Pancreatobiliary Pathology Society Journal Watch

Recent Articles that will be Selected

Last Update on 2019-12-27

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1 PBPath Journal Watch Articles

Wellcome to the PBPath Journal Watch!

This bi-monthly journal watch features exciting recently published pancreas and biliary pathology articles that will provide up to date medical knowledge in our field. These articles will be showcased in several convenient categories, including surgical pathology, cytopathology, and molecular pathology among others. The articles in each category are in no particular order. See the list of journals we search regularly here. Previous months' issues may be found in our *archive* and you may see drafts of the upcoming issue here.

We encourage members to actively participate by recommending new articles and providing feedback using the forms provided below.

We hope that you will enjoy the new PBPath Journal Watch!

1.1 Pancreas

- Diabetic Kidney Disease: Past and Present

Advances in anatomic pathology 2019 Dec;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31876542

Diabetes mellitus (DM) afflicting humans has been recognized as a disease for >3000 years. However, very little was known about its etiology and pathogenesis until about a century ago when increasing knowledge about anatomy and physiology of the human body gradually led to our understanding that the hormone insulin produced by the Islets of Langerhans in the pancreas plays a crucial role in the metabolism of glucose and maintaining the blood sugar level within a normal range. DM is caused by inadequate insulin production (type 1) or insulin resistance (type 2). For thousands of years, DM has been considered as a disease of the kidney; however, with the understanding of the pathogenesis of DM, it became clear that diabetic kidney disease (DKD) is a complication and not a cause of DM. DKD is associated with increased matrix expansion that manifests morphologically as a diffuse or nodular expansion of the mesangium and diffuse thickening of the glomerular and tubular basement membranes. Hyperglycemia plays a crucial role in the development of pathologic changes within the kidney. Once established, DKD usually undergoes a slow but relentless progression to end-stage renal disease. However, recent studies have shown that its progression can be slowed or even reversed by strict control of hyperglycemia. Morphologically, DKD may resemble several other glomerular diseases that must be ruled out before a definitive diagnosis. Patients with DM may also develop nondiabetic glomerular or interstitial diseases with or without DKD. The findings in nephrectomy specimens and the differential diagnoses are presented in detail.

doi: https://doi.org/10.1097/PAP.0000000000000257

- Loss of GATA4 causes ectopic pancreas in the stomach

The Journal of pathology 2019 Dec;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31875961

Pancreatic heterotopia is defined as pancreatic tissue outside its normal location in the body and anatomically separated from the pancreas. In this work we have analyzed the stomach glandular epithelium of Gata4flox/flox ; Pdx1-Cre mice (Gata4KO mice). We found that Gata4KO glandular epithelium displays an atypical morphology similar to the cornified squamous epithelium and exhibits upregulation of forestomach markers. The developing gastric units fail to form properly, and the glandular epithelial cells do not express markers of gastric gland in the absence of GATA4. Interestingly, the developing glands of the Gata4KO stomach express pancreatic cell markers. Furthermore, a mass of pancreatic tissue located in the subserosa of the Gata4KO stomach is observed at adult stages. Heterotopic pancreas found in Gata4-deficient mice contains all three pancreatic cell lineages, ductal, acinar and endocrine. Moreover, Gata4 expression is downregulated in ectopic pancreatic tissue of some human biopsy samples. This article is protected by copyright. All rights reserved.

doi: https://doi.org/10.1002/path.5378

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1.2 Gallbladder

- Pancreatic cancer organoids recapitulate disease and allow personalized drug screening

Proceedings of the National Academy of Sciences of the United States of America 2019 Dec;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31818951

