
- 50) Ekstedt M, Hagström H, Nasr P, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. *Hepatology.* 2015 May; 61(5):1547-54. PMID: 25125077. <https://doi.org/10.1002/hep.27368>.
- 51) Wanless IR, Lentz JS. Fatty liver hepatitis (steatohepatitis) and obesity: an autopsy study with analysis of risk factors. *Hepatology.* 1990 Nov; 12(5):1106-10. PMID: 2227807. <https://doi.org/10.1002/hep.1840120505>.
- 52) Zois CD, Baltayiannis GH, Bekiari A, et al. Steatosis and steatohepatitis in postmortem material from Northwestern Greece. *World J Gastroenterol.* 2010 Aug 21; 16(31):3944-9. PMID: 20712056. PMCID: PMC2923769. <https://doi.org/10.3748/wjg.v16.i31.3944>.
- 53) Lal A, Parai JL, Milroy CM. Liver pathology in first presentation diabetic ketoacidosis at autopsy. *Acad Forensic Pathol.* 2016 Jun; 6(2):271-80. <https://doi.org/10.23907/2016.028>.
- 54) Randall B. Fatty liver and sudden death. A review. *Hum Pathol.* 1980 Mar; 11(2):147-53. PMID: 6105125. [https://doi.org/10.1016/s0046-8177\(80\)80133-x](https://doi.org/10.1016/s0046-8177(80)80133-x).
- 55) Kramer K, Kuller L, Fisher R. The increasing mortality attributed to cirrhosis and fatty liver, in Baltimore (1957-1966). *Ann Intern Med.* 1968 Aug; 69(2):273-82. PMID: 5667768. <https://doi.org/10.7326/0003-4819-69-2-273>.
- 56) Clark JC. Sudden death in the chronic alcoholic. *Forensic Sci Int.* 1988 Jan; 36(1-2):105-11. PMID: 3338681. [https://doi.org/10.1016/0379-0738\(88\)90222-8](https://doi.org/10.1016/0379-0738(88)90222-8).
- 57) Milroy C. Sudden death and chronic alcoholism. *Acad Forensic Pathol.* 2014 Jun, 4(2):168-71. <https://doi.org/10.23907/2014.027>.
- 58) Targher G, Valbusa F, Bonapace S, et al. Association of nonalcoholic fatty liver disease with QTc interval in patients with type 2 diabetes. *Nutr Metab Cardiovasc Dis.* 2014 Jun; 24(6):663-9. PMID: 24594085. <https://doi.org/10.1016/j.numecd.2014.01.005>.
- 59) Ballestri S, Lonardo A, Bonapace S, et al. Risk of cardiovascular, cardiac and arrhythmic complications in patients with non-alcoholic fatty liver disease. *World J Gastroenterol.* 2014 Feb 21; 20(7):1724-45. PMID: 24587651. PMCID: PMC3930972. <https://doi.org/10.3748/wjg.v20.i7.1724>.



- 60) Mantovani A, Rigamonti A, Bonapace S, et al. Nonalcoholic fatty liver disease is associated with ventricular arrhythmias in patients with type 2 diabetes referred for clinically indicated 24-hour Holter monitoring. *Diabetes Care*. 2016 Aug; 39(8):1416-23. PMID: 27222503. <https://doi.org/10.2337/dc16-0091>.
- 61) Mantovani A, Ballestri S, Lonardo A, Targher G. Cardiovascular disease and myocardial abnormalities in nonalcoholic fatty liver disease. *Dig Dis Sci*. 2016 May; 61(5):1246-67. PMID: 26809873. <https://doi.org/10.1007/s10620-016-4040-6>.
- 62) Byrne CD, and Targher G. NAFLD: a multisystem disease. *J Hepatol*. 2015 Apr; 62(1 Suppl):S47-64. PMID: 25920090. <https://doi.org/10.1016/j.jhep.2014.12.012>.
- 63) Schwimmer JB, Deutsch R, Kahan T, et al. Prevalence of fatty liver in children and adolescents. *Pediatrics*. 2006 Oct; 118(4):1388-93. PMID: 17015527. <https://doi.org/10.1542/peds.2006-1212>.
- 64) Tominaga K, Kurata JH, Chen YK, et al. Prevalence of fatty liver in Japanese children and relationship to obesity. An epidemiological ultrasonographic survey. *Dig Dis Sci*. 1995 Sep; 40(9):2002-9. PMID: 7555456. <https://doi.org/10.1007/bf02208670>.
- 65) Schwimmer JB, Behling C, Newbury R, et al. Histopathology of pediatric nonalcoholic fatty liver disease. *Hepatology*. 2005 Sep; 42(3):641-9. PMID: 16116629. <https://doi.org/10.1002/hep.20842>.
- 66) Feldstein AE, Charatcharoenwitthaya P, Treeprasertsuk S, et al. The natural history of nonalcoholic fatty liver disease in children, a follow-up study for up to 20 years. *Gut*. 2009 Nov; 58(11):1538-44. PMID: 19625277. PMCID: PMC2792743. <https://doi.org/10.1136/gut.2008.171280>.
- 67) Howat AJ, Bennett MJ, Variend S, Shaw L. Deficiency of medium chain fatty acylcoenzyme A dehydrogenase presenting as the sudden infant death syndrome. *Br Med J (Clin Res Ed)*. 1984 Mar 31; 288(6422):976. PMID: 6423169. PMCID: PMC1442514. <https://doi.org/10.1136/bmj.288.6422.976>.
- 68) Bonnell HJ, Beckwith JB. Fatty liver in sudden childhood death. Implications for Reye's Syndrome? *Am J Dis Child*. 1986 Jan; 140(1):30-3. PMID: 3942104. <https://doi.org/10.1001/archpedi.1986.02140150032027>.
- 69) Berry PJ. Pathological findings in SIDS. *J Clin Pathol*. 1992 Nov; 45(11 Suppl):11-6. PMID: 1474151.



Postmortem Serum Amylase and Lipase Analysis in the Diagnosis of Acute Pancreatitis

Theodore T. Brown, Joseph A. Prahlow

ABSTRACT

The diagnosis of acute pancreatitis, which can occur due to natural and nonnatural causes, is usually made at autopsy based on gross and microscopic examination. However, some pathologists choose to measure serum amylase and lipase levels in postmortem blood samples, which may provide corroborating evidence of acute pancreatitis when evaluated in the context of the autopsy findings. A small series of autopsy cases of deaths related to acute pancreatitis with corresponding postmortem serum amylase and lipase levels and a review of the literature are used to highlight the potential benefits and interpretation issues of postmortem serum amylase and lipase. In autopsies without decomposition, elevated postmortem serum amylase (greater than 1000 U/L) and lipase can provide supportive evidence of acute pancreatitis as a cause of death. However, relying on postmortem serum amylase and lipase alone to diagnose acute pancreatitis is insufficient and unreliable. Rather, one must have the gross and histologic evidence of acute pancreatitis. *Acad Forensic Pathol.* 2018 8(2): 311-323

AUTHORS

Theodore T. Brown MD, Western Michigan University Homer Stryker MD School of Medicine - Pathology

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, principal investigator of the current study.

Joseph A. Prahlow MD, Western Michigan University Homer Stryker MD School of Medicine - Pathology

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, principal investigator of the current study.

CORRESPONDENCE

Theodore T. Brown MD, 300 Portage Street Kalamazoo Michigan 49008-1202, theodore.brown@med.wmich.edu

ETHICAL APPROVAL

As per Journal Policies, ethical approval was not required for this manuscript

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies conducted with animals or on living human subjects

STATEMENT OF INFORMED CONSENT

No identifiable personal data were presented in this manuscript

DISCLOSURES & DECLARATION OF CONFLICTS OF INTEREST

The authors, reviewers, editors, and publication staff do not report any relevant conflicts of interest

FINANCIAL DISCLOSURE

The authors have indicated that they do not have financial relationships to disclose that are relevant to this manuscript

KEYWORDS

Forensic pathology, Acute pancreatitis, Postmortem serum amylase and lipase, Autopsy, Gross and histologic examination

INFORMATION

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

©2018 Academic Forensic Pathology International • (ISSN: 1925-3621) • <https://doi.org/10.23907/2018.020>

Submitted for consideration on 7 Mar 2018. Accepted for publication on 13 Apr 2018

INTRODUCTION

Pancreatitis leading to death may be on the differential diagnosis for pathologists when performing an autopsy on a decedent with a clinical history that includes chronic alcoholism or known gallstones; however, pancreatitis can be caused by other natural conditions, including hyperlipidemia, as well as nonnatural conditions, including blunt abdominal injury, drugs, and hypothermia (1). The postmortem diagnosis of acute pancreatitis is often relatively straight forward. Various gross findings can suggest a possible diagnosis of acute pancreatitis, including pancreatic hemorrhage and evidence of fat necrosis. It should be highlighted, however, that nonspecific postmortem pancreatic hemorrhage (**Image 1**), probably related to autolysis, can be seen at autopsy; therefore, gross pancreatic hemorrhage is not sufficient to diagnose pancreatitis. Histologic examination of the pancreas, with identification of acute inflammatory cells, is essential for the diagnosis of acute pancreatitis. Depending on the circumstances of the case, acute pancreatitis may be considered a cause or contributing cause of death.

While the diagnosis of acute pancreatitis is largely dependent on gross and microscopic evaluation, some pathologists choose to measure serum amylase and lipase levels in postmortem blood samples. Although results must be evaluated in the context of the gross and histologic findings, elevated levels of serum amylase and lipase can provide adjunct laboratory confirmation of acute pancreatitis. Herein, the authors present a small series of autopsy cases of deaths related to acute pancreatitis wherein postmortem serum amylase and lipase levels are reported.

METHODS

In order to highlight the utility and limitations of measuring postmortem serum amylase and lipase, the authors have selected a series of five cases from their files where the cause of death of acute pancreatitis was complemented by postmortem serum amylase and lipase results. Refer to **Table 1** for a summary of the five cases.



Image 1: Nonspecific, postmortem pancreatic “hemorrhage,” related to autolysis, in a 44-year-old male who died from a drug overdose. There was no inflammation microscopically.

Table 1: Case Synopsis

Case Number	Decedent Information	Initial Presentation	Medical History	Pancreas Exam	Antemortem Testing	Postmortem Serum Testing	Cause of Death	Time Between LKA/Pronounced Dead to Autopsy
1	47 yowm	Found dead; two-day history of vomiting	Diabetes mellitus; obesity	Focal hemorrhage; + fat necrosis; acute inflammation	N/A	Amylase: 1817 U/L Lipase: 5080 U/L	I – Acute hemorrhagic pancreatitis II – DM; cardiomegaly; obesity	34 to > 40 hours
2	24 yowm	Found unresponsive; recent abdominal pain; drinking large amount of water	Obesity	Multifocal hemorrhage; + fat necrosis; acute inflammation	ED blood glucose: >1200 mg/dL TG: 1715 mg/dL	Amylase: 1920 U/L Lipase: 6606 U/L	I – Acute hemorrhagic pancreatitis with acute DM, due to hyper-triglyceridemia II – Morbid obesity	20 hours
3	46 yowm	Found unresponsive after complaining of abdominal pain; recent alcohol binge	Hypertension	Multifocal areas of fat necrosis, with fibrosis & scattered hemorrhage; acute and chronic inflammation	N/A	Amylase: 364 U/L Lipase: 1159 U/L	I – Acute & chronic pancreatitis II – Hypertensive & atherosclerotic cardiovascular disease	18 to 20 hours
4	57 yowm	Presented to ED after not feeling well for one week; increased thirst	None	Swollen and hemorrhagic; venous thrombosis; necrosis; acute inflammation	ED blood glucose: 1357 mg/dL Amylase: 119 U/L Lipase: 6485 U/L	Amylase: 268 U/L Lipase: >15 000 U/L	Acute hemorrhagic pancreatitis, with acute diabetic ketoacidosis, related to hyper-triglyceridemia	18 hours
5	30 yowm	Found dead on couch; recent complaints of feeling ill	Chronic alcoholism	Swollen and hemorrhagic; + fat necrosis; acute inflammation	N/A	Amylase: 2100 U/L Lipase: 9580 U/L	I – Acute hemorrhagic pancreatitis II – Chronic alcoholism	37 to 68 hours

LKA – Last known alive

yowm – Year old white male

N/A – Not applicable

DM – Diabetes mellitus

ED – Emergency department

TG – Triglycerides

Case 1

A 47-year-old, obese, diabetic male was found dead at home after a two-day history of vomiting. At autopsy, he was 71 inches tall and weighed 350 pounds (body mass index [BMI] of 48.8 kg/m^2). On gross internal exam, his heart weighed 480 g and contained multi-focal areas of mild to severe coronary artery atherosclerosis. His pancreas demonstrated marked central hemorrhage (**Image 2**), and there were multiple foci of yellow-tan chalky discolorations within the pancreas (**Image 3**) and the surrounding adipose tissue. Microscopic diagnoses consisted of cardiac myocyte hypertrophy and associated interstitial fibrosis, mild hepatic steatosis, mild emphysema, nodular glomerulosclerosis, and acute hemorrhagic pancreatitis with associated fat necrosis. Postmortem urine and blood drug screens were negative. Vitreous electrolytes were unremarkable except for a glucose of 396 mg/dL (acetone negative). Postmortem blood chemistry test results were as follows: serum amylase 1817 U/L (normal 25-105), serum lipase 5080 U/L (normal 16-63), cholesterol 149 mg/dL (normal 120-196), HDL 25 mg/dL (normal 40-85), LDL 72 mg/dL (normal 0-129), chol/HDL ratio 6.0 (normal 1-4), and triglycerides 258 mg/dL (normal 0-150). The cause of death was certified as acute hemorrhagic pancreatitis, with contributing factors of diabetes mellitus, cardiomegaly, and obesity. The manner of death was natural.



Image 2: Gross longitudinal section of the pancreas from Case 1. Note the patchy, but prominent areas of hemorrhage. Microscopically, there was acute inflammation and hemorrhage.

Case 2

An obese, 24-year-old male was found unresponsive and was emergently transported to a local hospital's emergency department, where a blood glucose level measured greater than 1200 mg/dL and his blood pH was 6.8. Despite all resuscitative efforts, the patient died. He had recently complained of abdominal pain and had been drinking a large amount of water.

At autopsy, the man weighed 400 pounds and was 75 inches tall (BMI of 50 kg/m^2). Significant gross findings included a 560 g heart with mild biventricular dilatation but no associated atherosclerosis, yellow discoloration of the liver, and areas of diffuse hemorrhage within the pancreas (**Image 4**) with associated white-yellow chalky foci, which extended to include the surrounding adipose tissue. Microscopic findings included cardiac myocyte hypertrophy with associated interstitial fibrosis, chronic bronchial inflammation, hepatic steatosis, and acute hemorrhagic pancreatitis with extensive fat necrosis (**Image 5**). A urine drug screen was negative. A serum drug screen was positive for acetone (60 mg/dL). Postmortem urinalysis was positive for protein (30 mg/dL), glucose (>1000 mg/dL), and ketones (15 ng/dL). Vitreous electrolytes revealed normal sodium, potassium, and chloride, and the following abnormal concentrations: urea 46 mg/dL; creatinine 1.48 mg/dL, and glucose



Image 3: Close-up of a different gross section of the pancreas from Case 1. Note the areas of distinct hemorrhage, as well as the foci of fat necrosis (arrows).

700 ng/dL. Postmortem blood chemistry tests included a serum amylase of 1920 U/L and a serum lipase of 6606 U/L. A lipid profile was performed on antemortem hospital blood samples, with the following results: cholesterol 258 mg/dL (normal 135-200), HDL cholesterol 66 mg/dL (normal 40-60), chol/HDL ratio 3.9 (normal 0-6), triglycerides 1715 mg/dL (normal 10-149), and LDL cholesterol unable to calculate due to elevated triglycerides. The cause of death was certified as acute hemorrhagic pancreatitis with acute diabetes mellitus, due to hypertriglyceridemia, with a contributing factor of morbid obesity. The manner of death was natural.

Case 3

A 46-year-old hypertensive male complained of abdominal pain. His wife went to the store to purchase a laxative, but upon her return, he was unresponsive. All resuscitative efforts failed. He had recently lost his job and had been consuming large amounts of ethanol. In addition, he was taking morphine for his pain.

At autopsy, the 69 inch, 175 pound man (BMI of 25.8 kg/m²) had the following significant gross findings: a 450 g heart, mild to moderate coronary artery atherosclerosis, yellow discoloration of the liver, and a pancreas with numerous areas of white-grey, lacelike fibrotic bands, with scattered surrounding hemorrhage (**Image 6**). Microscopic examination showed cardiac myocyte hypertrophy with interstitial fibrosis, hepatic steatosis, and patchy acute and chronic pancreatic inflammation with associated fibrosis, hemorrhage, and fat necrosis. Postmortem vitreous electrolytes were normal. A postmortem drug screen was positive for morphine (concentration of 183 ng/mL), but was negative for ethanol. Postmortem blood was also tested for amylase and lipase, with levels of 364 U/L and 1159 U/L, respectively. The cause of death was certified as acute and chronic pancreatitis, with contributing causes of hypertensive and atherosclerotic cardiovascular disease. The manner of death was natural.



Image 4: Gross longitudinal section of the pancreas from Case 2. The hemorrhage is more diffuse in this example.

Case 4

A 57-year-old male had not been feeling well for over a week, with noticeably increased thirst. He presented to a local hospital emergency department, where a blood glucose concentration was 1357 mg/dL. He was admitted with a diagnosis of diabetic ketoacidosis and was placed on insulin therapy. His condition rapidly deteriorated and he experienced cardiorespiratory arrest as he was being prepared for transport to a tertiary care facility. All resuscitative efforts failed and he died approximately 20 hours after initial presentation.

At autopsy, the 76 inch tall man weighed 237 pounds (BMI of 28.8 kg/m²). Significant gross findings included cardiomegaly (540 g), mild to moderate atherosclerosis, and a markedly swollen and hemorrhagic pancreas, with numerous pancreatic and peri-pancreatic veins, including the splenic vein, containing occlusive thrombi. Microscopic examination revealed myocyte hypertrophy with associated interstitial fibrosis, coronary artery atherosclerosis, mild emphysema, moderate steatosis, and acute hemorrhagic pancreatitis with extensive necrosis and venous thrombosis (**Image 7**). Toxicology testing of the original hospital admission

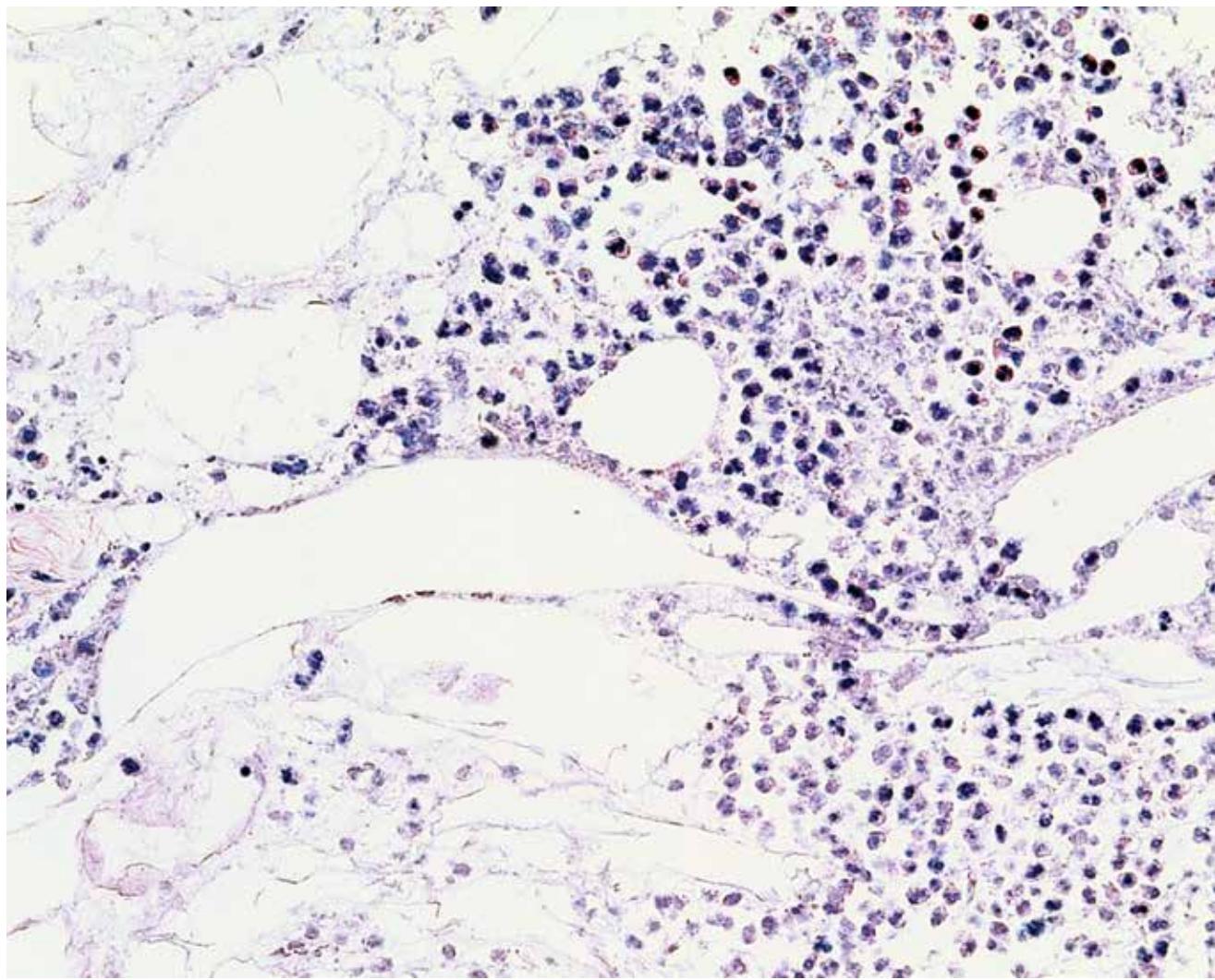


Image 5: Representative microscopic appearance of the pancreas from Case 2. Note the presence of acute inflammation as well as fat necrosis (H&E, x200).

blood was positive for acetone. Antemortem blood sample testing showed the following results: serum lipase 6485 U/L, serum amylase 119 U/L, cholesterol 247 mg/dL, HDL 17 mg/dL, LDL direct 75 mg/dL, non-HDL cholesterol 230 mg/dL, chol/HDL ratio 14.5, triglycerides 964 mg/dL. Postmortem blood sample testing showed the following results: serum lipase >15 000 U/L, serum amylase 268 U/L, cholesterol 248 mg/dL, HDL 12 mg/dL, LDL direct 68 mg/dL, non-HDL cholesterol 236 mg/dL, chol/HDL ratio 20.7, triglycerides 892 mg/dL. The cause of death was certified as acute hemorrhagic pancreatitis with acute diabetic ketoacidosis related to hypertriglyceridemia. The manner of death was natural.

Case 5

A 30-year-old chronic alcoholic male was found dead on his couch. He had recently complained of feeling ill. At autopsy, the 71 inch, 218 pound man (BMI of 30.4 kg/m²) had a 510 g, mildly-dilated heart, a grossly yellow liver, and a diffusely swollen and hemorrhagic pancreas with areas of white-tan discoloration within the surrounding retroperitoneal adipose tissue

(Image 8). Microscopic exam showed cardiac myocyte hypertrophy with interstitial fibrosis, hepatic steatosis with alcoholic hepatitis, and acute pancreatic inflammation with hemorrhage and fat necrosis **(Images 9 and 10).** Toxicology testing of postmortem blood samples showed therapeutic levels of diphenhydramine. Postmortem serum testing had the following results: amylase 2100 U/L (normal 0-88); lipase 9580 U/L (normal 16-63). Vitreous electrolytes were as follows: sodium 133 mEq/L, potassium 26.7 mEq/L, chloride 90 mEq/L, urea 18 mg/dL, creatinine 1.5 mg/dL, and glucose 125 mg/dL. The cause of death was certified as acute hemorrhagic pancreatitis with a contributing factor of chronic alcoholism. The manner of death was natural.

DISCUSSION

Causes of acute pancreatitis include obstructive etiologies, such as a biliary stone; toxins, such as alcohol; drugs; postsurgical complication; genetic predisposition; infections; metabolic abnormalities; autoimmune diseases; pregnancy; and idiopathic reasons (2). In the clinical setting, an elevated serum amylase and/



Image 6: Gross longitudinal section of the pancreas from Case 3. In this case, which demonstrated acute and chronic inflammation and fibrosis microscopically, note the widespread, lacelike fibrotic bands, with only focal, patchy areas of grossly-evident hemorrhage.

or lipase, in combination with the appropriate clinical presentation and radiographic findings, is strongly suggestive of pancreatitis. While amylase and lipase are typically elevated in this setting, certain etiologies may have serum amylase levels within normal limits due to an interference of the assay, for example by plasma lipids in hypertriglyceridemia (3-5). Furthermore, an increase in amylase and lipase is not necessarily specific to direct pancreatic pathology. Amylase is secreted by not only the pancreas, but also the salivary glands, small intestine, ovaries, adipose tissue, and skeletal muscle. Also, while an elevation in lipase can indicate acute pancreatitis, it may also represent chronic pancreatitis, acute cholecystitis, or

bowel obstruction (6-7). Other diagnoses in which an increase in amylase and lipase has been noted include head injury, abdominal aortic aneurysm, acute liver failure, macroamylasaemia, chronic renal failure, ruptured ectopic pregnancy, toxic epidermal necrolysis, and Stevens-Johnson syndrome (1).

In light of the nonspecificity of the tests, in the clinical setting, serum amylase or lipase greater than three times the upper limit of normal is considered supporting evidence of acute pancreatitis in the correct clinical context (8). Amylase rapidly increases within hours of symptoms and decreases to within normal limits within three to five days. Lipase concentrations

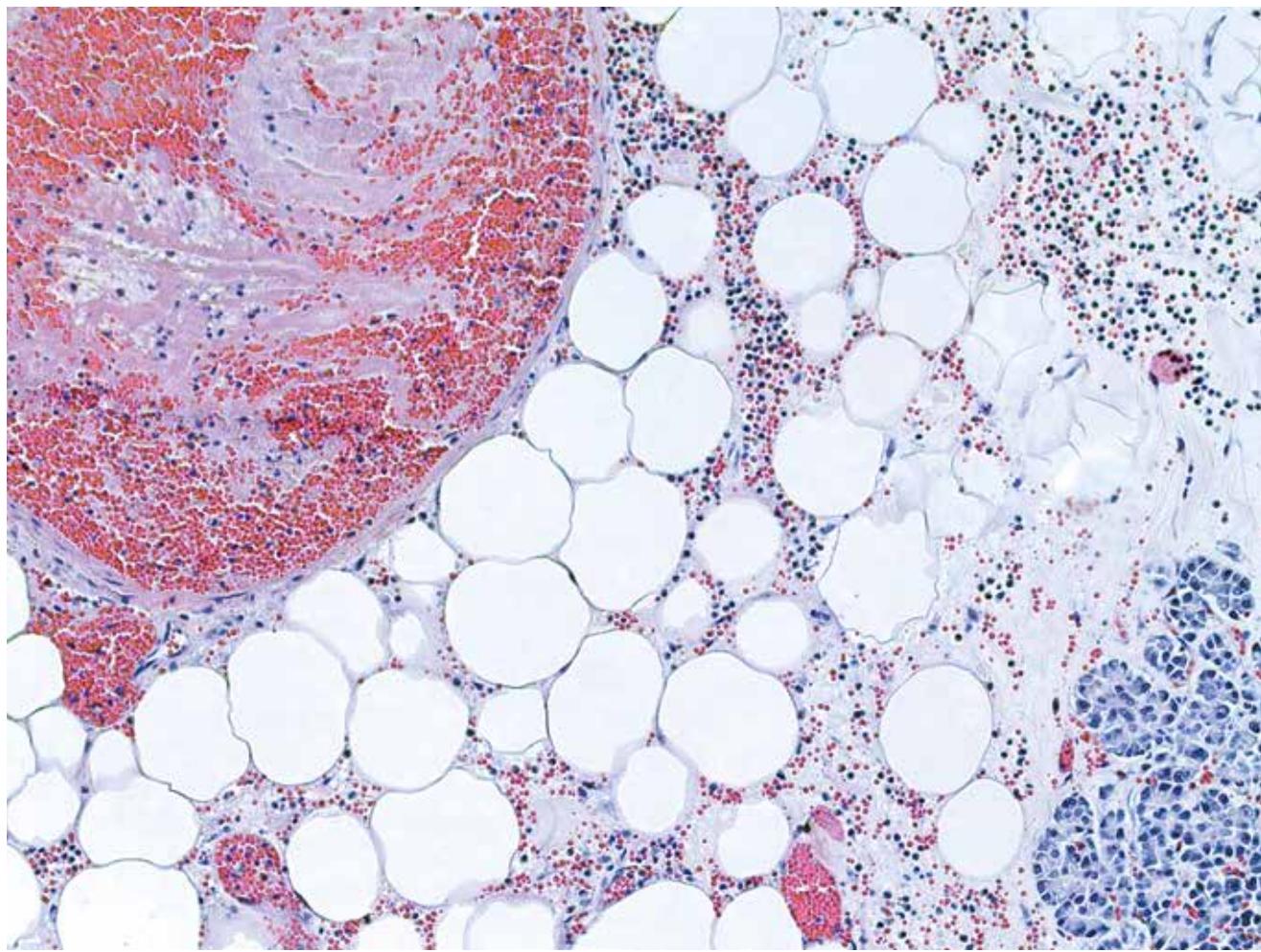


Image 7: Microscopic section of the pancreas from Case 4, showing an intravascular thrombus, as well as hemorrhage, inflammation, and fat necrosis (H&E, x100).

also become elevated in the setting of pancreatitis with serum concentrations remaining increased for up to 8 to 14 days after symptoms begin (9-11). As noted above, though, both amylase and lipase are not specific for the pancreas.

In the postmortem setting, amylase, and to a greater extent, lipase, are not reported as being commonly used by pathologists when considering a diagnosis of pancreatitis. Rather, at autopsy, pathologists rely on gross and microscopic findings to diagnose pancreatitis, including gross hemorrhage and edema, as well as microscopic hemorrhage, parenchymal destruction, acute inflammation, and fat necrosis (12). However, at autopsy, it may be challenging to differentiate pancreatitis from postmortem autolysis (13).

Grossly-identifiable, nonspecific pancreatic hemorrhage is a relatively common finding at autopsy, as seen in **Image 1**. Presumably, the postmortem extravasation of blood in this setting is related to autolysis involving digestive pancreatic enzymes. Microscopic identification of extravasated blood, without associated inflammation, is the key to recognizing this change as a postmortem artifact. It should also be noted that

pancreatic trauma, followed quickly by death, will have a similar histologic appearance (extravasated blood without inflammation).

Coe detailed that postmortem chemistry studies can provide valuable information, including documentation of biochemical changes in cases without significant gross and histologic autopsy findings (14-16). While some biochemical materials are stable following death, others display both known and unpredictable postmortem changes. Much of the biochemical changes known following death have been studied in the early postmortem period, between death and the start of intravascular hemolysis (14-16). As is done for routine toxicology testing, values detected from blood collected from femoral and/or subclavian veins are considered the closest representation of antemortem values (14). In the postmortem state, most enzymes, including amylase and lipase, display a rapid and unpredictable variation (14).

A study by Schoning and Strafuss compared canine antemortem versus postmortem serum amylase and lipase up to 48 hours after death (17). Postmortem serum amylase increased no more than 1.5 times the

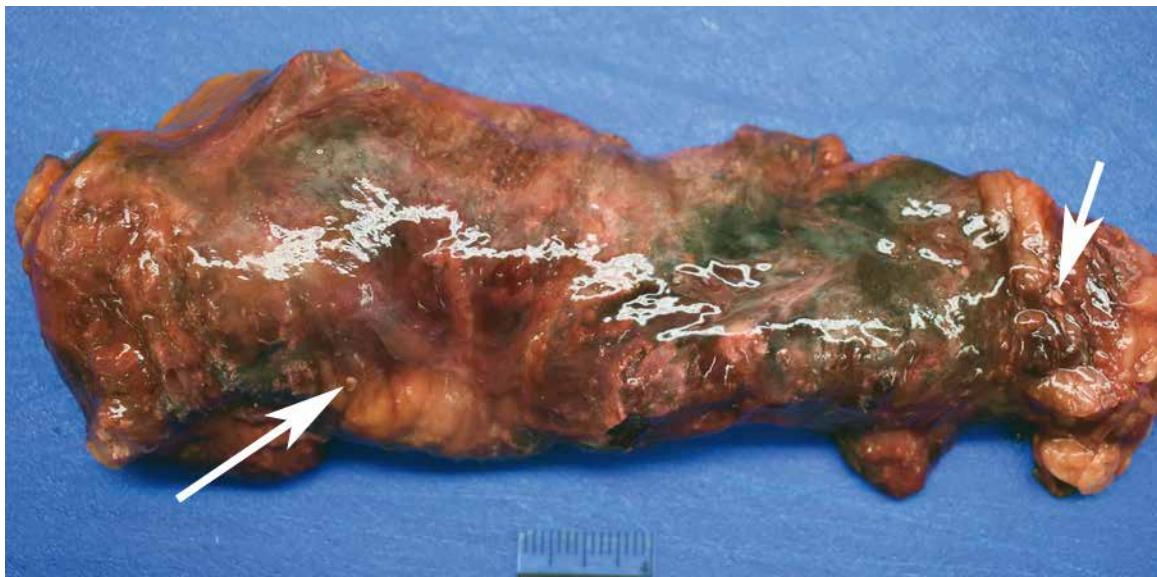


Image 8: Gross image of the intact (un-sectioned) pancreas from Case 5. Note the swollen and hemorrhagic appearance, as well as scattered yellow-white foci of fat necrosis, the largest two of which are indicated by arrows.

antemortem value and postmortem serum lipase increased up to 14.7 times the antemortem value (17). In humans, a study by Enticknap demonstrated that amylase has been documented to increase after death with values up to three to four times higher (mean of 370 Somogyi units or 684 U/L) on the second day after death (18). Specifically, amylase concentrations demonstrated a biphasic rise after death, increasing rapidly between two and 12 hours after death, followed by a decrease between 13 and 36 hours after death. Amylase then peaked to its highest level between 37 and 48 hours after death, followed by a decrease thereafter (18).

In order to understand the postmortem changes in amylase, a study by Michiue et al. collected postmortem serum amylase concentrations from bilateral cardiac blood specimens in deaths that did not directly involve the pancreas, have a preexisting condition or complication of the pancreas, or have a prolonged death (19). Causes of death in this study included intoxication, hyperthermia, hypothermia, acute brain injury, mechanical asphyxia, drowning, fire fatality, acute ischemic heart disease, and spontaneous cerebral hemorrhage. In most cases, the postmortem serum amylase concentrations in the bilateral cardiac blood specimens were higher than the clinical reference range, likely due to

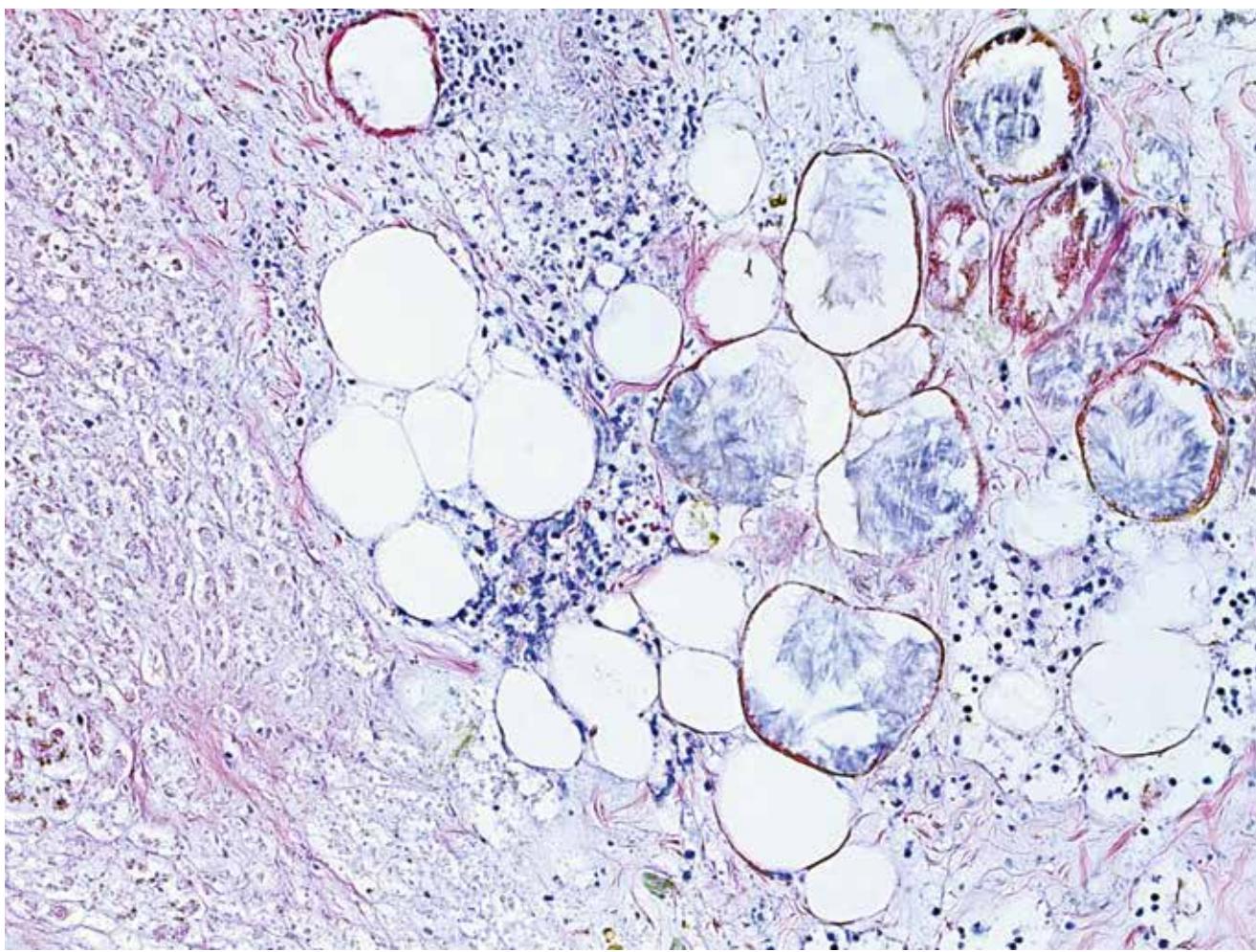


Image 9: Microscopic section of the pancreas from Case 5. A majority of the pancreas demonstrated severe autolysis/necrosis, with associated hemorrhage. Focally, there were areas demonstrating somewhat viable appearing inflammatory cells, as seen in this image, where fat necrosis is also evident; however, identification of definite neutrophils was compromised by severe autolysis (H&E, x100).

ischemia and hypoxia representing the severity of systemic organ damage (19). When intoxication causes of death were excluded, postmortem serum amylase concentrations were below 1000 U/L in most cases. Therefore, the study concluded that when postmortem serum amylase is greater than 1000 U/L, except in cases where intoxication is the cause of death, this may represent a high likelihood of significant pancreatic pathology, including pancreatitis (19). Similar studies evaluating the utility of lipase were not identified in the literature.

As demonstrated in this case series, all five cases had gross and microscopic evidence of acute pancreatitis. While postmortem serum amylase and lipase are largely supportive of a diagnosis of pancreatitis, relying on postmortem amylase alone, for example in Cases 3 and 4, would have led to missed diagnoses. As discussed previously, for Case 3 in the setting of acute and chronic pancreatitis, amylase decreases to within normal limits three to five days following presentation while lipase remains elevated. For Case 4, an explanation of why amylase is not elevated in the setting of

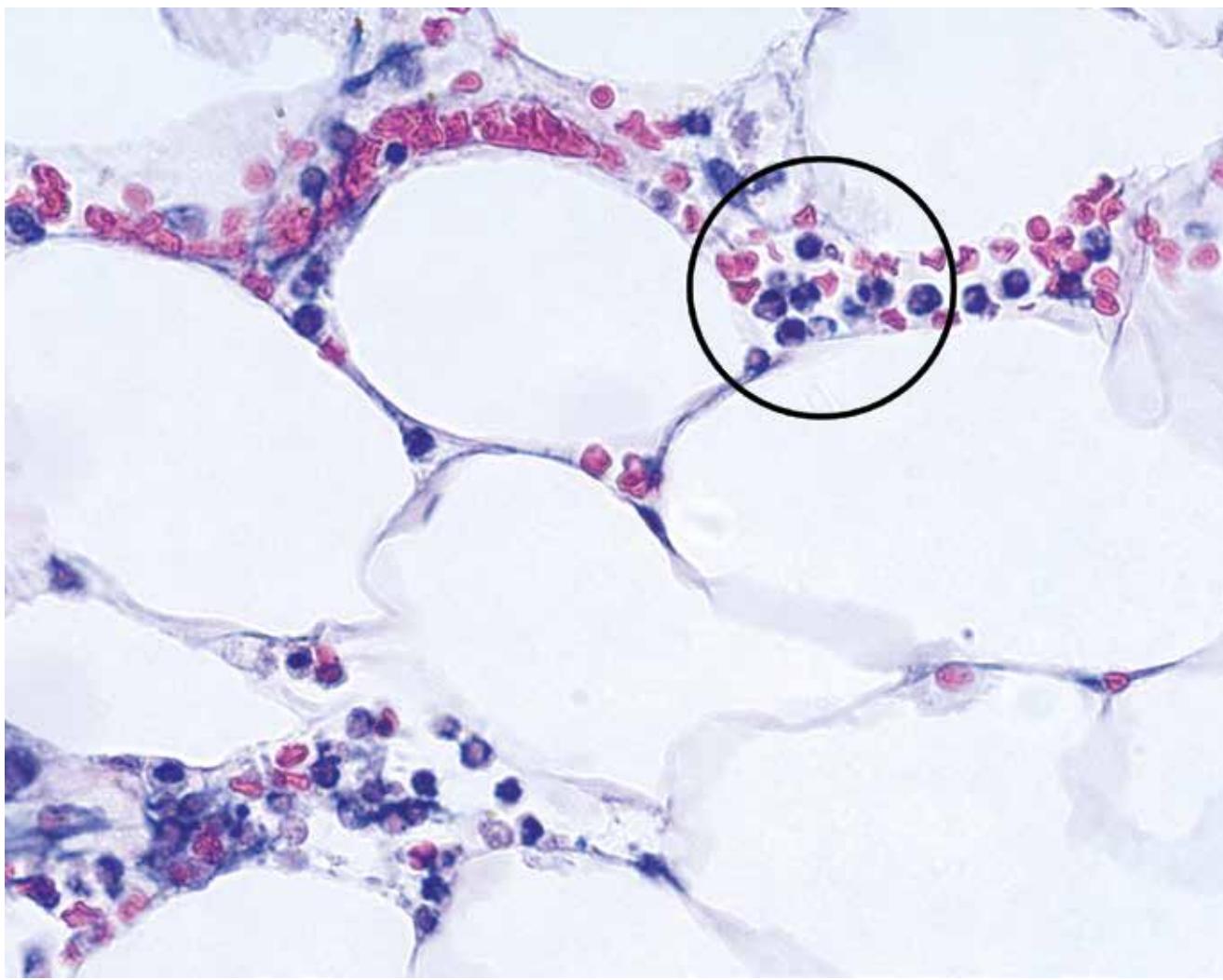


Image 10: Microscopic section of the peripancreatic adipose tissue from Case 5, showing rare intact and identifiable neutrophils (encircled). Most of the inflammatory cells (see elsewhere in image) contained nondefined, "smudged" nuclei, consistent with marked autolysis (H&E, x400).



gross and histologic evidence of acute pancreatitis and a greatly elevated lipase is likely due to interference from hypertriglyceridemia, as described previously. However, despite the limitations outlined, postmortem serum amylase and lipase can complement the autopsy gross and histologic findings of pancreatitis (20).

