OXFORD

INTERNATIONAL EDITION

Oxford Textbook of Medicine

SIXTH EDITION
VOLUME 3

EDITED BY
John D. Firth
Christopher P. Conlon
Timothy M. Cox

Oxford Textbook of Medicine

SIXTH EDITION

Volume 3: Sections 16–21

EDITED BY

John D. Firth

Christopher P. Conlon

Timothy M. Cox

OXFORD
UNIVERSITY PRESS

OXFORD
UNIVERSITY PRESS

Great Clarendon Street, Oxford, OX2 6DP,
United Kingdom

Oxford University Press is a department of the University of Oxford.
It furthers the University's objective of excellence in research, scholarship,
and education by publishing worldwide. Oxford is a registered trade mark of
Oxford University Press in the UK and in certain other countries

First Edition published in 1983
Second Edition published in 1987
Third Edition published in 1996
Fourth Edition published in 2003
Fifth Edition published in 2010
Sixth Edition published in 2020

Impression: 1

Published in the United States of America by Oxford University Press
198 Madison Avenue, New York, NY 10016, United States of America

British Library Cataloguing in Publication Data

Data available

Library of Congress Control Number: 2018933144

Set ISBN: 978–0–19–874669–0
Volume 1: 978–0–19–881533–4
Volume 2: 978–0–19–881535–8
Volume 3: 978–0–19–881537–2
Volume 4: 978–0–19–884741–0

Only available as part of a set

Printed in Malaysia by Vivar Printing

18.17

Pleural diseases

D. de Fonseka, Y.C. Gary Lee, and N.A. Maskell

ESSENTIALS

Pleural effusion—general considerations

This is a common clinical problem which can complicate a range of lung and systemic diseases. Most cases can be diagnosed by pleural fluid analysis and pleural biopsy. Light's criteria enables discrimination between transudates and exudates. These state that a pleural effusion is an exudate if any of the following are present: (1) pleural fluid to serum protein ratio greater than 0.5; (2) pleural fluid lactate dehydrogenase (LDH) greater than two-thirds of the upper limit of normal serum LDH; (3) pleural fluid to serum LDH ratio greater than 0.6.

Aetiology—common causes of a transudative effusion are heart failure and liver cirrhosis; common causes of an exudative effusion are malignancy, empyema/parapneumonic effusion, and tuberculosis.

Diagnosis—low pH and low glucose levels are found in pleural fluid caused by very intense inflammatory processes, most commonly pleural infection, or malignancy. A single cytological test of pleural fluid for malignant cells is about 50% sensitive for malignancy, with a second sample increasing the sensitivity to about 60%. Where cytology is negative, image-guided pleural cutting needle biopsy or thoracoscopy are the most sensitive techniques to identify malignancy (*c.*80%) and are superior to closed pleural biopsy (*c.*45%). A high pleural fluid adenosine deaminase (ADA) activity strongly supports the diagnosis of tuberculosis in TB endemic regions. A low pleural fluid ADA level effectively excludes TB pleuritis in a low incidence setting. Alternatively, tuberculosis can be diagnosed by pleural biopsy (closed biopsy *c.*80% sensitive vs. thoracoscopy *c.*100%). Where an effusion remains undiagnosed, specifically treatable conditions such as pulmonary embolism and drug-induced pleuritis should be reconsidered.

Pleural effusion—particular diseases

Pyogenic pleural infection—community-acquired infection is usually due to *Streptococci* (50% of cases, including the milleri group, and *S. pneumoniae*), enterobacteria, anaerobes, and *Staphylococci*; hospital-acquired infection is most commonly due to *Staphylococcus aureus* (50% of cases, of which many can be methicillin-resistant (MRSA)), enterobacteria, or enterococci. Clinical features can range from fulminant sepsis to an indolent presentation with weight loss. Diagnosis depends on sampling pleural fluid to identify purulence, the presence of bacteria or low pleural pH/glucose levels. The treatment depends on effective chest tube drainage, appropriate antimicrobials (usually for at least 3 weeks), adequate nutrition, and prompt thoracic surgical drainage where clinical recovery is delayed. The associated mortality is greater than 20%. A recent randomized trial has suggested the usefulness of intrapleural administration of tissue plasminogen activator (tPA) and deoxyribonuclease (DNase) in improving radiographic and clinical outcomes.

Tuberculous pleural effusion and empyema—hypersensitivity tuberculous pleurisy is due to a delayed hypersensitivity reaction to mycobacteria in the pleural space, often occurs in cases of primary infection, and is associated with a low pleural mycobacterial load. Diagnosis is often dependent on pleural histology revealing caseating granulomas. Tuberculous empyema is caused by rupture of cavitating tuberculosis into the pleural space and usually involves coinfection with mycobacteria and pyogenic bacteria (due to inoculation of the pleural space from the infected lung tissue). Treatment is as for tuberculosis elsewhere. Antibiotics for pyogenic bacteria are required in addition to antituberculous treatment in tuberculous empyema.

Chylothorax and pseudochylothorax—turbid or white pleural fluid has three common causes, with diagnosis established by lipid analysis of pleural fluid: (1) true chylothorax—due to leaking of chyle from a damaged thoracic duct, usually caused by lymphoma, other cancers, and trauma (including surgery); treatment is of the underlying disease where possible, and talc pleurodesis or thoracic duct repair for fluid control. Nutrition is a high priority; (2) pseudochylothorax—due to chronic pleural inflammation; and (3) empyema.

Haemothorax—most commonly caused by chest trauma or iatrogenically, haemothorax is distinguished from heavily blood stained pleural effusion by the pleural fluid haematocrit being greater than 0.5 of that in blood. Traumatic haemothorax is not detectable on a presentation chest radiograph in 20% of cases, when it subsequently evolves over a few days. Initial treatment is by large-bore chest tube drainage. About 20% of patients require surgery (video-assisted thoracoscopic surgery, or thoracotomy) to control blood loss, repair organ injury, and evacuate the blood. Failure to evacuate a large haemothorax can lead to late extensive pleural fibrosis ('fibrothorax').

Benign asbestos-induced pleural disease—the commonest benign asbestos-induced pleural disease is pleural plaque. These are fibrotic and sometimes calcified pleural thickenings on the lateral chest wall and the dome of the diaphragm that have no clinical significance. Diffuse pleural fibrosis is less common and occurs due to asbestos-mediated pleural inflammation, sometimes following benign asbestos pleural effusion. There is no specific treatment and care is supportive. When visceral pleural thickening causes the lung to enfold it forms a characteristic lesion known as 'rounded atelectasis'.

Pneumothorax

Pneumothoraces, defined as air in the pleural space, are classified as traumatic (including iatrogenic) or spontaneous, with the latter being primary (where the lung is largely normal) or secondary (where the pneumothorax is due to an underlying lung disease, most commonly chronic obstructive pulmonary disease). The diagnosis is usually established by visualization of a lung edge—a pleural line—on the chest radiograph. Treatment involves removing air from the pleural cavity and preventing recurrence.

Primary pneumothorax—associated with smoking, tall stature, and the presence of macroscopic subpleural apical lung blebs; generally a benign disease; usually treated conservatively. Supplementary oxygen can be given (where the patient is an inpatient) to hasten reabsorption. Aspiration is recommended for symptomatic large pneumothorax of greater than 50% of hemithoracic volume, with chest tube drainage required if this fails. Recurrence rate is approximately 40%, with video-assisted thoracic surgery typically recommended to prevent recurrence in patients who have had two events. All should be advised to stop smoking as this is a major risk factor for recurrence.

Secondary pneumothorax—can sometimes be difficult to differentiate from a large bulla; CT is useful in this setting. All patients require hospitalization for a period of observation and most require chest tube drainage and recurrence prevention.

Tension pneumothorax—a rare but important variant of pneumothorax where a 'flap valve' mechanism at the visceral pleural surface results in the development of increasing positive pressure in the pleural space. Diagnosis is based on the clinical features of a large pneumothorax with mediastinal shift away from the affected side, cardiovascular compromise, and severe progressive dyspnoea. Tension pneumothorax should be treated by urgent thoracic decompression, followed by placement of a chest tube.

Introduction

Pleural disease is a common problem, affecting 3000 per million population each year, contributing to a significant workload for every chest physician. Pleural effusion is the commonest pleural pathology, closely followed by pneumothorax.

Anatomy and physiology of the pleura

The pleura is a serous membrane that covers the lung parenchyma, rib cage, mediastinum, and the diaphragm. The visceral pleura covers the lung parenchyma, including the interlobar fissures. The parietal pleura covers the mediastinal structures, chest wall, and diaphragm. The pleural membrane consist of a monolayer of mesothelial cells that are metabolically active and are capable of synthesizing numerous inflammatory mediators in response to stimuli, which regulate biological responses within the pleural cavity and facilitate transport of molecular and particulate material across the pleural surfaces. The parietal pleura, particularly the costal and diaphragmatic portions has sensory nerve endings and is innervated by the intercostal nerves. Trauma or inflammation irritating the parietal pleura can be perceived as pain on the chest wall at this level. The visceral pleura, although contains sensory receptors, does not contain pain fibres.