We report the derivation of 30 patient-derived organoid lines (PDOs) from tumors arising in the pancreas and distal bile duct. PDOs recapitulate tumor histology and contain genetic alterations typical of pancreatic cancer. In vitro testing of a panel of 76 therapeutic agents revealed sensitivities currently not exploited in the clinic, and underscores the importance of personalized approaches for effective cancer treatment. The PRMT5 inhibitor EZP015556, shown to target MTAP (a gene commonly lost in pancreatic cancer)-negative tumors, was validated as such, but also appeared to constitute an effective therapy for a subset of MTAP-positive tumors. Taken together, the work presented here provides a platform to identify novel therapeutics to target pancreatic tumor cells using PDOs.

doi: https://doi.org/10.1073/pnas.1911273116

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1.3 Bile Ducts

- Pancreatic cancer organoids recapitulate disease and allow personalized drug screening

Proceedings of the National Academy of Sciences of the United States of America 2019 Dec;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31818951

We report the derivation of 30 patient-derived organoid lines (PDOs) from tumors arising in the pancreas and distal bile duct. PDOs recapitulate tumor histology and contain genetic alterations typical of pancreatic cancer. In vitro testing of a panel of 76 therapeutic agents revealed sensitivities currently not exploited in the clinic, and underscores the importance of personalized approaches for effective cancer treatment. The PRMT5 inhibitor EZP015556, shown to target MTAP (a gene commonly lost in pancreatic cancer)-negative tumors, was validated as such, but also appeared to constitute an effective therapy for a subset of MTAP-positive tumors. Taken together, the work presented here provides a platform to identify novel therapeutics to target pancreatic tumor cells using PDOs.

doi: https://doi.org/10.1073/pnas.1911273116

- Adult onset of genetic disorders in bile acid transport in the liver

Human pathology 2019 Dec;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31669892

Although severe deficiencies of canalicular transporter enzymes due to biallelic mutations are well known as causes of progressive cholestatic liver disease in children, it is increasingly recognized that milder disease may occur if a single, heterozygous gene mutation is present. This mild disease, generally presenting initially in adulthood, may have a variety of clinical and histological appearances. Bland canalicular cholestasis is the prototypic change, but it is now clear that some gene mutations, particularly in ABCB4 (encoding MDR3), can cause other patterns that include early cholesterol calculus formation, bile duct injury and disappearance, ductular reactions mimicking large duct obstruction, and, in rare cases, progressive fibrosis. Because the features can be subtle and not diagnostic in isolation, it is generally the combination of a biliary pattern of injury with a suggestive clinical and family history that allows the diagnosis to be suspected. Increased awareness and improved access to genetic testing are likely to result in more frequent diagnosis of these disorders.

doi: https://doi.org/10.1016/j.humpath.2019.10.006

- Landscape of distant metastasis mode and current chemotherapy efficacy of the advanced biliary tract cancer in the United States, 2010-2016

Cancer medicine 2019 Dec;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31876990

BACKGROUND: The distant metastasis (DM) mode and treatment efficacies in the advanced biliary tract cancer (BTC) were obscure, and a credible evaluation is urgently needed. METHOD: A total of 6348 advanced BTC patients (ICC, intrahepatic cholangiocarcinoma, n = 1762; PHCC, perihilar cholangiocarcinoma, n = 1103; GBC, gallbladder cancer, n = 2580; DCC, distal cholangiocarcinoma, n = 538; AVC, carcinoma of Vater ampulla, n = 365) were enrolled from the Surveillance, Epidemiology, and End Results (SEER) database. Propensity score matching (PSM) process was carried out for less bias. RESULT: The proportion of M1 patients in each subtype at first diagnosis was 26.4% (ICC), 37.2% (PHCC), 41. 0%

(GBC), 24.5% (DCC), and 12.7% (AVC), and the constitution of DM sites in different subtypes varied apparently. Moreover, the survival of metastasis sites was different ($P < .05$ in all the subtypes) where the multi-metastasis and distant lymph node (dLN) only always indicated the worst and best prognosis, respectively. Chemotherapy presented the most significant survival impact with the lowest hazard ratio by multivariate cox model and still provided a survival improvement after PSM (all $P < .001$) in all subtypes. However, the median months manifested different between patients with and without chemotherapy among the subtypes (ICC, from 5 to 9; PHCC, from 6 to 10; AVC, from 4 to 9; GBC, from 6 to 7; DCC from 6 to 8). CONCLUSION: We provided a landscape about the detailed DM mode of the advanced BTC in a large population, found the survival differences among DM sites, and revealed the different chemotherapy efficacies in the BTC subtypes.