Cases 2 and 4 are examples of cases in which acute pancreatitis developed as a complication of hypertriglyceridemia. In the setting of hyperlipidemic pancreatitis, triglyceride concentrations are often more than 1000 mg/dL (21). Clinically, individuals present with hyperlipidemic pancreatitis in multiple settings, including poorly controlled diabetes mellitus, alcohol use, obesity, or drug use, the most common of which is diabetes mellitus (22, 23). It can be inferred that individuals who present with hyperlipidemic pancreatitis associated with diabetes mellitus can have further destruction of islet cells, leading to a likely final mechanism of death related to acute diabetic ketoacidosis. In both cases, neither individual had a preexisting diagnosis of diabetes mellitus, despite the fact that ketoacidosis was unequivocally present at death. It could not be determined in either case if the diabetes was preexistent or if acute islet cell destruction related to the acute pancreatitis resulted in the acute onset of diabetes and ketoacidosis; however, either possibility seems possible for each case. No obvious renal histologic features of diabetes were identified, and tests were not performed to identify elevated hemoglobin A1C. The presence of either of these two findings would be supportive of preexisting diabetes.

The usefulness of postmortem biochemistry is, in large part, restricted to cases that have autopsy examinations performed within the first 48 hours after death due to increasing postmortem factors that include leakage from cell deterioration and denaturation, degradation, and decomposition of biochemical markers (24). The biochemical profile at the time of death represents multiple factors, including preexisting medical conditions, cause of death, associated complications, survival period, and postmortem changes (24, 25).

In autopsies without decomposition, postmortem serum amylase and lipase can provide supportive evidence of acute pancreatitis as a cause of death, especially when the serum amylase is greater than 1000 U/L without evidence of intoxication (19). However, relying on postmortem serum amylase and lipase alone to diagnose acute pancreatitis is insufficient and unreliable. Rather, one must have the gross and histologic evidence of acute pancreatitis. In cases that demonstrate extensive pancreatic autolysis, increased postmortem serum amylase and lipase can help trigger the pathologist to carefully look at the pancreas or peripancreatic adipose tissue, as demonstrated in Case 5, for any evidence of acute neutrophilic exudate within the autolytic pancreatic parenchyma and/or peripancreatic adipose tissue. An elevated lipase without a corresponding elevation of amylase may be explained by the timing of presentation/death, versus interference by hypertriglyceridemia.

For purposes of establishing the most accurate reflection of antemortem amylase and lipase concentrations, it seems intuitive to collect peripheral blood samples that are furthest from the pancreas, either subclavian or femoral vein, and in cases of trauma-related pancreatitis, at a site most distal from the pancreas and the bulk of the traumatic injuries. Developing a consistent means of sampling multiple sites, including vitreous humor, central and peripheral blood, cerebrospinal fluid, and urine is recommended in order to establish a database of the biochemical profile in individuals at death (24). In order to expand the database on postmortem serum amylase and lipase concentrations, especially when acute pancreatitis is in the differential diagnosis at autopsy, pathologists are encouraged to order postmortem serum amylase and lipase concentrations. Additional postmortem chemistry studies, such as lipid profiles and tests which identify ketoacidosis (vitreous glucose and ketones; blood ketones) may also help to clarify the cause and mechanism of death in cases of pancreatitis.



CONCLUSION

The diagnosis of acute pancreatitis requires histologic identification of acute pancreatic inflammation. Minor elevations of postmortem serum amylase and lipase are nonspecific, or, in the case of amylase, may be related to the timing of sample collection or artifactually low due to interfering substances. Markedly elevated postmortem serum amylase (greater than 1000 U/L) and lipase concentrations may provide corroborating evidence of acute pancreatitis. This may be especially useful when severe autolysis/necrosis results in difficulties in recognizing acute inflammation histologically. Pathologists should consider the possible causative role of hypertriglyceridemia in cases of acute pancreatitis. Postmortem lipid studies can assist in making such a diagnosis. Pathologists should also consider the possibility of acute diabetic ketoacidosis in persons dying from acute pancreatitis, even in persons without a previous diagnosis of diabetes, as the mechanism of death. Elevated postmortem vitreous glucose and ketones, as well as postmortem blood ketones, can assist in making such a diagnosis. Evidence of renal diabetic changes, or elevated hemoglobin A1C, may provide evidence that diabetes was preexistent.

REFERENCES

- 1) Muniraj T, Dang S, Pitchumoni CS. Pancreatitis or not?–Elevated lipase and amylase in ICU patients. *J Crit Care*. 2015 Dec; 30(6): 1370-5. PMID: 26411523. <https://doi.org/10.1016/j.jcrc.2015.08.020>.
- 2) Frossard JL, Steer ML, Pastor CM. Acute pancreatitis. *Lancet*. 2008 Jan 12; 371(9607):143-52. PMID: 18191686. [https://doi.org/10.1016/s0140-6736\(08\)60107-5](https://doi.org/10.1016/s0140-6736(08)60107-5).
- 3) Fallat RW, Vester JW, Glueck CJ. Suppression of amylase activity by hypertriglyceridemia. *JAMA*. 1973 Sep 10; 225(11):1331-4. PMID: 4740657. <https://doi.org/10.1001/jama.225.11.1331>.
- 4) Lesser PB, Warshaw AL. Diagnosis of pancreatitis masked by hyperlipemia. *Ann Intern Med*. 1975 Jun; 82(6):795-8. PMID: 1138589. <https://doi.org/10.7326/0003-4819-82-6-795>.
- 5) Warshaw AL, Bellini CA, Lesser PB. Inhibition of serum and urine amylase activity in pancreatitis with hyperlipemia. *Ann Surg*. 1975 Jul; 182(1):72-5. PMID: 1147712. <https://doi.org/10.1097/000000658-197507000-00014>.
- 6) Rompianesi G, Hann A, Komolafe O, et al. Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis. *Cochrane Database Syst Rev*. 2017 Apr 21; 4:CD012010. PMID: 28431198. <https://doi.org/10.1002/14651858.cd012010.pub2>.
- 7) Vissers RJ, Abu-Laban RB, McHugh DF. Amylase and lipase in the emergency department evaluation of acute pancreatitis. *J Emerg Med*. 1999 Nov-Dec; 17(6):1027-37. PMID: 10595892. [https://doi.org/10.1016/s0736-4679\(99\)00136-5](https://doi.org/10.1016/s0736-4679(99)00136-5).
- 8) Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013 Jan; 62(1):102-11. PMID: 23100216. <https://doi.org/10.1136/gutjnl-2012-302779>.
- 9) Matull WR, Pereira SP, O'Donohue JW. Biochemical markers of acute pancreatitis. *J Clin Pathol*. 2006 Apr; 59(4):340-4. PMID: 16567468. PMCID: PMC1860356. <https://doi.org/10.1136/jcp.2002.002923>.
- 10) Smotkin J, Tenner S. Laboratory diagnostic tests in acute pancreatitis. *J Clin Gastroenterol*. 2002 Apr; 34(4):459-62. PMID: 11907364. <https://doi.org/10.1097/00004836-200204000-00018>.
- 11) Yadav D, Agarwal N, Pitchumoni CS. A critical evaluation of laboratory tests in acute pancreatitis. *Am J Gastroenterol*. 2002 Jun; 97(6):1309-18. PMID: 12094843. [https://doi.org/10.1016/s0002-9270\(02\)04122-9](https://doi.org/10.1016/s0002-9270(02)04122-9).
- 12) Renner IG, Savage WT 3rd, Pantoja JL, Renner VJ. Death due to acute pancreatitis. A retrospective analysis of 405 autopsy cases. *Dig Dis Sci*. 1985 Oct; 30(10):1005-18. PMID: 3896700. <https://doi.org/10.1007/bf01308298>.
- 13) Siriwardana RC, Deen KI, Hevawesethi J. Postmortem sampling of the pancreas for histological examination: what is the optimum cut-off time? *JOP*. 2010 Jan 8; 11(1):87-8. PMID: 200655563.
- 14) Coe JI. Postmortem chemistry: practical considerations and a review of the literature. *J Forensic Sci*. 1974 Jan; 19(1):13-32. PMID: 4853713. <https://doi.org/10.1520/jfs10066j>.
- 15) Coe JI. Postmortem chemistry update. Emphasis on forensic application. *Am J Forensic Med Pathol*. 1993 Jun; 14(2):91-117. PMID: 8328447. <https://doi.org/10.1097/00000433-199306000-00001>.
- 16) Coe JI. Postmortem chemistry of blood, cerebrospinal fluid, and vitreous humor. *Leg Med Annu*. 1977; 1976:55-92. PMID: 325316.
- 17) Schoning P, Strafuss AC. Postmortem sera and cerebrospinal fluid enzymes. *J Forensic Sci*. 1980 Apr; 25(2):344-8. PMID: 6156226. <https://doi.org/10.1520/jfs12133j>.
- 18) Enticknap JB. Biochemical changes in cadaver sera. *J Forensic Med*. 1960; 7:135-46.
- 19) Michiue T, Ishikawa T, Kawamoto O, et al. Postmortem serum levels of amylase and gamma glutamyl transferase (GGT) as markers of systemic tissue damage in forensic autopsy. *Leg Med (Tokyo)*. 2013 Mar; 15(2):79-84. PMID: 23165248. <https://doi.org/10.1016/j.legalmed.2012.09.003>.
- 20) Palmiere C, Lesta Mdel M, Sabatasso S, et al. Usefulness of postmortem biochemistry in forensic pathology: illustrative case reports. *Leg Med (Tokyo)*. 2012 Jan; 14(1):27-35. PMID: 22177826. <https://doi.org/10.1016/j.legalmed.2011.10.004>.
- 21) Toskes PP. Hyperlipidemic pancreatitis. *Gastroenterol Clin North Am*. 1990 Dec; 19(4):783-91. PMID: 2269517.
- 22) Fortson MR, Freedman SN, Webster PD 3rd. Clinical assessment of hyperlipidemic pancreatitis. *Am J Gastroenterol*. 1995 Dec; 90(12): 2134-9. PMID: 8540502.
- 23) Yadav D, Pitchumoni CS. Issues in hyperlipidemic pancreatitis. *J Clin Gastroenterol*. 2003 Jan; 36(1):54-62. <https://doi.org/10.1097/00004836-200301000-00016>.
- 24) Maeda H, Ishikawa T, Michiue T. Forensic biochemistry for functional investigation of death: concept and practical application. *Leg Med (Tokyo)*. 2011 Mar; 13(2):55-67. PMID: 21269863. <https://doi.org/10.1016/j.legalmed.2010.12.005>.
- 25) Maeda H, Zhu BL, Ishikawa T, et al. Significance of postmortem biochemistry in determining the cause of death. *Leg Med (Tokyo)*. 2009 Apr; 11 Suppl 1:S46-9. PMID: 19269240. <https://doi.org/10.1016/j.legalmed.2009.01.048>.



The Utility of Bile in Postmortem Forensic Toxicology

Jolene Bierly, Laura M. Labay

ABSTRACT

Bile is one matrix type that may be collected at autopsy and submitted to the toxicology laboratory for analysis. Because it is an excretion product of the liver, it can be used for screening purposes and to determine what drugs an individual used or was exposed to prior to death. This paper presents collection and analytical considerations of bile, and provides an overview of its utility from a testing and interpretation perspective. *Acad Forensic Pathol.* 2018 8(2): 324-327

AUTHORS

Jolene Bierly MSFS D-ABFT-FT, NMS Labs - Toxicology

Roles: Data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, general supervision, general administrative support, writing assistance and/or technical editing.

Laura M. Labay PhD F-ABFT DABCC-TC, NMS Labs - Toxicology

Roles: Data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, general administrative support, writing assistance and/or technical editing.

CORRESPONDENCE

Laura M. Labay PhD, 3701 Welsh Road, Willow Grove PA 19090, Laura.Labay@nmslabs.com

ETHICAL APPROVAL

As per Journal Policies, ethical approval was not required for this manuscript

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies conducted with animals or on living human subjects

STATEMENT OF INFORMED CONSENT

No identifiable personal data were presented in this manuscript

DISCLOSURES & DECLARATION OF CONFLICTS OF INTEREST

The authors, reviewers, editors, and publication staff do not report any relevant conflicts of interest

FINANCIAL DISCLOSURE

The authors have indicated that they do not have financial relationships to disclose that are relevant to this manuscript

KEYWORDS

Forensic pathology, Bile, Toxicology, Postmortem

INFORMATION

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

©2018 Academic Forensic Pathology International • (ISSN: 1925-3621) • <https://doi.org/10.23907/2018.021>

Submitted for consideration on 28 Feb 2018. Accepted for publication on 12 Apr 2018



INTRODUCTION

Toxicology laboratories that perform postmortem testing must be able to process and handle matrices beyond the traditional blood and urine. Ideally, sufficient and varied biological material should be collected from the deceased individual; however, this is not always possible. Specimen source and quality impacts the ability of laboratories to provide the information required by the forensic pathologist or other death investigators. From an interpretation perspective, the challenge is that different matrix types have different utilities; one is not a complete substitute for another. For example, blood is used to determine if a drug was present at a therapeutic, toxic, or potentially lethal concentration at the time of death while positive findings in urine demonstrate past drug use and/or exposure. Forensic practitioners have no control over the condition of a body, or the choice and quality of the specimens that are available for removal and collection. When there is no blood or limited blood volume available, alternate matrix types need to be tested.

DISCUSSION

Bile in Forensic Toxicology

One alternative specimen that may be considered is bile. Bile is a body fluid that aids in the digestion of lipids. It is continuously produced by the liver, concentrated and stored in the gallbladder, and subsequently released into the duodenum. The consistency of bile varies among individuals, but it is typically has a yellow-greenish pigment with a slightly alkaline pH (1, 2). Some reasons for choosing bile as an alternative matrix include ease of collection, large sample volume, extended detection window relative to blood, and high concentrations of drugs and metabolites. Collection of bile is straightforward. It can be performed by syringe aspiration from the gallbladder or the more viscous samples can be obtained by excising the gallbladder and emptying its contents into a container of suitable size. A large volume of bile, approximately 50 mL, may be obtained from the gallbladder if the entire contents are collected. Like other toxicology specimens, if ethanol is an analyte of in-

terest, the sample should be mixed with 1% sodium fluoride to mitigate its neoformation (3).

Drugs and their metabolites are excreted by the liver into the bile, which is then stored and concentrated in the gallbladder. Once in the gallbladder, drugs may undergo a process known as enterohepatic circulation where drugs and/or metabolites are secreted from the bile into the intestine. Once in the intestine, drugs are available to be reabsorbed by the liver to either enter systemic circulation through the hepatic vein or be secreted back into the bile thus, increasing the concentration of drugs present in bile and the amount of time these drugs may be detected (4). While the processes that govern which drugs are excreted into the bile are complex and not completely understood, most abused drugs and many prescription medications have been detected in bile. Abused drugs such as cocaine, heroin, fentanyl, gamma hydroxybutyrate (GHB), ketamine, 3,4-methylenedioxymethamphetamine (MDA), 3,4-methylenedioxymethamphetamine (MDMA), methamphetamine, and marijuana in addition to medications such as amitriptyline, buprenorphine, duloxetine, nitrazepam, phenobarbital, and zolpidem have been confirmed and quantitated in bile from forensic cases (2, 4, 5).

Pharmacokinetic studies that serve to demonstrate expected concentrations, either peak (C_{max}) or steady-state, by dosage and route of administration are most often conducted in blood, serum, or plasma specimens. As a result, quantitative confirmation testing most often takes place in the blood matrix or samples (e.g., serum or plasma) collected at the time of hospital admission. This permits the comparison of analytical results to reference ranges established from drug time course studies. The utility of bile in forensic toxicology is limited due to variable bile-to-blood concentration ratios and limited published reference data. For these reasons, bile is more useful as a qualitative screening matrix similar to urine or vitreous fluid rather than a quantitative confirmatory matrix such as blood.



Testing

Laboratories have designed analytical approaches to accommodate the testing of bile. Even though it is a biological fluid, like blood and urine, it has long been recognized in the toxicology community that from an analytical perspective, a method shown to be suitable by proficiency testing for one matrix does not translate into suitability for another matrix. During the validation phase, method parameters such as accuracy, specificity, sensitivity, and recovery should be evaluated, and in accordance with requirements promulgated by those regulatory agencies that develop consensus standards and guidelines to ensure a sufficient scientific basis exists for work performed (6). A reality in the postmortem arena is that specimens may arrive for testing in a variety of non-ideal conditions including discolored, dried, viscous, and/or decomposed. In this regard, the laboratory must ensure that the method is robust in its ability to handle the non-ideal specimen. A review of the literature shows that several analytical options exist for preparing a bile sample for instrumental analysis including liquid-liquid extraction (LLE) and solid-phase extraction (SPE) (2, 7, 8). While it is possible to apply methods designed for the detection of drugs in blood directly to bile specimens, due to the potential for interference from drug metabolites concentrated in the specimen, additional sample purification is recommended to ensure appropriate identification of drugs.

Confirmations may be qualitative or quantitative, depending upon the intended use of results. In either circumstance, the use of analyte-specific labeled internal standards will best compensate for matrix variations from sample to sample. Another option, in the absence of commercial availability and to circumvent the cost associated with a custom synthesis, is to employ the technique of standard addition (6). Calibration performed using bile that has tested negative for the presence of the drug of interest can be used, but with the variety of specimens that often require analysis the approach of matrix-matched calibration standards is not practical and, by itself, still may not compensate for specimen-specific differences.

Another aspect of testing that, at least for some drugs, may influence the ability of the method to detect certain analytes is if the bile undergoes a hydrolysis step prior to analysis. Some drugs, via phase II metabolism, undergo conjugation to facilitate elimination. A classic example is seen with the opiate drug class. Opiates such as morphine, hydromorphone, and oxymorphone undergo extensive glucuronide conjugation. The worst case scenario is that the majority of drug is present in conjugated form(s) and is not detected because the analytical method only detects free or unconjugated drug. Acidic or enzymatic hydrolysis is often used to break this bond. Traditional hydrolysis methods have been used successfully in bile specimens (2, 6). Depending upon the sensitivity of the analytical technique, this may or may not be necessary.

Interpretation

Finally, interpretation of bile results is rather straightforward. Results go to demonstrate past use and/or exposure to a drug, and due to enterohepatic circulation may persist in bile for a longer time period as compared to blood, as previously described (2, 3). Another critical point is that bile drug concentrations can be influenced by water content and postmortem changes. As a consequence, quantitative concentrations in bile have limited direct correlation to circulating blood-drug concentrations (2, 9–12). Even though bile-to-blood drug ratios have been reported, the use of a bile concentration to mathematically calculate a blood concentration would be a risky endeavor. While it could be assumed that bile drug concentrations that appear elevated are indicative of an elevated blood concentration, this cannot be determined without analytical testing of the blood. Drug distribution studies, where drug and drug metabolite concentrations are determined in different bodily fluids including bile, may help to substantiate the cause of death determination.

CONCLUSION

Overall, the bile matrix is best utilized for screening purposes when limited blood sample is available. Under this circumstance, the bile should be used as



a qualitative indicator of what drugs are present in blood. Based upon factors such as the case history, autopsy findings, and the bile-drug concentrations relative to each other, selective quantitative confirmation testing can be performed in blood or an alternative matrix such as vitreous fluid.

REFERENCES

- 1) Rhoades RA, Tanner GA. *Medical physiology*. Boston: Little Brown; 1995. 839 p.
- 2) Bévalot F, Cartiser N, Bottinelli C, et al. State of the art in bile analysis in forensic toxicology. *Forensic Sci Int*. 2016 Feb; 259:133-54. PMID: 26773224. <https://doi.org/10.1016/j.forsciint.2015.10.034>.
- 3) Karch SB. Postmortem toxicology of abused drugs. Boca Raton: CRC Press; 2007. 212 p.
- 4) Roberts MS, Magnusson BM, Burczynski FJ, Weiss M. Enterohepatic circulation: physiological, pharmacokinetic and clinical implications. *Clin Pharmacokinet*. 2002; 41(10):751-90. PMID: 12162761. <https://doi.org/10.2165/00003088-200241100-00005>.
- 5) Agarwal A, Lemos N. Significance of bile analysis in drug-induced deaths*. *J Anal Toxicol*. 1996 Jan-Feb; 20(1):61-3. PMID: 8837955. <https://doi.org/10.1093/jat/20.1.61>.
- 6) Levine B. *Principles of forensic toxicology*. 4th ed. Washington: AACC Press; 2013. 550 p.
- 7) Yamaguchi K, Goda T, Yamaki S, Ohno Y. Structural analysis of quazepam metabolites in bile by ion trap time-of-flight mass spectrometry. *Forensic Sci Int*. 2015 Nov; 256:7-16. PMID: 26301753. <https://doi.org/10.1016/j.forsciint.2015.07.016>.
- 8) Amplatz B, Zöhrer E, Haas C, et al. Bile acid preparation and comprehensive analysis by high performance liquid chromatography-high-resolution mass spectrometry. *Clin Chim Acta*. 2017 Jan; 464: 85-92. PMID: 27838249. <https://doi.org/10.1016/j.cca.2016.11.014>.
- 9) Fernández P, Aldonza M, Bouzas A, et al. GC-FID determination of cocaine and its metabolites in human bile and vitreous humor. *J Appl Toxicol*. 2006 May-Jun; 26(3):253-7. PMID: 16389661. <https://doi.org/10.1002/jat.1130>.
- 10) Robertson MD, Drummer OH. Postmortem distribution and redistribution of nitrobenzodiazepines in man. *J Forensic Sci*. 1998 Jan; 43(1):9-13. PMID: 9456518. <https://doi.org/10.1520/jfs16082j>.
- 11) Fanton L, Bevalot F, Gustin MP, et al. Interpretation of drug concentrations in an alternative matrix: the case of meprobamate in bile. *Int J Legal Med*. 2009 Mar; 123(2):97-102. PMID: 18581126. <https://doi.org/10.1007/s00414-008-0259-x>.
- 12) Tominaga M, Michiue T, Oritani S, et al. Evaluation of postmortem drug concentrations in bile compared with blood and urine in forensic autopsy cases. *J Anal Toxicol*. 2016 Jun; 40(5):367-73. PMID: 27185819. <https://doi.org/10.1093/jat/bkw028>.



Autopsy Biosafety: Recommendations for Prevention of Meningococcal Disease

Erin G. Brooks, Suzanne R. Utley-Bobak, National Association of Medical Examiners Ad Hoc Committee for Bioterrorism and Infectious Disease

ABSTRACT

Introduction: As invasive meningococcal disease progresses rapidly, often affects youth, and has a fairly high mortality rate, such cases are likely to fall under medical examiner/coroner (ME/C) jurisdiction. Morgue personnel may be at risk of contracting secondary meningococcal disease. We review the current scientific literature regarding *Neisseria meningitidis* infection and provide recommendations for the prevention of meningococcal disease at autopsy.

Methods: A PubMed search utilizing applicable medical subject heading terms was performed retrieving articles for review from the preceding two decades. Pertinent current guidelines from multiple national organizations were also retrieved.

Results: Invasive meningococcal disease is transmitted by direct contact with large respiratory droplets or oral secretions. While a surgical mask would normally provide adequate protection from large droplet spread, it does not prevent inhalation of smaller aerosolized particles such as those generated at autopsy. Prosecutors are advised to routinely wear N-95 respirator masks or powered respirator hoods. All published cases of secondary meningococcal disease transmission to healthcare workers invariably arose in scenarios in which face masks/respirators were not employed; none of these cases involved meningococcal disease transmission to ME/C or other morgue staff.

Discussion: In the event that no mask—or inadequate coverage such as a surgical mask—is employed during autopsy of a decedent suspected/confirmed to have invasive meningococcal disease, antibiotic prophylaxis is advisable. Assuming appropriate personal protective equipment is utilized, chemoprophylaxis is unnecessary. Routine meningococcal vaccination is not recommended, except for ME/C with specified immunocompromising conditions or traveling to hyperendemic/endemic meningococcal regions. *Acad Forensic Pathol.* 2018 8(2): 328-339

AUTHORS

Erin G. Brooks MD, University of Wisconsin Hospital and Clinics - Pathology and Laboratory Medicine

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work.

Suzanne R. Utley-Bobak MD, District 12 Medical Examiner's Office (Florida)

Roles: Project conception and/or design, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work.

CORRESPONDENCE

Erin G. Brooks MD, 3147 Medical Foundation Centennial Building, 1685 Highland Avenue, Madison WI 53705, egbrooks@wisc.edu

ETHICAL APPROVAL

As per Journal Policies, ethical approval was not required for this manuscript

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies conducted with animals or on living human subjects

STATEMENT OF INFORMED CONSENT

No identifiable personal data were presented in this manuscript

DISCLOSURES & DECLARATION OF CONFLICTS OF INTEREST

The authors, reviewers, editors, and publication staff do not report any relevant conflicts of interest

FINANCIAL DISCLOSURE

The authors have indicated that they do not have financial relationships to disclose that are relevant to this manuscript



REVIEW ARTICLE

KEYWORDS

Forensic pathology, Autopsy, Biosafety, Biohazards, Meningococcus, Meningitis

INFORMATION

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

©2018 Academic Forensic Pathology International • (ISSN: 1925-3621) • <https://doi.org/10.23907/2018.022>

Submitted for consideration on 14 Feb 2018. Accepted for publication on 23 Mar 2018



INTRODUCTION

Invasive meningococcal disease can result in meningitis, disseminated intravascular coagulation, septic shock, and death (1-3). As meningococcal disease can have a fulminant course with a fairly high mortality rate and often affects youth, such cases are likely to fall under medical examiner/coroner (ME/C) jurisdiction. Medical examiners/coroners and other morgue personnel may be at risk of contracting secondary disease. The following review by the National Association of Medical Examiners (NAME) Ad Hoc Bioterrorism and Infectious Disease Committee is intended to educate ME/C and other morgue personnel regarding *Neisseria meningitidis* infection, as well as to provide evidence-based recommendations for the prevention of meningococcal disease at autopsy.

METHODS

A PubMed search utilizing terms “meningococcal” OR “meningococcus” AND “health-care worker” was performed. Common medical subject heading (MeSH) terms were also included in the search e.g., “*Neisseria meningitidis*” and “health personnel.” Limitations included English language-only and publication within the preceding two decades (i.e., 1/1/1998-1/1/2018). A total of 152 articles were retrieved; of these, 25 directly addressed the topic of meningococcal disease/disease prevention in healthcare employees and were reviewed. Also included in the review were pertinent national guidelines such as the Centers for Disease Control and Prevention (CDC) recommendations regarding immunization of healthcare personnel and meningococcal disease prevention, Occupational Safety and Health Administration (OSHA) respiratory protection recommendations, College of American Pathologists (CAP) general autopsy safety recommendations, and NAME biosafety recommendations. Additional references were sought, reviewed, and incorporated as necessary.

RESULTS

Incidence and Transmission

Neisseria meningitidis is an aerobic Gram-negative diplococcus that commonly colonizes the mucosal surfaces of the nasopharynx; the organism is transmitted via direct contact with respiratory tract droplets (1-3). In a recent systematic review and meta-analysis, age was found to be the key determinant of meningococcal carriage; prevalence was 4.5% in infants with a peak of 23.7% in 19-year-olds and subsequent decrease to 7.8% in 50-year-olds (4). Given these relatively high colonization rates, invasive meningococcal disease remains uncommon with historically low annual incidence. From 2005-2011, there were approximately 800-1200 cases of invasive meningococcal invasive disease annually in the United States (3, 5). In 2015 and 2016, this declined to 359 and 372 reported cases, respectively (6, 7). Despite the low incidence, however, the disease continues to have a 10-15% overall mortality with significant survivor morbidity including neurologic damage and complications of disseminated intravascular coagulation, such as digit or limb loss (1-3, 5-7).

The majority of young adults in the United States have detectable antibodies to pathogenic *N. meningitidis* serogroups (2). Invasive disease most commonly arises in seronegative individuals who are exposed to the organism. Scenarios in which transmission often occurs are those involving entry of a seronegative individual into a crowded new environment such as daycare center, college campus, military training camp, or nursing home (2, 5). In addition to crowding, other factors that may increase the likelihood of colonization include tobacco smoke inhalation (active or passive), recent upper respiratory tract infection, and chronic underlying illness (2, 3, 5). The highest rates of invasive meningococcal disease occur in children less than one year of age, followed by a second smaller peak in adolescents/young adults 16-23 years of age, and finally a third small peak in older adults > 65 years of age (5, 8). Of the five pathogenic *N. meningitidis* serogroups (A, B, C, Y, W-135), three (B, C, and Y) account for the majority of meningococcal disease



in the United States. While overall, serogroups B, C, and Y each cause approximately one-third of disease cases in the United States, serogroup B accounts for proportionately more of the childhood cases (2, 3, 5, 8).

At Risk Populations

Certain populations have been designated as being at increased risk of acquiring meningococcal disease by the CDC. For instance, individuals with persistent complement pathway deficiencies (i.e., C3, C5-C9, properdin, Factor D, or Factor H) have up to 10 000 times greater risk of acquiring meningococcal disease and are also at risk for recurrent disease (5, 9). The complement deficiency may be genetic or acquired. Eculizumab (Soliris, Alexion Pharmaceuticals), a terminal complement inhibitor approved for treatment of paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, and generalized myasthenia gravis may predispose to meningococcal infection (9, 10). Likewise, individuals with anatomic or functional asplenia are at increased risk for infection by encapsulated bacteria including *N. meningitidis*, and have an increased mortality rate (40-70%) if infected (5, 9). More recently, studies have confirmed an increased risk for meningococcal disease among HIV-infected individuals, who were found to be 5- to 24-fold more likely to become infected as compared to non-HIV infected individuals (11).

In addition to these populations with immune system compromise, individuals traveling to or residing in geographic regions in which meningitis is hyperendemic/epidemic (e.g., Saudi Arabia or sub-Saharan Africa) and microbiologists who are routinely exposed to *N. meningitidis* isolates are also considered at increased risk (2, 3, 5, 9, 12, 13). In one study, 16 cases of probable laboratory-acquired meningococcal disease were identified nationwide between the years 1985-2001; the vast majority of cases (15/16; 94%) arose in clinical microbiologists manipulating isolates without respiratory protection (14). The increased rates of laboratory-acquired meningococcal disease—as well as other infectious diseases—have been reported by multiple other authors as well (15-

19). Within the US it is estimated that the incidence of meningococcal disease among microbiologists is 50-fold higher than in the general population, i.e., 13 per 100 000 persons versus a general incidence rate of 0.2 per 100 000 (14, 15, 20). Due to their increased risk of meningococcal infection, augmented vaccination/boosters are recommended for these special populations.

Other than clinical microbiologists, healthcare personnel are not generally deemed a “high risk” population. Healthcare personnel are broadly defined as individuals providing health care services who:

...have the potential for exposure to patients and/or infectious materials, including body substances, contaminated medical supplies and equipment, contaminated environmental surfaces or contaminated air (20).

Autopsy pathologists and morgue staff would thus be included in this group. It is suspected that the relative rarity of occupationally-acquired meningococcal disease outside of the laboratory setting may be attributable to the widespread utilization of personal protective equipment by healthcare personnel (21). The few cases of secondary transmission of meningococcal disease to healthcare personnel that have been reported invariably entail unprotected exposure (i.e., lack of surgical mask or respirator) during respiratory procedures such as endotracheal intubation, airway suctioning, mouth-to-mouth resuscitation, or oxygen administration to infected patients (21-26). No reports of secondary transmission of meningococcal disease to autopsy pathologists or other morgue staff were found within the reviewed literature nor on additional PubMed searches.

Disease Manifestations

Invasive meningococcal disease typically manifests as meningitis and/or meningocephemia (2, 3, 5). The interval between acquisition of organism and invasive disease is relatively short, with an average incubation period of three to four days (range: two to ten days) (3). In many patients in whom *N. meningitidis* has



penetrated mucosal cells to enter the bloodstream, the organism will subsequently traverse the blood-brain barrier causing bacterial meningitis, which is the most common presentation of invasive meningococcal disease (3). Clinical history suggestive of meningococcal meningitis would include the classic triad of fever, neck stiffness, and headache. Additional disease manifestations such as altered mental status, photophobia, and nausea/vomiting may also be reported. Meningococcal sepsis without meningitis reportedly occurs in a minority (5-20%) of invasive meningococcal disease cases (3). Clinical history suggestive of meningococcal sepsis would include fever, myalgia, hypotension, shock, adrenal hemorrhage, and petechial rash. There is frequently overlap between meningococcal meningitis and meningococcemia: for instance, in a prospective cohort study of 258 adults with meningococcal meningitis, a rash was reported in 64% (27). Other presentations of meningococcal disease are far less common, e.g., pneumonia (5-15% of cases), arthritis (2%), otitis media (1%), and epiglottitis (< 1%) (3). While the overall mortality rate of invasive meningococcal disease is 10-15%, case fatality ratios are notably higher in cases of meningococcemia (up to 40%) and in patients > 65 years of age (23.8%) (3, 5).

Autopsy Biosafety

Because infectivity status is frequently unknown at the time of autopsy, all autopsies should be performed in a facility with adequate air handling systems and by personnel wearing appropriate personal protective equipment (PPE). Minimal PPE includes a surgical cap, impervious surgical gown with full sleeve coverage, shoe covers, mask/respirator, eye protection, and double gloves (**Image 1**) (28-32). *N. meningitidis* is transmitted primarily by means of direct contact with large respiratory droplets from a carrier. Surgical masks are intended to protect the wearer from transmission of infectious droplets to the mucous membranes of the wearer's nose or mouth, and thus are considered adequate droplet protection for healthcare personnel by the CDC and OSHA in cases of meningococcal disease (33). However, surgical masks do not protect against inhalation of aerosolized particles smaller than droplets, and certain medical procedures

are known to generate higher concentrations of smaller infectious airborne particles than would typically arise via coughed/sneezed droplets.

Autopsy is an aerosol-generating procedure by nature: oscillating saws, fluid aspirator hoses, and compression/dissection of lungs may all contribute to generate aerosols (30-34). Given that other aerosol-generating procedures (e.g., endotracheal intubation, airway suctioning) have been associated with meningococcal disease transmission, the CDC and OSHA suggest that utilizing respirators rather than surgical masks may be prudent in known or suspected cases of invasive meningococcal disease (33). Unlike surgical masks, N-95 particulate filter respirator masks are fitted, and contain a filter that is designed to filter 95% of particles that are one micron in diameter (**Image 2**) (30-33). Autopsy personnel who cannot be fitted for a respiratory mask due to facial hair or other fit issues should instead don a powered air-purifying respirator (PAPR) (**Image 3**) (30-33). It has also been established that utilization of a face shield rather than safety glasses can be helpful in further reducing the contamination of respirators by particles (35).

In addition to PPE, air-handling systems for autopsy suites can be key factors in minimizing personnel infectious exposures. It is recommended that autopsy suites have a minimum of 12 air exchanges per hour and be negatively pressurized relative to surrounding office spaces (30-32). Air should be exhausted outside of the facility and away from areas of high pedestrian traffic. Ideally, morgue laminar air flow would travel from clean to progressively less clean areas with downdraft table ventilation to decrease personnel exposure to aerosolized pathogens (30-32).

Vaccination

In general, forensic pathologists should not require meningococcal vaccination, as it is not routinely recommended after the age of 18 (2, 3, 5, 36). Exceptions to this would include pathologists at high risk of contracting meningococcal disease, e.g., functionally/anatomically asplenic, complement component deficient, or who are HIV positive (5, 9, 11, 36). Foren-



Image 1: Recommended personal protective equipment (PPE) includes a surgical cap, impervious surgical gown with full sleeve coverage, shoe covers, respirator mask, full face shield, and double gloves.

sic pathologists or autopsy assistants meeting any of these criteria are advised to receive a booster dose of quadrivalent conjugate meningococcal vaccine (Men-ACWY) every five years (3, 5, 11, 36). The Men-ACWY vaccine provides protection against meningococcal serogroups A, C, W-135 and Y. As it does not provide protection against serogroup B, vaccination with a MenB conjugate vaccine is also advised; the two vaccines may be administered concurrently (9). Also, any pathologist intending to travel to a geographic area in which meningococcal disease is hyperendemic/epidemic is advised to receive a booster dose of Men-ACWY if they have not already done so within the past five years; MenB vaccination is not recommended; however, as meningococcal disease is not typically caused by serogroup B in these regions (5, 9). Current CDC travel health recommendations, including meningococcal epidemic advisories, can be

accessed electronically at: <https://wwwnc.cdc.gov/travel>.

Chemoprophylaxis

Nosocomial transmission of meningococcal disease is uncommon (23, 26, 37). Since 1972, roughly 12 cases of secondary transmission to healthcare workers have been cited in the literature; no face mask/respirator utilization was reported in any of the cases (26). Currently in the US, post-exposure antibiotic prophylaxis is only recommended for healthcare personnel who have:

...intensive, unprotected contact (i.e., without wearing a mask) with infected patients (e.g., intubating, resuscitating, or closely examining the oropharynx of patients) (36).

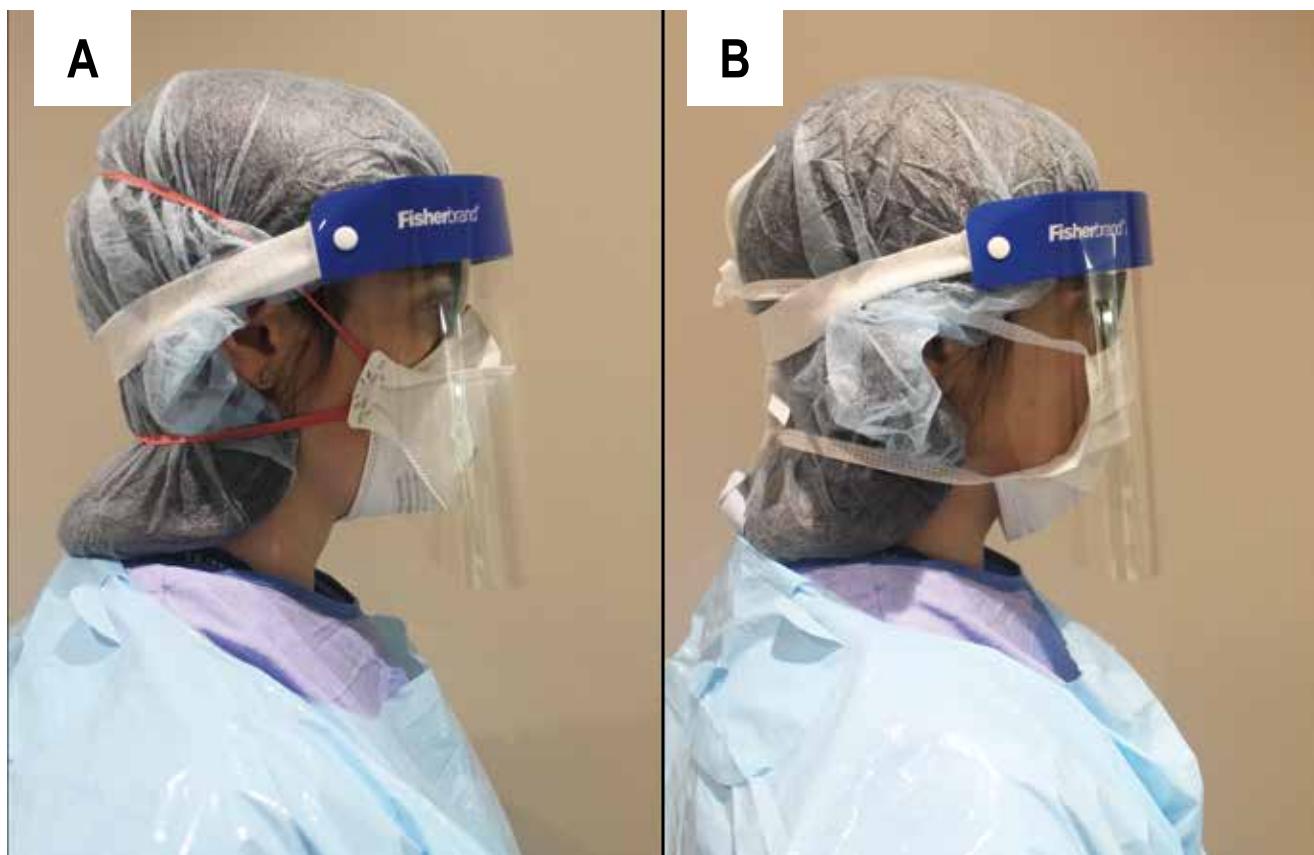


Image 2: An N-95 respirator mask provides protection against aerosolized infectious particles as well as larger droplets (A). Surgical masks provide infectious droplet protection only (B).



Image 3: A powered-air-purifying respirator (PAPR) is recommended for prosecutors with facial hair prohibiting tight respiratory mask fit.



Similar guidelines have been instituted in the United Kingdom and Australia (38, 39). Thus, in cases of suspected or confirmed invasive meningococcal disease in which autopsy is performed in a facility with adequate air handling systems and by personnel wearing appropriate personal protective equipment, antimicrobial prophylaxis would not be indicated.

Chemoprophylaxis can result in adverse reactions such as anaphylaxis and may cause antibiotic resistance (23, 38, 40-44). In a study of the risk of secondary meningococcal disease in healthcare workers in the United Kingdom, a total of three cases were identified in a 15-year span; all involved personnel who were not wearing surgical masks at the time of exposure. Overall, the relative risk of healthcare personnel has been established to be far lower than that of household contacts; whereas the attack rate among exposed healthcare personnel is 25 times higher than that of the general population, the rate among exposed household contacts is 500-800 times higher (3, 5, 23). It is estimated that if all healthcare workers in contact with patients having meningococcal disease received chemoprophylaxis, approximately 144 000 personnel would need to be treated to prevent a single case (23). The potential antibiotic resistance resulting from such an approach would far outweigh the benefits. Unfortunately, it appears unnecessary chemoprophylaxis may be all too common: in one survey, it was found that while antibiotic prescribing practices of hospital physicians in cases of meningococcal disease were largely in alignment with clinical guidelines, community general practitioners prescribed 118% more chemoprophylaxis than recommended (40). In addition to generating antibiotic resistance, antibiotics may eradicate commensal *Neisseria* species that help protect against colonization by pathogenic meningococci; normally, the incidence of invasive meningococcal disease is reciprocally related to antibody titers and antibodies are induced through the carriage of *Neisseria lactamica* as well as other similar commensal species (1, 38, 42).

In the event that appropriate personal protective equipment (i.e., N-95 respirator mask) is not worn at the time of autopsy of a decedent with invasive meningococcal disease, there may be exposure to infectious

droplet secretions and antibiotic prophylaxis would be advisable. Currently, recommended first-line antibiotic regimens for adults would include either rifampin (600 mg every 12 hours for two days), ciprofloxacin (500 mg single dose), or ceftriaxone (250 mg single intramuscular dose) (2, 3, 5, 36, 45). Both rifampin and ciprofloxacin are contraindicated in pregnancy (2, 5, 46). Ideally, the chemoprophylaxis would be administered within 24 hours of the exposure. If later than 14 days after exposure, antibiotics are unlikely to confer any added benefit (2, 3, 5, 20, 36).

DISCUSSION

Although incidence of invasive meningococcal disease in the US and other industrialized nations is low, epidemic outbreaks continue to occur (1, 3). As the disease progresses rapidly, often affects youth, and has a fairly high mortality rate, such cases are likely to fall under ME/C jurisdiction. Invasive meningococcal disease is transmitted by direct contact with oral secretions (e.g., kissing, mouth-to-mouth resuscitation) or direct exposure to infectious droplets (1-3). *Neisseria meningitidis* bacteria require a human host and cannot remain viable long in droplet form; the radius limit for large droplet spread is approximately 1 meter (3 feet) (1, 3, 38). While a surgical mask would normally be considered sufficient protection from large droplet spread, it does not prevent inhalation of smaller aerosolized particles such as those generated at autopsy (30-34). Prosector are thus advised to wear N-95 respirator masks or PAPRs at autopsy in cases in which invasive meningococcal disease is suspected/confirmed (33). Given that it may not be known prior to autopsy whether there is a potentially aerosolized infectious disease or not, prosector are encouraged to consider utilizing fitted N-95 respirator masks rather than surgical masks as a general practice (30, 31). The cost of disposable N-95 respirator masks vs. surgical masks is negligible while the aerosol-transmitted diseases against which surgical masks are deemed inadequate protection are myriad including *Mycobacterium tuberculosis*, measles, varicella (chickenpox), disseminated herpes zoster, severe acute respiratory syndrome (SARS), monkeypox, smallpox, and aerosolizable spore-containing powders (e.g., anthrax)



(33). Additionally, when engaged in an aerosolizing procedure such as autopsy, diseases that would normally require standard droplet precautions (i.e., a surgical mask) now instead require aerosol precautions (i.e., a respirator mask) (33).