The normal pleural cavity contains a very small volume of fluid for lubrication (c.0.13 ± 0.06 ml/kg body mass, per pleural cavity). The fluid is mostly filtered from the systemic blood supply of the intercostal arterial circulation of the parietal pleura, with a biochemical composition resembling that of other interstitial fluids. The bronchial circulation of the visceral pleura is unlikely to contribute significantly to the fluid formation process in humans as the visceral pleura is thick and the microvascular pressure for fluid filtration in the bronchial circulation is low. Fluid filters between mesothelial cells and into the pleural space according to the net hydrostatic–oncotic pressure gradient, and some molecules can be actively transported through the mesothelial cells. Pleural fluid accumulates when the rate of pleural fluid formation exceeds the rate of fluid reabsorption. The drainage capacity of the parietal pleural lymphatics can increase up to 30-fold from its baseline values observed during normal physiological states, hence significant increase in fluid formation and/or impairment of pleural fluid reabsorption is usually needed for diseases to produce a pleural effusion.

Pleural imaging

A chest radiograph (CXR) is a simple and easy imaging modality as a first assessment for suspected pleural disease. The normal parietal and visceral pleurae are not visible on the CXR, except for the double layer of visceral pleurae of the fissures.

CT, MRI, and PET

Three-dimensional imaging is very helpful in the differential diagnosis of pleural effusion. CT and MRI are equally effective in defining pleural anatomy, though CT is favoured for cost and convenience reasons. MRI is preferred where minimizing radiation dosage is particularly important (e.g. a young woman with benign disease, to avoid irradiating breast tissue).

CT technique is important to achieve effective delineation of pleural abnormality. Images should be gathered with pleural fluid *in situ* and following intravenous contrast administration. The contrast medium should be given time to enter the tissue phase (60–90 s after injection), to allow for the enhancement of abnormal parietal pleural tissue which is then easily seen against the lower attenuation pleural fluid (Fig. 18.17.1). Pleural thickening which is nodular and circumferential, extending over the mediastinal pleural surface, involving the interlobar fissures or is more than 1 cm in thickness is suggestive of malignant disease, and CT scan approaches 100% specificity for malignancy where all these criteria are fulfilled.

The use of MR imaging to differentiate between malignant and benign pleural disease is increasing. The absence of ionizing radiation and high soft tissue contrast and intrinsic flow sensitivity are

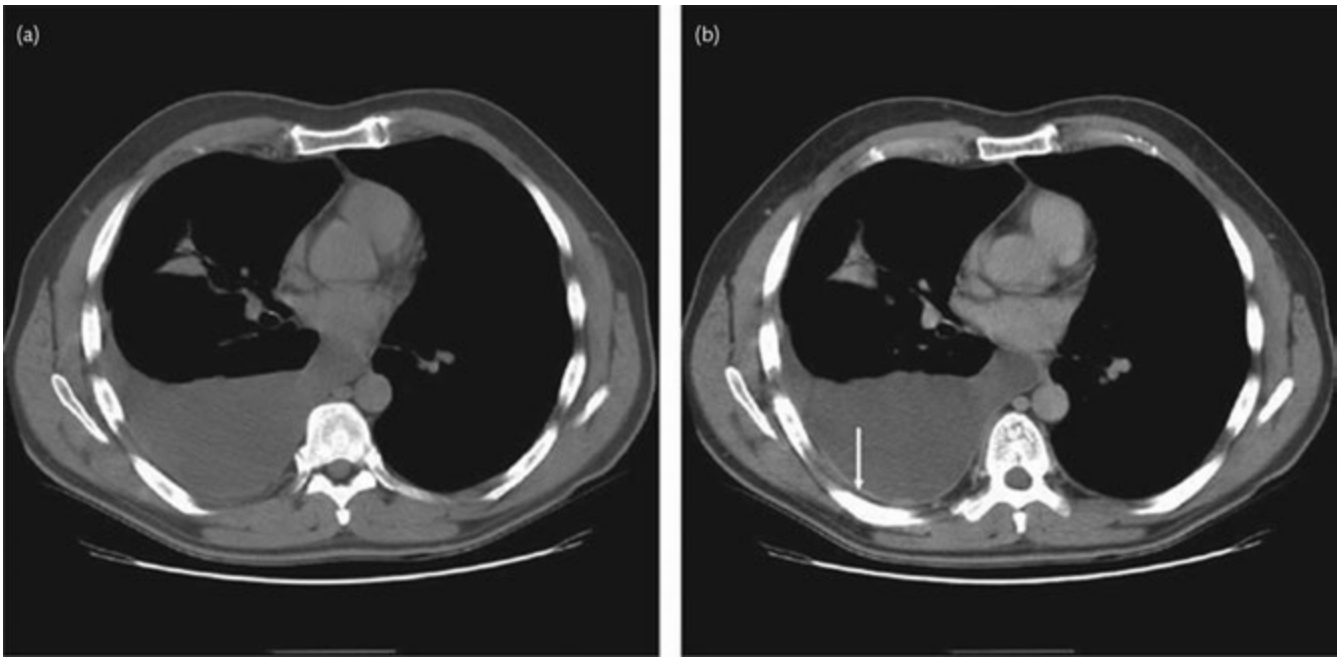

Fig. 18.17.1 Identification of malignant pleural tumour by CT scanning. Imaging was performed in the same patient without contrast administration (a) and 90 s after the administration of intravenous contrast to allow it to enter the 'tissue phase' (b). Parietal pleural thickening (due to pleural malignancy) which was invisible on the unenhanced images is clearly seen following contrast enhancement (arrow).

some of the features that make MRI more attractive. Combination of morphological and functional imaging sequences using diffusion weighted and dynamic contrast-enhanced MRI can increase the sensitivity and specificity of MRI when used to diagnose malignant pleural disease.

Positron emission tomography (PET) scanning is sensitive for pleural malignancy but of limited specificity as it cannot differentiate tumour from pleural inflammation (including empyema, tuberculosis, and the effects of pleurodesis). Some centres now use PET scanning in the staging of mesothelioma. It has a role in predicting survival in malignant mesothelioma, particularly when used to assess response to treatment for those having chemotherapy.

Ultrasound examination

Ultrasonography is simple portable and able to provide real-time point-of-care imaging with no radiation. It is increasingly performed at the bedside by appropriately trained respiratory physicians (Fig. 18.17.2). Following an unsuccessful 'blind' attempted pleural aspiration, subsequent ultrasound directed aspiration is successful in 87% of the cases. Pleural ultrasound offers vital information with regards to size of effusion, other characteristics such as septations and loculations, and location with regards to other nearby structures. Patients with effusions that are small or appear loculated on the chest radiograph should have pleural fluid sampling performed under ultrasound guidance. Pleural fluid that appears septated on ultrasound is consistently exudative, although

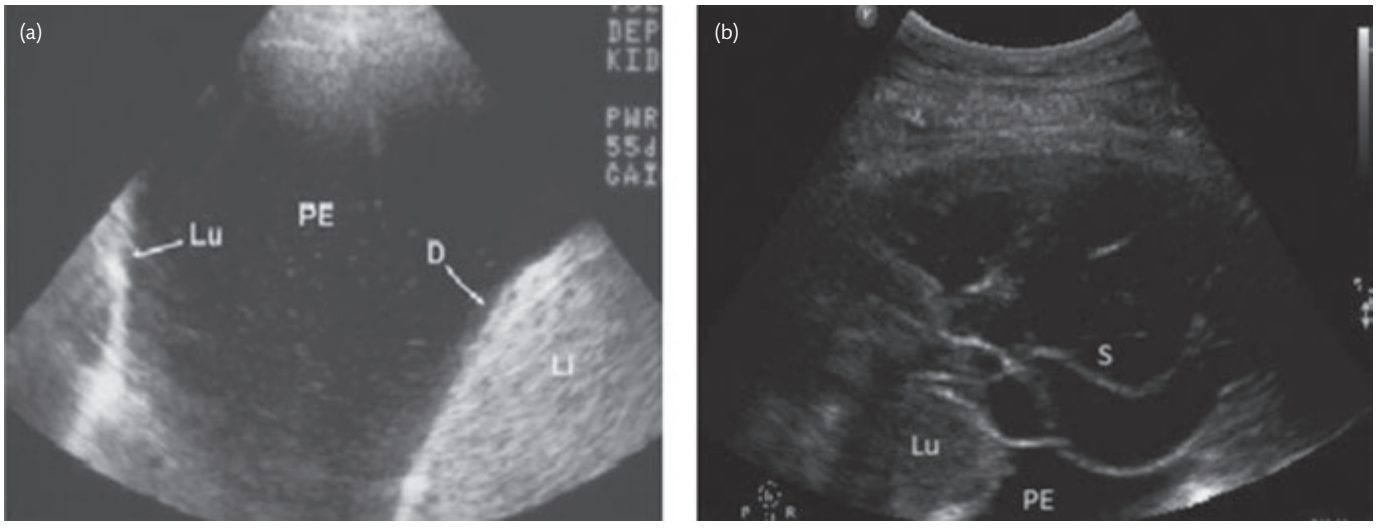

Fig. 18.17.2 The appearances of a free-flowing right pleural effusion on ultrasound (a) the large echo free area is the pleural effusion (PE). The diaphragm (D), liver (Li) and lung (Lu) are shown. Fig. (b) shows multiple septae (S) in a complicated parapneumonic effusion.

free-flowing effusions can be transudates or exudates. Nodularity of the pleura or diaphragm, which is suggestive of malignancy, can also be identified on ultrasound.