doi: https://doi.org/10.1002/cam4.2794

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1.4 Ampulla

- Microbial bile acid metabolites modulate gut ROR + regulatory T cell homeostasis

Nature 2019 Dec;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31875848

The metabolic pathways encoded by the human gut microbiome constantly interact with host gene products through numerous bioactive molecules1. Primary bile acids (BAs) are synthesized within hepatocytes and released into the duodenum to facilitate absorption of lipids or fat-soluble vitamins2. Some BAs (approximately 5%) escape into the colon, where gut commensal bacteria convert them into various intestinal BAs2 that are important hormones that regulate host cholesterol metabolism and energy balance via several nuclear receptors and/or G-protein-coupled receptors3,4. These receptors have pivotal roles in shaping host innate immune responses1,5. However, the effect of this host-microorganism biliary network on the adaptive immune system remains poorly characterized. Here we report that both dietary and microbial factors influence the composition of the gut BA pool and modulate an important population of colonic FOXP3+ regulatory T (Treg) cells expressing the transcription factor ROR . Genetic abolition of BA metabolic pathways in individual gut symbionts significantly decreases this Treg cell population. Restoration of the intestinal BA pool increases colonic ROR + Treg cell counts and ameliorates host susceptibility to inflammatory colitis via BA nuclear receptors. Thus, a pan-genomic biliary network interaction between hosts and their bacterial symbionts can control host immunological homeostasis via the resulting metabolites.

doi: https://doi.org/10.1038/s41586-019-1865-0

- Pathologic Evaluation of Endoscopically Resected Non-Ampullary Duodenal Lesions: A Single Center Experience

Turk patoloji dergisi 2019 Dec;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31825518

OBJECTIVE: Endoscopic resections are increasingly being used for superficial gastrointestinal lesions. However, application of these techniques in the duodenum remains challenging, due to the technical difficulties and high complication rates. This study projects a western tertiary center's experience in the endoscopic treatment and diagnostic workup of 19 cases of non-ampullary duodenal lesions. MATERIAL AND METHOD: Specimens (12 endoscopic mucosal resections, 6 endoscopic submucosal dissections, and one endoscopic full-thickness resection) were processed following a strict protocol (photographed, mapped digitally and submitted totally) for histopathologic examination. Clinicopathologic characteristics, margin status and follow-up information were analyzed. RESULTS: The mean age of the 16 patients was 52 years (range: 22-81). Mean lesion size was 1.4 cm (range: 0.3-3.6 cm) for all cases, 2 cm for endoscopic submucosal dissections and 1.1 cm for endoscopic mucosal resections. Mean number of blocks submitted was 4/case. Seven neuroendocrine tumors, 3 tubulovillous adenomas were diagnosed along with nine benign lesions. For endoscopic submucosal dissections, en-bloc and R0 resection rates were 100% (n=6/6) and 83% (n=5/6); for endoscopic mucosal resections, they were 92% (n=11/12) and 83% (n=10/12), respectively. Only one patient had procedure-related late perforation that was managed endoscopically. No mortality was encountered. CONCLUSION: Duodenal endoscopic resections proved successful, safe and feasible methods in a tertiary center. The pathologist's role is to designate the accurate diagnosis, related histopathologic parameters and margin status. The gross protocol was found to be essential in evaluating specimen margins and orientation, as well as in size measurement. We recommend following a standardized approach including gross photography and digital mapping when handling these specimens, for both diagnostic and data collection purposes.

doi: https://doi.org/10.5146/tjpath.2019.01474

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