In cases of invasive meningococcal disease at autopsy, PPE including N-95 respirator masks provides adequate protection for prosectors and no subsequent chemoprophylaxis is necessary. As chemoprophylaxis can result in adverse drug reactions, increased antibiotic resistance, and eradication of nonpathogenic *Neisseria* species that provide cross-reactive immunity, it should be utilized only when necessary (23, 38, 40-44). In cases in which no mask—or inadequate coverage such as a surgical mask—was employed at autopsy, chemoprophylaxis is advised due to the potential for large droplet or aerosol particle inhalation and subsequent infection. Rifampin, ciprofloxacin, or ceftriaxone are currently considered first-line therapies for meningococcal prophylaxis (2, 3, 5, 36, 45). Ideally, antibiotic prophylaxis should be initiated within 24 hours of exposure to be most efficacious (2, 3, 5, 20, 36). In the event that a patient has been given intravenous antibiotics 24 hours prior to death, infectivity is likely to be minimal thereafter (38). In general, morgue personnel are not considered to be a population at high-risk of acquiring secondary meningococcal disease. In the preceding 20 years, there have been no published cases of invasive meningococcal disease transmission to ME/C or other morgue staff. Accordingly, meningococcal vaccination is not recommended for forensic pathologists unless they are HIV positive, functionally/anatomically asplenic, deficient in complement components, or are planning travel to a hyperendemic/endemic meningococcal disease region (5, 9, 11, 36). Meningococcal disease is a nationally notifiable condition: medical examiners/coroners should immediately report suspected cases to the local health authority (21).

CONCLUSION

At autopsy, prosectors may be exposed to a wide array of infectious agents including *Neisseria meningitidis*. The risks of secondary transmission of disease can

be minimized, however, by adoption of appropriate pre- and post-exposure preventative measures. These would include vaccination of those with immunocompromising conditions placing them at high risk for invasive meningococcal disease, appropriate autopsy facility design with adequate air exchange/flow, regular utilization of personal protective equipment including an N-95 respirator mask, and chemoprophylaxis in the event appropriate PPE is not worn or malfunctions at autopsy (**Table 1**).

ACKNOWLEDGEMENTS

The modeling contributions of Jessica Gulliver, MD and Michael Schwalbe, MD of the University of Wisconsin Hospital and Clinics are gratefully acknowledged.

In addition to Drs. Brooks and Utley-Bobak, members of the National Association of Medical Examiners Ad Hoc Committee for Bioterrorism and Infectious Disease include:

Paul Chui DMJ (Health Sciences Authority, Singapore), Karen Kelly MD (Brody School of Medicine at East Carolina University), J. Matthew Lacy MD (Snohomish County Medical Examiner's Office), Micheline Lubin MD (King County Medical Examiner's Office), Lakshmanan Sathyavagiswaran MD FRCP(C) FACP FCAP (Los Angeles County Medical Examiner's Office: retired), Leah Schuppener DO (University of Wisconsin Hospital and Clinics), Steven White MD PhD (Cook County Medical Examiner's Office).

REFERENCES

- 1) Van Deuren M, Brandtzaeg P, van der Meer JW. Update on meningococcal disease with emphasis on pathogenesis and clinical management. *Clin Microbiol Rev.* 2000; 13(1):144-66. PMID: 10627495. PMCID: PMC88937. <https://doi.org/10.1128/cmrr.13.1.144-166.2000>.
- 2) Gardner P. Clinical practice. Prevention of meningococcal disease. *N Engl J Med.* 2006 Oct 5; 355(14):1466-73. PMID: 17021322. <https://doi.org/10.1056/nejmcp063561>.
- 3) Epidemiology and prevention of vaccine-preventable diseases. 13th ed. Washington: Public Health Foundation, c2015. Chapter 14, Meningococcal disease; p.231-46.
- 4) Christensen H, May M, Bowen L, et al. Meningococcal carriage by age: a systematic review and meta-analysis. *Lancet Infect Dis.* 2010 Dec; 10(12):853-61. PMID: 21075057. [https://doi.org/10.1016/S1473-3099\(10\)70251-6](https://doi.org/10.1016/S1473-3099(10)70251-6).

Table 1: Recommendations for Prevention of Meningococcal Disease at Autopsy

Chemoprophylaxis	<ol style="list-style-type: none"> 1. If full PPE (including an N-95 respirator mask or PAPR) is employed at autopsy in cases of suspected/confirmed invasive meningococcal disease, no chemoprophylaxis is indicated. 2. If no mask (or inadequate protection such as a surgical mask) is employed at autopsy in cases of suspected/confirmed invasive meningococcal disease, prompt chemoprophylaxis is recommended. 3. Current first-line chemoprophylaxis regimens are rifampin (600 mg every 12 hrs for two days), ciprofloxacin (500 mg single dose), or ceftriaxone (250 mg single intramuscular dose).
Vaccination	<ol style="list-style-type: none"> 1. Routine meningococcal vaccination is not recommended unless immunocompromised (i.e., HIV positive, functionally/anatomically asplenic, complement component deficient) or traveling to an area in which meningococcal disease is endemic. 2. Pathologists who are immunocompromised as defined above should receive booster doses of Men-ACWY quadrivalent conjugate vaccine every five years + MenB conjugate vaccine. 3. If travelling to a geographic area in which meningococcal disease is endemic, a booster dose of Men-ACWY quadrivalent conjugate vaccine is recommended if it has been greater than five years since last vaccination.
Facility Design	<ol style="list-style-type: none"> 1. It is recommended that autopsy suites have a minimum of 12 air exchanges per hour and be negatively pressure relative to surrounding office space. 2. Air should be exhausted outside of the facility and away from areas of high pedestrian traffic. 3. Downdraft table ventilation is recommended to decrease exposure to aerosolized pathogens.

PPE - Personal protective equipment

PAPR - Powered air purifying respirator

HIV - Human immunodeficiency virus

- 5) Cohn AC, MacNeil JR, Clark TA, et al. Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2013 Mar 22; 62(RR-2):1-28. PMID: 23515099 <https://doi.org/10.1037/e548762006-001>.
- 6) Enhanced meningococcal disease surveillance report, 2015 [Internet]. Atlanta: Centers for Disease Control and Prevention; 2017 Sep [cited 2018 Jan 7]. 2 p. Available from: <https://www.cdc.gov/meningococcal/downloads/NCIRD-EMS-Report-2015.pdf>.
- 7) Enhanced meningococcal disease surveillance report, 2016 [Internet]. Atlanta: Centers for Disease Control and Prevention; 2017 Sep [cited 2018 Jan 7]. 2 p. Available from: <https://www.cdc.gov/meningococcal/downloads/NCIRD-EMS-Report.pdf>.
- 8) Centers for Disease Control and Prevention [Internet]. Atlanta: US Department of Health & Human Services; c2018. Meningococcal disease: surveillance; [cited 2018 Jan 7]. Available from: <https://www.cdc.gov/meningococcal/surveillance/index.html>.
- 9) Folaranmi T, Rubin L, Martin SW, et al. Use of serogroup B meningococcal vaccines in persons aged \geq 10 Years at increased risk for serogroup B meningococcal disease: recommendations of the advisory committee on immunization practices, 2015. *MMWR Morb Mortal Wkly Rep*. 2015 Jun 12; 64(22): 608-12. PMID: 26068564. PMCID: PMC4584923.
- 10) United States Food and Drug Administration [Internet]. Silver Spring (MD): U.S. Department of Health and Human Services; c2018. Drugs@FDA: FDA Approved Drug Products. Alexion Pharmaceuticals Supplemental Approval-422; [cited 2018 Jan 7]. Available from: <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&AppN=125166>.
- 11) MacNeil JR, Rubin LG, Patton M, et al. Recommendations for use of meningococcal conjugate vaccines in HIV-infected persons — advisory committee on immunization practices, 2016. *MMWR Morb Mortal Wkly Rep*. 2016 Nov 4; 65(43):1189–1194. PMID: 27811836. <https://doi.org/10.15585/mmwr.mm6543a3>.
- 12) Boutet R, Stuart JM, Kaczmarski EB, et al. Risk of laboratory-acquired meningococcal disease. *J Hosp Infect*. 2001 Dec; 49(4): 282-4. PMID: 11740877. <https://doi.org/10.1053/jhin.2001.1084>.
- 13) Boutet R, Stuart JM, Jones DM, Kaczmarski EB. Prevention of meningococcal infection in laboratory workers—an audit of practice in England and Wales. *Commun Dis Public Health*. 2001 Jun; 4(2):130-2. PMID: 11525001.
- 14) Sejvar JJ, Johnson D, Popovic T, et al. Assessing the risk of laboratory-acquired meningococcal disease. *J Clin Microbiol*. 2005 Sep; 43(9):4811-14. PMID: 16145146. PMCID: PMC1234112. <https://doi.org/10.1128/JCM.43.9.4811-4814.2005>.
- 15) Singh K. Laboratory-acquired infections. *Clin Infect Dis*. 2009 Jul 1; 49(1):142-7. PMID: 19480580. <https://doi.org/10.1086/599104>.
- 16) Baron EJ, Miller JM. Bacterial and fungal infections among diagnostic laboratory workers: evaluating the risks. *Diagn Microbiol Infect Dis*. 2008 Mar; 60(3):241-6. PMID: 17997259. <https://doi.org/10.1016/j.diagmicrobio.2007.09.016>.
- 17) Kessler AT, Stephens DS, Somani J. Laboratory-acquired serogroup A meningococcal meningitis. *J Occup Health*. 2007 Sep; 49(5): 399-401. PMID: 17951972. <https://doi.org/10.1539/joh.49.399>.
- 18) Athlin S, Vikerfors T, Fredlund H, Olcén P. Atypical clinical presentation of laboratory-acquired meningococcal disease. *Scand J Infect Dis*. 2007; 39(10):911-3. PMID: 17852886. <https://doi.org/10.1080/00365540701367827>.



- 19) Omer H, Rose G, Jolley KA, et al. Genotypic and phenotypic modifications of *Neisseria meningitidis* after an accidental human passage. *PLoS One*. 2011 Feb 28; 6(2):e17145. PMID: 21386889. PMCID: PMC3046118. <https://doi.org/10.1371/journal.pone.0017145>.
- 20) Weber DJ, Rutala WA. Occupational health update: focus on preventing the acquisition of infections with pre-exposure prophylaxis and postexposure prophylaxis. *Infect Dis Clin North Am*. 2016 Sep; 30(3):729-57. PMID: 27515145. <https://doi.org/10.1016/j.idc.2016.04.008>.
- 21) Centers for Disease Control and Prevention (CDC). Occupational transmission of *Neisseria meningitidis* --- California, 2009. *MMWR Morb Mortal Wkly Rep*. 2010 Nov 19; 59(45):1480-3. PMID: 21085089.
- 22) Gehanno JF, Kohen-Couderc L, Lemeland JF, Leroy J. Nosocomial meningococcemia in a physician. *Infect Control Hosp Epidemiol*. 1999 Aug; 20(8):564-5. PMID: 10466560. <https://doi.org/10.1086/501672>.
- 23) Gilmore A, Stuart J, Andrews N. Risk of secondary meningococcal disease in health-care workers. *Lancet*. 2000 Nov 11; 356(9242): 1654-5. PMID: 11089828. [https://doi.org/10.1016/S0140-6736\(00\)03163-9](https://doi.org/10.1016/S0140-6736(00)03163-9).
- 24) Petsas A, Sharma A, Aghadiuno O, et al. A secondary case of meningococcal disease in an ambulance worker, Berkshire, November 2007. *Euro Surveill*. 2008 Jan 24; 13(4). pii: 8020. PMID: 18445400.
- 25) Fusco FM, Puro V. Meningococcal disease in an ambulance worker. *Euro Surveill*. 2008 Mar 6; 13(10). pii: 8061. PMID: 18445438. <https://doi.org/10.2807/es.13.10.08061-en>.
- 26) Ricciò M, Vezzosi L, Odone A, Signorelli C. Invasive meningococcal disease on the workplaces: a systematic review. *Acta Biomed*. 2017 Oct 23; 88(3):337-351. PMID: 29083344.
- 27) Heckenberg SG, de Gans J, Brouwer MC, et al. Clinical features, outcome, and meningococcal genotype in 258 adults with meningococcal meningitis: a prospective cohort study. *Medicine (Baltimore)*. 2008 Jul; 87(4):185-92. PMID: 18626301. <https://doi.org/10.1097/MD.0b013e318180a6b4>.
- 28) Aurelius MB. Autopsy Performance and Reporting. 3rd ed. Northfield, IL: College of American Pathologists; c2017. Chapter 12, Autopsy safety; p. 81-90.
- 29) Nine JS. Autopsy performance and reporting. 3rd ed. Northfield (IL): College of American Pathologists; c2017. Chapter 13, High-risk autopsy cases; p. 91-8.
- 30) Nolte KB, Taylor DG, Richmond JY. Biosafety considerations for autopsy. *Am J Forensic Med Pathol*. 2002 Jun; 23(2):107-22. PMID: 12040252. <https://doi.org/10.1097/00000433-200206000-00001>.
- 31) Nolte KB, Hanzlik RL, Payne DC, Kroger AT, et al. Medical examiners, coroners, and biologic terrorism: a guidebook for surveillance and case management. *MMWR Recomm Rep*. 2004 Jun 11; 53(RR-8):1-27. PMID: 15192550. <https://doi.org/10.1037/e548602006-001>.
- 32) Nolte KB, Guarner J, Shieh W, Zaki SR. Handbook of forensic pathology. 2nd ed. Northfield (IL): College of American Pathologists; c2003. Chapter 36, Emerging infectious diseases and the medical examiner; p. 345-60.
- 33) Hospital respiratory protection program toolkit: resources for respirator program administrators [Internet]. Washington: Occupational Safety and Health Administration; 2015 May [cited 2018 Jan 8]. 32 p. Available from: <https://www.osha.gov/Publications/OSHA3767.pdf>.
- 34) Wenner L, Pauli U, Summermatter K, et al. Aerosol generation during bone-sawing procedures in veterinary autopsies. *Vet Pathol*. 2017 May; 54(3):425-436. PMID: 28113035. <https://doi.org/10.1177/0300985816688744>.
- 35) Lindsley WG, Noti JD, Blachere FM, et al. Efficacy of face shields against cough aerosol droplets from a cough simulator. *J Occup Environ Hyg*. 2014; 11(8):509-18. PMID: 24467190. PMCID: PMC4734356. <https://doi.org/10.1080/15459624.2013.877591>.
- 36) Advisory Committee on Immunization Practices; Centers for Disease Control and Prevention (CDC). Immunization of health-care personnel: recommendations of the advisory committee on immunization practices (ACIP). *MMWR Recomm Rep*. 2011 Nov 25; 60(RR-7):1-45. PMID: 22108587.
- 37) Pollard AJ, Begg N. Meningococcal disease and healthcare workers. *BMJ*. 1999 Oct 30; 319(7218):1147-8. PMID: 10541486. PMCID: PMC1116940. <https://doi.org/10.1136/bmj.319.7218.1147>.
- 38) Stuart JM, Gilmore AB, Ross A, et al. Preventing secondary meningococcal disease in health care workers: recommendations of a working group of the PHLs meningococcus forum. *Commun Dis Public Health*. 2001 Jun; 4(2):102-5. PMID: 11524996.
- 39) Graham E, Dreimanis D. Chemoprophylaxis. *Collegian*. 1998 Apr; 5(2):9. PMID: 9644332.
- 40) Marks PJ, Neal KR. Variations in chemoprophylaxis for meningococcal disease: a retrospective case note review, analysis of routine prescribing data and questionnaire of general practitioners. *BMC Public Health*. 2001; 1:16. PMID: 11806758. PMCID: PMC64787. <https://doi.org/10.1186/1471-2458-1-16>.
- 41) Giovanetti F. Anaphylaxis following unnecessary meningococcal chemoprophylaxis of a healthcare worker. *Euro Surveill*. 2009 May 14; 14(19). pii: 19207. PMID: 19442400. <https://doi.org/10.2807/es.14.19.19207-en>.
- 42) Cowling P. Meningococcal disease in healthcare workers. Prophylaxis is not necessary. *BMJ*. 2000 Jan 22; 320(7229):247; author reply 248-9. PMID: 10712018.
- 43) Galloway A, Fulton B, Flood T. Meningococcal disease in healthcare workers. Long term effects and costs are unclear. *BMJ*. 2000 Jan 22; 320(7229):248; author reply 248-9. PMID: 10712020.
- 44) Gilmore A, Stuart J, Cartwright K, Patterson W. Meningococcal disease in healthcare workers. Recommendation will cause unease among healthcare staff. *BMJ*. 2000 Jan 22; 320(7229):247-8; author reply 248-9. PMID: 10712019.
- 45) Wilcox MH, Modi N. Meningococcal disease in healthcare workers. Ceftriaxone may be helpful. *BMJ*. 2000 Jan 22; 320(7229):248-9. PMID: 10712021.
- 46) Bazan JA, Mangino JE. Infection control and postexposure prophylaxis for the pregnant healthcare worker. *Clin Obstet Gynecol*. 2012 Jun; 55(2):571-88. PMID: 22510640. <https://doi.org/10.1097/grf.0b013e31824f3a07>.



Fatal Mitragynine-Associated Toxicity in Canada: A Case Report and Review of the Literature

Carol Wang, Alfredo E. Walker

ABSTRACT

Mitragynine is amongst the more than 40 natural indole alkaloids derived from the *Mitragyna speciosa*, or kratom tree, also referred to as ketum. The compound is unique in that it exhibits dose-dependent clinical outcomes with stimulant effects at lower doses but sedative effects at higher concentrations. It is indigenous to Southeast Asia, where the local population has had extensive experiences utilizing the substance for its medicinal as well as recreational effects. Mitragynine is advertised as an herbal remedy and is readily accessible via the Internet, resulting in its expansive distribution throughout the world. The addictive potential of this substance is quickly becoming recognized and mitragynine has been implicated in multidrug toxicity deaths.

We present a case of the first reported mitragynine-associated fatality in Canada where an independently fatal mitragynine concentration was detected in the postmortem femoral venous blood and the source drug was likely obtained as a powder from Indonesia. *Acad Forensic Pathol.* 2018 8(2): 340-346

AUTHORS

Carol Wang MD, Ottawa Hospital - Pathology and Laboratory Medicine, University of Ottawa Faculty of Medicine - Pathology and Laboratory Medicine

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, principal investigator of the current study.

Alfredo E. Walker MB BS FRCPath DMJ (Path) MFFLM MCSFS Dip Teach Train, Eastern Ontario Regional Forensic Pathology Unit - Department of Pathology and Laboratory Medicine - University of Ottawa

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, principal investigator of the current study, general supervision, writing assistance and/or technical editing.

CORRESPONDENCE

Alfredo E. Walker MB BS, 501 Smyth Road, Ottawa ON K1H 8L6, aewalker@toh.on.ca

ETHICAL APPROVAL

As per Journal Policies, ethical approval was not required for this manuscript

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies conducted with animals or on living human subjects

STATEMENT OF INFORMED CONSENT

No identifiable personal data were presented in this manuscript

DISCLOSURES & DECLARATION OF CONFLICTS OF INTEREST

The authors, reviewers, editors, and publication staff do not report any relevant conflicts of interest

FINANCIAL DISCLOSURE

The authors have indicated that they do not have financial relationships to disclose that are relevant to this manuscript

KEYWORDS

Forensic pathology, Mitragynine, Kratom, Mitragynine toxicity, Kratom deaths, Methadone-like powder

INFORMATION

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

©2018 Academic Forensic Pathology International • (ISSN: 1925-3621) • <https://doi.org/10.23907/2018.023>

Submitted for consideration on 1 Apr 2018. Accepted for publication on 7 May 2018

INTRODUCTION

Mitragynine is a natural indole alkaloid derived from *Mitragyna speciosa*, or kratom tree (**Image 1**) (1). This tropical plant is indigenous to the Philippine islands, New Guinea, and Southeast Asia including Indonesia, Malaysia, Thailand, and Borneo (1, 2). The alkaloid composition of the kratom plant varies geographically. Indonesian plants consist of higher mitragynine and alkaloid concentrations compared to its southeastern neighbors (1, 3). Mitragynine is among one of the more than 40 psychoactive diastereomers of the kratom plant, which vary in potency based on their structural differences (1, 3, 4). 7-hydroxymitragynine is another derivative that makes up 2% of the kratom plant and has more than 40 times the potency of mitragynine (1). Mitragynine is an agonist of the μ -, κ -, and δ -opioid receptors with a higher

affinity and potency than morphine (5). Its action on these opioid receptors allows this compound to exert analgesic and euphoric effects with the potential for respiratory depression (6). Compared with other opioid drugs, mitragynine is unique in its dose-dependent effects. At low concentrations it has stimulant effects, but behaves as a sedative at higher concentrations (1, 6). The exact doses for its stimulant, sedative, analgesic, and toxic thresholds remain unknown (6).

In Southeast Asia, kratom leaves (**Image 2**) are used by locals for both their medicinal effects against pain, diarrhea, fever, and as a recreational drug to reduce stress and enhance physical endurance and work capabilities (2, 5, 7, 8). Mitragynine has also been utilized as an affordable substitute to remedy withdrawal by those with opioid, amphetamine, and cannabis dependence (7, 9). The psychoactive compounds are most



Image 1: Kratom plant (Used under license from www.shutterstock.com).

commonly ingested by smoking, chewing, or brewing the kratom leaves (2, 10). Kratom-derived compounds are readily accessible via the Internet, which has aided in its spread to the United States, Europe, and Japan (11). In western countries, mitragynine is utilized as an herbal supplement for the self-management of chronic pain (2). Positive effects reported in western countries include euphoria, relaxation, increased energy, analgesia, and sensory enhancement (12). However, mitragynine's euphoric effect is addictive and is the reason for its abuse as a "legal" high. Its abuse potential is quickly becoming recognized (2, 11, 12).

Knowledge of the consequences of long-term mitragynine use is mostly derived from its countries of origin. In southeastern countries, chronic mitragynine use is complicated by weight loss, fatigue, constipation, dehydration, hand tremor, headache, and

hyperpigmentation (2, 8). Adverse effects reported in western countries include abdominal pain, nausea/vomiting, pruritus, mouth and throat numbness, sedation, dizziness, visual disturbances, cholestatic jaundice, seizures, and coma (2, 12). Interestingly, kratom-induced toxicity and death have not been reported previously in Southeast Asia and this may be secondary to either the underreporting of cases or the development of tolerance amongst chronic users (2). Persistent users eventually develop dependence and tolerance, complicated by both physical and psychological withdrawal symptoms upon cessation, which resolves within one to three days (2, 8, 9, 13). The reported withdrawal symptoms range from the physical (e.g., rhinorrhea, lacrimation, myalgia, and arthralgia) to the psychological (e.g., aggression, hostility, and inability to work) (8). At present, standardized therapy for kratom dependence has not been elucidated (2).



Image 2: Kratom leaves (Used under license from www.shutterstock.com).



Although marketed as a herbal preparation with medicinal benefits as described above, mitragynine toxicity-associated fatalities have been reported in the literature (14-17). We present a case of a mitragynine-associated fatality in Canada in the setting of mixed drug toxicity, although this case is distinguished by a potentially independently fatal blood concentration of mitragynine as measured postmortem.

CASE REPORT

A 56-year-old woman with a history of chronic obstructive pulmonary disease (COPD) was found dead in bed after recent complaints of dyspnea and cough. Her prescribed medications consisted of Percocet (acetaminophen and oxycodone) and lorazepam. Scene investigation indicated that the number of pills remaining in each prescription bottle was noticeably less than if they had been taken as prescribed. She was also known to use cannabidiol oil drops and relatives reported that she would use a “methadone-like” powder of unknown composition that was obtained from Indonesia. Given the sudden unexpected nature of her death, a medicolegal postmortem examination was requested to determine her cause and manner of death.

The medicolegal postmortem examination was performed on the day after her body was discovered. External examination indicated that the decedent was a slightly overweight, middle-aged woman with a body mass index of 25.3 kg/m². A white residue was on the outside of her lips. Internal examination demonstrated cardiomegaly (heart weight, 532 g) with biventricular hypertrophy and mild atheromatous disease of the coronary arteries with no myocardial scars or established acute myocardial infarction. Luminal pus was within the tracheobronchial tree and both lungs were heavy (left, 696 g; right, 658 g) and appeared hyperinflated with prominent fibrosis, consistent with the decedent’s history of COPD, but no features of bronchopneumonic consolidation were evident. The esophagus contained white residue similar to that seen on the lips, but only bile-stained mucoid fluid was in the stomach.

The liver exhibited a prominent “nutmeg appearance,” suggestive of congestive hepatopathy from passive venous congestion, attributable to right-sided heart failure. Fine and coarse granular cortical scarring of the kidneys was also noted. The urinary bladder contained 14 mL of urine.

Tissues from the main organs were processed into histological sections and examined microscopically. Cardiac blood, femoral venous blood, and urine were sent for standard toxicological analysis.

Histologic examination of the tissues revealed bilateral bronchopneumonia in a background of COPD changes in the lungs. Group B *Streptococcus* and *Staphylococcus aureus* were isolated from a swab of the pus in the trachea. Myocyte nuclear hypertrophy and patchy interstitial fibrosis were in the left ventricular myocardium. The liver exhibited mild portal inflammation with congestion of the terminal hepatic venules and perivenular regions. The kidneys exhibited scattered glomerulosclerosis and interstitial fibrosis.

Toxicological analysis of the femoral venous blood using a standardized panel detected oxycodone, lorazepam, and mitragynine; no other novel psychoactive substances were detected. Only oxycodone and lorazepam could be quantified by the reporting laboratory. The quantified concentrations of oxycodone (0.19 ± 0.01 mg/L) and lorazepam (63 ± 5 ng/L) were each not toxic in isolation, although the concentration of oxycodone was just under the reporting laboratory’s threshold of fatality (0.21 mg/L). As the reporting toxicology laboratory did not possess a quantification method for mitragynine, the femoral venous blood sample was sent to a referral laboratory with such capability in the United States. The referral toxicology laboratory reported an independently fatal concentration of mitragynine of 2500 ng/mL, based on previously published values from mixed drug toxicity case reports (range of 20-1060 ng/mL). The reported concentration of lorazepam was in the range consistent with therapeutic use and the reporting laboratory indicted that no reliable reports of fatalities solely attributable to lorazepam exist.



Analytical Toxicology

The analytical method employed in the quantification of the mitragynine was as follows:

Sample Preparation

A whole blood sample of postmortem femoral venous blood was prepared for analysis via liquid-liquid extraction with 0.1 M Borax buffer (pH 10.4) and n-butyl chloride:ethyl acetate in 70:30 ratio. The generated supernatant was transferred to auto sampler vials. Extracts were dried and reconstituted with 500 μ L 0.1% formic acid in acetonitrile.

Analysis

The analytical methods were validated on a Waters TQD Tandem Mass Spectrometer coupled to a Waters Acuity Ultra Performance LC system. The instrument was operated in positive electrospray, multiple reaction monitoring mode. Separation for blood method was performed on a Thermo Scientific BetaSil Silica-100 column, 2.1 x 100 mm column size, 5.0 μ m particle size. An isocratic gradient of 10% ammonium formate buffer, pH 4.0 to 90% acetonitrile was used for chromatographic separation.

LC-MS/MS Transitions

The transitions identified for the quantitative and qualitative determination of mitragynine were 399.3>174.1 and 399.3>226.2. Transitions for D3-mitragynine were 402.3>177.1 and 402.3 >226.2. The quantified value of mitragynine was then extrapolated.

Overall, the positive toxicological findings in the femoral venous blood were as stated in **Table 1**.

Clinicopathological considerations indicated that her cause of death was combined mitragynine, lorazepam, and oxycodone toxicity (given the potential for synergistic effects of all three detected drugs on depressing the central nervous system) in conjunction with bronchopneumonia. In the context of the clinical history, the identified bronchopneumonia was more likely to have been a preexistent entity that had developed as a complication of COPD rather than as a secondary phenomenon of her mixed drug toxicity. Bronchopneumonia was therefore listed as a contributory cause of death. The mitragynine concentration was potentially independently fatal and death may have occurred in the absence of the other detected drugs (oxycodone and lorazepam) or underlying bronchopneumonia.

DISCUSSION

The mitragynine concentration detected in this case is the highest reported in kratom-related fatalities to date when compared to the previously published value of 1060 ng/mL (4). To our knowledge, this is the first reported case of mitragynine-associated fatality in Canada. Echoing previous reports, mitragynine was not the sole substance detected on toxicological analysis (4, 14-17). However, the measured concentration can be independently fatal, although the lethal and toxic ranges of mitragynine has not yet been definitively established (17). Studies in rat models have put forth a single dose of 200 mg/kg of oral mitragynine as the lethal cut off (18, 19). The oxycodone and lorazepam concentrations did not independently reach lethal ranges, but they would have contributed synergistically to the mitragynine-induced opioid agonistic effect to produce profound central nervous system and respiratory depression. The combination of the lethal range mitragynine concentration and its interaction with the two other depressant/sedative hypnotic drugs would

Table 1: Summary of Toxicology Results on Femoral Venous Blood and Their Respective Reference Values

Drug	Measured Concentrations	Lethal Reference Value
Oxycodone	0.19 ± 0.01 mg/L	>0.21 mg/L
Lorazepam	63 ± 5 ng/mL	Not reliably defined
Mitragynine	2500 ng/mL	20-1060 ng/mL (based on published case reports)



have been primarily responsible for the decedent's demise from a synergistic "drug-drug interaction" (11).

The addictive properties of mitragynine through its induced euphoria, mood enhancement, and improved performance portends its potential for abuse (2, 12). Dependence and tolerance develops in association with chronic consumption of high doses (8, 9). In a web-based anonymous survey, kratom users reported tolerance and an inclination to increase their intake to achieve the same positive effects (12). However, a safe ceiling dose for chronic consumption in humans has not been established (10). Given the lethal-range mitragynine level detected in our case, the decedent may have been a chronic consumer with high tolerance. There is no history of previous suicidal attempts, expressed suicidal ideations, or evidence of foul play to suggest this was an intentional overdose. At present, a standard treatment protocol for kratom dependence or antidote for acute toxicity has not been developed (2). In a mouse model, withdrawal symptoms were induced by naloxone administration following development of tolerance to 7-hydroxymitragynine, suggesting a potential antidote for mitragynine associated toxicity (20).

In Thailand, Malaysia, Bhutan, and Myanmar, the planting, sale, and purchase of kratom are illegal and penalties are imposed for those in possession of the substance (2). However, locals may obtain their supplies from known suppliers in the form of trees, prepared solutions, or tea (2, 8). Since 2005, kratom usage has been illegal in Australia (21). In western countries, mitragynine may be purchased via the Internet from unknown suppliers in the form of capsules, tablets, gums, leaves, and extracts for smoking, often with little knowledge of its quality and content (2, 22). Internet sales have marketed mitragynine as herbal remedies or dietary supplements without acknowledgement of its adverse effects and toxicities (2). The United States Drug Enforcement Administration has categorized kratom as a "Drug and Chemical of Concern" under consideration for making it illegal if supporting evidence of its addiction potential and health hazards become available (4, 23, 24). In Canada, kratom products were voluntarily recalled by its

marketing company citing health risk concerns (25). Kratom-containing products are not authorized for sale by Health Canada, who recommended against its consumption in view of its adverse effects (25). Although marketed as a legal herb for its physiological and psychological benefits, its side effects and potential for lethality are increasingly recognized. The existing literature highlights the need for further supporting evidence and systematic review of kratom-associated health problems to help inform public health awareness and aid in development of regulations to prevent its adverse utilization (5). Furthermore, a reliable antidote for mitragynine-induced toxicity remains to be elucidated.

CONCLUSION

We present a case of an accidental death secondary to multidrug toxicity whereby mitragynine toxicity is primarily implicated. The measured mitragynine is likely independently fatal and appears to be the highest reported value in the medical literature to date. This is the first reported case of mitragynine-associated fatality in Canada. The only plausible source of the mitragynine lies in the report of the decedent's relatives that she would use a "methadone-like" powder of unknown composition which she had obtained from Indonesia, presumably via the Internet. Apart from contributing to the existing body of evidence on the adverse effects of mitragynine use, this case report is presented to help inform policy development to safeguard against the ease of accessibility of this easily available substance via the Internet to prevent further deaths.

REFERENCES

- 1) Domingo O, Roider G, Stover A, et al. Mitragynine concentrations in two fatalities. *Forensic Sci Int*. 2017 Feb; 271:e1-e7. PMID: 28089300. <https://doi.org/10.1016/j.forsciint.2016.12.020>.
- 2) Singh D, Narayanan S, Vicknasingam B. Traditional and non-traditional uses of Mitragynine (Kratom): a survey of the literature. *Brain Res Bull*. 2016 Sep; 126(Pt 1):41-46. PMID: 27178014. <https://doi.org/10.1016/j.brainresbull.2016.05.004>.
- 3) Orio L, Alexandru L, Cravotto G, et al. UAE, MAE, SFE-CO₂ and classical methods for the extraction of *Mitragyna speciosa* leaves. *Ultrason Sonochem*. 2012 May; 19(3):591-5. PMID: 22054912. <https://doi.org/10.1016/j.ulstchonch.2011.10.001>.

- 4) Karinen R, Fosen JT, Rogde S, Vindenes V. An accidental poisoning with mitragynine. *Forensic Sci Int.* 2014 Dec; 245:e29-32. PMID: 25453780. <https://doi.org/10.1016/j.forsciint.2014.10.025>.
- 5) Hassan Z, Muzaimi M, Navaratnam V, et al. From Kratom to mitragynine and its derivatives: physiological and behavioral effects related to use, abuse and addiction. *Neurosci Biobehav Rev.* 2013 Feb; 37(2):138-51. PMID: 23206666. <https://doi.org/10.1016/j.neubiorev.2012.11.012>.
- 6) Babu KM, McCurdy CR, Boyer EW. Opioid receptors and legal highs: salvia/divinorum and Kratom. *Clin Toxicol (Phila)*. 2008 Feb; 46(2):146-52. PMID: 18259963. <https://doi.org/10.1080/15563650701241795>.
- 7) Vicknasingam B, Narayanan S, Beng GT, Mansor SM. The informal use of Ketum (Mitragyna speciosa) for opioid withdrawal in the northern states of peninsular Malaysia and implications for drug substitution therapy. *Int J Drug Policy.* 2010 Jul; 21(4):283-8. PMID: 20092998. <https://doi.org/10.1016/j.drugpo.2009.12.003>.
- 8) Suwanlert S. A study of kratom eaters in Thailand. *Bull Narc.* 1975 Jul-Sep; 27(3):21-7. PMID: 1041694.
- 9) Henningfield JE, Fant RV, Wang DW. The abuse potential of Kratom according the 8 factors of the controlled substances act: implications for regulation and research. *Psychopharmacology (Berl).* 2018 Feb; 235(2):573-589. PMID: 29273821. PMCID: PMC5813050. <https://doi.org/10.1007/s00213-017-4813-4>.
- 10) Kruegel AC, Grundmann O. The medicinal chemistry and neuropharmacology of Kratom: a preliminary discussion of a promising medicinal plant and analysis of its potential for abuse. *Neuropharmacology.* 2017 Aug 19. pii: S0028-3908(17)30393-3. PMID: 28830758. <https://doi.org/10.1016/j.neuropharm.2017.08.026>.
- 11) Suhaimi FW, Yusoff NH, Hassan R, et al. Neurobiology of Kratom and its main alkaloid mitragynine. *Brain Res Bull.* 2016 Sep; 126(Pt 1): 29-40. PMID: 2708165. <https://doi.org/10.1016/j.brainresbull.2016.03.015>.
- 12) Swogger MT, Hart E, Erowid F, et al. Experiences of Kratom users: a qualitative analysis. *J Psychoactive Drugs.* 2015 Nov-Dec; 47(5):360-7. PMID: 26595229. <https://doi.org/10.1080/02791072.2015.1096434>.
- 13) Yusoff NH, Suhaimi FW, Vadivelu RK, et al. Abuse potential and adverse cognitive effects of mitragynine (Kratom). *Addict Biol.* 2016 Jan; 21(1):98-110. PMID: 25262913. <https://doi.org/10.1111/adb.12185>.
- 14) Kronstrand R, Roman M, Thelander G, Eriksson A. Unintentional fatal intoxications with mitragynine and O-desmethyltramadol from the herbal blend Krypton. *J Anal Toxicol.* 2011 May; 35(4):242-7. PMID: 21513619. <https://doi.org/10.1093/anatox/35.4.242>.
- 15) McIntyre IM, Trochta A, Stolberg S, Campman SC. Mitragynine 'Kratom' related fatality: a case report with postmortem concentrations. *J Anal Toxicol.* 2015 Mar; 39(2):152-5. PMID: 25516573. <https://doi.org/10.1093/jat/bku137>.
- 16) Holler JM, Vorce SP, McDonough-Bender PC, et al. A drug toxicity death involving propylhexedrine and mitragynine. *J Anal Toxicol.* 2011 Jan; 35(1):54-9. PMID: 21219704. <https://doi.org/10.1093/anatox/35.1.54>.
- 17) Neerman MF, Frost RE, Deking J. A drug fatality involving Kratom. *J Forensic Sci.* 2013 Jan; 58 Suppl 1:S278-9. PMID: 23082895. <https://doi.org/10.1111/1556-4029.12009>.
- 18) Azizi J, Ismail S, Mordini MZ, et al. In vitro and in vivo effects of three different Mitragyna speciosa korth leaf extracts on phase II drug metabolizing enzymes - glutathione transferases (GSTs). *Molecules.* 2010 Jan 20; 15(1):432-41. PMID: 20110902. <https://doi.org/10.3390/molecules15010432>.
- 19) Janchawee B, Keawpradub N, Chitrakarn S, et al. A high-performance liquid chromatographic method for determination of mitragynine in serum and its application to a pharmacokinetic study in rats. *Biomed Chromatogr.* 2007 Feb; 21(2):176-83. PMID: 17221920. <https://doi.org/10.1002/bmc.731>.
- 20) Matsumoto K, Horie S, Takayama H, et al. Antinociception, tolerance and withdrawal symptoms induced by 7-hydroxymitragynine, an alkaloid from the Thai medicinal herb Mitragyna speciosa. *Life Sci.* 2005 Nov 19; 78(1):2-7. PMID: 16169018. <https://doi.org/10.1016/j.lfs.2004.10.086>.
- 21) Philipp AA, Wissenbach DK, Zoernlein SW, et al. Studies on the metabolism of mitragynine, the main alkaloid of the herbal drug Kratom, in rat and human urine using liquid chromatography-linear ion trap mass spectrometry. *J Mass Spectrom.* 2009 Aug; 44(8):1249-61. PMID: 19536806. <https://doi.org/10.1002/jms.1607>.
- 22) Warner ML, Kaufman NC, Grundmann O. The pharmacology and toxicology of Kratom: from traditional herb to drug of abuse. *Int J Legal Med.* 2016 Jan; 130(1):127-38. PMID: 26511390. <https://doi.org/10.1007/s00414-015-1279-y>.
- 23) Drugs of abuse: a DEA resource guide 2017 [Internet]. Washington: Drug Enforcement Administration, US Department of Justice; 2017 [cited 2018 Jan 25]. 93 p. Available from: https://www.dea.gov/pr/multimedia-library/publications/drug_of_abuse.pdf#page=84.
- 24) Prozialeck WC, Jivan JK, Andurkar SV. Pharmacology of Kratom: an emerging botanical agent with stimulant, analgesic and opioid-like effects. *J Am Osteopath Assoc.* 2012 Dec; 112(12):792-9.
- 25) Health Canada [Internet]. Ottawa: Health Canada; c2018. Recalls and safety alerts: unauthorized 'High By Nature' kratom products recalled by Garnoff Botanicals as they may pose serious health risks; 2017 May 19 [cited 2018 Jan 25]. Available from: <http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2017/63338a-eng.php>.



Improving Forensic Pathologic Investigation of Sudden Death in the Young: Tools, Guidance, and Methods of Cardiovascular Dissection from the Sudden Death in the Young Case Registry

Sam P. Gulino, Kristin Burns, Wendy M. Gunther, Heather MacLeod

ABSTRACT

The Sudden Death in the Young (SDY) Case Registry, a prospective, population-based registry active in ten states, has developed tools to aid pathologists and death investigators in the evaluation and autopsy of unexplained, natural sudden deaths in the pediatric population. The tools were developed by a team of experts representing forensic pathology; pediatric-, cardiac-, and neuropathology; cardiology; neurology/epileptology; pediatrics; genetic counseling; and public health. These tools focus on collecting data relevant to determination of cause of death with a focus on dissection of the cardiovascular system. The tools provide an objective checklist format for ease of use and data extraction. By sharing the tools here and highlighting the examination of the cardiovascular system, the SDY Case Registry encourages a standardized approach to death investigation, autopsy, and data collection for sudden, unexpected deaths in the young towards a goal of informing prevention efforts. *Acad Forensic Pathol.* 2018 8(2): 347-391

AUTHORS

Sam P. Gulino MD, Philadelphia Medical Examiner's Office

Roles: Project conception and/or design, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work

Kristin Burns MD, National Institutes of Health - National Heart, Lung and Blood Institute

Roles: Project conception and/or design, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work

Wendy M. Gunther MD, Office of the Chief Medical Examiner - Tidewater District

Roles: Project conception and/or design, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work

Heather MacLeod MS CGC, SDY Case Registry

Roles: Project conception and/or design, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work

CORRESPONDENCE

Heather MacLeod MS CGC, 2479 Woodlake Circle, Okemos MI 48864, hmacleodgc@gmail.com

ETHICAL APPROVAL

As per Journal Policies, ethical approval was not required for this manuscript

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies conducted with animals or on living human subjects

STATEMENT OF INFORMED CONSENT

No identifiable personal data were presented in this manuscript

DISCLOSURES & DECLARATION OF CONFLICTS OF INTEREST

This study was made possible by the Sudden Death in the Young Case Registry, a collaboration between the National Heart, Lung, and Blood Institute and the National Institute of Neurologic Disorders and Stroke of the National Institutes of Health, and the Centers for Disease Control and Prevention, and its Data Coordinating Center at the Michigan Public Health Institute and SDY Biorepository at the University of Michigan. This work is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the Centers for Disease Control and Prevention. The authors, reviewers, editors, and publication staff do not report any relevant conflicts of interest

FINANCIAL DISCLOSURE

The authors have indicated that they do not have financial relationships to disclose that are relevant to this manuscript

KEYWORDS

Forensic pathology, Sudden death, Pediatrics, Cardiology, Cardiovascular pathology, Postmortem genetic testing

INFORMATION

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

©2018 Academic Forensic Pathology International • (ISSN: 1925-3621) • <https://doi.org/10.23907/2018.024>

Submitted for consideration on 1 Feb 2018. Accepted for publication on 18 Apr 2018



INTRODUCTION

The sudden death of a child is a devastating event that leaves family members, medical providers, and the community searching for answers. Some causes of sudden death in the young (SDY) are identifiable at autopsy (e.g., infections, motor vehicle accidents, suicide by hanging, or homicide by gunshot wound); but in many cases of sudden death that present to the medical examiner or coroner (ME/C), the history, autopsy, and death scene investigation do not reveal the cause of death (1).

Some medical conditions associated with SDY may be inherited (e.g., long QT syndrome and hypertrophic cardiomyopathy), and surviving family members may not know that they or their other children are at risk. Identifying heritable causes of death in SDY cases is critical to initiate cascade screening of surviving family members and to facilitate access to therapies that may lower their risk of sudden death. In cases of SDY with no identifiable cause at autopsy, there is a critical knowledge gap concerning mechanisms, clinically identifiable features, and epidemiology, fueled partly by a lack of standardized procedures in the United States for investigating, classifying, and reporting SDY. Medical examiners, coroners, and death scene investigators are critical partners in the effort to gather high-quality information to address this knowledge gap and to improve the understanding of SDY.

Most sudden deaths in infancy or childhood will fall under the jurisdiction of ME/C because they occur suddenly, unexpectedly, and in a person in apparently good health. In most states, the determination of whether to perform an autopsy on an SDY case is left to the discretion of the ME/C. Only a small minority of states specifically require an autopsy by law as part of the investigation of SDY (2). When an autopsy is performed, the extent of the autopsy and its ancillary testing may vary by jurisdiction (3, 4). This variation may be due to funding, ME/C preferences, prior experience and training of the ME or coroner's pathologist performing the autopsy, and ME/C workload. Funding for autopsies and ME/C staffing is determined by state or county budgets that may have limited resourc-

es and many competing priorities. In addition, most states are currently experiencing an increase in deaths due to the opioid epidemic, resulting in a significant burden on the death investigation system that reduces the time and resources that ME/C can spend on the investigation of natural deaths. Despite limits on the time and budgets, many ME/C are dedicated to improving the understanding of these unexpected infant and child deaths.