Pleural effusion—general considerations

Pleural effusions are common, with an incidence of greater than 0.3% of the population each year. It is a common medical problem complicating a range of lung and systemic diseases, hence establishing the cause can be challenging. Approximately 75% of pleural effusions are caused by malignancy, pneumonia, heart failure, and tuberculosis.

Formation of pleural effusion

Pleural fluid accumulates when the rate of pleural fluid formation exceeds the rate of pleural fluid removal due to a combination of intravascular pressures (positive driving pressure), increased pleural fluid protein levels (pleural oncotic pressure), and decreased intrapleural pressure (e.g. due to lung collapse). Changes in pressure gradients produce a transudate with a low protein concentration, and changes in vascular permeability produce an exudate with a high protein level. Inflammatory cellular debris and pleural fluid protein increase oncotic pressure, further promoting fluid collection.

Fluid may also enter the pleural cavity by leaking from other structures. Abdominal fluid (ascites or peritoneal dialysis fluid) may cross the diaphragm. Chyle can enter from a ruptured thoracic duct (chylothorax), blood from a blood vessel (haemothorax) or, rarely, urine from the kidney (urinothorax) or bile from the biliary tract (bilo or chylothorax). Occasionally a pleural effusion could be due to a direct communication with another organ such as an oesophagopleural fistula.

The most common cause of decreased pleural fluid absorption is parietal pleural malignancy or obstruction of the lymphatics draining the parietal pleura due to inflammation (e.g. empyema or tuberculosis). Pleural effusion development often involves both an increase in fluid formation and a decrease in its absorption.

Physiological consequences

The accumulation of pleural fluid is usually accompanied by an increase in pleural pressure in the thoracic cavity. The degree of dyspnoea induced by a pleural effusion is related to the effect of the increased pleural pressure on the hemidiaphragm and the loss of functioning lung parenchyma. If the hemidiaphragm is domed and is functioning normally, dyspnoea is mild and worsens as the hemidiaphragm flattens or everts.

High pleural pressures due to a large effusion can impair cardiac function by reducing venous return. In animals, right ventricular diastolic collapse begins when mean pleural pressure is increased about 5 mm Hg, and cardiac output falls about 30% if mean pleural pressure reaches 15 mm Hg.

Clinical features

Establishing a diagnosis begins with history and examination (Table 18.17.1), particularly seeking any history of asbestos or tuberculosis exposure, previous or current malignancy, smoking history, and a drug history (Box 18.17.1).

Table 18.17.1 Causes of transudative and exudative pleural effusions

Transudative effusion	Exudative effusion
Common	
Heart failure	Malignancy
Liver cirrhosis	Empyema/parapneumonic effusion
Hypoalbuminaemia	Tuberculosis
Uncommon	
Atelectasis	Pericardial diseases
Peritoneal dialysis	Pulmonary embolism
Nephrotic syndrome	Post-surgery (cardiac, thoracic, or abdominal)
Pulmonary arterial hypertension[a]	Post-cardiac injury syndrome
	Chylothorax[a] and cholesterol effusions
	Viral pleuritic
	Haemothorax
	Acute and chronic pancreatitis
	Autoimmune rheumatic diseases
Rare	
Glomerulonephritis	Drugs (see Box 18.17.1)
Superior vena cava obstruction	Fungal and parasitic infections
Hypothyroidism	Meigs' syndrome
Urinothorax[a]	

[a] These effusions may meet transudative or exudative criteria.

Clinical assessment can often reliably identify the causes of transudative effusions, and effusions in the context of heart failure do not need to be sampled unless there are atypical features (e.g. fever, chest pain, bilateral effusions of disparate sizes, and so on) or they fail to respond to therapy. Approximately 75% of effusions related to cardiac failure will resolve within a few weeks with optimum diuretic therapy. Effusions that persist require further investigation.

Investigation—imaging

The aim when investigating a patient with a pleural effusion is to reach an accurate diagnosis with the least invasive procedure and as few invasive pleural procedures as possible, thus reducing symptoms (i.e. dyspnoea, pain, cough), the risk of infection, the risk of pleural fluid loculation and septation (making later fluid control difficult), and the frequency of chest wall tumour invasion in patients who ultimately prove to have malignant pleural mesothelioma, which is common in the United Kingdom.

Box 18.17.1 Drugs particularly associated with pleural effusion

Cabergoline
Pergolide
Amiodarone
Dasatinib/Bosutinib
Nitrofurantoin
Phenytoin
Methotrexate

Chest radiography

The clinical history and examination are supplemented by an erect, plain chest radiograph (Fig. 18.17.3). Characteristically an effusion forms a basal opacity, drawn into a fluid meniscus by surface tension, and the costophrenic angle is lost, which helps differentiate pleural fluid from dense lung consolidation. The radiograph may also demonstrate pleural calcification, due to benign asbestos-related pleural plaques, or previous chronic pleural inflammation (particularly tuberculous treated with an artificial pneumothorax, or a chronic bacterial empyema, Fig. 18.17.4).

Failure of the pleural fluid to form a typical basal opacity suggests loculation of the fluid, which most commonly occurs in exudative effusions, particularly those that are heavily inflamed (see section on 'Pyogenic pleural infection', next).

In patients imaged supine, free-flowing pleural fluid lies posteriorly, and is seen as a hazy opacity of one hemithorax (Fig. 18.17.3). Bilateral effusions associated with an enlarged cardiac silhouette are usually due to heart failure, whereas the absence of cardiomegaly should raise suspicion of alternative diagnoses. Two-thirds of effusions that opacify the entire hemithorax have a malignant origin, although parapneumonic effusions, tuberculosis, and hepatic hydrothoraces may also manifest as massive effusions. Concurrent causes of pleural pathologies can coexist.

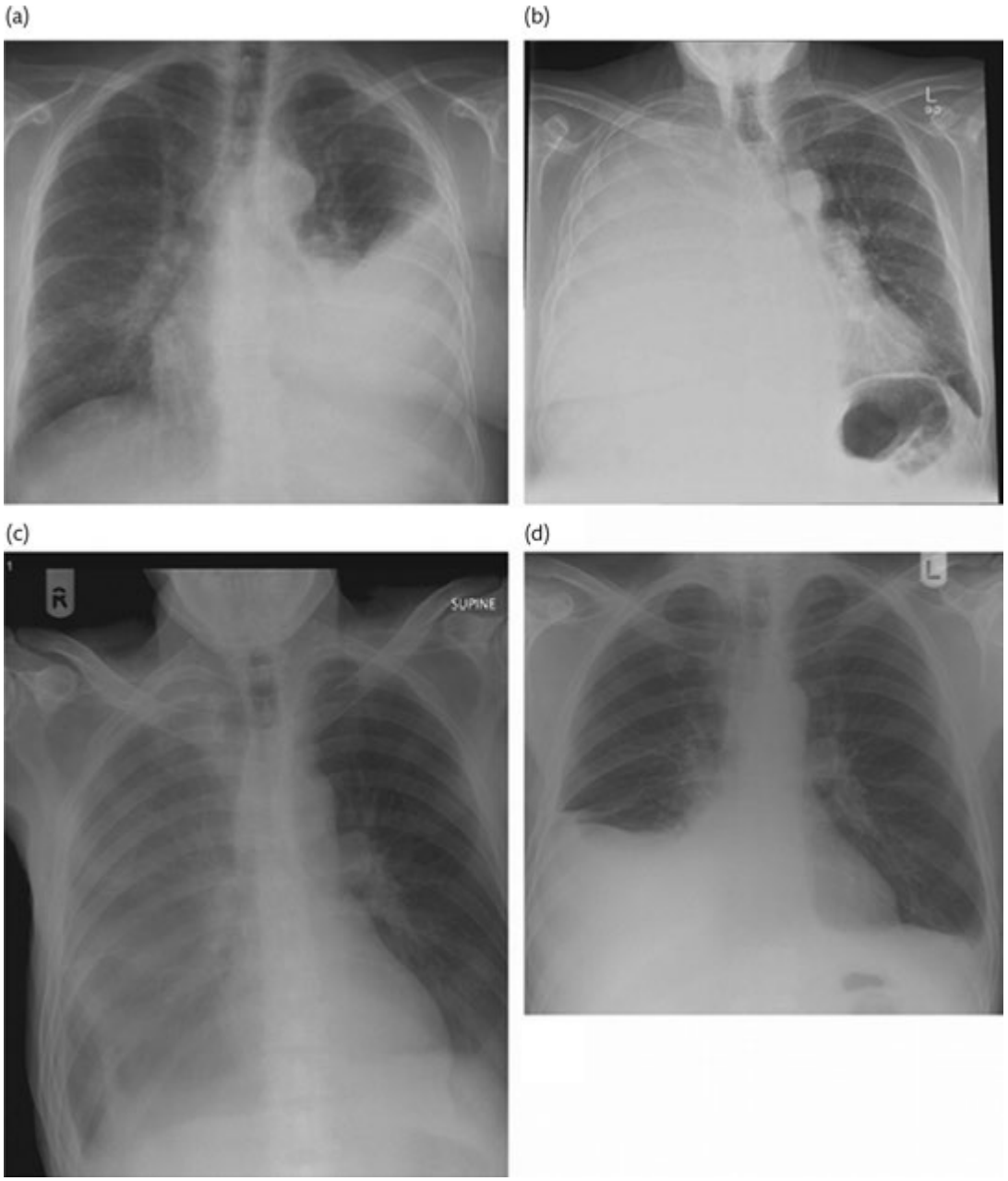

Fig. 18.17.3 Chest radiograph appearances of a free-flowing left pleural effusion imaged erect (a); a massive right pleural effusion with mediastinal shift (b); and a pleural effusion radiographed supine (c) and erect (d) in the same patient.