To facilitate improved understanding of SDY and ultimately inform prevention efforts, the Sudden Death in the Young Case Registry created tools and guidance to encourage standardized, comprehensive autopsies and death scene investigations for SDY cases. The tools focus on important elements of the autopsy that are relevant to sudden, unexpected, natural deaths in infants, children, and adolescents. We share these tools herein and provide specific guidance on the performance of the cardiac examination, given the high incidence of cardiac causes of SDY in children over one year of age. We hope that these tools may be useful in the ME/C community and may promote more standardized approaches to characterizing, classifying, understanding, and ultimately preventing sudden, unexpected natural deaths in the young.

DISCUSSION

The Sudden Death in the Young (SDY) Case Registry

The SDY Case Registry is a collaborative effort between the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the Michigan Public Health Institute (MPHI) to address the knowledge gaps in the epidemiology and causes of SDY in the United States (5). The SDY Case Registry includes infants and children from birth through 19 years of age in seven states and specific regions of three additional states. These selected jurisdictions cover 24% of the pediatric population in the United States and approximately 20% of SDY. The SDY Case Registry is one of the largest prospective, population-based cohorts to date of children who have died suddenly in the United States.

The goals of the SDY Case Registry are to: 1) determine the incidence of SDY using population-based surveillance in a large cohort in the United States; 2) compile data from SDY cases to create a resource of phenotypic and genotypic information for research; 3) encourage standardized approaches to investigation, autopsy, and categorization of SDY cases; 4) develop partnerships between local, state, and federal stakeholders towards the common goal of understanding and preventing SDY; and 5) support families who have lost loved ones to SDY by providing resources for bereavement and medical evaluation of surviving family members.

Figure 1 illustrates the flow of cases through the SDY Case Registry. Sudden deaths in infants and children are identified through ME/C offices, where the inclusion and exclusion criteria are applied. Since the SDY Case Registry is population-based, the decedent must have been a resident of the participating jurisdiction or state to be eligible. The registry does not discriminate between witnessed and unwitnessed deaths. Inclusion criteria include: sudden and unexpected death; age less than 20 years; death not explained by a homicide, suicide, drug overdose, or terminal illness; and death due to injury when there may have been an inciting natural cause (e.g., drowning or death of the driver in a motor vehicle accident, which may have been triggered by an underlying cardiac or neurological condition). “Sudden” is defined as death within 24 hours of the first symptom, or death under medical

care after resuscitation from an out-of-hospital cardiac arrest. Although some studies define the window of sudden death as one hour from symptom onset, the SDY Case Registry uses a window of 24 hours due to the high number of infant and childhood deaths that occur during sleep. Comorbid conditions with unrelated symptoms that might overlap this window are expected to have a low incidence, simply because sudden childhood deaths after infancy are so rare. “Unexpected” is defined as the death of an infant or child who was in good health, had either a stable, chronic condition, or had an acute illness that would not be expected to cause death.

Once included, each case is reviewed by a local or statewide child death review team (6), followed by an advanced review by a team of local clinical experts that also categorizes the case using a standardized algorithm to enable an SDY incidence rate to be calculated (5). Review teams are composed of experts in forensic pathology, cardiology, neurology/epileptology, pediatrics, genetic counseling, and public health, among other subject matter experts.

Use of the SDY Case Registry tools for death scene investigation and autopsy is encouraged to promote standardization, as well as to offer the chance of obtaining wide-ranging investigative and autopsy information. During the autopsy, pathologists collect samples of blood and tissue for DNA extraction. Blood in an EDTA tube is the preferred sample type, but



Figure 1: Case flow in the Sudden Death in the Young Case Registry.



fresh frozen liver and/or heart tissue serve as a back-up if the blood does not yield usable DNA. Currently, blood spot cards, formalin fixed tissue, and paraffin fixed tissue do not yield a reliable, adequate quality and quantity of DNA to allow for exome/genome sequencing. Blood and tissue samples are shipped to the SDY Case Registry Biorepository for DNA extraction and storage. The biorepository has a 99% success rate in obtaining adequate quality and quantity of DNA.

For all SDY cases, next of kin consent is sought for diagnostic genetic testing, future research studies that may or may not involve genetic testing, DNA banking, and return of genetic results. Although consent is not required for diagnostic genetic testing, the SDY Case Registry sought advice from ethicists and opted to obtain consent for diagnostic genetic testing as part of a menu of options due to the implications the results may have for the family (7).

The DNA may be used for genetic research by NIH-funded investigators focused on determining the causes of SDY as well as via diagnostic genetic testing. Invitae, a genetic testing company, has partnered with the MPHI and the Biorepository to offer in-kind (donated) diagnostic genetic testing to 900 cases in the SDY Case Registry over a three-year period. Genetic testing is offered on autopsy-negative cases as well as cases suggestive of cardiomyopathy using a panel of arrhythmia and cardiomyopathy genes. Such testing may provide additional information that may aid the ME/C in determining the cause of death and inform the approach to cascade screening of surviving family members. Access to such postmortem genetic testing for the ME/C community has previously been limited due to cost.

Tools to Assist With Autopsy and Death Scene Investigation of SDY

The SDY Case Registry sought guidance from an autopsy protocol task force comprised of ME/C; death investigators; pediatric-, cardiac-, and neuropathologists; genetic counselors; emergency room physicians; and public health experts (**Appendix 1**). After reviewing existing autopsy protocols for SDY from Australia

(8), Ireland (9), Canada (10), and the United Kingdom (11), the task force developed a standardized, comprehensive recommended approach to an SDY Case Registry autopsy and a protocol for sample collection for research and diagnostic genetic testing and DNA banking. The task force also developed tools to facilitate a standardized approach to death investigation. Materials and resources have been created by currently funded SDY states and the SDY technical assistance team for family referral for medical screening and genetic counseling for SDY cases (**Appendix 2 and 3**).

The SDY Field Investigation Guide and Family Interview Summary Sheet

The SDY Field Investigation Guide and Family Interview Tool (**Appendix 4**) was designed for death scene investigators and includes a series of questions, in both checklist and narrative formats, for the family and medical providers to obtain a comprehensive review of the history and circumstances surrounding the child's death. The tool begins with a list of suggested records to collect on the decedent before fatality review, and goes on to include questions ranging from general information about the family to specific information about the events leading up to the child's death. Although experienced investigators will ask many of these questions without the guide, the tool provides a helpful reminder of a comprehensive list of questions about triggers prior to death, symptoms within 24 and 72 hours of death, family history of sudden death, and clues that may help the pathologist identify genetic syndromes. Because the guide offers a standardized list of questions, the same comprehensive review can be performed for every SDY case.

The SDY Case Registry Autopsy Guidance and Summary Tools

The SDY Case Registry autopsy guidance tools focus on medical conditions and other anatomic findings that may be associated with SDY. They include a recommended comprehensive cardiovascular examination due to the high incidence of cardiac causes of SDY in children over age one. The tools are in checklist format to enable rapid and easy use by patholo-



gists. The checklist format also discourages narrative description to facilitate categorization of the cases and easier data mining.

The autopsy guidance tools are available in two forms: 1) the guidance tool and 2) the summary tool. The SDY Autopsy Guidance (**Appendix 5**) is 20 pages long, and although it is less practical for everyday use in the field, it is a valuable resource outlining the elements of a comprehensive SDY-related autopsy. Although the autopsy guidance form may seem at first glance to be time consuming because of its length, with its checklist format and repeated use, it becomes a rapid and easy form to fill out. The SDY Autopsy Summary (**Appendix 6**) is a checklist that is used to guide the pathologist in participating jurisdictions to the critical information that needs to be collected from the SDY Case Registry autopsy. The autopsy summary tool offers the forensic pathologist the chance to ask questions deemed important to the pediatric SDY autopsy by experts on the task force with additional training in several tissue and organ systems.

Many individual ME/C offices have their own existing forms for autopsies, and some offices participating in the SDY Case Registry have added questions from the SDY tools into their own forms. Integration of the SDY Autopsy Summary questions into an existing pediatric autopsy protocol may improve data collection on all pediatric cases for a given office, but states and jurisdictions participating in the SDY Case Registry are strongly encouraged to use the guidance and summary tools to improve data quality for the Registry. After becoming familiar with the tools, pathologists may incorporate elements of the SDY Case Registry summary tool into their routine practice and it may become easier to judge when an organ or system deserves additional expert consultation.

Recommended Practices for SDY Case Registry Autopsies

The following paragraphs describe the recommended practice by the SDY Case Registry to perform a comprehensive autopsy on cases of sudden, unexpected, natural death of a child. This section pays particular

attention to the cardiac examination, given the importance of cardiac causes in such deaths of children, especially over age one. This guidance also highlights some subtle features that deserve specific attention in such cases, and that may help to identify heritable diagnoses with implications for surviving family members.

The SDY Case Registry autopsy tools recommend a complete autopsy. Limited autopsy runs the risk of failing to detect information that may be critical to determining the cause and manner of death, as well as data that may be valuable for research.

After recording basic demographic and identifying information, record the sex, weight, body length, and a general description of body habitus and development. In children three years of age and under, record the head circumference. Use standardized growth charts to plot the anthropometric data and compare it to antemortem measurements, if any are available. These are used to provide a quick glimpse into the child's physical development and to identify a child whose development has been impaired by genetic or acquired chronic illnesses, abuse, neglect, or poor nutrition. The external examination includes the usual descriptions of scars, birthmarks, trauma, medical interventions, and physical stigmata of diseases and syndromes. Significant findings are often most effectively captured with photography as well as narrative; this may include pertinent negative findings.

Radiography is an important adjunct to the autopsy investigation of sudden death. Whole body radiography (so-called "babygrams") may be useful in demonstrating skeletal dysplasias, syndromes, and metabolic disorders (12), but they are technically inadequate for the demonstration of metaphyseal fractures (13). For this reason, a skeletal survey is recommended as part of the postmortem evaluation of infants and small children in cases suspicious for fatal abuse (14). Since the full circumstances of the child's death may not be known before the autopsy is performed, consideration should be given to performing a skeletal survey in all cases of sudden, unexplained death in infants and young children (13). In older children, in addition



to the demonstration of fractures, plain-film radiography of the chest can be useful in individual cases for demonstration of gas embolism, pneumothorax, and pneumomediastinum (15).

There has been much interest in the use of computed tomography (CT) and magnetic resonance imaging (MRI) as an adjunct to or replacement for autopsy, particularly in the setting of trauma. Few studies have been done on the use of so-called “virtual autopsy” specifically in cases of sudden unexplained deaths in infants and small children (16, 17). These studies did not demonstrate an ability to diagnose specific non-traumatic cardiovascular disease, aside from the presence of cardiac hypertrophy. This is inadequate, since a full understanding of the causes of SDY is needed, both in individual cases and across the population. In addition to the limited access most ME/C have to these expensive imaging modalities, interpretation by a radiologist who is experienced in interpreting postmortem CT/MRI images is required, as postmortem changes may produce artifacts that can mask or simulate pathology (18, 19). Thus, at present, postmortem CT/MRI imaging may be a useful adjunct to the autopsy evaluation of SDY, but should not replace it.

The SDY Case Registry autopsy guidance prompts careful examination of a variety of causes of SDY, including pulmonary etiologies (e.g., embolism, hypertension, pneumothorax), gastrointestinal catastrophe (e.g., volvulus, obstruction, intussusception), infection (e.g., meningitis, myocarditis, sepsis), and neurologic abnormalities (e.g., stroke, hemorrhage, herniation), among others. The SDY Case Registry encourages consultation with experts with additional training in pediatric-, cardiac-, and neuropathology, when feasible, to help identify subtle features of underlying disease.

Cardiovascular Examination

Detailed guides to the examination of the heart have been published elsewhere (20, 21). The following is intended to provide guidance that will suit the examination of most cases of SDY. However, in cases with complex pathology, especially cases involving

congenital heart disease or implanted cardiac devices, consultation with a cardiovascular pathologist is strongly recommended.

Prior to removal of the heart, the pericardium should be assessed for exudates, thickening, or calcification and any effusion or hemorrhage in the pericardial space should be noted and measured. The position and apical direction of the heart should then be documented. The heart may then be removed separately or in a block with the other thoracic organs. En bloc removal is particularly suited to situations in which congenital heart disease is suspected, as it facilitates examination of the arterial and venous connections of the heart, and for disorders involving the proximal portions of the aorta, such as aortic dissection.

After the removal of extraneous extra-cardiac soft tissue, the heart should be weighed. If, during subsequent dissection, it is found that the cardiac chambers contain abundant clotted blood, it is recommended that the heart be re-weighed after dissection and removal of the blood clots.

Prior to opening the heart, the epicardial arteries should then be evaluated by serial sectioning beginning near the aortic root and extending distally for as far as a distinct lumen can be identified. In older children and adolescents, the distance between sections should not exceed 5 mm. In addition, care should be taken not to cut into the ascending aorta and thus disrupt the coronary ostia. Coronary dominance should be noted by determining whether the posterior descending artery arises from the right coronary artery, left circumflex coronary artery, or both. While routine microscopic examination of the coronary arteries is not necessary in most SDY cases, any grossly-observed abnormalities should be submitted for histology.

Multiple specialized methods of cardiac dissection, including methods that reproduce standard echocardiographic views, have been described. However, for most SDY cases, the heart is best examined using the inflow-outflow method (i.e., cutting along the flow of blood), with or without first sectioning the heart along its short axis.



Serial short-axis sections expose the greatest surface area of myocardium and facilitate measurement of the ventricular chambers and walls. It is, therefore, the preferred method for demonstrating myocardial pathology that can result in changes in myocardial color or texture (e.g., infarction, fibrosis, myocarditis), ventricular wall thickness, and chamber size. However, there are circumstances in which it may be desirable to skip short-axis sectioning. This is true of cases of known or suspected congenital heart disease, especially where examination of the muscular ventricular septum for defects is desired (such as a child who was known to have an uninvestigated cardiac murmur during life). Short-axis sections also may be unnecessarily difficult to perform when examining very small hearts, such as those of infants. In these cases, it is reasonable simply to proceed with opening the heart along the flow of blood as described below. When performed, short-axis sections should be made parallel to the base of the heart, visibly identifiable as the atrioventricular groove, beginning just above the apex and continuing superiorly until just below the tips of the left ventricular papillary muscles. These short-axis slices should be no more than about 10 mm in thickness, and will necessarily be much thinner in smaller hearts.

Sectioning the heart along the flow of blood (the so-called “inflow-outflow” method) begins with opening the right atrium from the inferior vena cava orifice to the tip of the right atrial appendage. This permits inspection of the entire right atrium, the atrial septum, and the tricuspid valve. It is not recommended that a further cut be made connecting the inferior and superior vena cavae, since such a cut will pass through the terminal crest of the right atrium, disrupting the sinoatrial node and SA nodal artery and making histologic examination of this portion of the conduction system difficult or impossible in cases where such an examination might be desirable.

The second cut is made through the posterior wall of the right ventricle, just lateral to the septum. This permits examination of the tricuspid valve and the endocardial surface of the right ventricle.

The third cut extends along the anterior wall of the right ventricle and right ventricular outflow tract through the pulmonic valve. This cut affords a view of the outflow portion of the right ventricle and the band of myocardium (the parietal band) that separates the tricuspid and pulmonic valves. The presence of the parietal band confirms that the morphologic right ventricle is correctly sided. The parietal band will be absent in congenital conditions in which the right-sided ventricle is a morphologic left ventricle (e.g., congenitally-corrected transposition of the great arteries).

The fourth cut connects the pulmonary vein orifices, with an additional cut out to the tip of the left atrial appendage. This permits a view of the interior of the left atrium, the left side of the atrial septum, and the mitral valve. This is an ideal time to inspect the atrial septum for septal defects and to determine if there is a patent foramen ovale.

This is also an ideal time to confirm that the heart is demonstrating normal sidedness, which is defined by the morphology of the atria. A morphologic right atrium will have a smooth posterior portion (derived from the sinus venosus) and pectinate muscle in its anterior portion and appendage (derived from the embryologic atrium). The smooth and pectinated parts of the right atrium meet at a ridge of muscle (the terminal crest). In contrast, a morphologic left atrium is entirely smooth-walled (being derived from the confluence of pulmonary veins) except for the appendage, which has pectinate muscles. In normal sidedness (*situs solitus*), the right- and left-sided atria will have the appropriate morphologic features described above. In a mirror-image heart (*situs inversus*), the right-sided atrium will have a left atrial morphology and the left-sided atrium will have right atrial morphology. In heterotaxy syndromes (*situs ambiguus*), both atria may have right atrial morphology (right isomerism, asplenia syndrome) or left atrial morphology (left isomerism, polysplenia syndrome), or one or both atria may have indeterminate morphology. Disorders of cardiac sidedness are typically associated with not only congenital heart disease but also abnormalities in multiple other organ systems. Consultation with a pediatric pathologist or cardiac pathologist is crucial in such cases.



The fifth cut is along the lateral wall of the left ventricle, through the mitral valve, to expose the left ventricular endocardial surface, the mitral valve, and its chordae tendineae and papillary muscles.

The sixth and final cut is along the anterior wall of the left ventricle, turning slightly rightward at the left ventricular outlet to match the direction of takeoff of the ascending aorta. In a properly-sided morphologic left ventricle, it will be apparent at this point that there is direct continuity between the atrioventricular (mitral) valve and the semilunar (aortic) valve, contrasted with the morphologic right ventricle in which these structures are separated by the parietal band. This final cut also affords the ideal opportunity to look for defects in the ventricular septum and to assess the positioning of the coronary ostia.

Properly located coronary ostia will be at, or just below, the sinotubular junction in roughly the midportions of the left and right sinuses of Valsalva. Minor variations of positioning of the ostia are common, as is the co-location of a second small ostium immediately next to that of the right coronary artery (the conus artery which, when not arising from the right sinus, arises as the first branch of the right coronary artery). When major anomalies of the coronary arteries occur, the exact position of the anomalous ostium should be described, along with a statement of the angle at which the artery arises relative to the aortic wall and, if takeoff is at an acute angle, whether or not this results in the presence of an intimal flap that can potentially occlude the ostium. A very acute angle of origin, sometimes nearly parallel to the aortic wall, and an occlusive intimal flap are commonly seen in cases of sudden death caused by anomalous coronary arteries.

Cardiac measurements are useful for detecting and documenting the presence of cardiac pathology. It is therefore recommended in SDY cases that heart weight and ventricular wall thicknesses be routinely collected. Historically, valve circumferences have also been taken but their utility to diagnose pathology has not been proven. Data collected from the SDY Case Registry will be examined to better understand

the utility of valve measurements and thus, taking such measurements could be useful for contributing to a dataset.

Heart weight is the most important of these measurements, as it directly reflects the presence and degree of myocardial loss (atrophy) or excess (hypertrophy). In order to facilitate comparison with published normal heart weights, the heart should only be weighed after the removal of extraneous extracardiac tissue and intracavitory blood clots. As is true with the examination of adult hearts, the hearts of post-pubertal teenagers can reasonably be weighed to the nearest 5 or 10 grams, while the hearts of younger children are best weighed to the nearest gram and those of infants and toddlers to the nearest one-tenth of a gram.

The thicknesses of the left and right ventricular free walls and ventricular septum should be measured at the level of the tips of the left ventricular papillary muscles (20). These measurements should take into account only the compact myocardium and should not include the trabecular muscle or the epicardial fat. In the right ventricle, it is not uncommon for the inferior (posterior) wall to be slightly thicker than that anterior wall, in which case it is recommended that the greater thickness be recorded.

The circumferences of the atrioventricular and semilunar valves could be useful for demonstrating the presence and degree of annular dilation, which can result in regurgitation and stenosis. The recommended method is to use a piece of string or other flexible material that can conform to the curved contours of the valve annulus. The string can then be laid out flat on a ruler to get an accurate measure of the circumference.

These cardiac measurements must be compared with tables of normal values that take into account age, sex, and body size. Body size is typically represented by body weight. However, for situations in which the decedent is very obese or where the body weight has been artificially reduced (such as after organ and tissue donation) or increased (such as in decedents with anasarca), comparison with normal ranges based on body length is more appropriate (20). Many such



reference tables exist. This author (SG) prefers those from the Mayo Clinic (22), which contains reference ranges for heart weight, wall thickness, and valve circumference for individuals from birth to 19 years old.

The measurements must be interpreted in light of one another and the gross morphology of the heart. For example, a heart may have a left ventricular wall thickness in the published normal range. One might be tempted to interpret this as an absence of left ventricular hypertrophy. However, if the heart weight is significantly increased, a normal LV thickness implies that the left ventricle is both hypertrophied and dilated (the law of Laplace dictates that the wall will thin as the cavity dilates), which should be apparent in the gross appearance of the left ventricle and an increased circumference of the mitral valve.

The presence of structural congenital heart disease may be encountered at autopsy in approximately 1% of the population. Although there is a reported association between sudden death and some more complex forms of congenital heart disease (such as tetralogy of Fallot, transposition of the great arteries, and single ventricle anomalies), many types of congenital heart disease do not typically cause sudden death, and caution should be exercised in attributing cause of death to congenital heart disease in all cases if discovered at autopsy.

Call To Action

Feedback is welcome from the ME/C community on the value and utility of these autopsy and death scene investigation tools. ME/C are encouraged to use these tools and approaches in their routine practice to help improve standardization of investigation and characterization of SDY cases. All tools are available for download from the SDY Case Registry website: www.sdyregistry.org (23). Medical examiners and coroners are also encouraged to participate in child death reviews and/or advanced reviews for SDY Case Registry states/jurisdictions to help improve case review and categorization.

CONCLUSION

The SDY Case Registry tools and guidance documents promote standardization of death investigation and autopsy practices in funded jurisdictions. After informed consent from the next of kin, the SDY Case Registry permits collection of comprehensive information from investigation and autopsy as well as samples for DNA extraction that may inform the cause of death determination, guide cascade screening for families, and create a resource for research. We encourage use of the tools and guidance described herein to foster unified approaches to improving the understanding of sudden, unexpected natural deaths in the young and lead us towards more targeted approaches to prevention.

ACKNOWLEDGEMENTS

Steering Committee: Karon Abe PhD; Kristin M. Burns MD; Lena Camperlengo DrPH RN; Lauren Bienemann BS; Carri Cottengim MA; Theresa M. Covington MPH; Heather Dykstra MPA; Alexa Erck Lambert MPH; Meghan Faulkner MA; Jonathan R. Kaltman MD; Rosemarie Kobau MPH MAPP; Lori de Ravello MPH; Heather MacLeod MS; Alissa Novak, Christine K. Olson MD; Sharyn Parks Brown PhD MPH; Ellen Rosenberg RN; Mark W. Russell MD; Carrie K. Shapiro-Mendoza PhD MPH; Esther Shaw MSIS; Niu Tian MD PhD; and Vicky Whittemore PhD

External Committee of Experts: Lisa M. Bateman MD; Robert M. Campbell MD; Sumeet S. Chugh MD; Laura Crandall PT MA; Sam P. Gulino MD; Gardiner O. Lapham RN MPH; Martha Lopez-Anderson; Kurt B. Nolte MD; David J. Thurman MD MPH; and Victoria L. Vetter MD.

States/Jurisdictions: Delaware, Georgia, Minnesota, Nevada, New Hampshire, New Jersey, San Francisco County in California, Tennessee, Tidewater Region of Virginia, and Wisconsin



REFERENCES

- 1) Eckart RE, Scoville SL, Campbell CL, et al. Sudden death in young adults: a 25-year review of autopsies in military recruits. *Ann Intern Med.* 2004 Dec 7; 141(11):829-34. PMID: 15583223. <https://doi.org/10.7326/0003-4819-141-11-200412070-00005>.
- 2) Caucci L WM. Table 2: Selected characteristics of deaths requiring autopsy by state [Internet]. Atlanta: Centers for Disease Control and Prevention; 2015 [cited 2017 Nov 16]. 4 p. Available from: <https://www.cdc.gov/phlp/docs/coroner/table2-autopsy.pdf>.
- 3) Hanzlick RL. A perspective on medicolegal death investigation in the United States: 2013. *Acad Forensic Pathol.* 2014 Mar; 4(1):2-9. <https://doi.org/10.23907/2014.001>.
- 4) Peterson G, Clark, SC. Forensic Autopsy Performance Standards [Internet]. Walnut Shade (MO): National Association of Medical Examiners; 2016 [cited 2017 Nov 16]. 26 p. Available from: <https://netforum.avectra.com/public/temp/ClientImages/NAME/684b2442-ae68-4e64-9ecc-015f8d0f849e.pdf>.
- 5) Burns KM, Bienemann L, Camperlengo L, et al. The sudden death in the young case registry: collaborating to understand and reduce mortality. *Pediatrics.* 2017 Mar; 139(3). pii: e20162757. PMID: 28228502. PMCID: PMC5330401. <https://doi.org/10.1542/peds.2016-2757>.
- 6) National Center for Fatality Review and Prevention [Internet]. Washington: National Center for Fatality Review and Prevention; c2018. CDR Principles; [cited 2016 May 23]. Available from: <https://www.ncfrp.org/cdr-process/cdr-principles/>.
- 7) McGuire AL, Moore Q, Majumder M, et al. The ethics of conducting molecular autopsies in cases of sudden death in the young. *Genome Res.* 2016 Sep; 26(9):1165-9. PMID: 27412853. PMCID: PMC5052042. <https://doi.org/10.1101/gr.192401.115>.
- 8) Post-mortem in sudden unexpected death in the young: guidelines on autopsy practice [Internet]. Sydney (Australia): Trans-Tasman Response AGAinst sudden Death in the Young; 2008 [cited 2017 Nov 16]. 29 p. Available from: <http://www.laudafinem.org/wp-content/uploads/2016/06/Protocol-for-TRAGADY.pdf>.
- 9) Margey R, Roy A, Tobin S, et al. Sudden cardiac death in 14- to 35-year olds in Ireland from 2005 to 2007: a retrospective registry. *Europace.* 2011 Oct; 13(10):1411-8. PMID: 21798877. <https://doi.org/10.1093/europace/eur161>.
- 10) Porter B. Office of the Chief Coroner for Ontario. Guidelines for the investigation of sudden cardiac death. Memo #08-01.
- 11) Basso C, Burke M, Fornes P, et al. Guidelines for autopsy investigation of sudden cardiac death. *Virchows Arch.* 2008 Jan; 452(1): 11-8. PMID: 17952460. <https://doi.org/10.1007/s00428-007-0505-5>.
- 12) Arthurs OJ, Calder AD, Kiho L, et al. Routine perinatal and paediatric post-mortem radiography: detection rates and implications for practice. *Pediatr Radiol.* 2014 Mar; 44(3):252-7. PMID: 24202433. <https://doi.org/10.1007/s00247-013-2804-0>.
- 13) Kleinman PK, Blackbourne BD, Marks SC, et al. Radiologic contributions to the investigation and prosecution of cases of fatal infant abuse. *N Engl J Med.* 1989 Feb 23; 320(8):507-11. PMID: 2915652. <https://doi.org/10.1056/nejm198902233200807>.
- 14) Society for Pediatric R, National Association of Medical Examiners. The Society for Pediatric Radiology--National Association of Medical Examiners: Post-mortem radiography in the evaluation of unexpected death in children less than 2 years of age whose death is suspicious for fatal abuse. *Pediatr Radiol.* 2004 Aug; 34(8):675-7. PMID: 15221240. <https://doi.org/10.1007/s00247-004-1235-3>.
- 15) Ludwig J. Handbook of autopsy practice. 3rd ed. Totowa (NJ): Humana Press; 2002. Chapter 12, Autopsy roentgenology and other imaging techniques. p. 117-22.
- 16) Oyake Y, Aoki T, Shiotani S, et al. Postmortem computed tomography for detecting causes of sudden death in infants and children: retrospective review of cases. *Radiat Med.* 2006 Aug; 24(7):493-502. PMID: 17058143. <https://doi.org/10.1007/s11604-006-0061-y>.
- 17) Proisy M, Marchand AJ, Loget P, et al. Whole-body post-mortem computed tomography compared with autopsy in the investigation of unexpected death in infants and children. *Eur Radiol.* 2013 Jun; 23(6): 1711-9. PMID: 23242003. <https://doi.org/10.1007/s00330-012-2738-1>.
- 18) Burton JL, Underwood J. Clinical, educational, and epidemiological value of autopsy. *Lancet.* 2007 Apr 28; 369(9571):1471-80. PMID: 17467518. [https://doi.org/10.1016/s0140-6736\(07\)60376-6](https://doi.org/10.1016/s0140-6736(07)60376-6).
- 19) Christe A, Flach P, Ross S, et al. Clinical radiology and postmortem imaging (Virtopsy) are not the same: specific and unspecific postmortem signs. *Leg Med (Tokyo).* 2010 Sep; 12(5):215-22. PMID: 20630787. <https://doi.org/10.1016/j.legalmed.2010.05.005>.
- 20) Edwards ED. Handbook of autopsy practice. 3rd ed. Totowa (NJ): Humana Press; c2002. Chapter 3, Cardiovascular system; p. 21-43.
- 21) Maleszewski JJ Lai CK, Veinot JP. Cardiovascular pathology. 4th ed. New York: Elsevier; c2016. Chapter 1, Anatomic considerations and examination of cardiovascular specimens (excluding devices); p. 1-56.
- 22) Scholz DG, Kitzman DW, Hagen PT, et al. Age-related changes in normal human hearts during the first 10 decades of life. Part I (Growth): a quantitative anatomic study of 200 specimens from subjects from birth to 19 years old. *Mayo Clin Proc.* 1988 Feb; 63(2):126-36. PMID: 3276973. [https://doi.org/10.1016/s0025-6196\(12\)64945-3](https://doi.org/10.1016/s0025-6196(12)64945-3).
- 23) Sudden Death in the Young Case Registry [Internet]. Okemos (MI): Data Coordinating Center for the Sudden Death in the Young Case Registry (SDY); 2017 [cited 2017 Nov 16]. Available from: <https://www.sdyregistry.org/>.

APPENDIX 1

The SDY Case Registry Autopsy Protocol Task Force:
Karen Chancellor MD, Beau Clark MD D-ABMDI,
Timothy E. Corden MD, Kim Fallon, Corinne L.
Fligner MD, Sam P. Gulino MD, Wendy M. Gunther
MD, Jennifer L. Hammers DO, Owen L. Middleton
MD, and Michael Murphy DBA D-ABMDI.



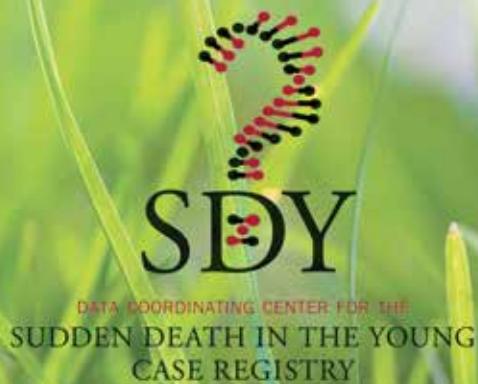
INFORMATION FOR FAMILIES

AGENCIES WORKING ON
THE REGISTRY

Tennessee Department of Health
West Tennessee Regional Forensic Center
Middle Tennessee Regional Forensic Center
Upper Northeast Regional Forensic Center

THE SUDDEN DEATH
IN THE YOUNG
CASE REGISTRY
WORKING TO COUNT,
UNDERSTAND, AND
PREVENT SUDDEN
DEATH IN THE YOUNG

Data Coordinating Center for the
Sudden Death in the Young (SDY) Registry
Telephone: 800-656-2434
Email: info@SDYregistry.org





RESOURCES

BEREAVEMENT SUPPORT GROUPS

The Compassionate Friends

compassionatefriends.org, 877-969-0010

MISS Foundation

missfoundation.org, 888-455-6477

The Tears Foundation

thetearsfoundation.org

SPECIFIC SUPPORT GROUPS

Sudden Unexplained Infant Death (SUID)/ Sudden Infant Death Syndrome (SIDS)

CJ First Candle Foundation

cjfirstcandle.org

Share Pregnancy and Infant Loss Support

nationalshare.org

Heart

Hypertrophic Cardiomyopathy Association

4hcm.org

Parent Heart Watch

parentheartwatch.org

Sudden Arrhythmia Death Syndrome (SADS) Foundation

sads.org

Epilepsy

Epilepsy Foundation SUDEP Institute

epilepsy.com/get-help/about-sudep-institute

The Danny Did Foundation

dannydid.org

Citizens United for Research in Epilepsy (CURE)

cureepilepsy.org/research/sudep.asp

FAMILY MEDICAL FOLLOW-UP

If heart disease is identified as cause of death
or if death remains unexplained

Vanderbilt University Medical Center

The Center for Inherited Heart Disease
Nashville, TN, Phone: 615-322-7602

If family history of epilepsy contact:

Vanderbilt Neurology, Nashville, TN
Phone: 615-936-0060.

WHAT KIND OF INFORMATION IS THE SDY CASE REGISTRY COMPILING?

The Sudden Death in the Young (SDY) Case Registry gathers information to learn more about children who die suddenly and unexpectedly. The project is funded by the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC). The SDY Data Coordinating Center located in Michigan is working to implement the SDY Case Registry.

The purpose of the SDY Case Registry is to try to understand the cause of these deaths and find ways to prevent these deaths.

You may be contacted in the future to consent to save your child's DNA and/or be re-contacted as part of the SDY Case Registry.

The SDY Case Registry is compiling information from the autopsy and death scene investigation, DNA from samples obtained at the time of autopsy and medical history of the child and the child's family. All of the information gathered for the SDY Case Registry will be kept confidential and private.

WHO DO I CONTACT FOR MORE INFORMATION?

Rachel Heitmann

615-741-0368

THIS PROJECT IS SUPPORTED BY:

Centers for Disease Control and Prevention

National Institutes of Health

FOR MORE INFORMATION ABOUT THE SDY CASE REGISTRY:

www.sdyregistry.org



APPENDIX 3

Date

X
X
X

Dear Mr./Mrs/Ms. BLANK

I would like to offer you my condolences on the loss of your child, NAME. At the time of their death, INSERT STAFF INFO talked with you about the Sudden Death in the Young (SDY) project designed to explore possible genetic causes of unexplained death in children. You consented to have your child's DNA tested. This testing was done to determine if your child had any known genetic abnormalities that might have contributed to their death. I am writing to you about those results.

The DNA sample we collected from your child was sent to INVITAE, a genetic testing lab. A CARDIOMYOPATHY and/or ARRHYTHMIA panel of genes were looked at to see if there were HEART STRUCTURAL/FUNCTIONAL ISSUES or ABNORMAL HEART RHYTHMS. This panel tested for changes (also known as variants) in genes.

Attached is the completed report for your review and for sharing with a genetic counselor, your family physician, family members, and anyone else you choose.

Insert if VUS identified

Genetic testing was inconclusive. The testing found a VARIANT (or variants) OF UNCERTAIN SIGNIFICANCE (VUS) in the [GENE] gene (or genes). This means the laboratory found a unique change in your child's DNA, but based on current knowledge, it is not known if these changes cause heart problems. This gene variant (or these gene variants) could increase the risk for heart problems, or it (or they) could be a harmless change that does not cause any heart problems. Thus, it is not clear if the variant is related to your child's sudden death. Talking with a genetic counselor and gathering more information on your family may help in better understanding the variant(s).

Insert if Mutation Negative

Genetic testing was normal. Testing found NO disease-causing gene changes. This testing cannot rule out a genetic cause of sudden death, but your child's death was most likely NOT related to a change in one of the genes she (or he) was tested for.

I highly recommend you reach out to a genetic counselor, geneticist, or your family physician for further explanation. Genetic counseling may also help you and your family understand which relatives might be at risk for an inherited disease, and what medical follow-up is recommended for your family.



METHODS AND PROCEDURES

AFP

Insert if Mutation Positive

Genetic testing showed a PATHOGENIC VARIANT(S) DETECTED. Thus, NAME's sudden death was most likely related to this gene change.

I highly recommend you reach out to a genetic counselor, geneticist, or your family physician for further explanation. Genetic counseling may also help you and your family understand which relatives might be at risk for an inherited disease, and what medical follow-up is recommended for your family.

For genetic counseling, I suggest you reach out to: INSERT LOCAL GENETICS Resource. Phone-based genetic counseling is also available through BLANK. The Office of BLANK is not affiliated with either of these offices or counselors, but they may be able to assist you further.

Enclosed is a brochure that contains additional information about the SDY registry as well as locally available bereavement resources. If you have any questions about the resources, the testing process, or the project please reach out to me. My phone number is BLANK and my email is BLANK.

Thank you for your time and for participating in the SDY project. We hope that this project has been helpful as we all search for the cause of sudden death in children. Again, please accept our condolences for the loss of your loved one.

Sincerely,

INSERT CONTACT INFO

Enclosure



METHODS AND PROCEDURES

AFP

APPENDIX 4

SDY FIELD INVESTIGATION GUIDE AND FAMILY INTERVIEW TOOL

2.0 | 1.2017



This is an optional tool to guide the information needed for the Sudden Death in the Young Case Registry Death Investigation and Family Interview. These questions mirror those in the Child Death Review Case Report and should be answered for sudden unexpected deaths in children in ages 0 through 19. It is important that you provide a copy of this tool to your Child Death Review Team, even if you were not able to obtain all the information. If the child whose death you are investigating is an infant (0 to 364 days old) also use the Sudden Unexplained Infant Death Investigation Reporting Form (SUIDIRF). <http://www.cdc.gov/sids/suidirfdownload.htm>

When introducing and using this tool, here are statements to share with families who are providing information: We would like to ask you additional questions about your child's and family's medical history. This information may assist the medical examiner/doctor in understanding why your child died. The questions are similar to what a doctor's office may ask you. This will take approximately 30-45 minutes. I understand that these questions may be difficult, or you may not know the answer, and that is ok. We can take breaks whenever you need. Would this be ok?

Some of the questions may not seem relevant or important since your child was so young. I still need to ask you to answer them the best you can. Even though it may not seem important, every little bit of information helps the medical examiner/doctor find out what happened. Remember it is okay to answer "I don't know."

We appreciate that this is a lot of information and we appreciate your time in helping us.

Name of person being interviewed: _____ Relationship to the deceased: _____

Name of Person conducting this interview: _____ Title: _____

Date/Time of Interview: _____ Signature: _____

Location of interview: _____ Interview Method (phone, in-person): _____

Medical records to collect

- Pediatric records for well and sick visits (including newborn screening results)
- If under 1 year of age, include mother's prenatal and obstetric reports
- Hospital birth records
- Emergency department records
- Emergency medical services/first responder records
- Immunization records
- Hospital records from day of death and from previous visits, if any
- Specialty health provider records (including any history of cardiac or neurological conditions)
- Any cardiac testing including previous electrocardiogram (EKG), echocardiogram, cardiac MRI, stress test, Holter monitors, and chest X-rays
- If child had epilepsy, records should include history of anti-epileptic drug levels, including frequency of monitoring of levels
- Any testing/records done as part of organ procurement
- Comprehensive family history records, if they exist



PAGE 1

Page 361



METHODS AND PROCEDURES

AFP

SDY FIELD INVESTIGATION GUIDE AND FAMILY INTERVIEW TOOL

General Information

Decedent Name:	Decedent Date of Birth:
Decedent Gender: <input type="radio"/> Male <input type="radio"/> Female	Decedent Ethnicity: <input type="radio"/> Hispanic/Latino <input type="radio"/> Non-Hispanic/Latino
Decedent Race: <input type="radio"/> Black <input type="radio"/> Asian, specify: <input type="radio"/> Alaskan Native, Tribe:	<input type="radio"/> American Indian, Tribe: <input type="radio"/> Pacific Islander, specify: <input type="radio"/> Native Hawaiian
Decedent Next of Kin's Name:	Decedent Next of Kin's Phone No:
Decedent Next of Kin's Email:	
Date of Death:	Time of Death:
Location of Death:	Time Decedent Was Last Seen Alive:
Was the incident witnessed? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	If yes, by whom:
Was a death scene investigation performed? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	

If yes, check all that apply: CDC's SUIDI Reporting Form or jurisdictional equivalent Narrative description of circumstances
 Scene Photos Scene recreation with doll Scene recreation without doll Witness interviews

Activities within 24 hours of death

Child's activity at time of incident? Check all that apply.

- Sleeping Playing Working Eating Driving/vehicle occupant Unknown
 Other, specify: _____

Did the child experience any of the following stimuli at the time of incident or within 24 hours of incident? Check all that apply.

- | | within 24 hrs | |
|--|--------------------------|--------------------------|
| | <u>at incident</u> | <u>of incident</u> |
| Physical activity | <input type="checkbox"/> | <input type="checkbox"/> |
| If yes to physical activity, specify: _____ | | |
| Sleep deprivation | <input type="checkbox"/> | <input type="checkbox"/> |
| Driving | <input type="checkbox"/> | <input type="checkbox"/> |
| Visual stimuli | <input type="checkbox"/> | <input type="checkbox"/> |
| Video game stimuli | <input type="checkbox"/> | <input type="checkbox"/> |
| Emotional stimuli | <input type="checkbox"/> | <input type="checkbox"/> |
| Auditory stimuli/startle (loud noises) | <input type="checkbox"/> | <input type="checkbox"/> |
| Physical trauma (direct blow to chest or head) | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> Other, specify: _____ | | |
| <input type="checkbox"/> Unknown | | |

Resuscitation

Resuscitation attempted?

- N/A Yes No Unknown

If yes, by whom?

If yes, type of resuscitation (CPR, Automated External Defibrillator (AED), rescue medications (e.g. atropine, epinephrine, other), specify: _____

If no AED, was AED available/accessible? Yes No

If an Automated External Defibrillator (AED) was used, was a shock administered? Yes No

How many shocks?

If yes, what rhythm was recorded? (e.g. ventricular fibrillation)

Describe the death, including: time lapse between collapse, 911 call, access to CPR and automated external defibrillator, EMS arrival, defibrillation, transit to hospital, death, etc.



METHODS AND PROCEDURES

AFP

SDY FIELD INVESTIGATION GUIDE AND FAMILY INTERVIEW TOOL

Symptoms within 72 hours of Death

check all that apply

Cardiac

- | | Yes | No | Unknown |
|------------------------------|--------------------------|--------------------------|--------------------------|
| 1. Chest pain | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. Dizziness/lightheadedness | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. Fainting | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. Palpitations | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Neurologic

- | | | | |
|--------------------------|--------------------------|--------------------------|--------------------------|
| 5. Concussion | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 6. Confusion | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 7. Convulsions/seizure | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 8. Headache | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 9. Head injury | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 10. Psychiatric symptoms | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 11. Paralysis (acute) | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Respiratory

- | | | | |
|--------------------------|--------------------------|--------------------------|--------------------------|
| 12. Asthma | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 13. Pneumonia | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 14. Difficulty breathing | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Other Acute Symptoms

- | | | | |
|---------------------------------|--------------------------|--------------------------|--------------------------|
| 15. Fever | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 16. Heat exhaustion/heat stroke | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 17. Muscle aches/cramping | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 18. Slurred speech | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 19. Vomiting | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 20. Other, specify: | <hr/> | | |

Previous Serious Injury

check all that apply

- | | Yes | No | Unknown |
|--------------------|--------------------------|--------------------------|--------------------------|
| 1. Near drowning | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. Car accident | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. Brain injury | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. Other, specify: | <hr/> | | |

If yes, describe

Symptoms prior to 72 hours of Death

check all that apply

Cardiac

- | | | | |
|------------------------------|--------------------------|--------------------------|--------------------------|
| 1. Chest pain | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. Dizziness/lightheadedness | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. Fainting | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. Palpitations | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Neurologic

- | | | | |
|------------------------|--------------------------|--------------------------|--------------------------|
| 5. Concussion | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 6. Confusion | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 7. Convulsions/seizure | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 8. Headache | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 9. Head injury | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Respiratory

- | | | | |
|--------------------------|--------------------------|--------------------------|--------------------------|
| 10. Difficulty breathing | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
|--------------------------|--------------------------|--------------------------|--------------------------|

Other

- | | | | |
|---------------------|--------------------------|--------------------------|--------------------------|
| 11. Slurred speech | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 12. Other, specify: | <hr/> | | |

Exercise

Did the child ever have any of the following uncharacteristic symptoms during or within 24 hours after physical activity?

- | | Yes | No | Unknown |
|---|--------------------------|--------------------------|--------------------------|
| 1. Chest pain | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. Confusion | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. Convulsions/seizure | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. Dizziness/lightheadedness | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 5. Fainting | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 6. Headache | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 7. Palpitations | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 8. Shortness of breath/difficulty breathing | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 9. Other, specify: | <hr/> | | |
| 10. Unknown | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

For children age 12 or older, did the child receive a pre-participation physical exam for a sport?

N/A Yes No Unknown

If yes, date:

Restrictions? N/A Yes No Unknown

If yes, specify:



METHODS AND PROCEDURES

AFP

SDY FIELD INVESTIGATION GUIDE AND FAMILY INTERVIEW TOOL

Medical History of Decedent - Symptoms/Medical History/Previous Injuries

Had the child ever been diagnosed by a medical professional for the following? Check all that apply.

Previous Diagnoses

Blood Disease

- | | Yes | No | Unknown |
|---|--------------------------|--------------------------|--------------------------|
| 1. Sickle cell disease | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. Sickle cell trait | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. Thrombophilia
(clotting disorder) | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Cardiac

- | | | | |
|---|--------------------------|--------------------------|--------------------------|
| 4. Abnormal electrocardiogram (EKG or ECG) | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 5. Aneurysm or aortic dilatation | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 6. Arrhythmia/arrhythmia syndrome (irregular heart rhythm, palpitations) (DD: long QT, Brugada, CPVT, WPW) | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 7. Cardiomyopathy (hypertrophic, dilated, arrhythmogenic right ventricular, left ventricular noncompaction) | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 8. Commotio cordis (blow to chest causing cardiac arrest or death) | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 9. Congenital heart disease | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 10. Coronary artery abnormality | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 11. Coronary artery disease (atherosclerosis) | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 12. Endocarditis | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 13. Heart failure | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 14. Heart murmur | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 15. High cholesterol | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 16. Hypertension | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 17. Myocarditis (heart infection) | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 18. Pulmonary hypertension | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 19. Sudden cardiac arrest | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Neurologic

- | | | | |
|--|--------------------------|--------------------------|--------------------------|
| 20. Anoxic brain injury (injury caused by lack of oxygen to the brain) | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 21. Traumatic brain injury/ head injury/concussion | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 22. Brain tumor | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 23. Brain aneurysm | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 24. Brain hemorrhage | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 25. Developmental brain disorder (cerebral palsy, structural brain malformation) | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 26. Epilepsy/seizure disorder | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 27. Febrile seizure | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 28. Mesial temporal sclerosis | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 29. Neurodegenerative disease | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

- | | Yes | No | Unknown |
|--|-----|----|---------|
|--|-----|----|---------|

- | | | | |
|---|--------------------------|--------------------------|--------------------------|
| 30. Stroke/mini stroke/ TIA- Transient Ischemic Attack | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 31. Central nervous system infection (meningitis or encephalitis) | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Respiratory

- | | | | |
|--------------------------|--------------------------|--------------------------|--------------------------|
| 32. Apnea | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 33. Asthma | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 34. Pulmonary embolism | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 35. Pulmonary hemorrhage | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 36. Respiratory arrest | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Other

- | | | | |
|---|--------------------------|--------------------------|--------------------------|
| 37. Connective tissue disease (Ehlers Danlos, Marfan syndrome, bicuspid aortic valve with aortic root dilation and/or cystic medial necrosis) | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 38. Diabetes | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 39. Endocrine disorder, other: thyroid, adrenal, pituitary | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 40. Hearing problems or deafness | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 41. Kidney disease | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 42. Mental illness/ psychiatric disease | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 43. Metabolic disease | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 44. Muscle disorder or muscular dystrophy | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 45. Oncologic disease treated by chemotherapy or radiation | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 46. Prematurity | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 47. Congenital disorder/ genetic syndrome | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 48. Other, specify: | | | |

Follow-up Testing and Evaluation for Diagnosis

(e.g. echo, EKG, neuro eval)

If a more specific diagnosis is known, provide any additional information:

Describe:

Routine treatment for diagnosis?



METHODS AND PROCEDURES

AFP

SDY FIELD INVESTIGATION GUIDE AND FAMILY INTERVIEW TOOL

Medical History of Decedent - Symptoms/Medical History/Previous Injuries (circle all that apply)

Medications

In the 72 hours prior to death was the child taking any prescribed medication(s)?

Yes No Unknown

If yes, describe:

Family History

Include information on 1st and 2nd degree relatives: *siblings, parents, grandparents, aunts, uncles and first cousins of the deceased as well as if they were older children if they had their own children.*

Family can be referred for genetic counseling at this center:

Unknown for all

Sudden Death

1. Sudden, unexpected death before age 50, describe (SIDS, drowning, relative who died in single and/or unexplained motor vehicle accident (driver of car))

Heart Disease

1. Heart condition/heart attack or stroke before age 50
2. Aortic aneurysm or aortic rupture
3. Arrhythmia (fast or irregular heart rhythm)
4. Cardiomyopathy
5. Congenital heart disease

Neurologic Disease

1. Epilepsy or convulsions/seizure
2. Other neurologic disease

Symptoms

3. Febrile seizures
4. Unexplained fainting

Other

1. Congenital deafness
2. Connective tissue disease (Ehlers Danlos Syndrome, Marfan syndrome)
3. Mitochondrial disease
4. Muscle disorder or muscular dystrophy
5. Thrombophilia (clotting disorder)
6. Other diseases that are genetic or run in families

Genetic Testing

Has any blood relative (siblings, parents, aunts, uncles, cousins, grandparents) had genetic testing?

Yes No Unknown

If yes, describe the results (disease, gene, mutation)



METHODS AND PROCEDURES

AFP

SDY FIELD INVESTIGATION GUIDE AND FAMILY INTERVIEW TOOL

Epilepsy/Seizure Disorder

Answer only if child was diagnosed with an epilepsy/seizure disorder.

How old was the child when diagnosed with epilepsy/seizure disorder?

Describe the child's epilepsy/seizures.

Check all that apply.

Yes No Unknown

Last less than 30 minutes

Last more than 30 minutes

(status epilepticus)

Occur in the presence of fever

(febrile seizure)

Occur in the absence of fever

Occur when exposed to strobe lights, video game, or flickering light (reflex seizure)

What was the underlying cause of the child's seizures?

Check all that apply.

Yes No Unknown

Brain injury/trauma

Brain tumor

Cerebrovascular

Central nervous system infection

Degenerative process

Developmental brain disorder

Inborn error of metabolism

Genetic/chromosomal

Mesial temporal sclerosis

Idiopathic or cryptogenic

Other acute illness or injury
other than epilepsy, other, specify:

What type(s) of seizures did the child have?

Check all that apply.

Yes No Unknown

Non-convulsive

Convulsive (grand mal seizure
or generalized tonic-clonic seizure)
or

Occur when exposed to strobelights, video game, or
flickering light (reflex seizure)

How may seizures did the child have in the year preceding death?

Did treatment for seizures include anti-epileptic drugs?

If yes, how many different types of anti-epilepsy drugs (AED)
did the child take?

Was night surveillance used?



DATA COORDINATING CENTER FOR THE
SUDDEN DEATH IN THE YOUNG
CASE REGISTRY

Sudden Death in the Young Case Registry Data Coordinating Center
c/o Michigan Public Health Institute, 2479 Woodlake Circle, Okemos, MI 48864

Telephone: 800-656-2434 Email: info@SDYregistry.org
Web: www.sdyregistry.org Fax: 844-816-9662

PAGE 6

Page 366

Gulino et al. • SDY Case Registry Pathologic Investigation

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS
©2018 Academic Forensic Pathology International

Downloaded from www.afpjournals.com by an AFP Journal subscriber
This article is for personal use only and may not be shared or distributed in any fashion



METHODS AND PROCEDURES

AFP

APPENDIX 5

SUDDEN DEATH IN THE YOUNG AUTOPSY GUIDANCE SUBJECT ID:



Introduction

This Guidance is a reference to assist you in completing the Sudden Death in the Young (SDY) Autopsy Summary. This summary sheet of autopsy results should be completed following your investigation of a sudden and unexpected death in a child or youth under age 20. It includes instructions for specific components of the autopsy.

The SDY Autopsy Guidance was developed as part of the SDY Case Registry, an initiative of the National Institutes of Health (NIH) and the US Centers for Disease Control and Prevention (CDC). This summary, the guidance and instructions were developed by the SDY Autopsy Protocol Committee composed of medical examiners with experience in pediatric, cardiac and/or neuro pathology; physician coroners, death investigators, and other medical professionals with experience in cardiology, neurology, emergency medicine, public health and genetics.

Your jurisdiction is participating in the Sudden Death in the Young Case Registry with funding from the NIH and CDC. The autopsy findings will be summarized with other case review information and biospecimen data (upon family consent) in the SDY Case Registry. This Registry of de-identified data will be used to better understand the etiologies and risk factors for sudden death in the young so that improved prevention strategies may be developed.

Additional instructions and information are provided throughout this document in italics and footnotes.

SDY Definitions and Inclusion/Exclusion Criteria for the SDY Case Registry

"Sudden" implies death within 24 hours of the first symptom, or those resuscitated from cardiac arrest and dying during the same hospital admission.

"Unexpected" refers to a death in someone who dies from an accidental injury or someone who was believed to have been in good health, or had a stable chronic condition or had an illness but death was not expected. Examples could include hypertrophic or dilated cardiomyopathy, congenital heart disease, epilepsy, asthma and pneumonia.

Inclusion and Exclusion Criteria

This autopsy results summary sheet is a key component of the SDY Case Registry and should be used for all cases that meet all of the following inclusion criteria and none of the following exclusion criteria:

Inclusion Criteria

- | | | |
|---|---------------------------------------|--------------------------------------|
| Is the child under 20 years old? | <input type="checkbox"/> Yes, Include | <input type="checkbox"/> No, Exclude |
| Was the death sudden and unexpected and/or unwitnessed? | <input type="checkbox"/> Yes, Include | <input type="checkbox"/> No, Exclude |

Exclusion Criteria

- | | | |
|---|---------------------------------------|--------------------------------------|
| Was the death caused by an accident in which the external cause was <u>the obvious and only</u> reason* for the death? | <input type="checkbox"/> Yes, Exclude | <input type="checkbox"/> No, Include |
| *Exception: All infants under 1 year of age whose death was caused by suffocation | <input type="checkbox"/> Include | |
| Was the death an obvious homicide? | <input type="checkbox"/> Yes, Exclude | <input type="checkbox"/> No, Include |
| Was the death an obvious suicide? | <input type="checkbox"/> Yes, Exclude | <input type="checkbox"/> No, Include |
| Was the death caused by an accidental or intentional overdose of drugs even if this caused cardiac or respiratory arrest? | <input type="checkbox"/> Yes, Exclude | <input type="checkbox"/> No, Include |
| Was the death caused by a terminal illness in which the death was reasonably expected to occur within 6 months? | <input type="checkbox"/> Yes, Exclude | <input type="checkbox"/> No, Include |



METHODS AND PROCEDURES

AFP

SUDDEN DEATH IN THE YOUNG AUTOPSY GUIDANCE

General

Sex: Male Female

Body weight: _____ kg Body length: _____ cm

Head circumference: _____ cm

External Exam: If abnormalities suggest trauma, disease/syndrome, or medical intervention, please describe:

Photography (external): Yes No

Imaging

(Circle all that were performed and describe the location)

X-Ray, single:

X-Ray, multiple views:

CT scan:

MRI:

Describe any abnormalities found on imaging:

Detailed Review of Specified Organs

Thorax/Lungs

Thorax/Lungs Imaging:

Radiographs of chest Prior to death (hospital, emergency room, other) Postmortem

- If there is a question about the possibility of extra lobar or intra-lobar sequestration, or congenital pulmonary adenomatoid malformation (CPAM; old name CCAM), remove the heart, lungs, central diaphragm, inferior vena cava, and descending aorta as a block, and send for pediatric pathology consultation.

Thorax/Lungs - External Gross Examination

Chest

Contour Normal Abnormal

If abnormal: Increased anteroposterior diameter Asymmetry

Costal margin flaring Other:

Injuries Absent Present:

Axillary lymphadenopathy Absent Present

Other:

Nasal choanae (infants)¹ Patent Obstructed

¹Testing to see if the nasal choanae are patent may be performed by sounding each nostril with a flexible probe. This can be performed with the nasopharyngeal swab for viral culture.



METHODS AND PROCEDURES

AFP

SUDDEN DEATH IN THE YOUNG AUTOPSY GUIDANCE

Thorax/Lungs – Internal Gross Examination

- **Photography:** (optional) In situ On cutting board • **Testing:** sampling for viral and bacterial cultures (as indicated)

Tracheal deviation Absent Present: Left Right

Lungs

Pneumothorax Absent Present: Left Right Bilateral

If present, diagnosed by: X-ray

Other means: _____

Hypoventilation² Absent Present: Left Right Bilateral

Lung(s) sunken towards the back Absent Present: Left Right Bilateral

Hyperinflation Lungs do not approach midline Approach midline Meet in midline

Color Pink Dark red Alternating pink and purple Fibrinous/purulent exudate

Dark red in all lobes, posterior only³ Other: _____

Pleural effusion Absent Present: Left Right Bilateral

If present, appearance: Clear Bloody Straw Purulent Other: _____

Amount: _____ ml

Hemidiaphragm elevation: Absent Present: Left Right Bilateral

Thorax/Lungs – Gross Dissection

- Take heart and lungs out as a block after inspecting aorta for vascular ring around trachea, and inspecting pulmonary arteries and veins (see heart section).

- The trachea / upper respiratory tract should be removed as a block with the lungs.

Vascular ring (aorta around trachea) Absent Present

Lungs

Blood on the pleural surface (adherent hemothorax) Absent Present: Acute Chronic

Blood beneath the pleura Absent Present: Petechiae Confluent/Large hemorrhages

Necrotic exudate on the pleural surface Absent Present

Prominent/discolored/dilated lymphatics visible through the pleura Absent Present

Cobblestoning⁴ Absent Present

Rib markings on the pleura Absent Present

Other: _____

- Perform the initial examination of the heart/lung block. If a cardiovascular pathology or pediatric pathology consultation is requested, send the heart/lung block to the consultant. If consultation is not requested, separate the lungs from the heart following the initial examination.

Lung weights within normal range for age Yes No: Increased Decreased

Right lung approximately 1/3 heavier than the left lung Yes No: _____

Resuscitation-related changes Absent Present: _____

Pulmonary edema, NOS Absent Present: _____

Neurogenic pulmonary edema⁵ Absent Present: _____

Pulmonary infection Absent Present: _____

Pulmonary hemorrhage Absent Present: _____

If present: Diffuse Focal, location: _____ Aspiration pattern (follows bronchi)

Pulmonary hypertension⁶ Absent Present

Other: _____

²Do the lungs approach each other or meet in the midline?

³Consider SUDEP

⁴Probable postmortem change

⁵Muscle layers in subpleural arterioles

⁶Areas of pink hyperinflation and purple hypoventilation



METHODS AND PROCEDURES

AFP

SUDDEN DEATH IN THE YOUNG AUTOPSY GUIDANCE

Thorax/Lungs – Gross Dissection (continued)

Abnormalities/disease processes visible at the hilum of either lung:

- Pulmonary artery thromboemboli⁷ Absent Present, location: _____
Bronchial mucus/purulence Absent Present: _____
Bronchial aspirated food, foreign object Absent Present: _____
Other: _____

Is the right lung anatomically right-sided, and is the left lung left-sided?⁸ Yes No

If no, partially divided lobes: Absent Present: _____

Relationship of mainstem bronchus to mainstem pulmonary artery:⁹

- Normal: left hyparterial bronchus and right eparterial bronchus
 Left side is normal but right side is not (two left lungs)¹⁰
 Right side is normal but left side is not (two right lungs)¹¹
 Neither side is normal¹²

* *Section through all lobes, central and peripheral, including mainstem bronchi.*

- Hilar lymph nodes Normal Abnormal
If abnormal: Enlarged Anthracotic Granulomatous disease Hemorrhagic
 Gross infection Tumor deposits Other: _____
Aspiration Absent Present: _____
Atelectasis Absent Present: _____
Hyperinflation with/without mucus plugs¹³ Absent Present: _____
Rib markings on pleura Absent Present: _____
Cobblestoning Absent Present: _____
Copious clear fluid Absent Present: _____
Copious blood-tinged fluid (from bronchi and/or parenchyma on sectioning) Absent Present
Hemorrhage Absent Present:
If present: Diffuse Focal, location: _____ Aspiration pattern (follows bronchi)
Pneumonia/consolidation, exudate in bronchi, abscesses, or other signs of infection Absent Present
Cavitation Absent Present: _____
Granulomatous process¹⁴ Absent Present: _____
Infarction/thromboemboli¹⁵ Absent Present: _____
Tumor or suspected benign
or neoplastic process Absent Present: _____
Congenital anomaly Absent Present: _____
Other: _____

⁷If there is any question whether blood clots in the mainstem pulmonary artery branches are antemortem thromboemboli or postmortem clot, histology is definitive.

⁸Three lobes on the right and two lobes on the left

⁹Does the main bronchus enter the hilum above, or approximately level with, the mainstem pulmonary artery branch on the right side (normal right eparterial bronchus), and below the mainstem pulmonary artery branch on the left side (normal left hyparterial bronchus)? If abnormal, consider pediatric pathology consultation.

¹⁰Look for polysplenia.

¹¹Look for asplenia.

¹²Look for Kartagener syndrome.

¹³Consider asthma.

¹⁴Consider infection or sarcoidosis

¹⁵Propagation of thromboemboli causes red-purple "sausages" to exude from cross-sectioned pulmonary artery branches.



METHODS AND PROCEDURES

AFP

SUDDEN DEATH IN THE YOUNG AUTOPSY GUIDANCE

Thorax/Lungs - Microscopic Examination

- Central
- Peripheral: including pleura and subpleural pulmonary artery branches and medium-sized bronchi
- Through areas of grossly evident or suspected disease processes
- There is no definitive number of lung sections supported by research that can be stated as required in every case. Peripheral and central lung samples each yield different diagnoses, and both should be sampled. Sampling from multiple areas may detect patchy diseases. Grossly suspicious areas are likely to reward sampling. Storage of multiple lung segments allows further sampling if disease processes are detected that require it. If in doubt, consult a pediatric pathologist.

- Obtain special stains as indicated for:
 - Bacterial infection
 - Granulomatous disease (acid-fast bacteria, sarcoidosis, fungi)
 - Autoimmune disease
 - Neoplasia
 - Resolving hemorrhage (iron)

Aspiration	<input type="checkbox"/> Absent	<input type="checkbox"/> Present:	<input type="checkbox"/> Food	<input type="checkbox"/> Blood	<input type="checkbox"/> Other: _____
Pulmonary edema	<input type="checkbox"/> Absent	<input type="checkbox"/> Present: _____			
Alveolar hemorrhage	<input type="checkbox"/> Absent	<input type="checkbox"/> Present: _____			
Hemorrhage in bronchial lumens	<input type="checkbox"/> Absent	<input type="checkbox"/> Present: _____			
Red cell morphology	<input type="checkbox"/> Normal	<input type="checkbox"/> Typical postmortem	<input type="checkbox"/> Sickle cells on formalin-exposed tissue		
Inflammation	<input type="checkbox"/> Absent	<input type="checkbox"/> Present			
If present, location:	<input type="checkbox"/> Bronchi/bronchioles	<input type="checkbox"/> Alveoli	<input type="checkbox"/> Alveolar walls		
Bronchus-associated lymphoid tissue	<input type="checkbox"/> Normal	<input type="checkbox"/> Abnormal: _____			
Pulmonary thromboemboli	<input type="checkbox"/> Absent	<input type="checkbox"/> Present: _____			
Secondary pneumonia around obstructed bronchi/infarcted lung parenchyma		<input type="checkbox"/> Absent	<input type="checkbox"/> Present		
Chronic lung disease following prematurity	<input type="checkbox"/> Absent	<input type="checkbox"/> Present			
Pulmonary hypertension or evidence of persistent fetal circulation ¹⁶	<input type="checkbox"/> Absent	<input type="checkbox"/> Present			
Asthma or other eosinophilic diseases	<input type="checkbox"/> Absent	<input type="checkbox"/> Present			
Foreign bodies	<input type="checkbox"/> Absent	<input type="checkbox"/> Present			

Trachea:

- Methods of examining the trachea should include opening along the long axis and cross-sectioning.
- The neck contents (proximal esophagus, trachea, thyroid gland, and overlying strap muscles) may be cross-sectioned together in one piece for histologic examination, particularly if tracheal/bronchial infection or narrowing of the lumen are of concern.
- Areas not cross-sectioned may be opened along the long axis. The epiglottis is easily sectioned. The aryepiglottic folds may be sectioned to look for eosinophils.
- The carina lends itself to a triangle-shaped sagittal cross-section that includes the carinal nodes.
- Trachea should be removed, including the hyoid bone, epiglottis, aryepiglottic folds, arytenoid cartilage, thyroid cartilage, trachea, and carina.

Epiglottis	<input type="checkbox"/> Symmetrical	<input type="checkbox"/> Asymmetrical	Tracheal contents	<input type="checkbox"/> Absent	<input type="checkbox"/> Present
Erythema	<input type="checkbox"/> Absent	<input type="checkbox"/> Present	If present:		
Exudate	<input type="checkbox"/> Absent	<input type="checkbox"/> Present	White foam, pink foam	<input type="checkbox"/> Absent	<input type="checkbox"/> Present
Aryepiglottic folds	<input type="checkbox"/> Symmetrical	<input type="checkbox"/> Asymmetrical	Mucus	<input type="checkbox"/> Absent	<input type="checkbox"/> Present
	<input type="checkbox"/> Flat (normal)	<input type="checkbox"/> Swollen	Necrotic exudate	<input type="checkbox"/> Absent	<input type="checkbox"/> Present
	<input type="checkbox"/> Obstruct the lumen	<input type="checkbox"/> Do not obstruct the lumen	Thin layer of liquid blood along the mucosa	<input type="checkbox"/> Absent	<input type="checkbox"/> Present
Vocal cords	<input type="checkbox"/> Symmetrical	<input type="checkbox"/> Asymmetrical	Pieces of food, vomitus streaking the mucosa	<input type="checkbox"/> Absent	<input type="checkbox"/> Present
Abnormalities	<input type="checkbox"/> Absent	<input type="checkbox"/> Present: _____	Obstructing blood clots	<input type="checkbox"/> Absent	<input type="checkbox"/> Present
Tracheal mucosa			Obstructing food bolus	<input type="checkbox"/> Absent	<input type="checkbox"/> Present
Erosion	<input type="checkbox"/> Absent	<input type="checkbox"/> Present	Foreign object	<input type="checkbox"/> Absent	<input type="checkbox"/> Present
Erythema	<input type="checkbox"/> Absent	<input type="checkbox"/> Present			
Inflammation	<input type="checkbox"/> Absent	<input type="checkbox"/> Present			

¹⁶Including muscle layers in subpleural arterioles; other abnormalities of pulmonary artery branches



METHODS AND PROCEDURES

AFP

SUDDEN DEATH IN THE YOUNG AUTOPSY GUIDANCE

Heart – Gross Dissection

- Weigh the heart
- Make note of epicardial adhesions, exudate, or discoloration
 - Make note of amount and distribution of epicardial fat
- Section the epicardial coronary arteries at 3-5 mm intervals, avoiding cutting into great arteries and cardiac chambers
 - Note arterial dominance (right/left/shared) and locations and degrees of obstructions
- Make transverse (short axis) slices through the ventricles beginning 1 cm above the apex and at 1 cm intervals; do not section above the level of the tips of the left ventricular papillary muscles
 - Note all gross lesions in the myocardial sections including scars, discolorations, and softening
 - Lesions should be described by the usual descriptors (e.g., size, color, firmness) as well as:
- Vertical location (e.g., basal, midventricular, apical)
- Lateral location (e.g., anteroseptal, inferolateral)
- Distribution (e.g., subendocardial, transmural, subepicardial)
 - Take measurements of left ventricular thickness, right ventricular thickness, and septal thickness in the uppermost (most basal) slice
- When taking measurements, include only the compact myocardium; do not include trabecular muscle or papillary muscles
 - Examine the right ventricular wall for fat infiltration
 - It is recommended that the myocardial slices be photographed, especially if there are grossly visible lesions
- Open the heart in the direction of blood flow:
 - Open the right atrium from the inferior vena cava orifice to the tip of the atrial appendage
- Do not open through the superior vena cava orifice; doing so may cut through the SA node, hampering dissection of the conduction system if that is desired later
 - Open from the right atrium to the right ventricle along the posterior or lateral wall
 - Open the right ventricular outflow tract anteriorly
 - Open the left atrium by connecting all of the pulmonary veins and cutting to the tip of the atrial appendage
 - Open from the left atrium to the left ventricle along the lateral wall
 - Open the left ventricular outflow tract anteriorly
- Remove postmortem clot from all chambers
 - If large amount of postmortem clot is present, consider re-weighing heart after the clot is removed
- Describe degree of dilation of chambers, if any, and document presence/absence of mural thrombi
- Document presence/absence of patent foramen ovale, atrial septal defect, or ventricular septal defect (describe size and location if present)
- Examine the valves, noting number of leaflets/cusps of each and presence of any abnormalities (e.g., myxoid change, calcification, vegetations)
- Examine the coronary ostia
 - If ectopic origin is present, note acuity of the origin (e.g., sharp angle of origin), course of the proximal segment of the artery (e.g., within aortic adventitia), and presence/absence of an occlusive ostial flap
- If any of the above findings are present, it is recommended that they be photographed in addition to being described in the autopsy guidance

Heart – Gross Examination

Heart weight _____ g	<input type="checkbox"/> Unfixed	<input type="checkbox"/> Fixed	
Thoracic position	<input type="checkbox"/> Left (normal)	<input type="checkbox"/> Right	<input type="checkbox"/> Midline <input type="checkbox"/> Ectopic: _____
Apex	<input type="checkbox"/> Leftward (normal)		<input type="checkbox"/> Rightward <input type="checkbox"/> Other: _____
Spleen	<input type="checkbox"/> Single	<input type="checkbox"/> Accessory	<input type="checkbox"/> Polysplenia <input type="checkbox"/> Asplenia
Liver	<input type="checkbox"/> Right (normal)	<input type="checkbox"/> Left	<input type="checkbox"/> Midline/ambiguous
Pericardial effusion	<input type="checkbox"/> Absent	<input type="checkbox"/> Present	If present: Amount: _____ ml
– Appearance	<input type="checkbox"/> Clear	<input type="checkbox"/> Straw	<input type="checkbox"/> Purulent <input type="checkbox"/> Other: _____
Hemopericardium	<input type="checkbox"/> Absent	<input type="checkbox"/> Present	
Vascular Ring	<input type="checkbox"/> Absent	<input type="checkbox"/> Present	
Epicardium – Exudate	<input type="checkbox"/> Absent	<input type="checkbox"/> Present: _____	
– Adhesions	<input type="checkbox"/> Absent	<input type="checkbox"/> Present: _____	
– Fat	<input type="checkbox"/> Present, normal amount	<input type="checkbox"/> Increased <input type="checkbox"/> Decreased	
Right atrium – Morphology	<input type="checkbox"/> Right ¹⁷ (normal)	<input type="checkbox"/> Left	<input type="checkbox"/> Ambiguous/other: _____
– Venoatrial connections (SVC/IVC)	<input type="checkbox"/> Normal	<input type="checkbox"/> Abnormal	: _____
– Coronary sinus OS	<input type="checkbox"/> Patent	<input type="checkbox"/> Stenotic	<input type="checkbox"/> Atretic
– Dilation	<input type="checkbox"/> Absent	<input type="checkbox"/> Present: <input type="checkbox"/> Mild	<input type="checkbox"/> Moderate <input type="checkbox"/> Severe
– Cavitary thrombus ¹⁸	<input type="checkbox"/> Absent	<input type="checkbox"/> Present	

¹⁷Right atrial morphology includes presence of terminal crest, smooth endocardial surface posterior to terminal crest, pectinate muscles anterior to terminal crest and in atrial appendage.

¹⁸Antemortem thrombus; excludes perimortem/postmortem clot.



METHODS AND PROCEDURES

AFP

SUDDEN DEATH IN THE YOUNG AUTOPSY GUIDANCE

Heart - Gross Examination (continued)

Left atrium

- Morphology Left (normal)¹⁹ Right Ambiguous/other: _____
- Coronary sinus OS Patent Stenotic Atretic
- Dilatation Absent Present: _____
- Cavitary thrombus Absent Present: _____

Atrial septum

- Intact Probe-patent foramen ovale Atrial septal defect:²⁰ _____

Atrioventricular valves

- Two valves (right and left) Common valve (atrioventricular canal²¹)

Right atrioventricular valve

- Morphology Tricuspid (normal) Prosthetic: (type) _____ Other: _____
- Abnormalities Absent Present: If present, circle/describe all that apply:
 - Vegetations _____
 - Prolapse/ballooning _____
 - Commissural fusion _____
 - Other: _____
- Leaflet thickening _____
- Leaflet perforation _____
- Apical displacement of septal leaflet (Ebstein's anomaly) _____

Left atrioventricular valve

- Morphology Mitral (bicuspid, normal) Prosthetic: (type) _____ Other: _____
- Abnormalities Absent Present: If present, circle/describe all that apply:
 - Vegetations _____
 - Prolapse/ballooning _____
 - Commissural fusion _____
 - Chordal stretching/rupture _____
- Leaflet thickening _____
- Leaflet perforation _____
- Chordal thickening _____
- Other: _____

Right ventricle

- Morphology Right²² (normal) Left Ambiguous/other: _____
- Wall thickness²³ Anterior: _____ cm Posterior: _____ cm
- Fat infiltration²⁴ Absent Present If present, which wall: Anterior Posterior
 - Maximum % thickness of wall involved: _____
- Right ventricular thinning²⁴ Absent Present, location: _____
- Dilation Absent Present: Mild Moderate Severe
- Cavitary thrombus Absent Present: _____
- Endocardium Thin, translucent (normal) Abnormal: _____

Left ventricle

- Morphology Left²⁵(normal) Right Ambiguous/Other
- Wall thickness²³ Anterior: _____ cm Lateral: _____ cm Inferior/posterior: _____ cm
- Dilation Absent Present: Mild Moderate Severe
 - If present, chamber diameter (at same level as wall thicknesses): _____ cm
- Cavitary thrombus Absent Present: _____
- Endocardium Thin, translucent (normal) Abnormal: _____
- Myocardial infarction (acute/recent) Absent Present: _____
- Myocardial scar²⁶ Absent Present: _____
- Myocardial discoloration Absent Present: _____

¹⁹Left atrial morphology includes absence of terminal crest and smooth endocardial surface throughout atrium except for pectinate muscles in atrial appendage.

²⁰Description should include location, size, and any intervention.

²¹Describe morphology and pathology under "Left atrioventricular valve" section.

²²Right ventricular morphology includes coarse endomyocardial trabeculations and presence of a moderator band.

²³Measurements should be taken at the level of the tips of the ventricular papillary muscles and should include only the compact myocardium (not epicardial fat or papillary/trabecular muscle).

²⁴Concerning for arrhythmogenic right ventricular cardiomyopathy

²⁵Left ventricular morphology includes fine endomyocardial trabeculations and absence of a moderator band.

²⁶Includes remote myocardial infarctions



METHODS AND PROCEDURES

AFP

SUDDEN DEATH IN THE YOUNG AUTOPSY GUIDANCE

Heart – Gross Examination (continued)

Ventricular septum

– Septal thickness²⁷ _____ cm Intact Ventricular septal defect²⁸ _____

Semilunar valves

– If two valves: Two valves Single valve²⁹ (truncus arteriosus, pulmonary or aortic atresia)
– Aorta posterior and rightward of the pulmonary valve (normal)
– D-malposed³⁰ Other arrangement: _____

Right semilunar valve

– Number of cusps 3 (normal) Other: _____ Prosthetic (type) _____
– Abnormalities Absent Present: If present, circle/describe all that apply:
– Vegetations _____
– Thickening _____
– Calcification _____
– Perforation _____
– Commissural fusion _____
– Other: _____

Left semilunar valve

– Number of cusps 3 (normal) 2 (bicuspid) Other: _____ Prosthetic (type) _____
– Abnormalities Absent Present: If present, circle/describe all that apply:
– Vegetations _____
– Thickening _____
– Calcification _____
– Perforation _____
– Commissural fusion _____
– Other: _____

Great vessels

– Pulmonary artery Normal Dilated Hypoplastic
– Discontinuous branch pulmonary arteries Absent Present
– Supravalvar pulmonary stenosis Absent Present: Mild Moderate Severe
– Thromboemboli Absent Present:
– Aorta³¹ Leftward arch (normal) Rightward arch
– Other arch anomaly (e.g., vascular ring) Absent Present: _____
– Root dilatation Absent Present: _____ cm (circumference)
– Dissection Absent Present: (type) _____ Ruptured? Yes No
– Coarctation/Interruption Absent Present
– Supravalvar aortic stenosis Absent Present: Mild Moderate Severe
– Ductus arteriosus Ligamentous (ligamentum arteriosum) Present, closed
– Ductus arteriosus Probe patent Visibly patent: _____ mm (diameter)

Coronary arteries

– Ostia Normal³² Abnormal: (e.g., stenosis) _____
– Distribution Normal, right dominant Normal, left dominant³³ Abnormal
If abnormal Single Left anterior descending from right Circumflex from right
– Other: _____
– Aneurysm Absent Present: _____
– Dissection Absent Present: _____
– Narrowing Absent Present: _____ Atherosclerotic Non-atherosclerotic

²⁷Measurement should be taken at the level of the tips of the left ventricular papillary muscles.

²⁸Description should include location, size, and any intervention. If malalignment is present (e.g., as in tetralogy of Fallot), describe extent and direction – anterior or posterior.

²⁹Describe morphology/pathology in "Left semilunar valve" section.

³⁰D-malposition is commonly referred to as "complete transposition" (i.e., aorta is anterior and rightward of the pulmonary artery).

³¹The aorta is the vessel that gives rise to the coronary arteries.

³²"Normal" includes origin of the conus artery adjacent to right coronary ostium (normal variant).

³³The right coronary artery may be small in left-dominant hearts. Describe in further detail in "Other" section if absent/hypoplastic or if downstream sequelae exist (e.g., myocardial infarction).



METHODS AND PROCEDURES

AFP

SUDDEN DEATH IN THE YOUNG AUTOPSY GUIDANCE

If atherosclerosis is present, fill out the following table:

Coronary Artery	Greatest % obstruction	Proximal ✓	Mid ✓	Distal ✓	Thrombus +/-	Calcification +/-
Left main						
Left anterior descending						
Diagonal						
Left circumflex						
Obtuse marginal						
Right						
Posterior descending						
Other						

Hypertrophic cardiomyopathy Absent Present

Dilated cardiomyopathy Absent Present

Left ventricular noncompaction Absent Present

Restrictive cardiomyopathy Absent Present

Congenital heart disease^{34,35} Absent Present: (type) _____

Valve disease

– Mitral valve prolapse Absent Present

– Valve stenosis Absent Present: (location, severity) _____

Cardiovascular interventions

present at autopsy³⁶ Absent Present

– Pacemaker: (make, model, type) _____

Interrogated? Yes No Results: _____

– Implantable cardioverter defibrillator: (make, model) _____

Interrogated? Yes No Results: _____

– Implanted loop recorder: (make, model) _____

Interrogated? Yes No Results: _____

– Ventricular assist device: (type, location) _____

– Evidence of congenital heart surgery: (type, location) _____

– Stents/coils/plugs/occluder devices: (location) _____

– Other: _____

³⁴Probe patent foramen ovale is considered a normal variant and should not be included under congenital heart disease.

³⁵Surgical status will be recorded under evidence of cardiovascular interventions

³⁶With the exception of valve prostheses, which should be described in the valve sections above.



METHODS AND PROCEDURES

AFP

SUDDEN DEATH IN THE YOUNG AUTOPSY GUIDANCE

Heart - Microscopic Examination (Describe findings on page 17)

The extent of microscopic examination is guided by the available history and the gross findings.

For a grossly normal heart, at a minimum:

- 2 sections of left ventricle that include the anterolateral and posteromedial papillary muscles
 - 1 section of basilar ventricular septum
 - 1 section of right ventricle
 - An additional 4-6 sections of myocardium taken from a variety of locations in the ventricles and septum (to look for myocarditis, which can be patchy; if there is recent history of viral illness, it is advisable to take more)
- Myocardium:**
- Take sections of any areas of discoloration, softening, or mass.
 - Taking sections of old myocardial infarction scars is usually uninformative, but areas of myocardium with randomly dispersed interstitial scars should be sampled.
 - In cases of suspected hypertrophic cardiomyopathy, the ventricular septum should be carefully sampled to look for myocyte disarray.
 - In cases of suspected arrhythmogenic right ventricular cardiomyopathy, multiple sections of the anterior and posterior walls of the right ventricle should be taken.
 - Make note of:
 - Hypertrophy
 - Myocyte disarray
 - Necrosis (coagulative vs. contraction-band; focal vs. geographic; specific distribution)

- Fibrosis (replacement vs. interstitial; specific distribution)

- Inflammation (prominent cell type(s); presence/absence of myocyte necrosis)

- Infiltrate (e.g., fat, amyloid)

- Epicardial surface (e.g., presence/absence of inflammation and exudate)

- Epicardial arteries (atherosclerosis)

- Intramyocardial arteries (thrombi, fibromuscular dysplasia)

Coronary arteries:

- Take sections of the greatest area of obstruction of each artery.
- Take sections of any other grossly visible lesion (e.g., aneurysm, dissection); consider including elastic stain.

Valves:

- Take sections of any vegetations (consider including Brown & Brenn tissue gram stain).
- Take a section of a mitral leaflet if it appears to have myxoid degeneration (include an Alcian Blue (AB)-Periodic acid-Schiff (PAS) stain).

Conduction system:

- Examination of the conduction system³⁷ should be done in all cases where:
 - There is documented history of heart block, OR
 - The decedent is an infant/small child and there is a known history of maternal lupus, OR
 - Myxoid valvular disease is present.
- If number of histology blocks is not a financial consideration, doing microscopic examination of the conduction system should be considered in any apparent sudden cardiac death case.

Brain - Gross Examination (Describe findings on page 17)

- Photographs should be taken with the brain in place and cranial vault removed. This is helpful for evaluation of brain swelling. All photographs should be made with a ruler.

-Photographs: Vertex view Right view Left view Base View

- Photographs
 - Epidural surface of dura mater -Subdural surface of dura mater
 - Dorsal brain -Ventral brain
 - Right side of brain -Left side of brain
 - Evidence of surgical intervention

Evidence of surgical intervention Absent Present: If present, circle/describe all that apply:

– Craniotomy: _____

– Cranectomy: _____

– Hardware in skull: _____

– Dural grafts: _____

– Tubes, drains: _____

Dural sinus thrombosis Absent Present: Sagittal Transverse

Subdural hemorrhage Absent Present: Left Right Bilateral

– If present:

Amount _____ ml

Color _____

Appearance: Clotted Liquid Shiny surface

³⁷A stepwise description of the technique can be found in Gulino SP. Examination of the cardiac conduction system: forensic application in cases of sudden cardiac death. Am J Forensic Med Pathol 2003;24(3):227-38.



METHODS AND PROCEDURES

AFP

SUDDEN DEATH IN THE YOUNG AUTOPSY GUIDANCE

Brain – Gross Examination (continued)

Purulent material in subdural space Absent Present

– If present, bacterial culture obtained Yes, results: _____ No

Subarachnoid hemorrhage Absent Present

– If present Pattern: Diffuse Scattered Focal, location: _____

Severity: Mild Moderate Severe _____

Leptomeninges

– Clear Yes No:

If no:

– Purulent material Absent Present

If present, bacterial culture obtained Yes, results: _____ No

– Clouding Absent Present

If present, bacterial and viral culture obtained Yes, results: _____ No

– Congestion Absent Present

Brain removed³⁸ No Yes: By pathologist By pathology resident By technician

Brain weight (unfixed)³⁹ _____ g

• Fix brain in 10 – 20% buffered formalin for 2 weeks or longer.^{40,41}

• Suspend brain so that is not deformed by container. This can be done by suspension with a thread under the basilar artery or by using concentrated formalin until the brain floats

• Request antemortem imaging reports if available for review prior to cutting.

Brain weight (fixed): _____ g

Photographs: -Epidural surface of dura mater -Subdural surface of dura mater -Dorsal brain -Ventral brain
-Right side of brain -Left side of brain -Evidence of surgical intervention

Intradural hemorrhage Absent Present

– If present Location: _____

Severity: Mild Moderate Severe

Subdural neomembrane Absent Present

– If present Location: Right cerebral Left cerebral Superior tentorium Inferior tentorium Posterior fossa
Color: _____

Gyral pattern Normal Aberrant: _____

– Polymicrogyria Absent Present, location(s): _____

Circle of Willis:

– Distribution Normal Abnormal: _____

– Obstruction Absent Present

– Size Normal Small Large Vessel(s): _____

– Aneurysm Absent Present

If present: Size _____ mm

Location: _____

Cranial nerves All present: Yes No: _____

Symmetric: Yes No: _____

Cingulate herniation Absent Present: Right Left

Uncal herniation Absent Present: Right Left Bilateral

Tonsillar herniation Absent Present: Right Left Bilateral Chronic⁴² Acute

³⁸Removal by forensic pathologist is recommended. This decreases the chances of artifacts, such as tearing of cranial nerves.

⁴¹In some jurisdictions the family must be notified if the brain is retained for fixation.

³⁹Skip this step if the brain is very fragile and the brain can be fixed.

⁴²As in a malformation such as Arnold Chiari

⁴⁰Except in jurisdictions in which this is not allowed.



METHODS AND PROCEDURES

AFP

SUDDEN DEATH IN THE YOUNG AUTOPSY GUIDANCE

Brain - Gross Examination (continued)

Pontomedullary tear	<input type="checkbox"/> Absent	<input type="checkbox"/> Present: _____	Depth _____ mm
Cerebral hemispheres	<input type="checkbox"/> Symmetric	<input type="checkbox"/> Asymmetric:	<input type="checkbox"/> Right larger <input type="checkbox"/> Left larger
Cerebellar hemispheres	<input type="checkbox"/> Symmetric	<input type="checkbox"/> Asymmetric:	<input type="checkbox"/> Right larger <input type="checkbox"/> Left larger
Cerebellar folial sclerosis	<input type="checkbox"/> Absent	<input type="checkbox"/> Present, location:	_____
Areas of softening	<input type="checkbox"/> Absent	<input type="checkbox"/> Present, location:	_____
Areas of firmness	<input type="checkbox"/> Absent	<input type="checkbox"/> Present, location:	_____
Surgical drains or other materials	<input type="checkbox"/> Absent	<input type="checkbox"/> Present	

– If present: Location: _____ Type of material:
Drains patent Yes No N/A
Shunts patent Yes No N/A

- Separate brainstem/cerebellum by horizontal cut through the midbrain.⁴³

Aqueduct: Normal Obstructed Dilated

- Cut the cerebrum in the coronal plane at 1.5 – 2.0 cm intervals.

- Separate the brainstem from the cerebellum by cutting the cerebellar peduncles.

- Divide the cerebellum in midline; slice each hemisphere with sagittal cuts at 0.5 cm intervals.

- Section the brainstem at 0.3 cm intervals.

- Photograph the cut brain sections.⁴⁴

Brain Symmetric Asymmetric: _____

Lateral ventricles Symmetric Asymmetric: Right larger Left larger
 Not Dilated Dilated: Mild Moderate Severe

Mass Absent Present: _____

Third ventricle Normal Dilated Obstructed

Fourth ventricle Normal Dilated Obstructed

Cortical ribbon

– Size Normal Narrow: _____ Diffuse Focal, location(s): _____
– Discoloration Absent Present: _____ Diffuse Focal, location(s): _____

White matter

– Distribution Symmetric Asymmetric: _____
– Discoloration Absent Present: _____ Diffuse Focal, location(s): _____

Myelination Normal for age Abnormal for age: _____

Hippocampi Symmetric Asymmetric: Right smaller Left smaller

Deep nuclei

– Distribution: Symmetric Asymmetric: _____
– Discoloration: Absent Present: _____ Diffuse Focal, location(s): _____

Pituitary

– Size Normal Small Large
– Necrosis Absent Present: _____
– Mass Absent Present: _____
– Areas of softness Absent Present

If present: Location(s): _____ Size: _____ mm

⁴³Other techniques may be useful (e.g., sagittal sectioning of brainstem if pontomedullary tear suspected; sagittal sectioning of brainstem with cerebellum if Arnold Chiari suspected)

⁴⁴Photographs of cut brain can be done in 2 to 6 photos with multiple sections in each. If abnormalities are found, photograph the involved brain section(s) with possible close-up views of the abnormalities.