Fig. 18.17.4 Right pleural calcification following treatment of tuberculosis with an artificial pneumothorax in the prechemotherapy era.

Investigation—Pleural fluid analysis

The first investigation of an undiagnosed pleural effusion should be a diagnostic aspiration, whereby a small volume of pleural fluid is aspirated through a fine bore (*c.*21 G) needle, under ultrasound guidance. In a very large symptomatic effusion, 1–2 litres of fluid may be removed to reduce breathlessness, but the thorax should not be completely drained as leaving some fluid can help with subsequent CT or pleural biopsy if necessary.

The odour and colour of pleural fluid should be noted. Bloodstained pleural fluid suggests malignancy, trauma, pulmonary infarction or embolism, benign asbestos effusion, or post-cardiac surgery syndrome. Milky pleural fluid suggests a chylothorax, pseudochylothorax (see later in this chapter) or occasionally, empyema. Foul-smelling fluid suggests anaerobic pleural infection and pleural fluid that smells like urine suggests urinothorax.

Fluid should be sent for estimation of protein and lactate dehydrogenase (LDH) concentrations (to differentiate pleural transudates and exudates); cytological assessment for malignant cells, and dominant cell type (e.g. neutrophilic vs. lymphocytic) and pH and/or glucose levels, Gram smear for bacteria, and microbial culture. Additional tests can be ordered if clinically appropriate, including adenosine deaminase (ADA) and TB culture for TB, and flow cytometry for lymphoma.

Transudative and exudative effusions

Differentiating if an effusion is a transudate or an exudate is a useful first step as this can guide the best investigational pathway to obtain a diagnosis. A transudate is unlikely to be due to a primary pleural pathology and usually resolves when the underlying cause is treated. Exudative effusions with a high protein and/or LDH content are commoner and can be manifestation of range of pleural and systemic diseases.

Transudative and exudative effusions are usually differentiated using 'Light's criteria'. A pleural effusion is an exudate if it satisfies any of the following criteria:

- Pleural fluid to serum protein ratio more than 0.5
- Pleural fluid LDH more than 2/3 of the upper limit of normal serum LDH
- Pleural fluid to serum LDH ratio more than 0.6

Analysing pleural fluid protein and LDH concentrations as continuous variables improves their diagnostic accuracy slightly, but the traditional simple threshold criteria are generally robust in clinical practice.

The leading causes of transudates are heart failure (80%) and liver cirrhosis (13%). Light's criteria are highly sensitive (98%) in identifying exudates, but misclassify 20–30% of transudates as exudates, almost exclusively in patients receiving diuretic therapy. In those thought to have heart failure or cirrhosis whose pleural fluid meet exudative Light's criteria, a serum to pleural fluid albumin gradient more than 1.2 g/dl or a pleural fluid to serum albumin ratio less than 0.6, respectively, points to a truly transudative effusion. Serum or pleural fluid levels of the natriuretic peptide NT-proBNP more than 1300 pg/ml indicates that the effusion is almost certainly secondary to heart failure.

Pleural fluid cytology for malignant cells

Overall, only 60% of patients with malignant pleural disease will have a positive diagnosis established by a single cytological test of pleural fluid. This is increased if both cell blocks and smears are prepared. A further 5–10% are identified by a second fluid sample, but a third examination adds little.

The sensitivity of pleural cytology depends on tumour cell type, a low yield being common for diseases like lymphoma and malignant mesothelioma. Malignant mesothelioma is particularly difficult to diagnose with cytology, and only about 20% of cases are positive. Immunocytochemistry helps distinguish between benign and malignant cells, as well as between different cancer types.

Diagnosis of pleural infection

Pleural fluid Gram's smear for bacteria and microbial culture should be performed in all cases of exudative pleural effusion. Inoculation of pleural fluid into culture medium bottles (widely used for blood cultures) will improve the sensitivity of bacterial culture but at least 40% of cases of pleural infection are negative by standard culture techniques. Where there is a reasonable suspicion of mycobacterial disease, pleural fluid should be tested for acid- and alcohol-fast bacilli, ADA, and TB culture ordered.

Intense pleural inflammation reduces pleural fluid pH as lactate is produced by leucocyte and bacterial metabolism. A pleural fluid pH of less than 7.2 (measured on a heparinized pleural fluid sample with a blood gas analyser), in association with a clinical presentation suggestive of pleural infection, is a clinically robust diagnostic test that predicts the need for pleural effusion drainage, as well as antibiotic therapy, hence measurement of pleural fluid pH should be routine in the assessment of all non-purulent pleural effusions. The interpretation of a pleural acidosis should always consider the differential diagnosis of other diseases that cause intense pleural inflammation and so lower pleural pH, particularly rheumatoid disease, oesophageal perforation

(which is causing pleural infection), advanced malignancy, and tuberculosis.

The inflammatory processes that produce pleural acidosis also reduce pleural fluid glucose as it is consumed by metabolically active cells and bacteria, and raise the pleural fluid LDH level as this is released from apoptotic leucocytes. Quantifying these indices are alternative ways of identifying intense pleural inflammation, but in practice they add little to the measurement of pleural fluid pH alone.

Other pleural fluid analyses to diagnose exudative pleural effusion

A pleural fluid amylase level is useful for diagnosing the cause of exudative pleural effusion associated with pancreatitis, which can sometimes occur without abdominal pain. Isoenzyme analysis shows that the amylase is pancreatic in origin. Oesophageal perforation allows amylase of salivary origin to enter the pleural space, and identification of this can suggest an oesophageal leak. Some adenocarcinomas also secrete amylase (usually salivary), hence amylase rich effusions are seen in some cases of carcinoma.

Measurements of pleural fluid triglyceride, lipid profiles, and cholesterol levels are valuable in the differential diagnosis of chylo/pseudochylothorax.

Adenosine deaminase levels are raised in pleural tuberculosis, which is diagnostically valuable in TB endemic areas. However, even in areas with low prevalence of tuberculosis, a low pleural ADA test is useful for ruling out the disease due to its high negative predictive value. High pleural fluid ADA activity can also occur with empyema, connective tissue diseases, and lymphoma.

The demonstration of a pleural fluid to serum creatinine ratio greater than 1 is diagnostic of the rare syndrome of urinothorax, where urine has extravasated from an obstructed kidney through the retroperitoneal space and into the pleural cavity. Similarly, the finding of a very elevated glucose level in a pleural effusion in a patient on peritoneal dialysis suggests the presence of a diaphragmatic leak.

In general, the measurement of tumour markers for the evaluation of patients with suspected malignant effusions is not recommended. When 100% specific cut-off levels are set, tumour markers are very insensitive. Mesothelin is a potential biomarker of mesothelioma that can be measured in pleural fluid or serum (sensitivity 70–80%, specificity 90%).

Investigation—pleural biopsy

Pleural malignancy

Exudative pleural effusions where pleural fluid analysis has not yielded a diagnosis usually require the sampling of pleural tissue to make a specific diagnosis, particularly of malignancy, tuberculosis, and some rarer conditions such as amyloidosis and sarcoidosis. There are three common approaches to gaining this tissue: thoracoscopy (under general or local anaesthesia), image-guided pleural biopsy (where pleural thickening or nodules have been shown on contrast-enhanced CT), or blind closed pleural biopsy (using an Abrams or Cope's biopsy needle).

For malignant pleural disease, thoracoscopic and image-guided cutting needle biopsy of pleural tissue are 95% and 87% sensitive, respectively, which is superior to the sensitivity of closed pleural biopsy (about 45%). Whereas image-guided pleural biopsy is a less invasive procedure, thoracoscopy allows for drainage of pleural effusion and pleurodesis in order to control pleural fluid recurrence, all in one setting.

The histological differential diagnosis of malignant pleural mesothelioma from reactive mesothelium and metastatic carcinoma by morphological examination is not reliable: accurate diagnosis often relies on a panel of immunohistochemical markers. Prophylactic radiation to pleural puncture sites to reduce the risk of tumour invasion into needle tracts is controversial, with conflicting results from three small randomized trials. If used, radiotherapy should be administered within 2 weeks of the biopsy or drainage procedure.

Tuberculosis

The choice of biopsy method is more finely balanced when possible tuberculosis is the indication for the procedure. Closed (Abrams) pleural biopsy with acid-fast bacillus staining and culture of a biopsy sample for mycobacteria is diagnostic of tuberculosis in about 90% of cases when histological appearances and mycobacterial culture results are combined. This is less sensitive than thoracoscopic pleural biopsy, which is nearly 100% sensitive, although the diagnostic advantage to thoracoscopy is smaller than it is in malignant disease.

Pleural effusion—specific conditions

Pyogenic pleural infection

Infection of the pleural space has been known for millennia. Hippocrates was credited for its recognition as long ago as 500 BC, and it remains a significant problem with an incidence of more than 65 000 cases in the United Kingdom and United States combined.

Pleural infection is still associated with a high mortality and morbidity. The median length of stay in hospital is 12–15 days, and 25% of patients stay in hospital for over one month, with a mortality rate of up to 20%. The incidences of pleural infection have been rising worldwide in recent decades despite the introduction of multivalent pneumococcal vaccines.

Aetiology

Risk factors for developing empyema are similar to those for pneumonia, with paediatric and elderly populations being particularly susceptible. Men are affected twice as often as women. Diabetes mellitus, immunocompromise, alcohol abuse, and intravenous drug use are all risk factors for the development of empyema. Poor orodental hygiene is commonly seen in anaerobic pleural infections.

Most cases of pleural infection are secondary to underlying parenchymal lung infection. Up to half the cases of pneumonia will develop a parapneumonic effusion, and up to 10% of these can subsequently become infected. However, there is no radiological evidence of pneumonia in a third of cases, raising the likelihood of other routes of entry (e.g. micro-aspiration, haematogenous or transdiaphragmatic invasion). Other causes of pleural infection include trauma, iatrogenic causes, and proximal bronchial tree obstruction.

Pathophysiology

An uncomplicated sterile exudative effusion is formed as a result of increased vascular permeability of the visceral pleural membranes

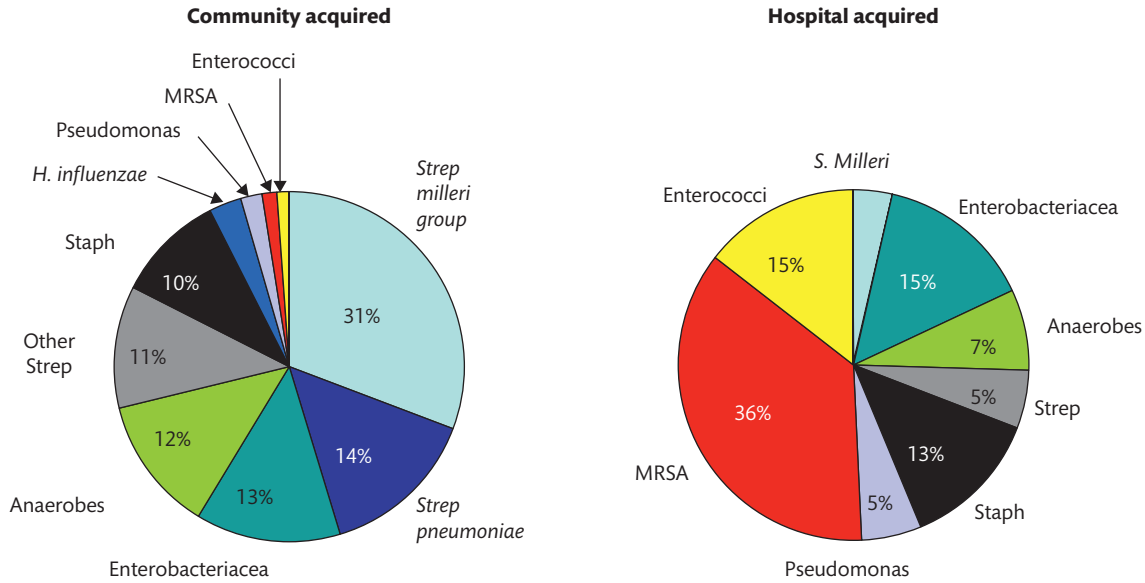

Fig. 18.17.5 Pie charts showing the proportions of different bacterial classes in community-acquired and hospital-acquired pleural infection.

during the parenchymal infection. Pro-inflammatory cytokines such as interleukin (IL)–6, IL-8 and tumour necrosis factor alpha (TNFα) facilitate the formation of pleural fluid. At this initial stage, the sterile effusion can be managed with antibiotic treatment alone. However, secondary bacterial infection of the effusion leads to the pleural infection syndrome, which often fails conservative management.

With invasion of the pleural space the bacteria multiply leading to increased metabolic activity and neutrophil phagocytic activity, resulting in increased production of lactic acid and consumption of pleural fluid glucose. The characteristic features in the diagnosis of pleural infection; pH less than 7.2, pleural fluid glucose less than 3.0 mmol/litre, and LDH less than 1000 IU/litre are a result of the increased metabolic activity. Along with the increased production of pro-inflammatory cytokines, a rising level of inhibitors of fibrinolysis such as tissue plasminogen activator inhibitor leads to increased production of fluid and deposition of fibrin. This thin fibrin layer coats the visceral and parietal pleural surfaces which can lead to formation of pockets or locules that complicates the management of these effusions even further.

Bacteriology

Pleural fluid microbiological culture is only positive in approximately 45% of cases. The yield can be increased significantly by placing a pleural fluid sample in blood culture bottles. The bacteriology of pleural infection varies significantly between community- and hospital-acquired pleural infection (Fig. 18.17.5), and empirical antibiotics should be tailored accordingly. The mortality of hospital-acquired pleural infection is twice that of community-acquired infection.

Community-acquired pleural infections are predominantly Streptococcal and Staphylococcal species with up to 65% culture positive cases being attributable to these two groups. In addition, at least 20% of cases are associated with anaerobic organisms. In contrast *Staphylococcus aureus* (including MRSA) and Gram negative organisms are often associated with hospital-acquired cases.

Clinical features and investigations

Pleural infection commonly present with cough, breathlessness, chest pain, fever, and a clinical examination suggestive of effusion. Occasionally a more indolent course may follow with lethargy and anorexia where diagnosis and hence treatment can be delayed. A chest radiograph may give information as to the presence of fluid or parenchymal infection. CXR appearance in pleural infection may be of a simple effusion with blunting of the costophrenic angle with a meniscus sign confirming fluid or it may have a lobulated appearance depicting a mass, which is not uncommon in a loculated empyema (Fig. 18.17.6).

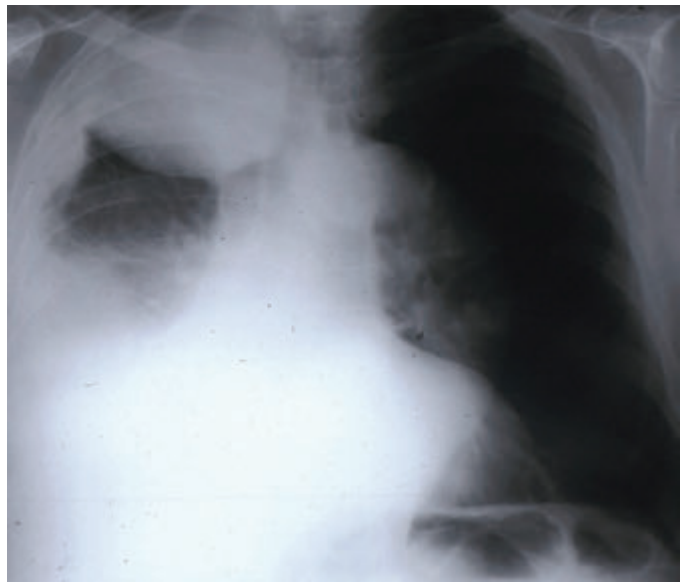

Fig. 18.17.6 Chest radiograph showing a typical pleural infection with a severely loculated pleural effusion, which mimics a lung mass.