METHODS AND PROCEDURES

AFP

SUDDEN DEATH IN THE YOUNG AUTOPSY GUIDANCE

Brain - Gross Examination (continued)

- Areas of firmness Absent Present
If present: Location(s): _____ Size: _____ mm
- Areas of discoloration Absent Present
If present: Location(s): _____ Size: _____ mm
Color: _____
- Hemorrhage Absent Present
If present: Location(s): _____ Size: _____ mm
- Encephomalacia Absent Present
If present: Location(s): _____ Size: _____ mm
- Stroke Absent Present, location: _____
- Heterotopia Absent Present, location: _____
- Arterio-venous malformation Absent Present, location: _____
- Compression of cerebral hemisphere Absent Present
- Anoxic ischemic encephalopathy Absent Present
- Other congenital anomalies of the brain Absent Present, describe: _____

Brain - Microscopic Examination (Describe findings on page 17)

- Take sections of any abnormal areas⁴⁵
- Also take sections of:
 - Dura⁴⁶
 - Frontal cortex including subcortical white matter
 - Parietal cortex including subcortical white matter
 - Temporal cortex including subcortical white matter and ependymal surface
 - Right hippocampus at level of lateral geniculate nucleus
 - Left hippocampus at level of lateral geniculate nucleus
- Amygdala
- Hypothalamus
- Cerebellum including dentate nucleus and folia
- Midbrain
- Pons
- Medulla
- Keep sectioned brain in formalin until histologic examination is complete.
- Retain brainstem and hippocampi.⁴⁷

Gastrointestinal Tract - Gross Examination

External Examination

Abdominal distention Absent Present

If present: Postmortem gas Asymmetry Fluid wave

Scar(s) from previous abdominal surgery Absent Present: _____

External feeding tube Absent Present: _____

Internal Examination

- Photography: optional *In situ* *On cutting board*
- Testing: sampling for viral and bacterial cultures (as indicated)

Peritoneal Cavity

- Evidence of peritonitis Absent Present: _____
- Ruptured abdominal organ Absent Present: _____
- Fluid accumulation Absent Present: _____
- Injury from resuscitation Absent Present: _____

⁴⁵Sections should include borders between normal and abnormal areas.

⁴⁶If subdural hemorrhage/neomembrane present, include interface with the normal dura.

⁴⁷If jurisdiction allows.



METHODS AND PROCEDURES

AFP

SUDDEN DEATH IN THE YOUNG AUTOPSY GUIDANCE

Gastrointestinal Tract - Gross Examination (continued)

- Adhesions Absent Present: _____
- Previous surgery Absent Present: _____
- Hernia Absent Present: _____
 If present: Incarceration: Absent Present: _____
- Volvulus Absent Present: _____
- Intussusception Absent Present: _____
- Appendicitis Absent Present: _____
- Foreign object in
 the peritoneum Absent Present: _____

- Examine the tongue. During examination look for tongue bites if the child has teeth; examine the area of the foramen cecum for a visible or microscopic trace of the origin of the thyroid gland.

Liver weight within normal range for age Yes No: Larger Smaller

If the liver is enlarged, does it appear to be a sequela of right heart failure (not a primary liver problem)? Yes No

- Look at the epiglottis (may fall under respiratory/trachea).
- Open the esophagus, stomach, and duodenum, and consider opening the jejunum and ileum (strongly recommended).
- Open the large bowel.
- Use dissection or the squeeze test to evaluate whether the biliary tree passes bile.
- Open the gallbladder; optional, obtain bile for later evaluation.
- Section the liver and the pancreas.
- The pancreas may be sectioned with the duodenum and ampulla (preferred), or after separation from the duodenum.

Pancreatitis Absent Present: _____

Adhesions/sequelae of surgery

Absent Present: _____

Bleeding Absent Present: _____

Thrombosis Absent Present, vessel: _____

Obstruction Absent Present: _____

Dilatation Absent Present: _____

Stenosis Absent Present: _____

Fistulas Absent Present: _____

Foreign objects

Absent Present: _____

Masses - wall, including reduplications

Absent Present: _____

Masses in the lumen

Absent Present: _____

Intussusception

Absent Present: _____

Volvulus Absent Present: _____

Toxic megacolon

Absent Present: _____

Prolapse (rectal or other)

Absent Present: _____

Reflux

Absent Present: _____

Inflammation

Absent Present: _____

Diarrhea

Absent Present: _____

Constipation

Absent Present: _____

Sequelae of necrotizing enterocolitis

Absent Present: _____

Sequelae of G.I. diseases/infections⁴⁸

Absent Present: _____

Congenital abnormalities

Absent Present: _____

⁴⁸In neonates, systemic Herpes infection may include hepatitis.



METHODS AND PROCEDURES

AFP

SUDDEN DEATH IN THE YOUNG AUTOPSY GUIDANCE

Gastrointestinal Tract - Microscopic Examination (Describe findings on page 17)

- Take sections of any abnormal areas.
- Also take sections of:
 - Tongue at foramen cecum (optional)
 - Epiglottis (optional)
 - Proximal esophagus (optional)
 - Gastroesophageal junction, for reflux (required in infants; optional in children/young adults)
 - Gastric wall (optional)
 - Pyloroduodenal junction (recommended in infants; optional in children and young adults)
 - Proximal duodenum (if evaluating for villous atrophy, some immunodeficiency syndromes, or parasites; optional otherwise)
 - Ampulla of Vater with adjacent duodenum and head of the pancreas (optional)
- Tail of the pancreas (optional)
- Liver
- Gallbladder, biliary tree (optional)
- Jejunal and ileal sections (if evaluating for villous atrophy, enteritis, or parasites; optional otherwise)
- Ileocecal junction (recommended in infants; optional in children and young adults)
- Appendix tip or base (optional)
- Ascending or transverse colon (optional)
- Descending or rectosigmoid colon (recommended in infants and children; optional in children and young adults)
- Anorectum (optional)

Infectious Diseases

Neurologic			Gastrointestinal		
– Encephalitis	<input type="checkbox"/>	Absent	<input type="checkbox"/>	Present	
– Meningitis	<input type="checkbox"/>	Absent	<input type="checkbox"/>	Present	
Respiratory			Other		
– Pharyngitis	<input type="checkbox"/>	Absent	<input type="checkbox"/>	Present	
– Epiglottitis	<input type="checkbox"/>	Absent	<input type="checkbox"/>	Present	
– Bronchitis/bronchiolitis	<input type="checkbox"/>	Absent	<input type="checkbox"/>	Present	
– Pneumonia	<input type="checkbox"/>	Absent	<input type="checkbox"/>	Present	
Cardiac			– Enterocolitis		
– Myocarditis	<input type="checkbox"/>	Absent	<input type="checkbox"/>	Absent	<input type="checkbox"/>
– Endocarditis	<input type="checkbox"/>	Absent	<input type="checkbox"/>	Present	
			– Diffuse rash		
			<input type="checkbox"/>	Absent	<input type="checkbox"/>
			– Soft tissue lesion		
			<input type="checkbox"/>	Absent	<input type="checkbox"/>
			– Lymphadenitis		
			<input type="checkbox"/>	Absent	<input type="checkbox"/>
			– Sepsis syndrome (e.g., disseminated intravascular coagulopathy)		
			<input type="checkbox"/>	Absent	<input type="checkbox"/>
			– Urinary tract infection		
			<input type="checkbox"/>	Absent	<input type="checkbox"/>
			– Other: _____		

Specimens

The following should not be construed as requiring every sample for every examination, but should guide the autopsy physician's selection of specimens recovered based upon antemortem signs and symptoms and postmortem anatomic findings.

- Nasopharyngeal swab for viral culture
- Cerebrospinal fluid
 - Blood cultures Aerobic Anaerobic
 - Trachea Culturette Fresh tissue (obtained in a sterile fashion)
 - Bronchus Culturette Fresh tissue (obtained in a sterile fashion)
 - Lung culturette(s)
 - Right upper lobe Right middle lobe Right lower lobe
 - Left upper lobe Left lower lobe
 - Sterilely obtained fresh lung tissue
 - Right upper lobe Right middle lobe Right lower lobe
 - Left upper lobe Left lower lobe
- Stool sample

Were additional specialists consulted on this autopsy (e.g., cardiac pathologist, neuropathologist)? Yes No

If yes, specify: _____



METHODS AND PROCEDURES

AFP

SUDDEN DEATH IN THE YOUNG AUTOPSY GUIDANCE

Gross Examination of Organs Summary Table

Organ	In situ exam	Gross weight of organ	Fixed or fresh (check)	Gross inspection (check box if normal; if not, describe abnormalities)	Sections retained?*
Brain (including leptomeninges)				<input type="checkbox"/> Normal	<input type="checkbox"/> Yes <input type="checkbox"/> No
Neck structures ⁵⁰		Thyroid gland ⁵¹	<input type="checkbox"/> Fresh <input type="checkbox"/> Fixed	<input type="checkbox"/> Normal	<input type="checkbox"/> Yes <input type="checkbox"/> No
		Thymus			
Body cavities ⁵²			<input type="checkbox"/> Fresh <input type="checkbox"/> Fixed	<input type="checkbox"/> Normal	<input type="checkbox"/> Yes <input type="checkbox"/> No
Heart			<input type="checkbox"/> Fresh <input type="checkbox"/> Fixed	<input type="checkbox"/> Normal	<input type="checkbox"/> Yes <input type="checkbox"/> No
Kidneys			<input type="checkbox"/> Fresh <input type="checkbox"/> Fixed	<input type="checkbox"/> Normal	<input type="checkbox"/> Yes <input type="checkbox"/> No
Liver			<input type="checkbox"/> Fresh <input type="checkbox"/> Fixed	<input type="checkbox"/> Normal	<input type="checkbox"/> Yes <input type="checkbox"/> No
Lungs			<input type="checkbox"/> Fresh <input type="checkbox"/> Fixed	<input type="checkbox"/> Normal	<input type="checkbox"/> Yes <input type="checkbox"/> No
Pancreas			<input type="checkbox"/> Fresh <input type="checkbox"/> Fixed	<input type="checkbox"/> Normal	<input type="checkbox"/> Yes <input type="checkbox"/> No
Spleen			<input type="checkbox"/> Fresh <input type="checkbox"/> Fixed	<input type="checkbox"/> Normal	<input type="checkbox"/> Yes <input type="checkbox"/> No
Gastrointestinal tract			<input type="checkbox"/> Fresh <input type="checkbox"/> Fixed	<input type="checkbox"/> Normal	<input type="checkbox"/> Yes <input type="checkbox"/> No

*Small tissue samples in formalin.

⁵⁰Neck structures include: epiglottis, aryepiglottic folds, arytenoid and thyroid cartilage to include the vocal cords, cricothyroid membrane, the cricoid cartilage and the tracheal rings, thyroid gland, strap muscles, and the vessels and nerves including those within the carotid sheath and tongue. Under 1 year old include the subglottic musculature.

⁵¹In infants the thyroid may be too small to weigh.

⁵²Body cavities include the pleural, peritoneal and pericardial cavities and pelvis.



SUDDEN DEATH IN THE YOUNG AUTOPSY GUIDANCE

Tissue Sampling and Histology

Sampled Tissue	Number of Sections	Describe Abnormalities
Airways		
Brain (including leptomeninges)		
Heart		
Kidneys		
Liver		
Lungs		
Pancreas		
Spleen		
Thymus		
Bone or costochondral tissue		Location: Abnormalities:
Endocrine organs ⁵³		
Gastrointestinal tract		

⁵³Endocrine organs include: adrenal glands, pituitary gland, and the thyroid gland. The testes/ovaries can also be included.



METHODS AND PROCEDURES

AFP

SUDDEN DEATH IN THE YOUNG AUTOPSY GUIDANCE

Ancillary Testing

Testing	Describe Testing Performed	Results
	Lab name and type of testing (toxicology panel or genetic testing for Long QT, etc.)	
Microbiology/cultures for infectious disease		<input type="checkbox"/> Normal <input type="checkbox"/> Abnormal If abnormal, describe:
Postmortem metabolic screen		<input type="checkbox"/> Normal <input type="checkbox"/> Abnormal If abnormal, describe:
Toxicology		<input type="checkbox"/> Normal <input type="checkbox"/> Abnormal If abnormal, describe:
Vitreous testing		<input type="checkbox"/> Normal <input type="checkbox"/> Abnormal If abnormal, describe:
Genetic testing		<input type="checkbox"/> Normal <input type="checkbox"/> Abnormal If abnormal, describe:
Other, specify:		<input type="checkbox"/> Normal <input type="checkbox"/> Abnormal If abnormal, describe:

Final Pathologic Diagnosis

Was the family referred to a tertiary care center with subspecialty expertise relevant to the cause of death (e.g., cardiology, neurology) for screening of at-risk relatives and genetic counseling?

Yes No N/A Where:



METHODS AND PROCEDURES

AFP

APPENDIX 6

SDY AUTOPSY SUMMARY

SUBJECT ID:



Instructions

This summary sheet of autopsy results should be completed following your investigation of a sudden and unexpected death in a child or youth under age 20. Once completed, please share this summary with your local or state Child Death Review Team for its SDY case review process. We hope you are able to participate in the reviews. Your jurisdiction is participating in the Sudden Death in the Young Case Registry, funded by the National Institutes of Health and the Centers for Disease Control and Prevention. The autopsy findings will be summarized with other case review information and biospecimen data (upon family consent) into the SDY Case Registry. Analysis of this comprehensive data will help us better understand the etiologies and risk factors for sudden death in the young.

Limited guidance is provided throughout this summary sheet in italics and footnotes. Please try to complete all elements by circling the appropriate responses and most importantly describing any abnormalities.

A longer and more detailed document called the SDY Autopsy Guidance is also available to you for further direction and instructions. If you do not have a copy you can request one from your SDY State Coordinator.

"Sudden" implies death within 24 hours of the first symptom, or those resuscitated from cardiac arrest and dying during the same hospital admission.

"Unexpected" refers to a death in someone who dies from an accidental injury or someone who was believed to have been in good health, or had a stable chronic condition or had an illness but death was not expected. Examples could include hypertrophic or dilated cardiomyopathy, congenital heart disease, epilepsy, asthma and pneumonia.

This summary, the guidance and instructions were developed by the SDY Autopsy Protocol Committee composed of medical examiners with experience in pediatric, cardiac and neuropathology, physician coroners, death investigators, and other medical professionals with experience in cardiology, neurology, emergency medicine, public health and genetics.

Inclusion and Exclusion Criteria

This autopsy results summary sheet is a key component of the SDY Case Registry and should be used for all cases that meet all of the following inclusion criteria and none of the following exclusion criteria:

Inclusion Criteria

- | | | |
|---|---------------------------------------|--------------------------------------|
| Is the child under 20 years old? | <input type="checkbox"/> Yes, Include | <input type="checkbox"/> No, Exclude |
| Was the death sudden and unexpected and/or unwitnessed? | <input type="checkbox"/> Yes, Include | <input type="checkbox"/> No, Exclude |

Exclusion Criteria

- | | | |
|---|---------------------------------------|--------------------------------------|
| Was the death caused by an accident in which the external cause was <u>the obvious and only reason*</u> for the death? | <input type="checkbox"/> Yes, Exclude | <input type="checkbox"/> No, Include |
| *Exception: All infants under 1 year of age whose death was caused by suffocation | <input type="checkbox"/> Include | |
| Was the death an obvious homicide? | <input type="checkbox"/> Yes, Exclude | <input type="checkbox"/> No, Include |
| Was the death an obvious suicide? | <input type="checkbox"/> Yes, Exclude | <input type="checkbox"/> No, Include |
| Was the death caused by an accidental or intentional overdose of drugs even if this caused cardiac or respiratory arrest? | <input type="checkbox"/> Yes, Exclude | <input type="checkbox"/> No, Include |
| Was the death caused by a terminal illness in which the death was reasonably expected to occur within 6 months? | <input type="checkbox"/> Yes, Exclude | <input type="checkbox"/> No, Include |



METHODS AND PROCEDURES

AFP

SDY AUTOPSY SUMMARY

SUBJECT ID:

SDY Autopsy Guidance and Instructions consulted?

Yes No

Were additional specialists consulted on this autopsy (e.g., cardiac pathologist, neuropathologist)?

Yes No

If yes, specify:

General

Sex: Male Female

Body weight: _____ kg Body length: _____ cm

Head circumference: _____ cm

External Exam: If abnormalities suggestive of trauma, disease/syndrome, or medical intervention, please describe:

Photography (external) yes no

Imaging

(Circle all that were performed and describe the location)

X-Ray, single:

X-Ray, multiple views:

CT scan:

MRI:

Describe any abnormalities found on imaging:

PAGE 2

Page 386

Gulino et al. • SDY Case Registry Pathologic Investigation

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

©2018 Academic Forensic Pathology International

Downloaded from www.afpjournals.com by an AFP Journal subscriber

This article is for personal use only and may not be shared or distributed in any fashion



METHODS AND PROCEDURES

AFP

SDY AUTOPSY SUMMARY

SUBJECT ID:

Gross Examination of Organs

Organ	In situ exam	Gross weight of organ	Fixed or fresh (check)	Gross inspection (check box if normal; if not, describe abnormalities)	Sections retained ¹ ?
Brain (including leptomeninges)				<input type="checkbox"/> Normal	<input type="checkbox"/> Yes <input type="checkbox"/> No
Neck structures ²		Thyroid gland ³	<input type="checkbox"/> Fresh <input type="checkbox"/> Fixed	<input type="checkbox"/> Normal	<input type="checkbox"/> Yes <input type="checkbox"/> No
		Thymus			
Body cavities ⁴			<input type="checkbox"/> Fresh <input type="checkbox"/> Fixed	<input type="checkbox"/> Normal	<input type="checkbox"/> Yes <input type="checkbox"/> No
Heart			<input type="checkbox"/> Fresh <input type="checkbox"/> Fixed	<input type="checkbox"/> Normal	<input type="checkbox"/> Yes <input type="checkbox"/> No
Kidneys			<input type="checkbox"/> Fresh <input type="checkbox"/> Fixed	<input type="checkbox"/> Normal	<input type="checkbox"/> Yes <input type="checkbox"/> No
Liver			<input type="checkbox"/> Fresh <input type="checkbox"/> Fixed	<input type="checkbox"/> Normal	<input type="checkbox"/> Yes <input type="checkbox"/> No
Lungs			<input type="checkbox"/> Fresh <input type="checkbox"/> Fixed	<input type="checkbox"/> Normal	<input type="checkbox"/> Yes <input type="checkbox"/> No
Pancreas			<input type="checkbox"/> Fresh <input type="checkbox"/> Fixed	<input type="checkbox"/> Normal	<input type="checkbox"/> Yes <input type="checkbox"/> No
Spleen			<input type="checkbox"/> Fresh <input type="checkbox"/> Fixed	<input type="checkbox"/> Normal	<input type="checkbox"/> Yes <input type="checkbox"/> No
GI tract			<input type="checkbox"/> Fresh <input type="checkbox"/> Fixed	<input type="checkbox"/> Normal	<input type="checkbox"/> Yes <input type="checkbox"/> No

¹Small tissue samples in formalin.

²Neck structures include: epiglottis, aryepiglottic folds, arytenoid and thyroid cartilage to include the vocal cords, cricothyroid membrane, the cricoid cartilage and the tracheal rings, thyroid gland, strap muscles, and the vessels and nerves including those within the carotid sheath and tongue. Under 1 y.o. include the subglottic musculature.

³In infants the thyroid may be too small to weigh.

⁴Body cavities include the pleural, peritoneal and pericardial cavities and pelvis.



METHODS AND PROCEDURES

AFP

SDY AUTOPSY SUMMARY

SUBJECT ID:

Detailed Review of Specified Organs

Thorax/Lungs

Aspiration

Pneumonia/consolidation	<input type="checkbox"/> Absent	<input type="checkbox"/> Present
Pulmonary artery thromboemboli ⁵	<input type="checkbox"/> Absent	<input type="checkbox"/> Present (location): _____
Hemorrhage	<input type="checkbox"/> Absent	<input type="checkbox"/> Present
If present: Diffuse	Focal, location: _____	Aspiration pattern (follows bronchi)
Pulmonary hypertension ⁶	<input type="checkbox"/> Absent	<input type="checkbox"/> Present

Heart

Hemopericardium	<input type="checkbox"/> Absent	<input type="checkbox"/> Present	
Vascular ring	<input type="checkbox"/> Absent	<input type="checkbox"/> Present	
Right ventricular fat infiltration ⁷	<input type="checkbox"/> Absent	<input type="checkbox"/> Present	
If present, circle which wall	<input type="checkbox"/> Anterior	<input type="checkbox"/> Posterior	Maximum % thickness of wall involved: _____
Right ventricular thinning ⁸	<input type="checkbox"/> Anterior	<input type="checkbox"/> Posterior	Location: _____
Hypertrophic cardiomyopathy	<input type="checkbox"/> Absent	<input type="checkbox"/> Present	
Ventricular septal thickness ⁹ :	_____ cm		
Dilated cardiomyopathy	<input type="checkbox"/> Absent	<input type="checkbox"/> Present	
Left ventricular noncompaction	<input type="checkbox"/> Absent	<input type="checkbox"/> Present	
Restrictive cardiomyopathy	<input type="checkbox"/> Absent	<input type="checkbox"/> Present	
Congenital heart disease ^{10,11}	<input type="checkbox"/> Absent	<input type="checkbox"/> Present (type) _____	
Valve disease:			
Mitral valve prolapse	<input type="checkbox"/> Absent	<input type="checkbox"/> Present	
Valve stenosis	<input type="checkbox"/> Absent	<input type="checkbox"/> Present (location, severity) _____	
Myocardial infarction (recent)	<input type="checkbox"/> Absent	<input type="checkbox"/> Present (location) _____	
Coronary arteries: <input type="checkbox"/> Ostia:	<input type="checkbox"/> Normal ¹²	<input type="checkbox"/> Abnormal: (location)	
Distribution:	<input type="checkbox"/> Normal, right dominant	<input type="checkbox"/> Normal, left dominant ¹³	<input type="checkbox"/> Co-dominant
<input type="checkbox"/> Single	<input type="checkbox"/> Left anterior descending from right	<input type="checkbox"/> Circumflex from right	
<input type="checkbox"/> Other:			
Aneurysm:	<input type="checkbox"/> Absent	<input type="checkbox"/> Present	
Dissection:	<input type="checkbox"/> Absent	<input type="checkbox"/> Present	
Atherosclerosis:	<input type="checkbox"/> Absent	<input type="checkbox"/> Present	

⁵If there is any question whether blood clots in the mainstem pulmonary artery branches are antemortem thromboemboli or postmortem clot, histology is definitive.

⁶Muscle layers in subpleural arterioles

⁷Concerning for arrhythmogenic right ventricular cardiomyopathy

⁸Concerning for arrhythmogenic right ventricular cardiomyopathy

⁹"Normal" includes origin of the conus artery adjacent to right coronary ostium (normal variant).

¹⁰Probe patent foramen ovale is considered a normal variant and should not be included under congenital heart disease.

¹¹Surgical status will be recorded under evidence of cardiovascular interventions.

¹²"Normal" includes origin of the coronary artery adjacent to right coronary ostium (normal variant).

¹³The right coronary artery may be small in left-dominant hearts. Describe in further detail in "Other" section if absent/hypoplastic or if downstream sequelae exist (e.g., myocardial infarction).



METHODS AND PROCEDURES

AFP

SDY AUTOPSY SUMMARY

SUBJECT ID:

Heart (continued)

Evidence of cardiovascular interventions Absent Present

Pacemaker (make, model, type) _____

Interrogated? Yes No Results: _____

Implanted defibrillator (make, model) _____

Interrogated? Yes No Results: _____

Implanted loop recorder (make, model) _____

Interrogated? Yes No Results: _____

Ventricular assist device (type, location) _____

Evidence of congenital heart surgery (type, location) _____

Stents/coils/plugs/occluder devices (type, location) _____

Prosthetic valves (type, location) _____

Other: _____

Brain

Dural sinus thrombosis Absent Present Sagittal Transverse

Epidural hemorrhage Absent Present

Subdural hemorrhage Absent Present Left Right Bilateral

If present: Amount: _____ ml

Color: _____

Appearance: Clotted Liquid Shiny surface

Subarachnoid hemorrhage Absent Present

If present: Pattern: Diffuse Scattered Focal, location: _____

Severity: Mild Moderate Severe

Circle of Willis Distribution: Normal Abnormal: _____

Obstruction: Absent Present

Size: Normal Small Large Vessel(s): _____

Aneurysm: Absent Present

If present: Size: _____ mm Location: _____

Cingulate herniation Absent Present Right Left

Uncal herniation Absent Present Right Left Bilateral

Tonsillar herniation Absent Present Right Left Bilateral

Chronic¹⁴ Acute

Stroke Absent Present Location: _____

Heterotopia Absent Present Location: _____

Arterio-venous malformation Absent Present Location: _____

Compression of cerebral hemisphere Absent Present

Anoxic ischemic encephalopathy Absent Present

Other congenital anomalies of the brain Absent Present Describe: _____

¹⁴As in a malformation such as Arnold Chiari



SDY AUTOPSY SUMMARY

SUBJECT ID:

Detailed Review of Specified Organs

Gastrointestinal Tract

Intussusception	<input type="checkbox"/>	Absent	<input type="checkbox"/>	Present
Obstruction	<input type="checkbox"/>	Absent	<input type="checkbox"/>	Present
Ruptured abdominal organ	<input type="checkbox"/>	Absent	<input type="checkbox"/>	Present
Volvulus	<input type="checkbox"/>	Absent	<input type="checkbox"/>	Present

Infectious Diseases

Epiglottitis	<input type="checkbox"/>	Absent	<input type="checkbox"/>	Present
Encephalitis	<input type="checkbox"/>	Absent	<input type="checkbox"/>	Present
Meningitis	<input type="checkbox"/>	Absent	<input type="checkbox"/>	Present
Myocarditis	<input type="checkbox"/>	Absent	<input type="checkbox"/>	Present
Endocarditis	<input type="checkbox"/>	Absent	<input type="checkbox"/>	Present
Pneumonia	<input type="checkbox"/>	Absent	<input type="checkbox"/>	Present
Urinary tract infection	<input type="checkbox"/>	Absent	<input type="checkbox"/>	Present

Tissue Sampling and Histology

Sampled Tissue	Number of Sections	Describe Abnormalities	
Airways			
Brain including leptomeninges			
Heart			
Kidney			
Liver			
Lungs			
Pancreas			
Spleen			
Thymus			
Bone or costochondral tissue		Location:	Abnormalities:
Endocrine organs ¹⁵			
Gastrointestinal tract			

¹⁵Endocrine organs include: adrenal glands, pituitary gland, and the thyroid gland. The testes/ovaries can also be included.



METHODS AND PROCEDURES

AFP

SDY AUTOPSY SUMMARY

SUBJECT ID:

Ancillary Testing

Testing	Describe Testing Performed	Results
	E.g. lab name and type of testing (toxicology panel or genetic testing for Long QT, etc...)	Circle Normal or Abnormal If Abnormal, Describe
Microbiology/cultures for infectious disease		<input type="checkbox"/> Normal <input type="checkbox"/> Abnormal If abnormal, describe:
Postmortem metabolic screen		<input type="checkbox"/> Normal <input type="checkbox"/> Abnormal If abnormal, describe:
Toxicology		<input type="checkbox"/> Normal <input type="checkbox"/> Abnormal If abnormal, describe:
Vitreous testing		<input type="checkbox"/> Normal <input type="checkbox"/> Abnormal If abnormal, describe:
Genetic testing		<input type="checkbox"/> Normal <input type="checkbox"/> Abnormal If abnormal, describe:
Other, specify:		<input type="checkbox"/> Normal <input type="checkbox"/> Abnormal If abnormal, describe:

Final Pathologic Diagnosis

Was the family referred to a tertiary care center with subspecialty expertise relevant to the cause of death (e.g. cardiology, neurology) for screening of at-risk relatives and genetic counseling?

Yes No N/A

Where:

PAGE 7

Page 391

Gulino et al. • SDY Case Registry Pathologic Investigation

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

©2018 Academic Forensic Pathology International

Downloaded from www.afpjournals.com by an AFP Journal subscriber

This article is for personal use only and may not be shared or distributed in any fashion



A Case Series of Anterograde and Retrograde Vascular Projectile Embolization

Jennifer Chao, Jeffrey Barnard, Joyce L. deJong, Joseph A. Prahlow

ABSTRACT

Deaths related to firearms are common within the United States, with most cases having conspicuous projectile wounds found at autopsy. Individual gunshot wounds may be perforating or penetrating. In most cases with penetrating wounds, projectiles are relatively easily found via radiography and by following the pathway on internal examination. When a projectile is not detected in the expected region, intravascular embolization of the projectile should be suspected. Embolization may be arterial or venous, as well as anterograde or retrograde. Typically, such emboli involve small caliber bullets or shot pellets. The authors present three unusual cases of intravascular projectile embolization at autopsy, one involving shotgun slug fragment embolization, one where death was delayed, and one with retrograde embolization into the liver. *Acad Forensic Pathol.* 2018 8(2): 392-406

AUTHORS

Jennifer Chao MD, Western Michigan University Homer Stryker MD School of Medicine

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, principal investigator of the current study.

Jeffrey Barnard MD, University of Texas-Southwestern Medical School - Forensic Pathology

Roles: Data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, general supervision, writing assistance and/or technical editing.

Joyce L. deJong DO, Western Michigan University Homer Stryker MD School of Medicine - Pathology

Roles: Data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, general supervision, general administrative support, writing assistance and/or technical editing.

Joseph A. Prahlow MD, Western Michigan University Homer Stryker MD School of Medicine - Pathology

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, general supervision, general administrative support, writing assistance and/or technical editing.

CORRESPONDENCE

Joseph A. Prahlow MD, 300 Portage Street, Kalamazoo MI 49008, joseph.prahlow@med.wmich.edu

ETHICAL APPROVAL

As per Journal Policies, ethical approval was not required for this manuscript

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies conducted with animals or on living human subjects

STATEMENT OF INFORMED CONSENT

No identifiable personal data were presented in this manuscript

DISCLOSURES & DECLARATION OF CONFLICTS OF INTEREST

The authors, reviewers, editors, and publication staff do not report any relevant conflicts of interest

FINANCIAL DISCLOSURE

The authors have indicated that they do not have financial relationships to disclose that are relevant to this manuscript

KEYWORDS

Forensic pathology, Firearms, Vascular projectile embolization, Bullet embolus, Emboli

INFORMATION

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

©2018 Academic Forensic Pathology International • (ISSN: 1925-3621) • <https://doi.org/10.23907/2018.025>

Submitted for consideration on 1 Feb 2018. Accepted for publication on 21 Mar 2018



INTRODUCTION

Deaths related to firearms are common within the United States with most cases having conspicuous projectile-related wounds evident at autopsy. Individual gunshot wounds may be perforating, having both entrance and exit wounds, or penetrating, having only an entrance wound, with the projectile remaining within the body. In most cases with penetrating wounds, projectiles are relatively easily found via a combination of radiography exam and by following the bullet pathway on internal examination. However, occasionally in cases involving a penetrating wound, there is failure to discover a projectile in the expected region. When this occurs, vascular bullet/projectile embolization should be suspected. The occurrence rate of vascular bullet embolization is reported to be approximately 0.3% in penetrating trauma (1). Arterial bullet embolization is most common, while approximately one-third of the cases involve venous embolization (2). Anterograde movement within the vessel, in the direction of normal blood flow, is typical; however, paradoxical bullet embolism, or embolization that occurs against the flow of blood (also known as retrograde movement or embolization), may also occur. In this small case series, the authors present details regarding three cases of bullet/projectile embolization at autopsy. The ensuing discussion focuses on the current literature and review of vascular bullet/projectile embolization.

METHODS

The cases were selected from the cases of the authors (JB, JD, and JP). Two cases demonstrate bullet/projectile emboli that travel in an anterograde fashion, whereas a single case demonstrates a bullet/projectile embolus that travels in a retrograde fashion.

CASE REPORTS

Case 1

A 10-year-old male child was found dead along with his mother and another female in a burning trailer. At autopsy, his entire body was extensively charred with

heavy soot deposition (**Image 1**). He was shot before the fire, with radiographic images demonstrating shotgun slug fragments within the posterior cranial cavity and the right side of his neck (**Image 2**). Due to his extensively fractured skull and thermal damage, a distinctive entry wound could not be discerned. However, the wound path was thought to have traversed through the scalp, skull, and brain, with a fragment of projectile subsequently embolizing to his jugular vein in an anterograde fashion, where it was recovered (**Image 3**).

Case 2

A 16-year-old male was found experiencing seizure-like activity while he was eating. He was rushed to the emergency department (ED), but was pronounced dead. Approximately one month prior to death, the teenager had reportedly sustained a gunshot wound to the back, but was alert, oriented, and had no complaints or symptoms of concern on evaluation at an ED. A chest radiograph was negative, but a bullet was present on radiograph of his abdomen/pelvis (**Image 4**). He underwent an exploratory laparotomy, which was negative, with no free blood in the abdominal cavity. It was presumed that the bullet had a markedly downward trajectory, entering the back, staying behind the peritoneal cavity, and lodging within the buttock. No further surgical exploration for the projectile was attempted, and he was discharged to home. At autopsy, a healing cutaneous entrance defect was on the left mid-to-low back. On internal examination, it was apparent that the bullet had entered the posterior subpleural aspect of the left chest wall, grazing the superior aspect of the tenth rib and the tenth thoracic vertebra, before entering the aorta (**Image 5**). There was a large (8 x 9 x 4 cm) hematoma adjacent to the defect in the aorta, a portion of which is visible in **Image 6**. This hematoma had ruptured into the left chest cavity, producing a massive hemothorax, composed of 2750 mL of liquid and clotted blood. The small caliber bullet had previously embolized downward within the aorta in an anterograde fashion and became embedded in the proximal aspect of the left internal iliac artery (**Image 7**). Postmortem blood toxicology testing was negative. The cause of death was

determined to be complications of the gunshot wound of the trunk, leading to the formation of a hematoma that subsequently ruptured. The manner of death was homicide.

Case 3

A 21-year-old man's decomposing body (**Image 8**) was found floating in the water in a drainage area along the south bank of a river. He was on probation for drug-related offences and reportedly owed money for drugs. When he was unable to pay the suspect the money he owed, he was reportedly shot with a M-16/AR-15 rifle. On external examination at autopsy, he had eight gunshot wounds with bullets entering the left side of his neck, left anterior chest, left central chest (**Image 9**), left lateral upper back, right mid-back, right lower back, right lower lateral buttock, and dorsal aspect of the right hand. On internal examina-

tion, the penetrating wound of the anterior chest wall demonstrated the following pathway: perforation of the left chest wall between anterior left ribs three and four, the anterior pericardial sac, the superior aspect of the anterior right ventricular wall, and the atrioventricular septum, with the pathway ending within the right atrium. The bullet could not be identified anywhere within the heart, lungs, inferior vena cava, or superior vena cava. A radiograph of the removed, but still intact liver, revealed the presence of a bullet (**Image 10**). Careful dissection of the hepatic vein, from its connection to the inferior vena cava, revealed that the projectile had embolized in a retrograde fashion into the hepatic venous system (**Image 11**). A partially deformed, small caliber, non-jacketed, gilded bullet was recovered from within the right lobe of the liver, where it was found wedged into a tributary of a hepatic vein (**Image 12**). The cause of death was multiple rifle wounds. The manner of death was homicide.



Image 1: Head, neck, and upper chest of extensively burned 10-year-old child in Case 1. Thermal injuries obscure the shotgun wound.



Image 2: Postmortem radiograph of extensively fractured skull in Case 1, with arrows pointing to shotgun slug fragments.

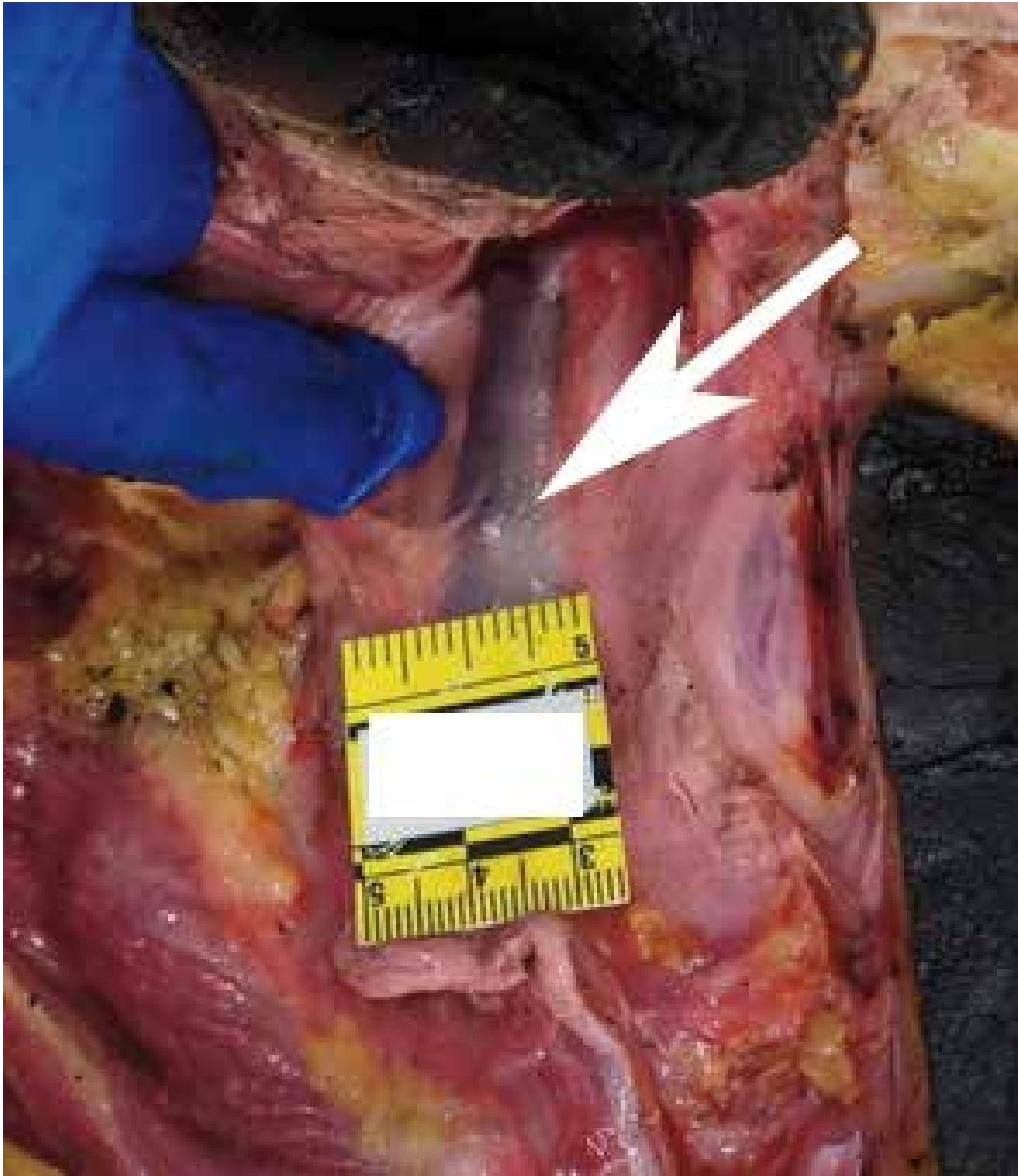


Image 3: Gross view of embolized fragment of shotgun slug (arrow) within the jugular vein in Case 1. Note that the projectile is visible through the intact, translucent venous wall.



Image 4: Postmortem radiograph of pelvis from Case 2, with bullet.

DISCUSSION

A bullet/projectile from a modern firearm typically follows a relatively straight course within a body, either exiting the body (a perforating wound) or being recovered from within the body at the end of the bullet pathway/track (a penetrating wound). However, in some cases, vascular embolization of a bullet/projectile or fragment occurs, such that there is failure to discover the bullet in the expected region, radiologically or during autopsy dissection.

Intravascular embolization can occur within the arterial or venous systems. The most common sites of entrance for a bullet into the arterial system are the aorta

and the heart, whereas entrance into the venous system typically occurs via the vena cava and iliac veins (3). Although embolization usually occurs immediately following entrance of the bullet into the circulation, delays as long as 26 days have been reported (4). According to DiMaio, bullet emboli are usually associated with small-caliber, lightweight, low-velocity missiles that possess low kinetic energy—and if these missiles lose their forward velocity on penetration of a major blood vessel or the heart, they are able to enter the circulation and embolize to a distant site (3). In addition to small caliber projectiles, birdshot pellets and small fragments of projectiles are also capable of embolization. A projectile or fragment that has a specific gravity greater than blood is capable of traveling

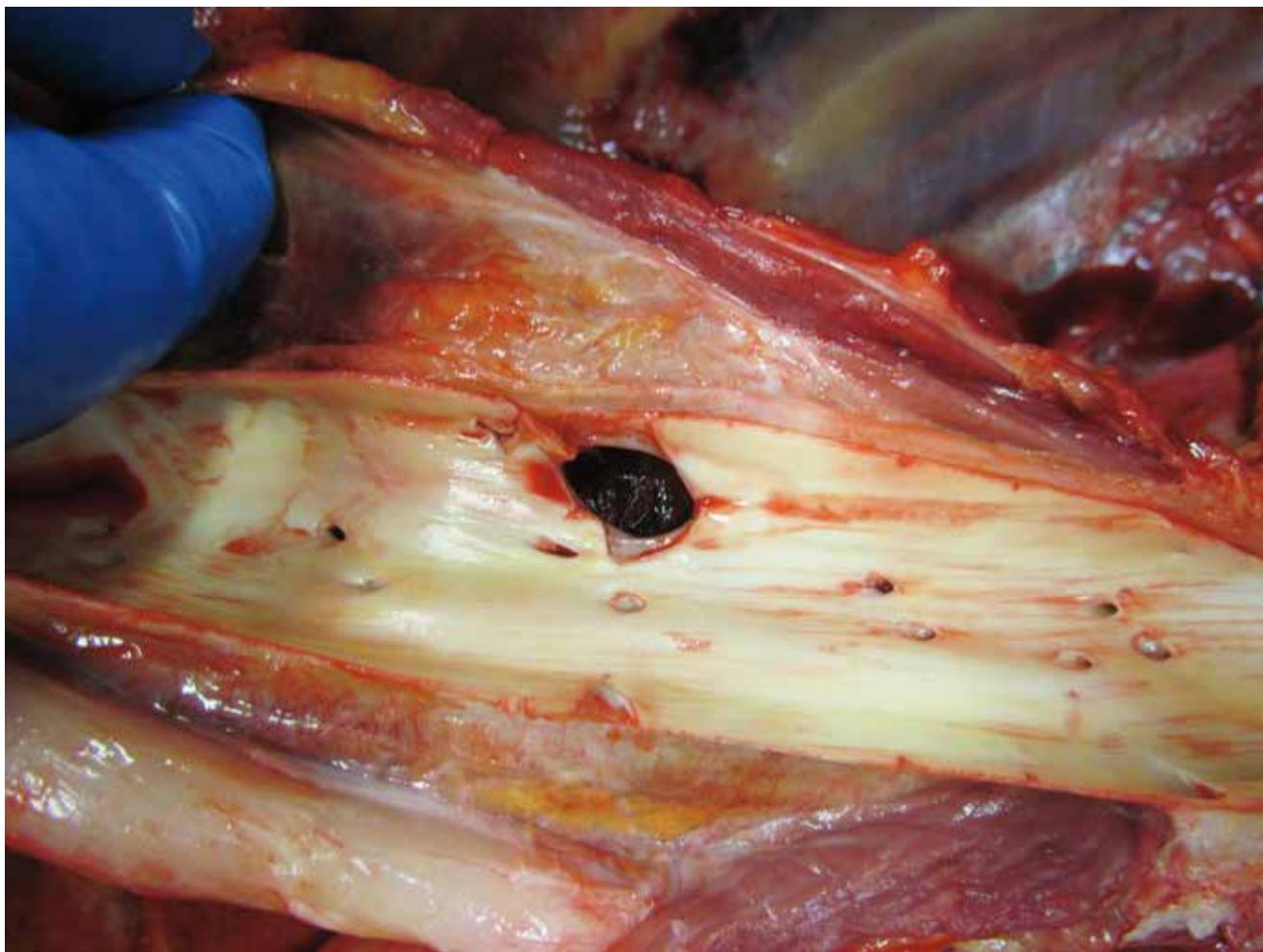


Image 5: Bullet perforation site of the aorta in Case 2, as discovered at autopsy.

against the flow of blood in a retrograde fashion, also known as “paradoxical bullet embolism”(5). Thus, depending on the trajectory and the properties of the projectile itself, it may travel in an anterograde or retrograde fashion through the arterial or venous system.