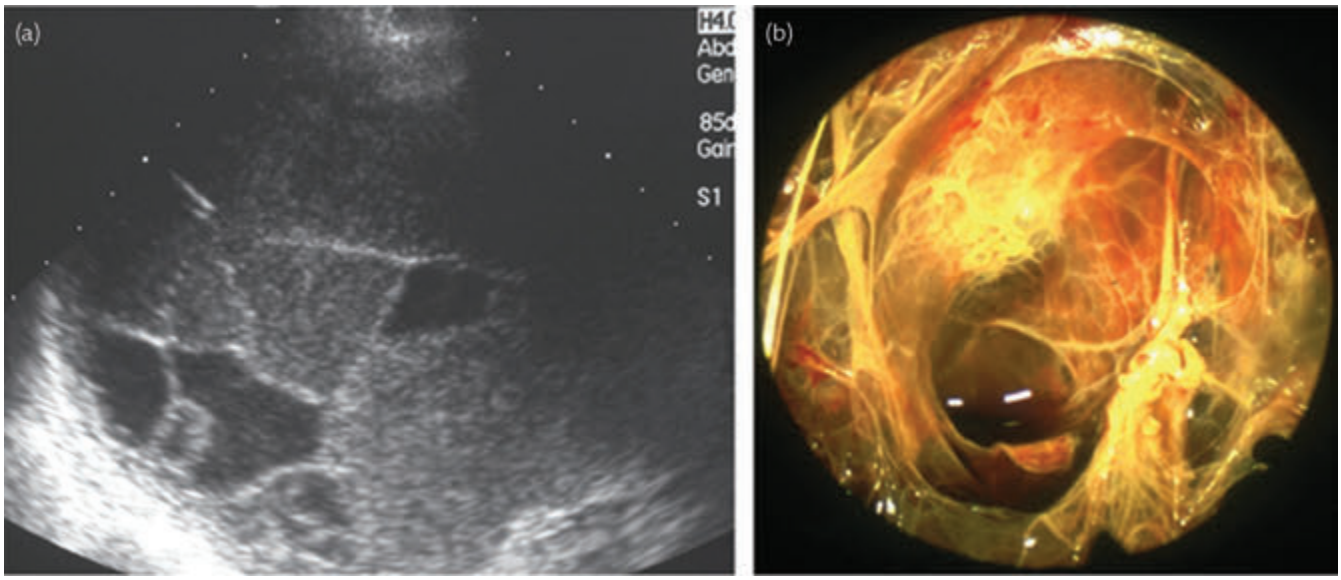

Fig. 18.17.7 Fibrinous septations due to pleural infection shown on ultrasonography (a) and directly observed at thoracoscopy (panel b).

Thoracic ultrasound is useful when investigating pleural infection, not only to confirm the presence of fluid in the pleural space and guide a diagnostic aspiration, but also to characterize the nature of the effusion as to the presence or absence of septations and loculations (Fig. 18.17.7). Diagnostic aspiration is essential to exclude pleural infection when there is clinical suspicion of this diagnosis (Fig. 18.17.8).

CT can be useful where diagnostic uncertainty remains following the investigations described earlier (Fig. 18.17.9). CT with contrast swallow is particularly useful where oesophageal perforation is suspected as the cause of low pleural fluid pH, or advanced malignancy. A contrast CT acquired in the pleural phase, approximately 60 seconds post contrast injection, will provide good pleural enhancement. Smooth pleural thickening, parietal pleural enhancement, and attenuation of the extrapleural fat are common features seen in pleural infection.

Fig. 18.17.8 Pleural fluid samples obtained from locules with varying echogenicity on ultrasound in a case of pyogenic bacterial pleural infection. Those with greater echogenicity contain fluid of greater purulence, thus emphasizing that the pleural inflammatory process is not uniform.

Risk stratification

A recently published prediction model (the RAPID score) derived from two large prospective randomized trials of patients with pleural infection offers some promise in prognostication in pleural infection. Increasing age, raised blood urea level, low serum albumin, hospital-acquired infection, and nonpurulence of the pleural fluid were all associated with a poorer outcome. (See Table 18.17.2). This score is now the subject of a large multicentre observational study aimed at validating it.

Management

Timely diagnosis and initiation of treatment is crucial in the management of pleural infection. Empirical intravenous antibiotic treatment, directed by likely source of acquisition, is required

Fig. 18.17.9 Thoracic CT scan showing an empyema complicating an aspirated foreign body (marked A). A piece of lamb chop was later removed at bronchoscopy. A chest drain is also seen (marked B).

Table 18.17.2 RAPID risk stratification score for pleural infection

Parameter	Measure	Score
Renal		
– Urea (mM)	<5 5–8 >8	0 1 2
Age (years)	<50 50–70 >70	0 1 2
Purulence of pleural fluid		
– purulent – nonpurulent	– –	0 1
Infection source		
– community-acquired – hospital acquired	– –	0 1
Dietary factors		
– Albumin (g/litre)	≥27 <27	0 1
Risk categories Score 0–2 Score 3–4 Score 5–7	 – – –	 Low risk Medium risk High risk

ahead of pleural fluid culture results. Community-acquired infections should be treated with an antibiotic agent that has good Gram-positive and anaerobic cover. Hospital-acquired infections will require both Gram-positive (including possible MRSA) cover, Gram-negative cover, and anaerobic cover.

Early nutritional support is an important cornerstone of management and often overlooked at initial presentation. While it has not been subject to a randomized controlled trial in this setting, nutritional support is likely to be important in counteracting the catabolic state associated with infection. Early full nutrition assessment is strongly advised in all cases.

Frank pus on aspiration is diagnostic of pleural infection and tube drainage should be initiated to drain the pleural space. Pleural fluid culture positive for organisms, a positive Gram stain or low pleural fluid pH/glucose with history suggestive of pleural infection would necessitate intercostal tube drainage of the fluid. There is no consensus on the optimum size of the chest tube, but smaller bore chest tubes (10–14 F) are just as effective as larger bore drains, and are better tolerated due to less discomfort. It is important to note that small bore chest tubes must be flushed regularly with normal saline to maintain tube patency.

The MIST2 study, a double-dummy, double-placebo, randomized, controlled trial in pleural infection, utilizing tPA as a directly-acting fibrinolytic to disrupt septations and DNase to reduce fluid viscosity within the pleural space and enhance drainage. This four arm study (n = 210) showed that intrapleural tPA and DNase therapy resulted in significant reduction in chest radiographic opacification, whereas single-agent tPA or DNase had no effect compared to placebo. A recently published prospective series of over 100 patients treated with this regime highlighted its safety. The need for surgical intervention was limited to only a handful of patients, and the mortality rate was extremely low.

In some cases resolution following tube drainage can be slow (Fig. 18.17.10), but patients with ineffective tube drainage and persistent clinical features of sepsis will require assessment by thoracic surgery. Most pleural infection cases requiring surgical intervention are now treated with video-assisted thoracoscopic surgery (VATS). VATS allows disruption of the adhesions and clearance of the infected pleural collection, although some cases still require open thoracotomy and decortication. Rib resection with open drainage is an option in those that are very frail.

Tuberculous pleural effusion and empyema

The general treatment of tuberculosis is discussed in detail elsewhere (see Chapter 8.6.26).

Tuberculous related pleural effusions are predominantly due to a delayed hypersensitivity reaction to mycobacteria or mycobacterial

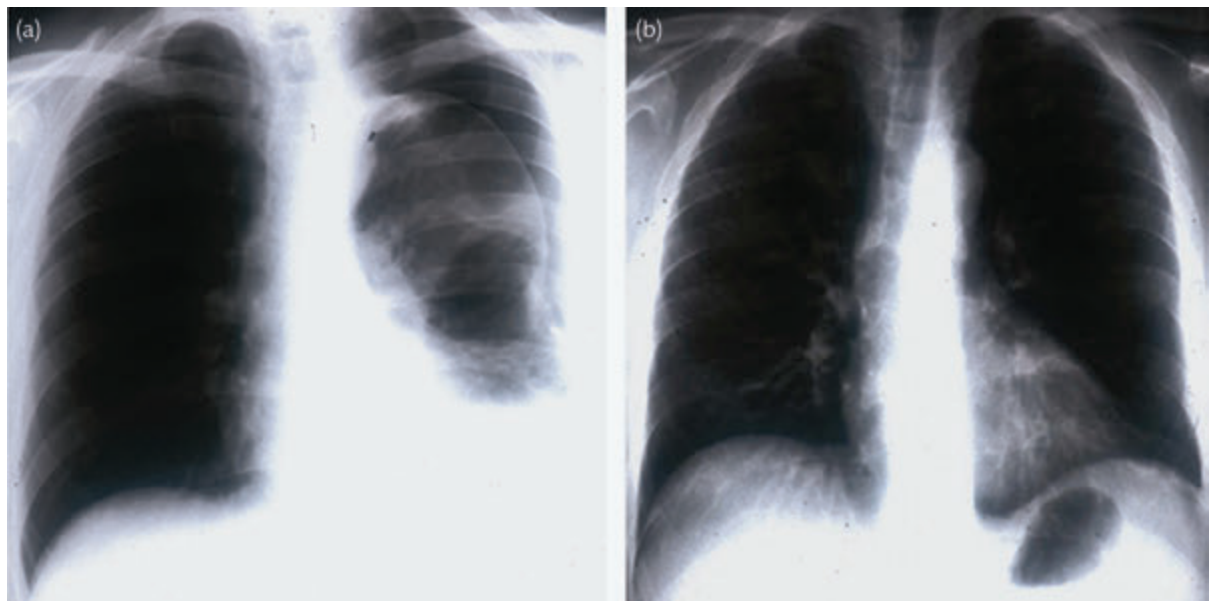

Fig. 18.17.10 Chest radiographs in a patient with a left lung that has not re-expanded due to visceral pleural thickening following drainage and treatment of a pleural infection (a). The patient was clinically well and the radiographic changes resolved spontaneously over 3 months (b).

antigens in the pleural space. In most cases these effusions resolve spontaneously without treatment. Rarely, patients can develop tuberculous empyema due to direct communication between infected lung parenchyma and the pleural space, such as a ruptured cavity.

Clinical features and diagnosis

Hypersensitivity pleuritis may be asymptomatic in some cases, or acute or subacute symptoms may develop depending on the duration of the inflammation of the pleura and presence of effusion. Patients may have symptoms of cough, pleuritic chest pain, and fever.