The definition of “embolism” is the lodging of an “embolus,” a blockage-causing piece of material, inside a blood vessel (6). Although uncommon, migratory intraluminal bullets may produce complex nonvascular “embolization” scenarios in patients with gunshot wounds. A rare case of gastrointestinal bullet “embolism” was described where a small-caliber bullet perforated the small bowel, migrated distally, and eventually

was discovered in the distal colon, which resulted in a missed injury, leading to sepsis and the demise of the patient (7). Smalls and Siram have reported a unique case of a “wandering” bullet in which the bullet caused esophageal injury and was found lodged in the stomach (8). DiMaio has depicted two interesting cases of bullets expelled through the oral orifice—in the first case, a bullet from an entry point in the back was recovered from the oral cavity, whereas in the second case, a bullet from a chest wound that halted within the lungs was eventually coughed-up into the mouth (3). Another rare case involved the spontaneous migration of a bullet within the spinal subarachnoid space, which caused delayed radicular symptoms (9).

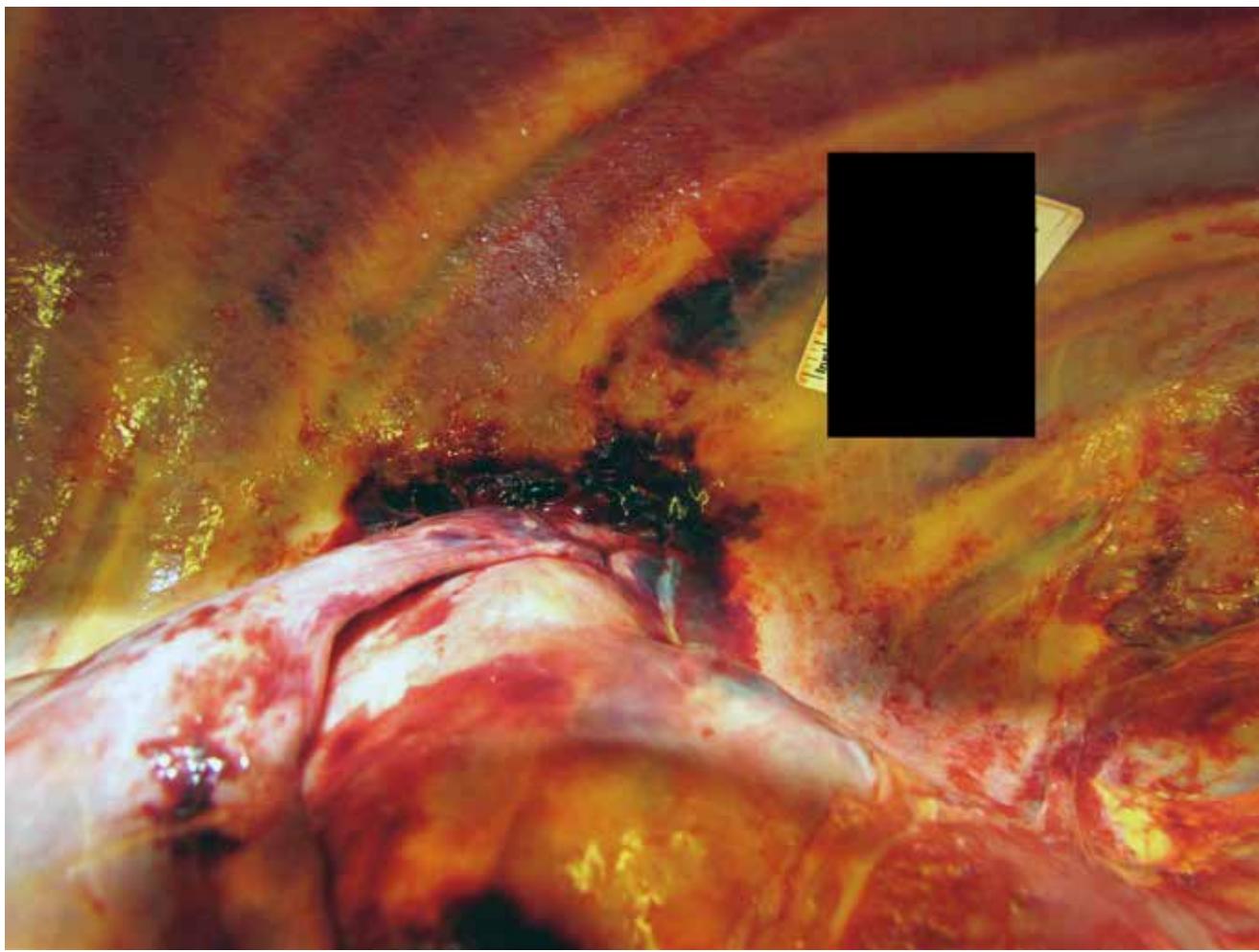


Image 6: The site of hematoma rupture into the left chest cavity as seen at autopsy from Case 2. Note that most of the large hematoma is hidden from view in this photograph, as it is behind the aorta.



Image 7: Gross view of small caliber bullet recovered from within the proximal left internal iliac artery in Case 2.

The vascular embolization phenomenon is not limited to detection at autopsy, as intravascular bullet embolization also occurs in living survivors of gunshot injuries. The clinical medical literature has numerous reports of intravascular bullet emboli, including cases of arterial embolization (2, 10-13), venous embolization (2, 10, 14, 15), and retrograde embolization (16). Several unique cases have been reported, including shotgun pellet embolization to a coronary artery and a projectile paradoxical embolization via a patent foramen ovale from the left external iliac vein to the left common iliac artery (17, 18). In a 1990 review of the English language literature, Michelassi et al. describe 153 cases of bullet emboli, of which 100 were arterial and 53 were venous (2). In their review, most bullet emboli followed the normal direction of blood flow; however, 15% of venous bullets embolized in a retro-

grade manner (2). One in ten arterial emboli occurred following a right-heart or venous injury and 80% of arterial emboli were symptomatic, while only one third of venous emboli were symptomatic (2).

A variety of potential explanations may account for a discrepancy when attempting to account for the number of entry and exit wounds, the number of projectiles accounted for at the scene of the shooting, and the number of projectiles evident on radiographic examination. A recent review provides a relatively complete list of the various situations and possible explanations for when such a discrepancy exists (19). If there is any discrepancy between the number of entry and exit wounds, or if the clinical signs and radiographic imaging do not correlate with the injuries, suspected bullet embolism should be one of



Image 8: The decomposed body of the man from Case 3, after being removed from the water.

several possible explanations. The missing projectile should be thoroughly accounted for by a meticulous search. As such, a high degree of suspicion and diligent evaluation of patients with gunshot wounds is of critical importance in order to identify situations where projectile embolism may have occurred. Case 2 exemplifies this fact within a person who initially survived his injuries. Had the clinicians and surgeon in this case recognized the fact that the bullet seen in the pelvis region on radiograph actually represented an intra-arterial embolic phenomenon, they would have realized that a vascular (aortic) injury had occurred. Knowing this, they would have likely explored the chest in order to identify and repair the aortic injury, thus possibly preventing the delayed death related to the gunshot wound.

CONCLUSION

The cases presented serve as examples of somewhat unique variations of bullet/projectile intravascular embolization. Such cases can involve arteries or veins, and be anterograde or retrograde. Intravascular projectile embolism can cause difficulty at forensic autopsy, while pathologists attempt to account for projectile pathway and location. The first case, involving an anterograde venous embolism, highlights the fact that shotgun slug fragments may embolize. The location of the projectile fragment within the jugular vein might be explained by a combination of gravity (child was presumably standing or sitting upright when shot) and possibly the “vacuum action” created within the severed vein as the heart continued to



Image 9: Entrance wound on the left central chest from Case 3.

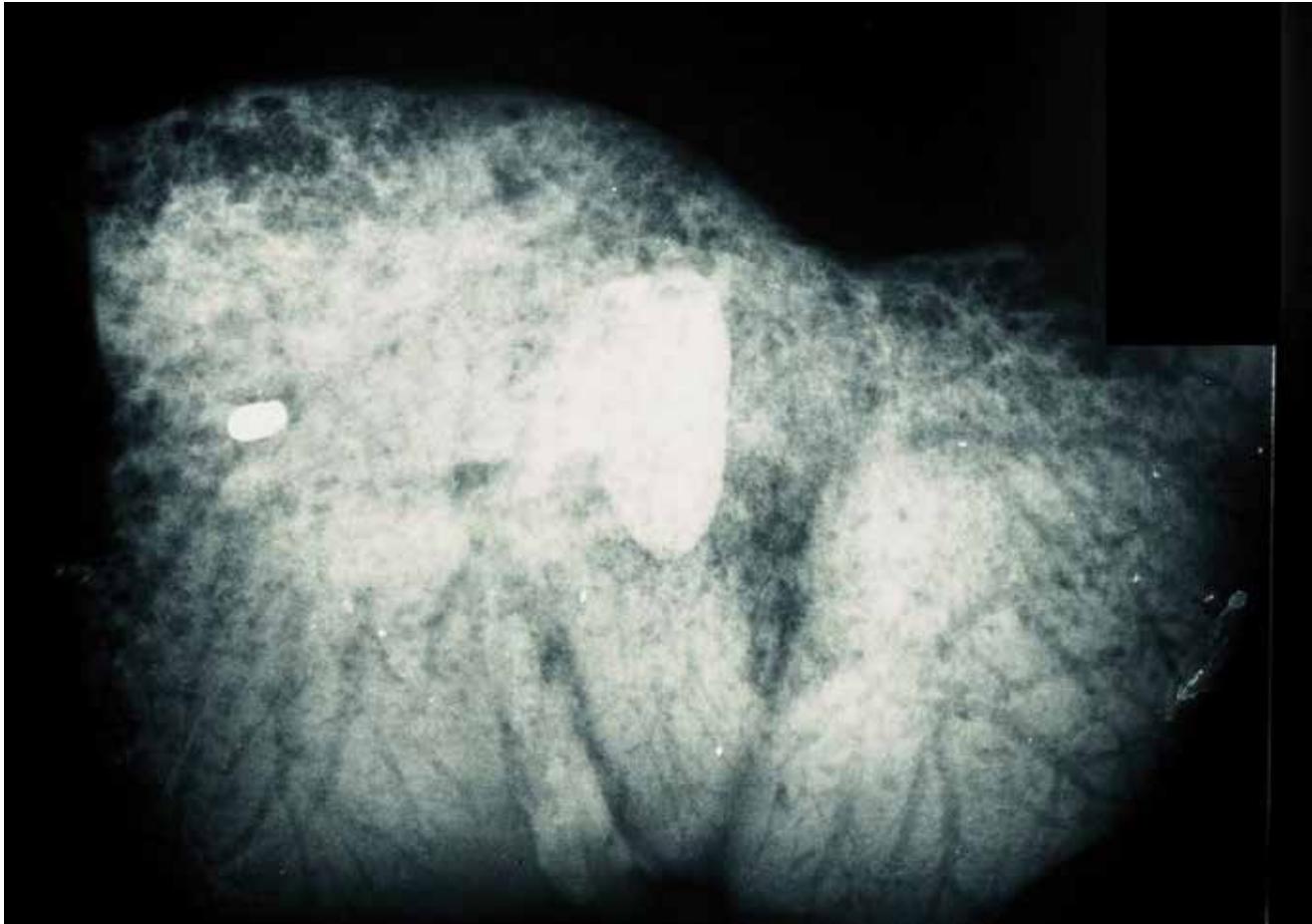


Image 10: Radiograph of liver from Case 3, showing the presence of a small caliber bullet.

pump for a short time. The second case, which involved an anterograde arterial embolism, represents a unique case where embolization was not recognized until several weeks following the shooting. The third case involved a retrograde venous embolism into a branch of the hepatic vein within the liver. The exact explanation for the retrograde venous embolism could not be ascertained with certainty; however, possible factors might include passive gravitational forces and increased “back-pressure” on the inferior vena cava,

via the pumping action of the heart, with forces transmitted via the bullet track through the atrioventricular septum. In addition to presenting challenges for forensic pathologists at autopsy, projectile emboli can pose problems for clinicians and surgeons. Case 2 in this series highlights the importance of identifying bullet emboli in patients who initially survive a gunshot wound. Failure to recognize projectile embolism in the clinical setting can have lethal consequences.

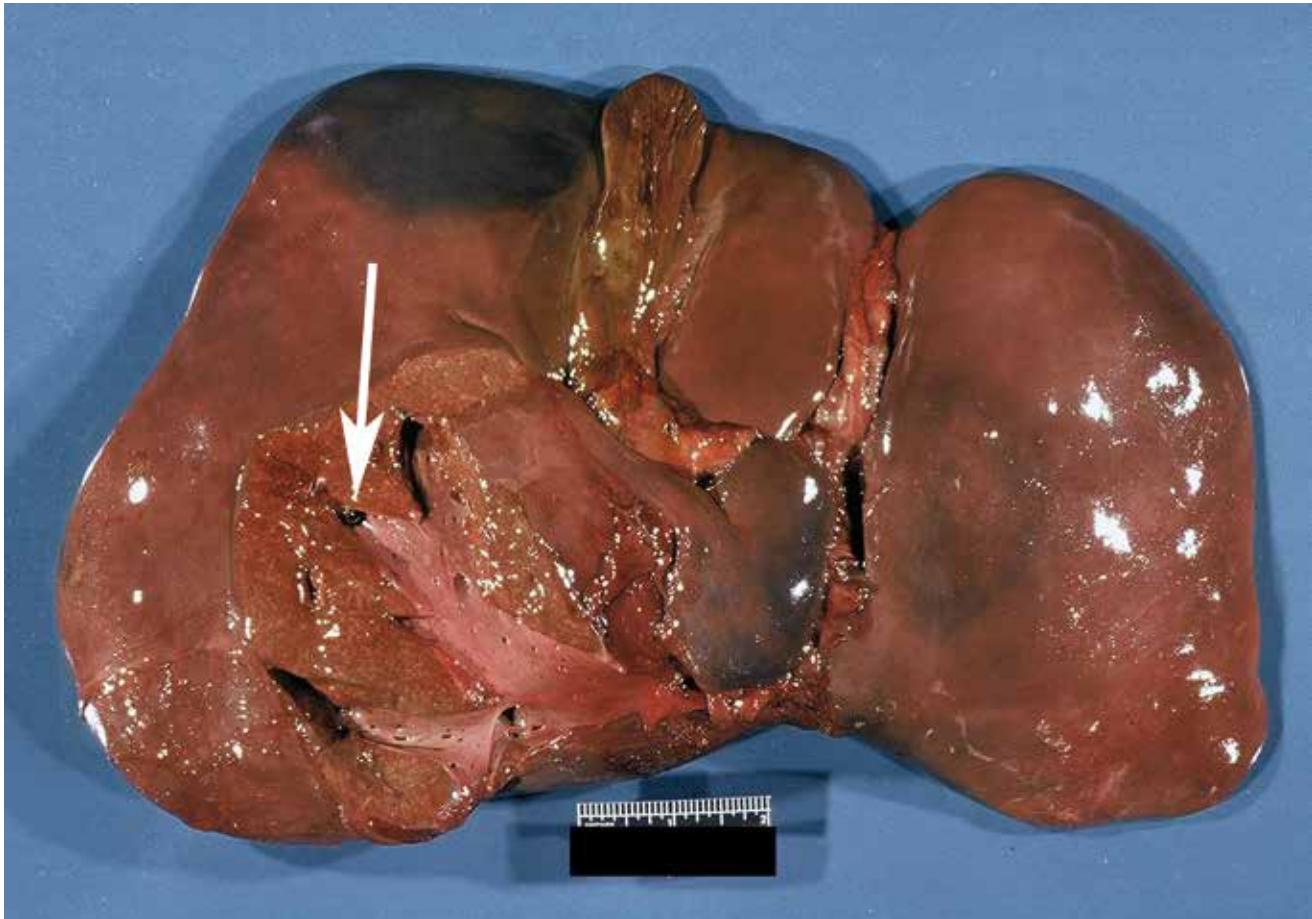


Image 11: Careful dissection of the hepatic vein in Case 3, from its connection to the inferior vena cava, revealed that the projectile (arrow) had embolized in a retrograde fashion into the hepatic venous system.



Image 12: Close-up view of the small caliber bullet found wedged into a tributary of a hepatic vein, after opening the vein at autopsy in Case 3.

REFERENCES

- 1) Schroeder ME, Pryor HI 2nd, Chun AK, et al. Retrograde migration and endovascular retrieval of a venous bullet embolus. *J Vasc Surg.* 2011 Apr; 53(4):1113-5. PMID: 21215588. <https://doi.org/10.1016/j.jvs.2010.11.046>.
- 2) Michelassi F, Pietrabissa A, Ferrari M, et al. Bullet emboli to the systemic and venous circulation. *Surgery.* 1990 Mar; 107(3):239-45. PMID: 2408175.
- 3) DiMaio VJM. Gunshot wounds: practical aspects of firearms, ballistics, and forensic techniques. Boca Raton: CRC Press; 2016. 422 p.
- 4) Keeley JL. A bullet embolus to the left femoral artery following a thoracic gunshot wound; probable entrance through thoracic aorta; case report and résumé of peripheral arterial bullet emboli. *J Thorac Surg.* 1951 Jun; 21(6):608-20. PMID: 14841797.
- 5) Adelson L. The pathology of homicide: A vade mecum for pathologist, prosecutor and defense counsel. Springfield (IL): Charles C Thomas; 1974. 976 p.
- 6) Dorland's Illustrated Medical Dictionary (32nd ed). Burlington (MA): Elsevier; 2012. 2147 p.
- 7) Biswas S, Price C, Abrol S. An elusive bullet in the gastrointestinal tract: a rare case of bullet embolism in the gastrointestinal tract and a review of relevant literature. *Case Rep Crit Care.* 2014; 2014:689539. PMID: 24829839. PMCID: PMC4009998. <https://doi.org/10.1155/2014/689539>.
- 8) Smalls NM, Siram SM. The wandering bullet. *J Natl Med Assoc.* 1988 Jun; 80(6):678-9, 682. PMID: 3292777. PMCID: PMC2625665.
- 9) Karim NO, Nabors MW, Golocovsky M, Cooney FD. Spontaneous migration of a bullet in the spinal subarachnoid space causing delayed radicular symptoms. *Neurosurgery.* 1986 Jan; 18(1):97-100. PMID: 3945385. <https://doi.org/10.1097/00006123-198601000-00018>.
- 10) Nolan T, Phan H, Hardy AH, et al. Bullet embolization: multidisciplinary approach by interventional radiology and surgery. *Semin Intervent Radiol.* 2012 Sep; 29(3):192-6. PMID: 23997411. PMCID: PMC3577595. <https://doi.org/10.1055/s-0032-1326928>.
- 11) Nguyen R, Ouedraogo A, Deneuville M. Gunshot wounds to the chest with arterial bullet embolization. *Ann Vasc Surg.* 2006 Nov; 20(6): 780-3. PMID: 17086482. <https://doi.org/10.1007/s10016-006-9128-6>.



CASE OF THE MONTH

AFP

- 12) Echeverria A, Feliciano DV, Vercruyse G. Pulmonary artery bullet embolism necessitating operative removal. *Am Surg.* 2015 Feb; 81(2):E80-1. PMID: 25642865.
- 13) Huang J, Pandey V, Shah R, et al. Popliteal artery embolism of bullet after abdominal gunshot wound. *Radiol Case Rep.* 2016 Nov; 11(4): 282-6. PMID: 27920844. PMCID: PMC5128195.
<https://doi.org/10.1016/j.radcr.2016.04.011>.
- 14) Nazir Z, Esufali ST, Rao NS, Rizvi I. Venous bullet embolism: a case report and review of the literature. *Injury.* 1992; 23(8):561-3. PMID: 1286915. [https://doi.org/10.1016/0020-1383\(92\)90163-m](https://doi.org/10.1016/0020-1383(92)90163-m).
- 15) Miller KR, Benns MV, Sciarretta JD, et al. The evolving management of venous bullet emboli: a case series and literature review. *Injury.* 2011 May; 42(5):441-6. PMID: 20828693.
<https://doi.org/10.1016/j.injury.2010.08.006>.
- 16) Bertoldo U, Enrichens F, Comba A, et al. Retrograde venous bullet embolism: a rare occurrence – case report and literature review. *J Trauma.* 2004 Jul; 57(1):187-92. PMID: 15284574.
<https://doi.org/10.1097/01.ta.0000135490.10227.5c>.
- 17) Hopkins HR, Pecirep DP. Bullet embolization to a coronary artery. *Ann Thorac Surg.* 1993 Aug; 56(2):370-2. PMID: 8347026.
[https://doi.org/10.1016/0003-4975\(93\)91181-l](https://doi.org/10.1016/0003-4975(93)91181-l).
- 18) Schurr M, McCord S, Croce M. Paradoxical bullet embolism: case report and literature review. *J Trauma.* 1996 Jun; 40(6):1034-6. PMID: 8656462.
<https://doi.org/10.1097/00005373-199606000-00034>.
- 19) Prahlow SP, Wolfenbarger R, Prahlow JA. Tandem bullet homicide. *Acad Forensic Pathol.* 2016 Mar; 6(1):130-9.
<https://doi.org/10.23907/2016.014>.



A Case of Severe Cardiac Sarcoidosis with Minimal Pulmonary Involvement: A Case Report with Literature Review

Mark R. Fowler, Nobby C. Mambo

ABSTRACT

Sarcoidosis is a granulomatous disease of unknown etiology. Although sarcoidosis is a systemic disease, there appears to be a predilection for involvement of certain organs. The pulmonary system is the most commonly affected system among all racial groups. Cardiac and respiratory complications are the leading causes of death due to sarcoidosis and in certain patient populations about half of these deaths are attributed to cardiac sarcoidosis. There are few autopsy case reports of cardiac sarcoidosis with minimal respiratory involvement making this case report relevant to the importance of the recognition and awareness of this entity. *Acad Forensic Pathol.* 2018 8(2): 407-415

AUTHORS

Mark R. Fowler MD, University of North Carolina Health Care System - Pathology

Roles: Project conception and/or design, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, principal investigator of the current study.

Nobby C. Mambo MD, Galveston County Medical Examiner's Office - Pathology

Roles: Project conception and/or design, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, principal investigator of the current study, general supervision.

CORRESPONDENCE

Mark R. Fowler MD, 101 Manning Dr., Chapel Hill NC 27514-4220, fowler5152@gmail.com

ETHICAL APPROVAL

As per Journal Policies, ethical approval was not required for this manuscript

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies conducted with animals or on living human subjects

STATEMENT OF INFORMED CONSENT

No identifiable personal data were presented in this manuscript

DISCLOSURES & DECLARATION OF CONFLICTS OF INTEREST

The authors, reviewers, editors, and publication staff do not report any relevant conflicts of interest

FINANCIAL DISCLOSURE

The authors have indicated that they do not have financial relationships to disclose that are relevant to this manuscript

KEYWORDS

Forensic pathology, Cardiac sarcoidosis, Splenic sarcoidosis, Noncaseating granuloma, Autopsy

INFORMATION

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

©2018 Academic Forensic Pathology International • (ISSN: 1925-3621) • <https://doi.org/10.23907/2018.026>

Submitted for consideration on 11 Feb 2018. Accepted for publication on 16 Apr 2018



INTRODUCTION

Sarcoidosis is a granulomatous disease of unknown etiology with variable clinical presentations and medical courses ranging from spontaneous resolution to chronic progression. Its dermatologic manifestation was first described by Jonathan Hutchinson in 1869 as a clinicopathologic entity causing persistent skin lesions. He described one patient with non-painful, symmetrically-purple skin plaques on the legs and hands. Another patient was described with raised, dusky-red skin lesions on the face and forearms without ulceration (1, 2). Schaumann, later in 1914, recognized sarcoidosis as a systemic, nonmalignant, and non-tuberculoid granulomatous disorder (3). The etiology of sarcoidosis has been attributed to genetic, environmental, infectious, and immune dysregulation causes. Current thought is that sarcoidosis is a common endpoint granulomatous disease caused by a heterogeneous group of agents in a genetically susceptible patient (4).

In the United States, predilection of this disease towards African Americans has been reported. The age-adjusted annual incidence in the US ranges from 10.9 cases per 100 000 for Caucasians to 35.5 cases per 100 000 for African Americans (5). Incidence has been reported to be highest in individuals between the ages of 20 and 40, and in females of all ethnic and racial groups (5, 6).

Cardiac and respiratory complications are the leading causes of death, with an estimated overall mortality between 1-5% (7). In certain patient populations, about half of these deaths are attributed to cardiac sarcoidosis (8). The prevalence of cardiac sarcoidosis varies between studies. In one study, the prevalence of cardiac sarcoidosis was reported as 40% in outpatients with documented sarcoidosis, with greater than half being asymptomatic (9). In the ACCESS study of 736 patients with sarcoidosis, an expected vast majority at 95% had lung involvement; however, only 2-7% demonstrated cardiac manifestations (10).

Here, we present an autopsy case of sarcoidosis with significant involvement of the heart and spleen, and

with minimal lung involvement in a 42-year-old African American male.

CASE REPORT

The decedent was found at home by his aging mother with whom he resided. He had just been released from the county jail for a minor offense. He had no known documented medical history and an old albuterol rescue inhaler was found at the scene. His mother had severe dementia and vaguely recalled that the decedent had been diagnosed with asthma many years prior to his death but could not recall additional details. The case was taken to the medical examiner for autopsy.

External Findings

The decedent was a well-developed and nourished male at 86.6 kg and 185 cm tall. He had no outward evidence of trauma and his skin was free of any dermatologic lesions.

Gross Findings

Autopsy demonstrated a 690 g heart covered by a thickened pericardium that was markedly adherent to the tan, firm epicardium (**Image 1**). Coronal sections showed almost total replacement of the left and right ventricular myocardium by firm, tan tissue most prominent in the left lateral ventricle and nearly completely replacing the ventricular septum (**Image 2**). A thin rim of normal looking endocardium was on the posterior walls of both ventricles.

The hilar and peribronchial lymph nodes were enlarged, constituting a pattern consistent with the lambda sign seen on chest imaging. Their cut surfaces demonstrated small, irregular firm tan nodules. The lungs (603 g, right; 550 g, left) were hyperinflated and collapsed on puncturing. Their parenchyma had a few barely visible and palpable greyish nodules. Thick mucus clogged some small airways. The 300 g spleen had tan-grey capsular scarring and irregular, firm tan parenchymal nodules (**Image 3**). The rest of the autopsy was unremarkable.

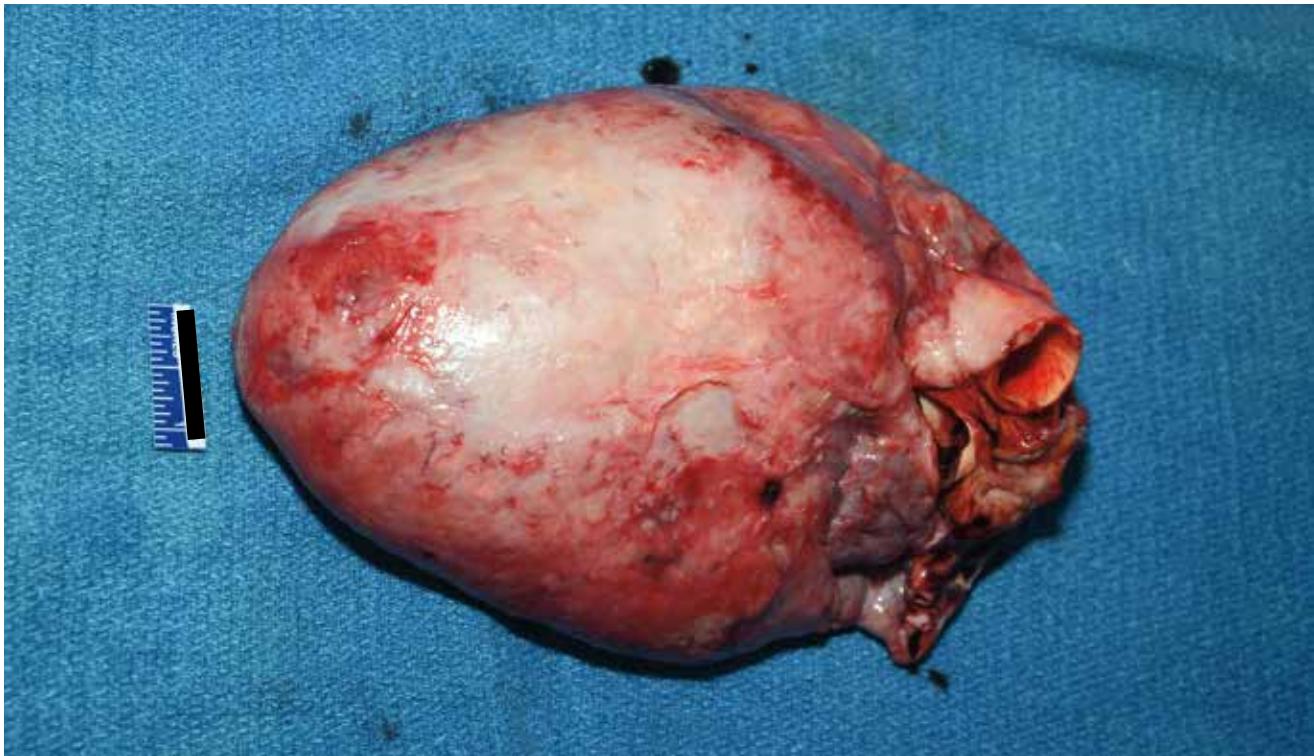


Image 1: Thickened epicardium with adhesions.



Image 2: Cross sections of the heart showing replacement of myocardium with tan tissue.

Microscopic Findings

Histologic examination of the affected organs showed noncaseating granulomatous inflammation with epithelioid cells, giant cells, diffuse chronic inflammatory cells, and perilesional dense fibrosis. The inflammation was negative for infective organisms including mycobacterium and fungal organisms.

The organ most affected was the heart, where the inflammation was associated with marked scarring (**Image 4**). The sinoatrial and atrioventricular nodes were severely affected and could not be identified be-

cause of the inflammation and scarring. Sections of the spleen and lymph nodes showed a granulomatous inflammation with marked scarring.

The lungs showed granulomatous inflammation around small airways, some of which were distended with mucus and others markedly distorted accompanied by extravasation of mucus. No histologic features of bronchial asthma such as bronchial smooth muscle hyperplasia, eosinophilic infiltrates in the walls of the airways, or thickening of the basement membrane of the airways were identified. Histologic examination of remaining organs was unremarkable.



Image 3: Splenic involvement with many tan nodules.

DISCUSSION

Although sarcoidosis is a systemic disease, there appears to be a predilection for involvement of certain organs with some variability between race and geography. The pulmonary system is the most commonly and significantly affected organ system among racial groups (11). Iwai and coworkers, in their autopsy study of 503 patients (109 Caucasians, 74 African Americans, 320 Japanese), reported cardiac sarcoid prevalence of 69.1% in Japanese, 18% in Caucasians, and 14.3% in African Americans. Pulmonary sarcoidosis was the major cause of death in African American patients, but Japanese patients had the highest incidence of death caused by cardiac sarcoidosis (8). Ex-

trathoracic lymphadenopathy, eye disease, and liver disease are also not uncommon in sarcoidosis. Splenic involvement is less frequent, occurring in approximately 7% of patients in one large multicenter study (12). The splenic sarcoid granulomas may be small or coalesce to form strikingly apparent macroscopic nodules (13).

William C. Robert and colleagues, in their study of 113 autopsy cases of cardiac sarcoidosis, reported that the myocardium is the most frequently involved site of sarcoid granuloma formation (2). Additionally, the most frequent location of myocardial involvement is the free wall of the left ventricle, followed by the ventricular septum, right ventricle, and atria (2).

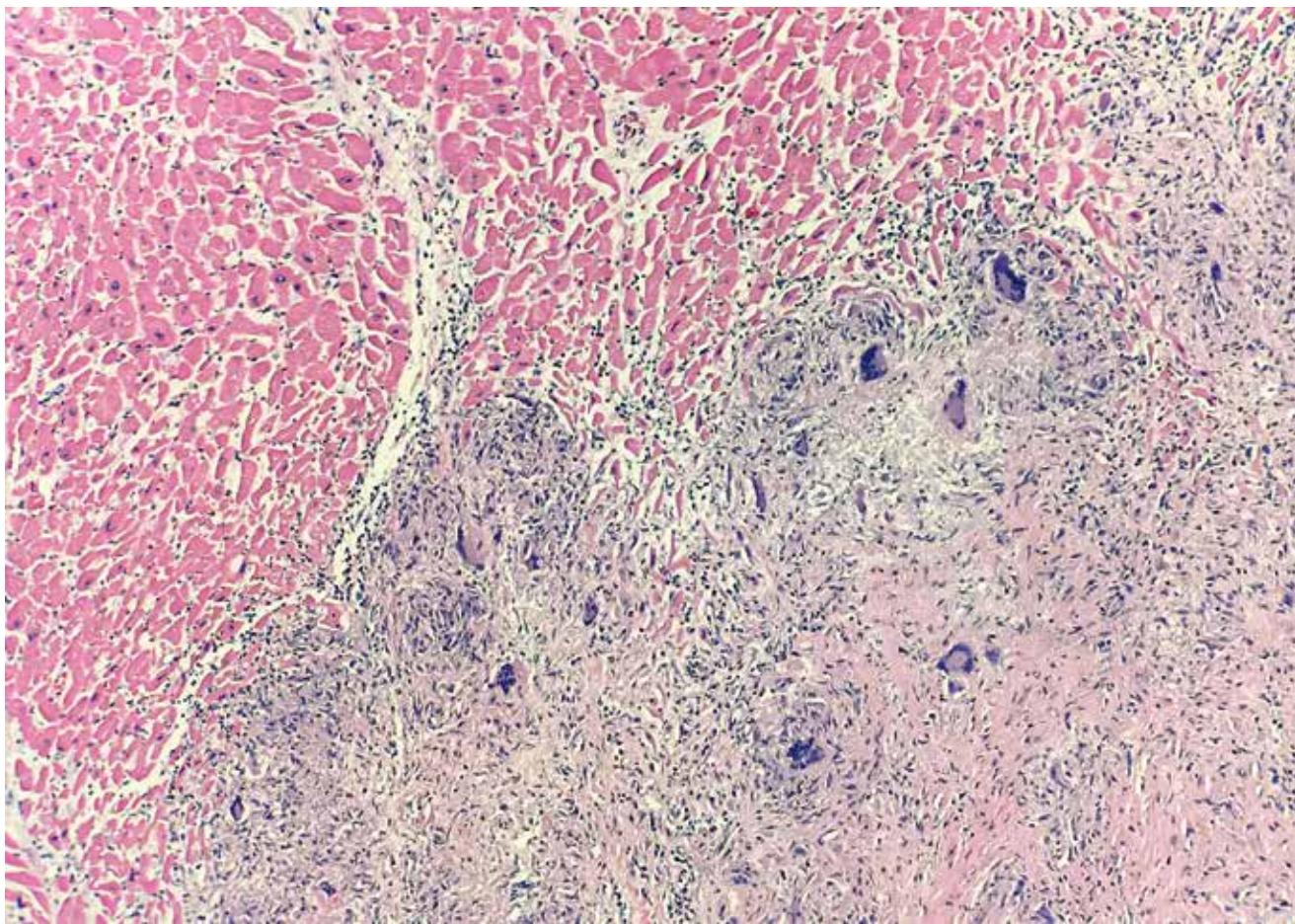


Image 4: Noncaseating granulomatous inflammation affecting the myocardium. Note the diffuse interstitial fibrosis with cardiac myocyte loss. Langerhans type giant cells are seen (H&E, x200).



Grossly, the granulomatous lesions can appear as yellow, white, tan, or grey nodules of varying sizes and shapes. Granulomatous inflammation elicits scarring that is randomly distributed, unlike that of a myocardial infarction where scarring is maximal in the subendocardial region extending out (14). In clinically suspected cases, an endomyocardial biopsy can provide a definitive diagnosis of cardiac sarcoidosis; however, its sensitivity is low because of the patchy distribution and the lower incidence of anterior right ventricle and septum involvement (15).

In the differential, it is of import to consider both primary cardiac tumors and metastatic tumors that may involve the heart, with the latter being significantly more common (16). The most common primary tumors of the heart are myxomas, comprising over half of primary cardiac tumors, followed by sarcomas, which comprise slightly less than a quarter (17). Primary cardiac sarcomas typically originate in the right atrium and are grossly multi-lobular, hemorrhagic, and spread along the epicardial surface (18). Though less common, primary cardiac lymphomas typically affect the right side of the heart with diffuse large B cell lymphoma being the most common type. Grossly, these tumors appear as single or multiple firm white nodular masses and may show focal necrosis (19).

Carcinomas are the most common metastatic malignancy to the heart, comprising over 50% of metastatic heart tumors with lung, esophagus, and breast cancers forming the vast majority of these (20, 21). The pericardium is the most frequent site of cardiac metastasis, comprising upwards of 69% of all cardiac metastases, followed by the epicardium and myocardium (22). Metastases to the heart typically manifest in patients with advanced disease, with cardiac tumor deposits ranging from single to diffuse (23).

Lymphoma metastatic to the heart is not uncommon among those with a history of malignant lymphoma. One autopsy study identified metastatic lymphoma to the heart in 13 of 150 patients with malignant lymphoma. The gross distribution of metastatic lymphoma on presentation ranged from an infiltrating mass to diffuse involvement of the myocardium (24).

The hallmark microscopic feature of sarcoidosis is the presence of noncaseating granulomas in the affected organs. Granulomas occur in response to a number of inciting agents and may be classified according to clinical etiologies: vascular (e.g., granulomatosis with polyangiitis, giant cell arteritis), infectious (e.g., mycobacteria, brucellosis, histoplasmosis), immunologic (e.g., Crohn's disease, primary biliary cirrhosis), leukocyte oxidase defects (e.g., chronic granulomatous disease), hypersensitivity pneumonitis (e.g., bird fanciers', Farmer's lung), neoplasia (e.g., pinealoma, dysgerminoma), and foreign substance (e.g., beryllium, zirconium, aluminum) (25). Early sarcoid granulomas may be loose and consist of macrophages and abundant lymphocytes (14, 26). Macrophages become epithelioid cells and may fuse to form multinucleated giant cells. These giant cells typically resemble those of the foreign body type, with haphazardly arranged nuclei initially and later form into Langhans type with peripherally arranged nuclei (27). The giant cells may contain cytoplasmic inclusion bodies. Schaumann bodies have been reported as being present in 70%-88% of sarcoid cases and are identified as oval concentrically laminated intracellular inclusion bodies consisting of calcified proteins (14). Asteroid inclusion bodies are not uncommon in sarcoid giant cells and are identified as stellate inclusion bodies with cytoplasmic clearing thought to be made of non-collagenous filaments and myelinoid membranes that stain with anti-ubiquitin antibodies (28).

A primary histologic differential diagnosis for cardiac sarcoidosis includes giant cell myocarditis, idiopathic granulomatous myocarditis, tuberculous myocarditis, fungal myocarditis, and Whipple disease (27). Idiopathic granulomatous myocarditis is characterized by non-necrotizing granulomas limited to the heart and may be regarded as sarcoidosis limited to the heart (29). Giant cell myocarditis is characterized by an inflammatory infiltrate of eosinophils, macrophages, and lymphocytes. The macrophages of which are not epithelioid, nor do they aggregate into granulomas. The giant cells are associated with myocyte necrosis (29). The macrophages of Whipple disease are generally foamy or granular and typically do not aggregate into granulomas.



Several cellular constituents of the reticuloendothelial cell lineage are involved in granuloma formation and maintenance. Macrophages differentiate to form epithelioid cells under the influence of cytokine production, which then fuse to form multinucleated giant cells. Macrophage chemokine secretions recruit lymphocytes from lymph nodes and monocytes from the local circulation while inciting epithelioid and fibroblast proliferation at the site of granuloma formation. Granulomas are maintained by the regulatory influence of cytokines produced by mononuclear cells, T cells, dendritic cells, and fibroblasts, which perpetuate ongoing inflammation and cytokine release (30, 31). Sarcoid granulomas typically have CD4 T cells in their center and CD8 T cells and B lymphocytes in the periphery (32, 33). The cytokines primarily involved in granuloma formation are of the TH1 lineage (interleukin IL-2, interferon γ , IL-12) with paucity of the TH2 cytokines (IL-4, IL-5) (34, 35). Conversely, sarcoidosis remission has been found in association when TH2 cytokines predominate, which are thought to be antiinflammatory, with granuloma regression (36).

Sarcoid myocardial involvement may be asymptomatic or can cause sudden death. The prognosis of symptomatic cardiac sarcoidosis is unclear, with a range of survival outcomes reported between studies (37). Involvement of the conduction system by cardiac sarcoid may cause conduction disturbances resulting in fatal arrhythmias. Alternatively, sarcoid involvement of the myocardium may cause symptomatic congestive heart failure, aneurysm, and valve dysfunction (2). Symptomatic cardiac sarcoidosis may enter remission or continue to progressive heart failure, myocardial infarction, or sudden cardiac death (38, 39). Serum markers may be useful in aiding the diagnosis and monitoring systemic sarcoidosis and include elevated serum angiotensin-converting enzyme, elevated lysozyme, and hypercalcemia. Hypercalcemia is thought to be attributed to calcitriol production by activated macrophages comprising the sarcoid granuloma (40). However, these markers lack specificity and their utility in the diagnosis and management of sarcoidosis is questionable.

The classic respiratory finding in sarcoidosis is restrictive pulmonary function due to replacement of lung parenchyma with granulomatous inflammatory nodules and scar tissue. The lungs are therefore traditionally found to be firm. However, the decedent's lungs were hyperinflated and demonstrated few barely appreciated nodules in the lung parenchyma. With the extensive replacement of the myocardium by scar tissue, it is surprising that the lungs were not congested. One might surmise that such replacement of myocardial tissue with noncontractile fibrous scar tissue would have resulted in a restrictive cardiomyopathy-type presentation resulting in pulmonary congestion and edema. Perhaps the decedent's condition, given additional time, would have presented as such.

Histologically, features of bronchial asthma, including bronchial smooth muscle hyperplasia, eosinophilic infiltrates in the walls of the airways, and thickening of the basement membrane of the airways were not identified. However, granulomatous inflammation was around the small airways, possibly impairing effective removal of mucus debris. This would be consistent with the finding that some of the small airways were distended with mucus and others markedly distorted and accompanied by extravasation of mucus. One may postulate that impaired mucus removal secondary to granulomatous inflammation would narrow the small airways causing a similar presentation to that of an asthmatic.

CONCLUSION

Sarcoidosis demonstrates a predilection for organ involvement with the pulmonary system and lymphatics involved in most cases. Though less common, cardiac sarcoidosis may occur in tandem with respiratory and lymph node involvement or in isolation. Due to the high morbidity and mortality associated with cardiac sarcoidosis, there must be an increased awareness of this disease entity and the extent to which it can affect the heart. Otherwise, this important disease entity may remain underdiagnosed or mistaken for another disease etiology if not adequately investigated. There are few autopsy case presentations of patients with isolated cardiac sarcoidosis with minimal respiratory



involvement making this case report relevant to the importance of the recognition and awareness of this entity.