Pleural fluid analysis reveals high protein and lactate dehydrogenase level content. Pleural fluid glucose level can be moderately depressed. Lymphocyte predominant effusions are common where the effusions have been present for a few days. It is not uncommon to see a neutrophil predominance at early stages of effusion or in empyema.

Pleural fluid ADA levels have a role in excluding a diagnosis of tuberculous pleuritis where the level is less than 35 U/litre in low endemic areas. Sensitivity of ADA is low as it can be elevated in non-tuberculous related empyema and in patients with HIV.

Pleural fluid smear and culture yields are low especially in immunocompromised patients. Pleural biopsy with Abrams needle is a relatively safe procedure with a high sensitivity, with granuloma of the parietal pleura demonstrated in 95% of cases due to pleural TB (Fig. 18.17.11). Thoracoscopy is nearly 100% sensitive for diagnosing pleural TB, but it is a more invasive procedure.

Management

Most cases of tuberculous related pleural effusions resolve spontaneously. Left untreated, half the cases may develop some form of active tuberculosis, mostly pulmonary, over the ensuing few years. Treatment is therefore mainly aimed at preventing recurrence. The

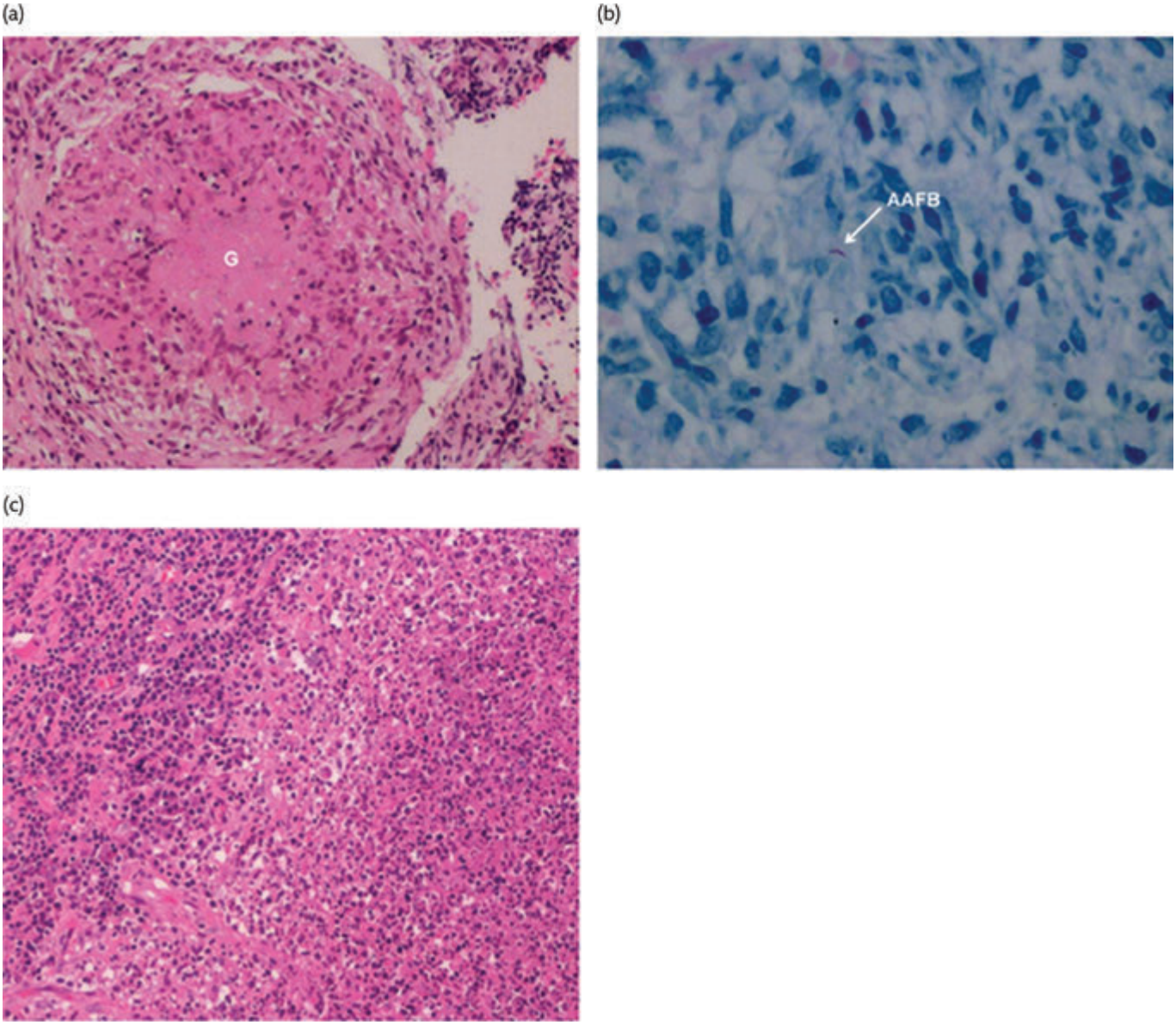

Fig. 18.17.11 Histological appearances of pleural biopsies in patients with tuberculosis. The appearance in an immunocompetent patient (a) shows a typical caseating granuloma (G). Panel b shows staining for acid- and alcohol-fast bacilli (AAFB) and demonstrates *Mycobacterium tuberculosis* (later confirmed by culture). The appearance in a patient with immunosuppression due to HIV disease (c) shows no granulomas.

same antibiotic regimes as per pulmonary TB are used to treat tuberculous pleural effusions (see Chapter 8.6.26).

Use of corticosteroids for tuberculous pleuritis and effusions remain controversial. Small studies and a recent Cochrane review failed to show sufficient evidence to recommend adjuvant use of corticosteroids in TB pleurisy. A short course of steroid can be justified in those with large recurrent effusions, and those with troublesome symptoms (e.g. fever and chest pain). Steroid may increase the risk of subsequent Kaposi's sarcoma in HIV patients.

Coinfections of the pleural space with other bacteria are not uncommon in TB empyema, hence adequate cover should be instigated for these patients alongside their TB treatment. Tuberculous empyema can cause significant pleural thickening/calcification and long-term disabling sequalae in some patients. Surgery is an option for these patients, but can be difficult due to underlying parenchymal infection and poor respiratory reserve.

Other specific causes of exudative pleural effusion

Rheumatoid arthritis

Up to 5% of patients with rheumatoid arthritis can develop pleural effusions. They are more common in men and those with subcutaneous nodules. The timing of the effusions in relation to the diagnosis of rheumatoid arthritis can be variable: they can rarely precede joint symptoms, but often occur more than 10 years after the initial joint symptoms.

One of the most striking features of rheumatoid related effusions is the very low glucose level. It is postulated that this is due to the significant inflammatory reaction of the pleura. Rheumatoid related effusions can also contain a high level of cholesterol leading to rheumatoid related pseudochylothoraces (see later). Cytological analysis of fluid reveals one or more of the following features: slender elongated multinucleated macrophages, giant round multinucleated macrophages, or necrotic background material.

Many agents (e.g. NSAIDS, steroids—oral or intrapleural—and pleurodesis) have been attempted for the management of recurrent rheumatoid effusions; none have been well studied. Pleural thickening may develop over time.

Systemic lupus erythematosus

The pleura is often involved in systemic lupus erythematosus (SLE), with reports of up to 56% of patients experiencing pleuritic pain at some point during the course of their disease. Reports of SLE related pleural effusions range widely from 9% to 44% of patients in some case series, although these tend to be of patients with severe disease.

Joint symptoms usually precede pleuritis. Pleural fluid levels of antinuclear antibody (ANA) and lupus erythematosus (LE) cells are not useful in diagnosis. Differential white cell count reflects a high proportion of polymorphonuclear leucocytes. Nonsteroidal anti-inflammatory drugs and corticosteroids often control mild and severe SLE pleurisy, respectively. Occasionally cyclophosphamide may be tried.

Pleural effusion secondary to IgG_4 related disease

IgG_4 related pleural effusion is a newly recognized entity that has been increasingly cited in case series. This is a systemic fibro-inflammatory disease associated with elevated circulating levels of IgG_4. The underlying pathophysiology involves dense lymphoplasmacytic infiltrates containing IgG_4 positive plasma cells. It is more common in men, with an average age 69 years old at presentation. Most patients respond to steroids.

Pulmonary embolism

Pleural effusions are present in up to 50% of cases of pulmonary embolism. These effusions have no specific diagnostic features, but most tend to be small, and larger effusions should be investigated for other underlying causes. Pleural fluid analysis is important to exclude concurrent malignancy or pleural infection. Analysis of fluid often reveals a high polymorphonuclear leucocyte count and occasionally an elevated eosinophil count. Physicians must maintain a high index of suspicion for this diagnosis and should pursue appropriate diagnostic tests as required.

Persisting but undiagnosed pleural effusion

About 15% of exudative pleural effusions remain undiagnosed, even after careful investigation, including thoracoscopic biopsy. About 10% of these will eventually prove to have a malignant cause, particularly mesothelioma. In cases of undiagnosed effusion, those diagnoses where there is specific therapy to prevent significant morbidity/mortality should be reconsidered. CT pulmonary angiography for pulmonary embolism, ADA testing for tuberculosis, and lymphocyte subset analysis of the pleural fluid to help exclude lymphoma are particularly worthy of consideration.