REFERENCES

- 1) Sharma OP. Sarcoidosis: a historical perspective. *Clin Dermatol*. 2007 May-Jun; 25(3):232-41. PMID: 17560300. <https://doi.org/10.1016/j.cldermatol.2007.03.013>.
- 2) Roberts WC, McAllister HA, Ferrans VJ. Sarcoidosis of the heart. A clinicopathologic study of 35 necropsy patients (group 1) and review of 78 previously described necropsy patients (group 11). *Am J Med*. 1977 Jul; 63(1):86-108. PMID: 327806.
- 3) Longcope WT, Freiman DG. A study of sarcoidosis; based on a combined investigation of 160 cases including 30 autopsies from The Johns Hopkins Hospital and Massachusetts General Hospital. *Medicine (Baltimore)*. 1952 Feb; 31(1):1-132. PMID: 14899212. <https://doi.org/10.1097/00005792-195202000-00001>.
- 4) Reich JM. What is sarcoidosis? *Chest*. 2003 Jul; 124(1):367-71. PMID: 12853546. <https://doi.org/10.1378/chest.124.1.367>.
- 5) Rybicki BA, Major M, Popovich J, et al. Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization. *Am J Epidemiol*. 1997 Feb 1; 145(3):234-41. PMID: 9012596. <https://doi.org/10.1093/oxfordjournals.aje.a009096>.
- 6) Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. *N Engl J Med*. 2007 Nov 22; 357(21):2153-65. PMID: 18032765. <https://doi.org/10.1056/nejmra071714>.
- 7) Costabel U, Hunninghake GW. ATS/ERS/WASOG statement on sarcoidosis. Sarcoidosis Statement Committee. American Thoracic Society. European Respiratory Society. World Association for Sarcoidosis and Other Granulomatous Disorders. *Eur Respir J*. 1999 Oct; 14(4):735-7. PMID: 10573213. <https://doi.org/10.1034/j.1399-3003.1999.14d02.x>.
- 8) Iwai K, Tachibana T, Takemura T, et al. Pathological studies on sarcoidosis autopsy. I. Epidemiological features of 320 cases in Japan. *Acta Pathol Jpn*. 1993 Jul-Aug; 43(7-8):372-6. PMID: 8372682. <https://doi.org/10.1111/j.1440-1827.1993.tb01148.x>.
- 9) Mehta D, Lubitz SA, Frankel Z, et al. Cardiac involvement in patients with sarcoidosis: diagnostic and prognostic value of outpatient testing. *Chest*. 2008 Jun; 133(6):1426-1435. PMID: 18339784. <https://doi.org/10.1378/chest.07-2784>.
- 10) Semenzato G. ACCESS: a case control etiologic study of sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis*. 2005 Jun; 22(2):83-6. PMID: 16053022.
- 11) Sharma OP. Sarcoidosis around the world. *Clin Chest Med*. 2008 Sep; 29(3):357-63, vii. PMID: 18539231. <https://doi.org/10.1016/j.ccm.2008.03.013>
- 12) Baughman RP, Teirstein AS, Judson MA, et al. Clinical characteristics of patients in a case control study of sarcoidosis. *Am J Respir Crit Care Med*. 2001 Nov 15; 164(10 Pt 1):1885-9. PMID: 11734441.
- 13) Warshauer DM. Splenic sarcoidosis. *Semin Ultrasound CT MR*. 2007 Feb; 28(1):21-7. PMID: 17366705. <https://doi.org/10.1053/j.sult.2006.10.004>.
- 14) Rosen Y. Pathology of sarcoidosis. *Semin Respir Crit Care Med*. 2007 Feb; 28(1):36-52. PMID: 17330191. <https://doi.org/10.1055/s-2007-970332>.
- 15) Uemura A, Morimoto S, Hiramitsu S, et al. Histologic diagnostic rate of cardiac sarcoidosis: evaluation of endomyocardial biopsies. *Am Heart J*. 1999 Aug; 138(2 Pt 1):299-302. PMID: 10426842. [https://doi.org/10.1016/s0002-8703\(99\)70115-8](https://doi.org/10.1016/s0002-8703(99)70115-8).
- 16) Butany J, Leong SW, Carmichael K, Komeda M. A 30-year analysis of cardiac neoplasms at autopsy. *Can J Cardiol*. 2005 Jun; 21(8):675-80. PMID: 16003450.
- 17) Greb ML, Rosado de Christenson ML, Burke AP, et al. Primary cardiac and pericardial neoplasms: radiologic-pathologic correlation. *Radiographics*. 2000 Jul-Aug; 20(4):1073-103; quiz 1110-1, 1112. PMID: 10903697. <https://doi.org/10.1148/radiographics.20.4.g00j081073>.
- 18) Burke A, Virmani R. Tumors of the heart and great vessels. Fascicle 16, 3rd Series. In: *Atlas of tumor pathology*. Washington, DC: Armed Forces Institute of Pathology; 1996.
- 19) Miguel CE, Bestetti RB. Primary cardiac lymphoma. *Int J Cardiol*. 2011 Jun 16; 149(3):358-63. PMID: 20227122. <https://doi.org/10.1016/j.ijcard.2010.02.016>.
- 20) Chiles C, Woodard PK, Gutierrez FR, Link KM. Metastatic involvement of the heart and pericardium: CT and MR imaging. *Radiographics*. 2001 Mar-Apr; 21(2):439-49. PMID: 11259706. <https://doi.org/10.1148/radiographics.21.2.g01mr15439>.
- 21) Hudzik B, Miszalski-Jamka K, Glowacki J, et al. Malignant tumors of the heart. *Cancer Epidemiol*. 2015 Oct; 39(5):665-72. PMID: 26239627. <https://doi.org/10.1016/j.canep.2015.07.007>.
- 22) Goldberg AD, Blankstein R, Padera RF. Tumors metastatic to the heart. *Circulation*. 2013 Oct 15; 128(16):1790-4. PMID: 24126323. <https://doi.org/10.1161/circulationaha.112.000790>.
- 23) Ekmektzoglou KA, Samelis GF, Xanthos T. Heart and tumors: location, metastasis, clinical manifestations, diagnostic approaches and therapeutic considerations. *J Cardiovasc Med (Hagerstown)*. 2008 Aug; 9(8):769-77. PMID: 18607239. <https://doi.org/10.2459/jcm.0b013e3282f88e49>.
- 24) McDonnell PJ, Mann RB, Bulkley BH. Involvement of the heart by malignant lymphoma: a clinicopathologic study. *Cancer*. 1982 Mar 1; 49(5):944-51. PMID: 7037154. [https://doi.org/10.1002/1097-0142\(19820301\)49:5<944::aid-cncr2820490519%3E3.0.co;2-c](https://doi.org/10.1002/1097-0142(19820301)49:5<944::aid-cncr2820490519%3E3.0.co;2-c).
- 25) James DG. A clinicopathological classification of granulomatous disorders. *Postgrad Med J*. 2000 Aug; 76(898):457-65. PMID: 10908370. PMCID: PMC1741697. <https://doi.org/10.1136/pmj.76.898.457>.
- 26) Sakthivel P, Bruder D. Mechanism of granuloma formation in sarcoidosis. *Curr Opin Hematol*. 2017 Jan; 24(1):59-65. PMID: 27755127. <https://doi.org/10.1097/moh.0000000000000301>.
- 27) Lagana SM, Parwani AV, Nichols LC. Cardiac sarcoidosis: a pathology-focused review. *Arch Pathol Lab Med*. 2010 Jul; 134(7):1039-46. PMID: 20586635. <https://doi.org/10.1043/2009-0274-RA.1>.
- 28) Gal AA, Koss MN. The pathology of sarcoidosis. *Curr Opin Pulm Med*. 2002 Sep; 8(5):445-51. PMID: 12172451. <https://doi.org/10.1097/00063198-200209000-00018>.
- 29) Okura Y, Dec GW, Hare JM, et al. A clinical and histopathologic comparison of cardiac sarcoidosis and idiopathic giant cell myocarditis. *J Am Coll Cardiol*. 2003 Jan 15; 41(2):322-9. PMID: 12535829. [https://doi.org/10.1016/s0735-1097\(02\)02715-8](https://doi.org/10.1016/s0735-1097(02)02715-8).
- 30) Agostini C, Adami F, Semenzato G. New pathogenetic insights into the sarcoid granuloma. *Curr Opin Rheumatol*. 2000 Jan; 12(1):71-6. PMID: 10647958. <https://doi.org/10.1097/00002281-200001000-00012>.
- 31) Lazarus A. Sarcoidosis: epidemiology, etiology, pathogenesis, and genetics. *Dis Mon*. 2009 Nov; 55(11):649-60. PMID: 19857640. <https://doi.org/10.1016/j.dismonth.2009.04.008>.
- 32) Ma Y, Gal A, Koss MN. The pathology of pulmonary sarcoidosis: update. *Semin Diagn Pathol*. 2007 Aug; 24(3):150-61. PMID: 17882899. <https://doi.org/10.1053/j.semdp.2007.06.002>.



CASE OF THE MONTH

AFP

- 33) Gerke AK, Hunninghake G. The immunology of sarcoidosis. *Clin Chest Med.* 2008 Sep; 29(3):379-90, vii. PMID: 18539233. <https://doi.org/10.1016/j.ccm.2008.03.014>.
- 34) Schoppet M, Pankuweit S, Maisch B. Cardiac sarcoidosis: cytokine patterns in the course of the disease. *Arch Pathol Lab Med.* 2003 Sep; 127(9):1207-10. PMID: 12946220. [https://doi.org/10.1043/1543-2165\(2003\)127<1207:CSCPIT>2.0.CO;2](https://doi.org/10.1043/1543-2165(2003)127<1207:CSCPIT>2.0.CO;2).
- 35) Wahlström J, Katchar K, Wigzell H, et al. Analysis of intracellular cytokines in CD4+ and CD8+ lung and blood T cells in sarcoidosis. *Am J Respir Crit Care Med.* 2001 Jan; 163(1):115-21. PMID: 11208635. <https://doi.org/10.1164/ajrccm.163.1.9906071>.
- 36) Smedema JP, Snoep G, van Kroonenburgh MP, et al. Cardiac involvement in patients with pulmonary sarcoidosis assessed at two university medical centers in the Netherlands. *Chest.* 2005 Jul; 128(1): 30-5. PMID: 16002912. <https://doi.org/10.1378/chest.128.1.30>.
- 37) Yeboah J, Lee C, Sharma OP. Cardiac sarcoidosis: a review 2011. *Curr Opin Pulm Med.* 2011 Sep; 17(5):308-15. PMID: 21743332. <https://doi.org/10.1097/mcp.0b013e328349637a>.
- 38) Kim JS, Judson MA, Donnino R, et al. Cardiac sarcoidosis. *Am Heart J.* 2009 Jan; 157(1):9-21. PMID: 19081391. <https://doi.org/10.1016/j.ahj.2008.09.009>.
- 39) Kandolin R, Lehtonen J, Airaksinen J, et al. Cardiac sarcoidosis: epidemiology, characteristics, and outcome over 25 years in a nationwide study. *Circulation.* 2015 Feb 17; 131(7):624-32. PMID: 25527698. <https://doi.org/10.1161/circulationaha.114.011522>.
- 40) Yotsumoto H. Fever, hypercalcemia and tuberculosis. *Intern Med.* 2007; 46(6):259-60. PMID: 17379990. <https://doi.org/10.2169/internalmedicine.46.0176>.



Coronary Artery Aneurysms and Thrombosis in Kawasaki Disease

Linda J. Szymanski, Julie Huss-Bawab, James K. Ribe

Acad Forensic Pathol. 2018 8(2): 416-423

AUTHORS

Linda J. Szymanski DO, Los Angeles County Department of Medical Examiner-Coroner

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, principal investigator of the current study.

Julie Huss-Bawab MD, Los Angeles County Department of Medical Examiner-Coroner

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, writing assistance and/or technical editing.

James K. Ribe MD, Los Angeles County Department of Medical Examiner-Coroner

Roles: Project conception and/or design, data acquisition, analysis and/or interpretation, manuscript creation and/or revision, approved final version for publication, accountable for all aspects of the work, general supervision, writing assistance and/or technical editing.

CORRESPONDENCE

Linda J. Szymanski DO, 1104 N. Mission Road, Los Angeles CA 90033, LSzymanski@coroner.lacounty.gov

ETHICAL APPROVAL

As per Journal Policies, ethical approval was not required for this manuscript

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies conducted with animals or on living human subjects

STATEMENT OF INFORMED CONSENT

No identifiable personal data were presented in this manuscript

DISCLOSURES & DECLARATION OF CONFLICTS OF INTEREST

The authors, reviewers, editors, and publication staff do not report any relevant conflicts of interest

FINANCIAL DISCLOSURE

The authors have indicated that they do not have financial relationships to disclose that are relevant to this manuscript

KEYWORDS

Forensic pathology, Pediatrics, Coronary artery aneurysms, Kawasaki disease

INFORMATION

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

©2018 Academic Forensic Pathology International • (ISSN: 1925-3621) • <https://doi.org/10.23907/2018.027>

Submitted for consideration on 12 Feb 2018. Accepted for publication on 12 Apr 2018

Kawasaki disease (KD) is an acute vasculitis of unknown etiology occurring in infants and young children and affecting medium-sized muscular arteries. It is a systemic disease, with possibly morbid to mortal manifestations in the cardiovascular system, including lymphocytic myocarditis and acute vasculitis associated with thrombosis and/or aneurysm formation. In regards to aneurysm formation, coronary artery involvement occurs in up to 40% of patients and can range from transient, mild dilatation or ectasia to giant coronary artery aneurysm. Treatment with aspirin and intravenous immunoglobulin (IVIG) therapy greatly reduces the occurrence of coronary artery aneurysm. Patients with large or giant coronary artery aneurysms are especially at risk for cardiac events including coronary artery thrombosis or stenosis, myocardial infarction, arrhythmias, and death (1).

A 7-month-old male infant was brought to the hospital after being found by his foster parents to be inconsolable and crying. He was up-to-date on his immunizations and met all his developmental milestones. Significant birth history included intrauterine exposure to methamphetamine, with a positive methamphetamine drug screen at birth, and subsequent removal from his mother and placement with a foster family.

A month earlier, he presented to an emergency department with symptoms of diarrhea for one week, loss of appetite, fever, pink eye, and rash on his entire body. A pediatrician diagnosed him with gastroenteritis secondary to adenovirus, he was treated with intravenous fluids, and he was released three days later with instructions to continue with oral rehydration with Pedialyte.

He continued to have intermittent loss of appetite and diarrhea, change of personality from being a happy baby to one with low energy, and significant weight loss. Worried, his foster parents brought him to the emergency department.

At the emergency department, he became tachycardic, displayed decreased capillary refill, and had episodes of apnea necessitating bag-mask ventilation. A complete blood count showed the white blood cell count

was elevated, but without profound left-shift, and he had mild anemia. While in the pediatric intensive care unit, an emergency bedside echocardiogram was done that showed markedly dilated coronary arteries consistent with Kawasaki disease. Despite aggressive management, he had multiple episodes of respiratory arrest without loss of pulse and was pronounced dead.

Autopsy examination revealed a pale infant with pale organs and an enlarged heart with thrombosed giant coronary artery aneurysms involving the proximal portions of the right coronary and the entire left anterior descending arteries (**Image 1A**). Both kidneys had multiple wedge-shaped acute cortical infarcts. Histopathologically, there were thrombosed aneurysms of the coronary arteries along with panvasculitis of the coronary arterial wall (**Images 1B and 1C**), lymphocytic epicarditis, lymphocytic myocarditis, and multifocal contraction band necrosis (**Image 1D**). An interlobular aneurysm with thrombus formation was identified with panarteritis was seen in one of the kidneys (**Image 1E**).

The cause of death was determined to be complications of Kawasaki disease and the manner of death was natural.

The clinical diagnosis of Kawasaki disease, or mucocutaneous lymph node syndrome, requires the presence of a fever lasting for five or more days, accompanied by four out of five principal clinical findings including bilateral conjunctival congestion, oral changes such as strawberry tongue and cracked and erythematous lips, acute non-purulent cervical lymphadenopathy, extremity changes such as erythema or palm and sole desquamation, and polymorphous rash. Incomplete (atypical) Kawasaki disease occurs in patients with fevers lasting five or more days and with less than four of the clinical findings. A clinical diagnosis of Kawasaki disease can be made in patients with the incomplete form when coronary artery disease is detected by coronary angiography or two-dimensional echocardiography (2). Histologic descriptions are largely based on the most severe cases, as they reflect findings at the time of autopsy (1).

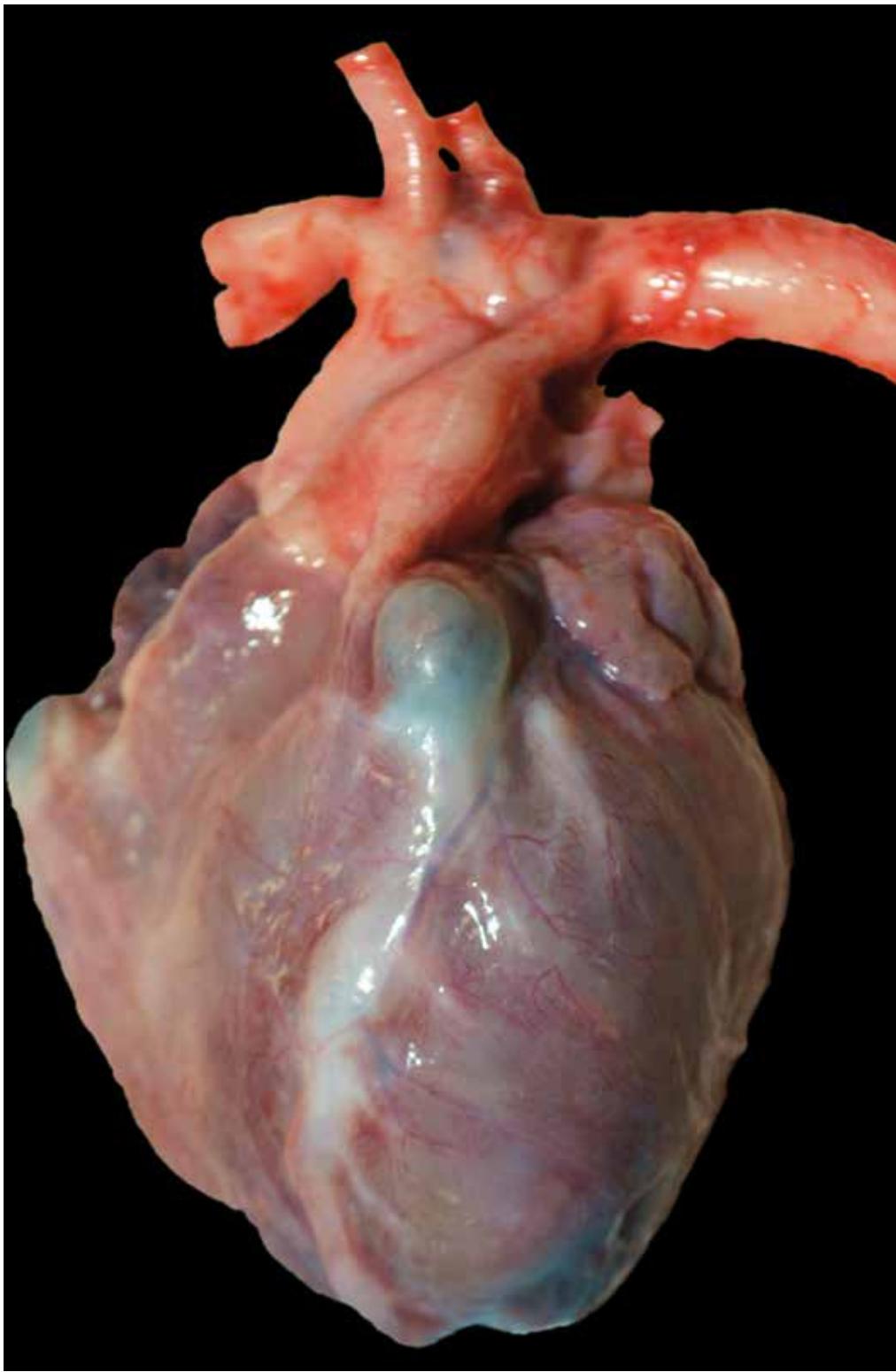


Image 1A: Enlarged heart with giant coronary artery aneurysms of the right coronary and left anterior descending arteries.

Prompt and early diagnosis within ten days of illness is imperative, so treatment with aspirin and intravenous immunoglobins can be initiated. In nearly 15 to 25% of untreated patients, coronary artery aneurysms develop. If treated properly, the incidence of coronary artery aneurysm decreases to approximately 5% and development of giant coronary aneurysms to 1% (2). Giant coronary artery aneurysms are defined as aneurysms that measure greater than 8 mm in diameter. This finding is strongly associated with poor patient

outcome as the large aneurysm size increases the risk of thrombosis, rupture, stenosis, myocardial infarction, and sudden death (3, 4).

Diagnosis of Kawasaki disease can be challenging as it mimics other common illnesses and drug reactions, and thus diagnosis is often delayed. Infants presenting with incomplete (atypical) Kawasaki disease are at a heightened risk for delayed diagnosis and the development of coronary artery aneurysms (5, 6). Risk fac-

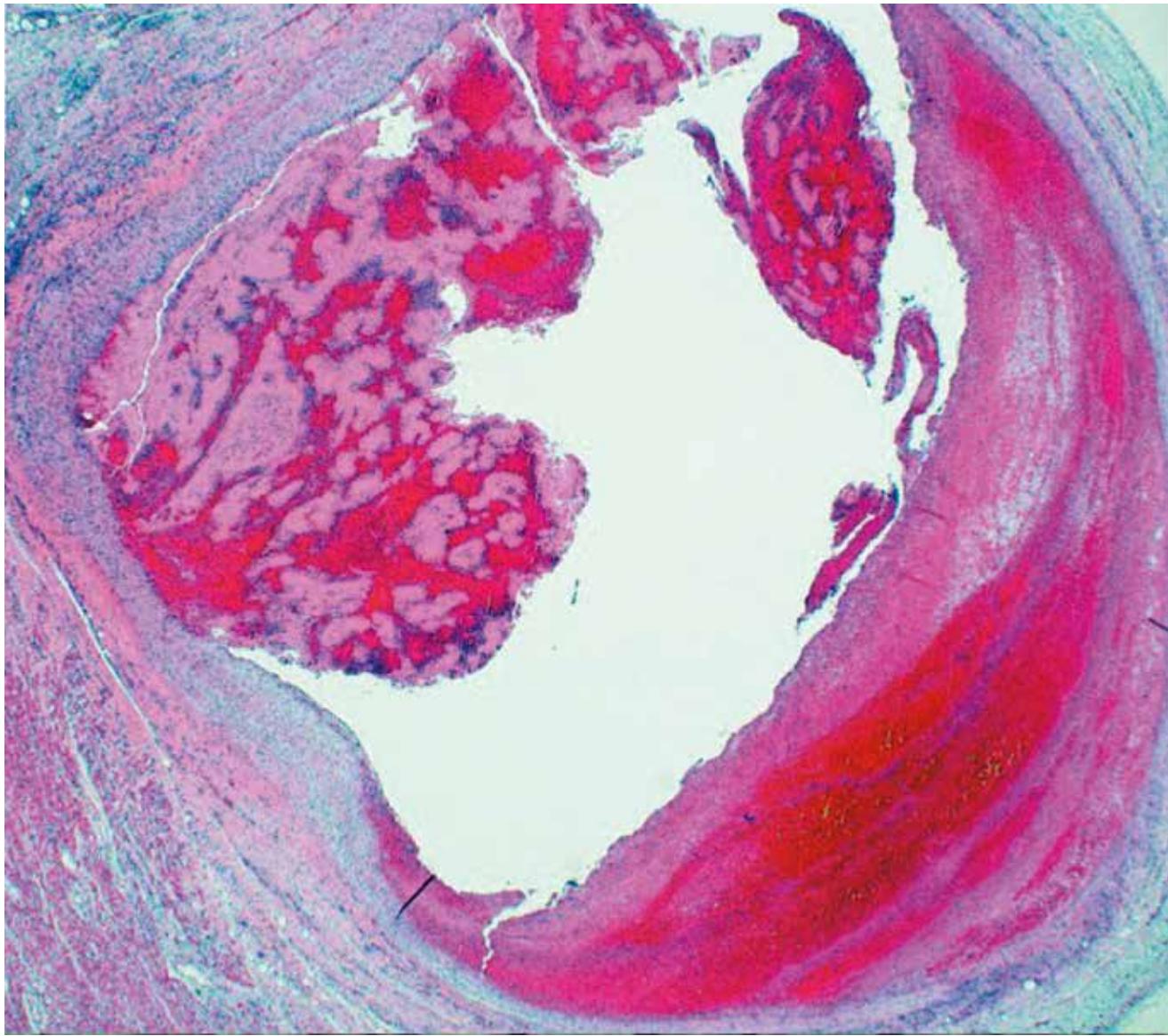


Image 1B: Coronary artery with aneurysm, thrombus and panvasculitis (H&E, x20).

tors for development of coronary artery aneurysms, particularly giant coronary artery aneurysms, include young infants, males, persistent fevers, laboratory signs of inflammation, Asian ancestry, Hispanic children (intermediate risk), longer interval to diagnosis and treatment, and recurrent disease (7-10). Giant coronary artery aneurysm confers a high risk for thrombosis, as was seen in this patient (3, 4).

There is a progression to the histopathology findings in the coronary arteries in Kawasaki disease that mir-

rors patient risk and disease state. Coronary arteritis is first seen six to eight days after the onset of disease. Beginning at day ten, the arterial walls are infiltrated by lymphocytes and macrophages with subsequent panvasculitis and damage of the internal elastic lamina and medial smooth muscle cells. Around day 12, aneurysms start to form, if the damage is severe, and thrombosis may occur since blood pools in the aneurysms. Inflammatory infiltrates continue to be present until the 25th day of the disease, and then will gradually decrease and be almost completely gone

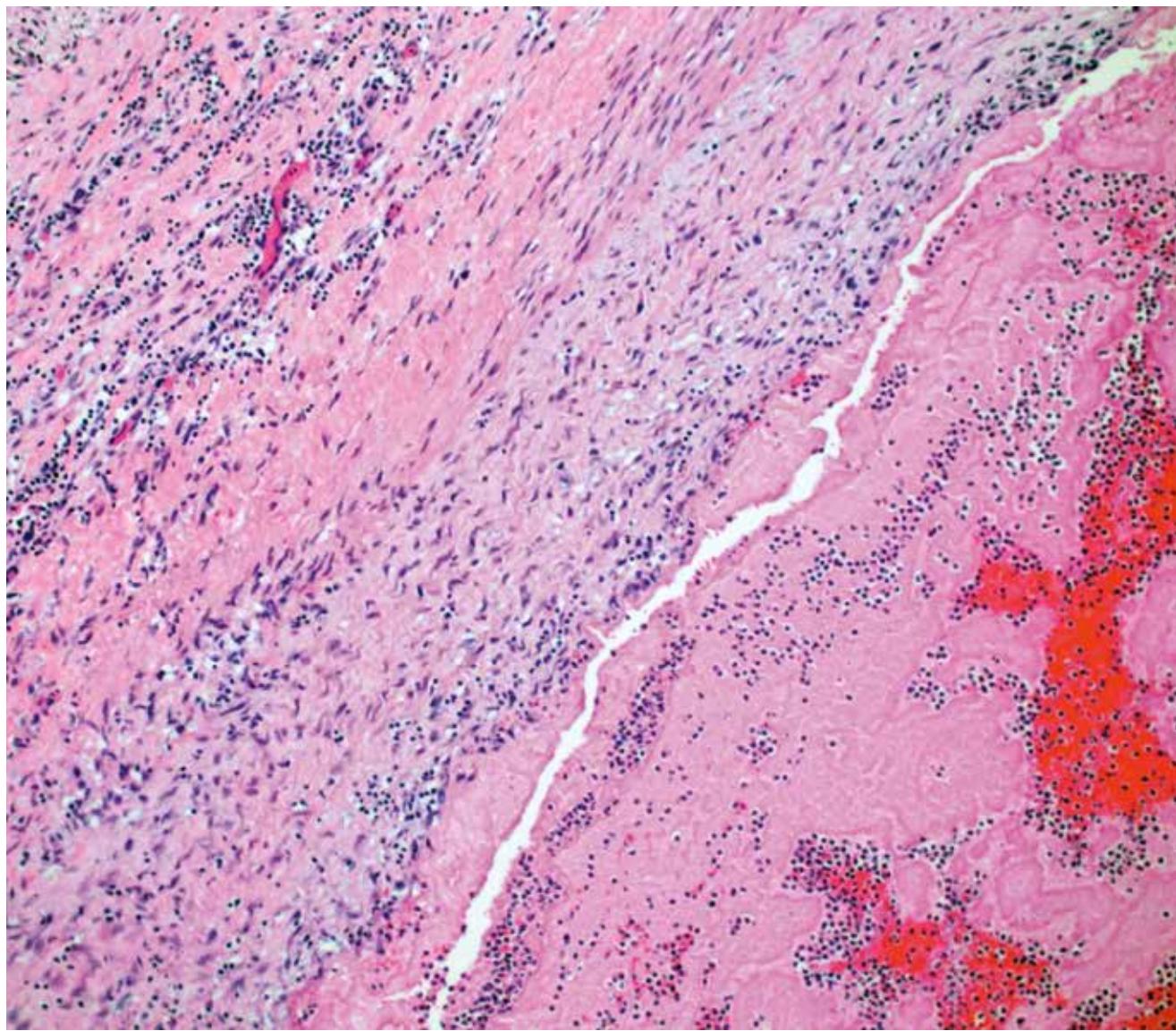


Image 1C: Higher magnification of thrombus with lymphocytic panvasculitis and surrounding epicarditis (H&E, x100).

by day 40. Scars from the inflammation will remain (11). Lymphocytic myocarditis is commonly found in Kawasaki disease and can be responsible for cardiac dysfunction (12).

Kawasaki disease is an infrequent entity seen in the medical examiner setting. Delay in clinical diagnosis can lead to coronary artery aneurysm and thrombosis and sudden death. Mortality/morbidity due to sequelae of persistent/remodeled cardiac damage can be seen in the adult population (13).

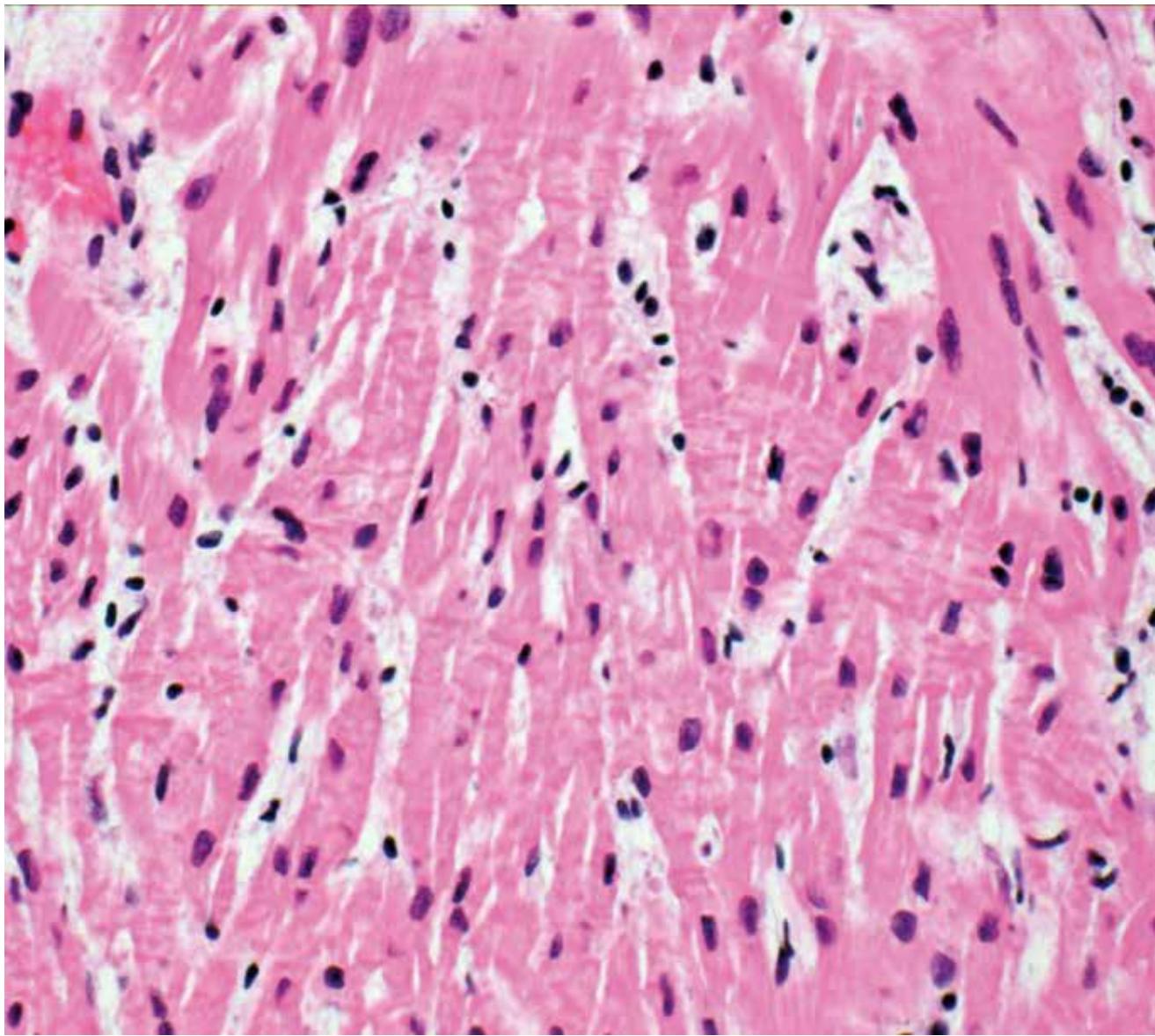


Image 1D: Myocardium with contraction band necrosis (H&E, x400).

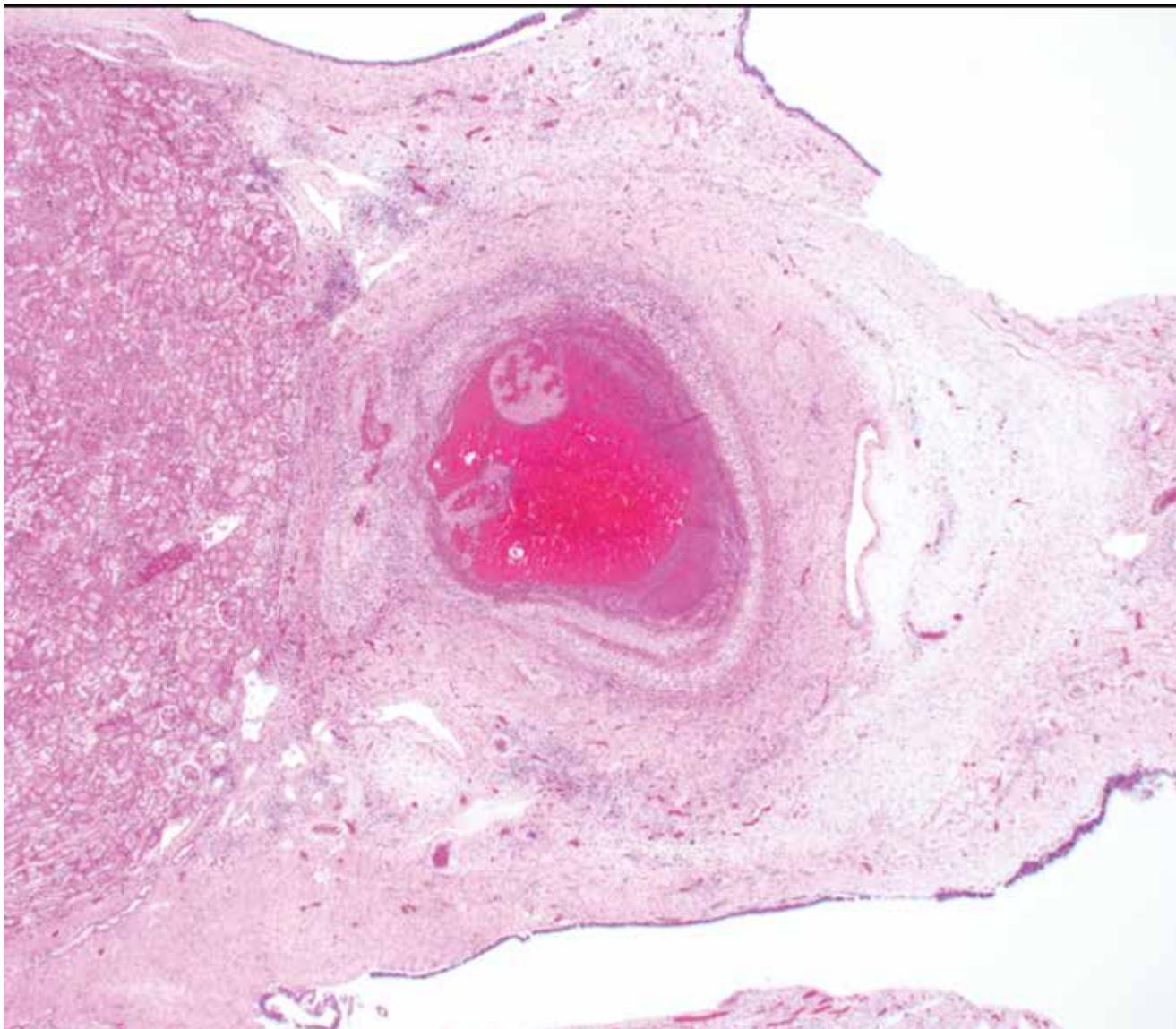


Image 1E: Kidney with thrombus in arcuate artery and associated vasculitis (H&E, x20).

REFERENCES

- 1) Newburger JW, Takahashi M, Burns, JC. Kawasaki disease. *J Am Coll Cardiol.* 2016 Apr 12; 67(14):1738-49. PMID: 27056781. <https://doi.org/10.1016/j.jacc.2015.12.073>.
- 2) Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation.* 2004 Oct 26; 110(17):2747-71. PMID: 15505111. <https://doi.org/10.1161/01.CIR.0000145143.19711.78>.
- 3) Patil S, Shirodkar S, Pinto RJ, Dalvi B. Giant coronary artery aneurysm with a thrombus secondary to Kawasaki disease. *Ann Pediatr Cardiol.* 2008 Jan; 1(1):59-61. PMID: 20300241. PMCID: PMC2840734. <https://doi.org/10.4103/0974-2069.41059>.
- 4) Kato H, Sugimura T, Akagi T, et al. Long-term consequences of Kawasaki disease. A 10- to 21-year follow-up study of 594 patients. *Circulation.* 1996 Sep 15; 94(6):1379-85. PMID: 8822996. <https://doi.org/10.1161/01.cir.94.6.1379>.
- 5) Chang FY, Hwang B, Chen SJ, et al. Characteristics of Kawasaki disease in infants younger than six months of age. *Pediatr Infect Dis J.* 2006 Mar; 25(3):241-4. PMID: 16511387. <https://doi.org/10.1097/01.inf.0000202067.50975.90>.



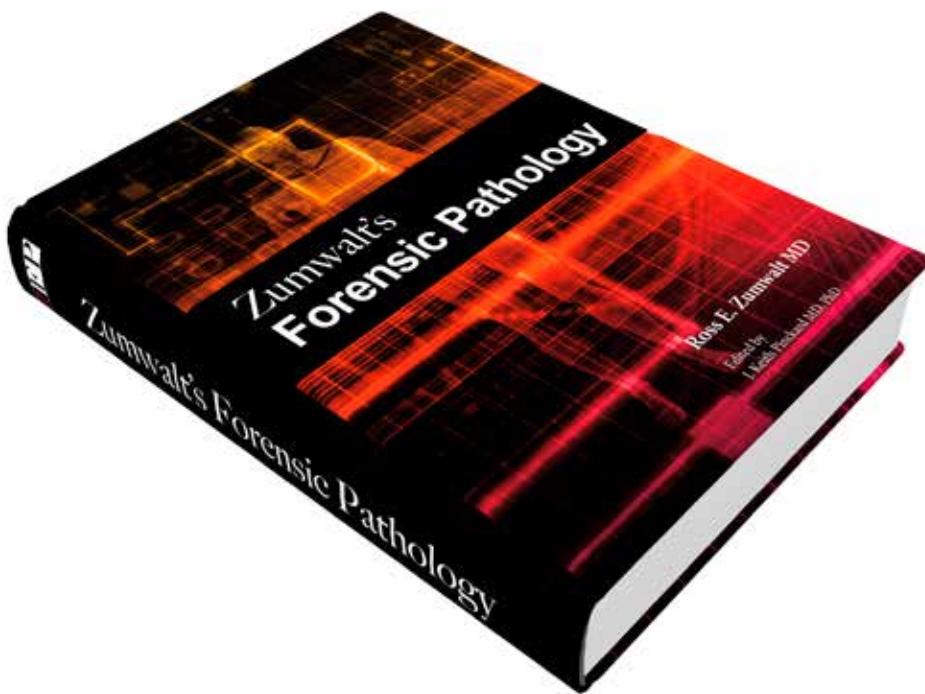
- 6) Liu HC, Lo CW, Hwang B, Lee PC. Clinical manifestations vary with different age spectrums in infants with Kawasaki disease. *Scientific World Journal*. 2012; 2012:210382. PMID: 22454602. PMCID: PMC3289979. <https://doi.org/10.1100/2012/210382>.
- 7) Minich LL, Sleeper LA, Atz AM, et al. Delayed diagnosis of Kawasaki disease: What are the risk factors? *Pediatrics*. 2007 Dec; 120(6):e1434-40. PMID: 18025079. <https://doi.org/10.1542/peds.2007-0815>.
- 8) Belay ED, Maddox RA, Holman RC, et al. Kawasaki syndrome and risk factors for coronary artery abnormalities: United States, 1994-2003. *Pediatr Infect Dis J*. 2006 Mar; 25(3):245-9. PMID: 16511388. <https://doi.org/10.1097/INF.00000202068.30956.16>.
- 9) Nakamura Y, Yashiro M, Uehara R, et al. Case-control study of giant coronary aneurysms due to Kawasaki disease. *Pediatr Int*. 2003 Aug; 45(4):410-3. PMID: 12911476. <https://doi.org/10.1046/j.1442-200x.2003.01744.x>.
- 10) McCrindle BW, Li JS, Minich LL, et al. Coronary artery involvement in children with Kawasaki disease: risk factors from analysis of serial normalized measurements. *Circulation*. 2007 Jul 10; 116(2):174-9. PMID: 17576863. <https://doi.org/10.1161/CIRCULATIONAHA.107.690875>.
- 11) Takahashi K, Oharaseki T, Yokouchi Y. Pathogenesis of Kawasaki disease. *Clin Exp Immunol*. 2011 May; 164 Suppl 1:20-2. PMID: 21447126. PMCID: PMC3095860. <https://doi.org/10.1111/j.1365-2249.2011.04361.x>.
- 12) Harada M, Yokouchi Y, Oharaseki T, et al. Histopathological characteristics of myocarditis in acute-phase Kawasaki disease. *Histopathology*. 2012 Dec; 61(6):1156-67. PMID: 23134515. <https://doi.org/10.1111/j.1365-2559.2012.04332.x>.
- 13) Daniels LB, Gordon JB, Burns JC. Kawasaki disease: late cardiovascular sequelae. *Curr Opin Cardiol*. 2012 Nov; 27(6):572-7. PMID: 23075819. <https://doi.org/10.1097/HCO.0b013e3283588f06>.

Dr. Zumwalt practiced forensic pathology for 40 years — instead of practicing one year of forensic pathology 40 times...

A book about HOW and WHY we practice the way we do, and how to GROW as we practice...

ORDER NOW

<https://store.academicfp.com>



Foreword by Randy Hanzlick MD

Published by Academic Forensic Pathology International



Ross Zumwalt MD

(Former) Chief Medical Investigator
New Mexico OMI

Zumwalt's Forensic Pathology includes:

- *Death certification*
- *Death investigation*
- *The forensic autopsy*
- *Ancillary laboratory studies*
- *Apparently natural death*
- *Apparently accidental death*
- *Apparently suicidal death*
- *Apparently homicidal death*
- *Deaths whose manner cannot be determined*
- *Other topics*

Approximately 500 pages

Published in brilliant full color

Estimated release: Mid-2018

Retail price \$350 USD