Chylothorax

Pleural fluid that is white or milky in colour and does not clear with centrifugation almost always has a high lipid content. This occurs when chyle enters the pleural space following disruption of the thoracic duct (a true chylothorax), or large amounts of cholesterol or lecithin–globulin complexes accumulate in a long-standing inflammatory effusion (a pseudochylothorax).

Pathophysiology

About 2 litres of chyle is created daily, with the volume of chyle transported in the thoracic duct increasing by 2–10 times following a high-fat meal. The predominant cell type in chyle is small T-lymphocytes. Chyle is bacteriostatic, hence the risk of developing empyema in the presence of a chylous effusion is low. It is non-irritant to the pleura and thus development of significant pleural thickening is uncommon.

Chyle travels in the thoracic duct, which usually passes through the aortic hiatus of the diaphragm on the right, crosses between the T4 and T6 vertebrae to the left, and then continues cephalad on the left side of the oesophagus. A chylothorax forms when the thoracic duct is disrupted, either before or after it crosses the midline, tending to produce right- and left-sided chylothoraces, respectively.

Aetiology

The leading cause of chylothorax is trauma, often secondary to oesophageal surgical procedures (incidence nearly 4%) or cardiothoracic surgical procedures (incidence less than 1%). Malignancy is the second commonest cause, with up to 75% of being secondary to lymphoma. Paediatric chylothorax is rare, but when it occurs it tends to be in relation to surgical intervention such as repair of congenital diaphragmatic hernia, and is usually left sided.

Penetrating injuries of the neck or thorax, and nonpenetrating trauma with spine hyperextension or vertebral fracture, can cause thoracic duct damage. Rupture after weightlifting, severe coughing or vomiting, childbirth, and vigorous stretching while yawning are also occasionally reported.

Chylothorax can follow chylous ascites. Pulmonary lymphangioleiomyomatosis is one of the common causes of chylothorax and this is discussed in Chapter 18.14.6. Other precipitants include intestinal lymphangiectasis, yellow nail syndrome, superior vena cava, or subclavian vein thrombosis/obstruction, filariasis, lymph node enlargement, mediastinal fibrosis, lymphangitis of the thoracic duct, tuberous sclerosis, amyloidosis, and Gorham's syndrome (disappearing bone disease; massive osteolysis).

Clinical features

The clinical features are those of a pleural effusion, but chest pain and fever are rare. In traumatic chylothorax, effusion onset is typically delayed for 2–10 days: during this time chyle may accumulate in the posterior mediastinum as a 'chyloma'—sometimes visible on the chest radiograph—which resolves when it ruptures into the pleural space. The main threat to life with chylothorax is malnutrition if the chyle is drained externally, as the daily loss of 1500–2500 ml of fluid containing substantial amounts of protein, fats, electrolytes, and lymphocytes rapidly makes a patient malnourished and immunocompromised.

Diagnosis

Diagnosis is usually easy from the distinctive white, odourless, milky appearance of aspirated pleural fluid (Fig. 18.17.12) that remains opulent on centrifuging. Chylous effusions may occasionally appear bloody, turbid, or clear yellow. The usual differential diagnoses are empyema fluid and pseudochylothorax. In empyema, the milky appearance is from suspended white blood cells and debris, which sediment on centrifugation and the supernatant remains clear. In pseudochylothorax, the lipids are cholesterol crystals or lecithin–globulin complexes rather than chylomicrons (Fig. 18.17.13).

Biochemical assessment of the pleural fluid is key to accurate diagnosis. Patients who have a true chylothorax usually have a pleural fluid triglyceride level above 110 mg/dl (1.24 mmol/litre), a ratio of pleural fluid to serum triglyceride of greater than 1.0, and a ratio of the pleural fluid to serum cholesterol of less than 1.0. The demonstration of chylomicrons on pleural fluid lipoprotein electrophoresis is diagnostic of a chylothorax. Fasting may significantly reduce the triglyceride level in the pleural fluid and lead to a false-negative result, hence fluid sampling after a high-fat meal is helpful if diagnostic doubt persists.

CT scanning of the chest should be obtained in all patients with nontraumatic chylothorax to look for thoracic and abdominal lymphadenopathy suggestive of lymphoma (Fig. 18.17.14). In young women the appearance on CT scanning of cystic lung disease may indicate lymphangioleiomyomatosis. Unlike most other pleural effusions, examination of the pleura is not usually diagnostic, and pleural biopsy or thoracoscopy is usually only indicated for fluid control.

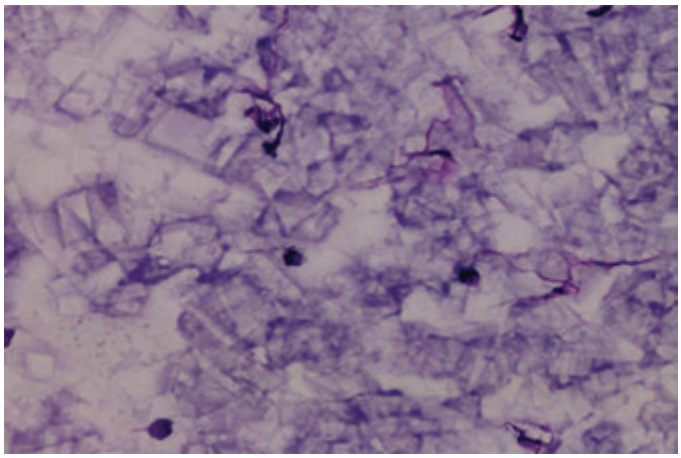

Fig. 18.17.13 Microscopy of pleural fluid from a pseudochylothorax showing multiple cholesterol crystals (Giemsa stain with birefringence).

Fig. 18.17.12 Typical milky pleural fluid from a true chylothorax.

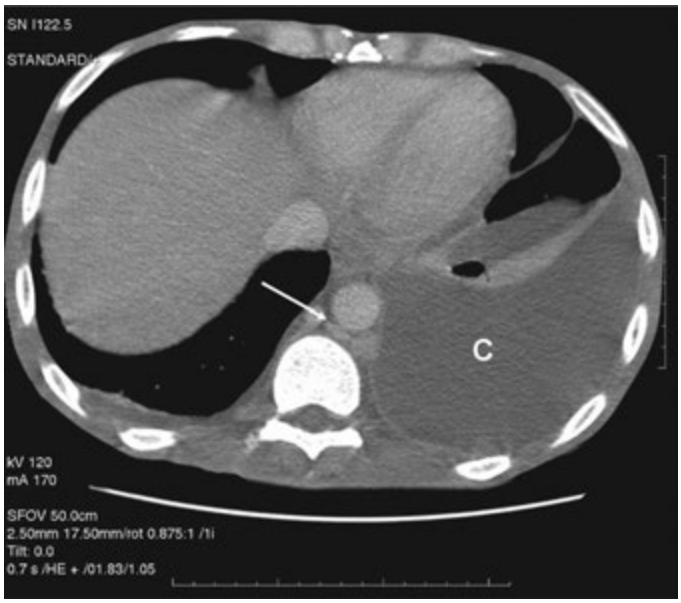

Fig. 18.17.14 A case of chylothorax (C) where the thoracic duct has been ruptured by enlarged mediastinal lymph nodes (arrowed).

Site of injury to the thoracic duct can be localized using lymphoscintigraphy with Technetium-99 diethylenetriaminepentaacetic acid human serum albumin (99mTc-DTPAHSA, 185 MBq/0.5 ml) injected into the subcutaneous tissue of the dorsum of the foot. A single photon emission computed tomography/computed tomography (SPECT/CT) performed immediately after the injection will allow localization of the chyle leak. Lymphangiography using lipiodol (iodinated poppy-seed oil) is a novel method of isolating the site of chyle leakage. Some studies have shown this method may heal the leak where the chyle leak is of small volume: the mechanism of this is unclear but an inflammatory effect of the lipiodol has been postulated.

Treatment

Treatment aims to correct the underlying disease, maintain nutrition, reduce the flow of chyle, relieve dyspnoea, and (sometimes) close the thoracic duct defect. Malnutrition and a compromised immunological status can quickly follow chest tube drainage through loss of large amounts of protein, fat, electrolytes, and lymphocytes. This means that definitive control of the effusion is required before the patient becomes too debilitated. Spontaneous closure of a thoracic duct leak may follow reduction of the flow of chyle by parenteral feeding or use of a low-fat diet rich in medium-chain triglycerides that are absorbed directly into the blood, but this diet is often difficult to tolerate as it tastes unpleasant.

Octreotide, a somatostatin analogue, may be effective in hastening the closure of a thoracic duct leak: the mechanism of its action is not clear, but may be through reduced intestinal fat absorption and increased faecal fat excretion.

If the cause is lymphoma or metastatic carcinoma, a chylothorax often responds to effective chemotherapy or mediastinal radiotherapy. Pleuroperitoneal shunts can be used if a chylothorax fails to settle, which avoids malnourishment and immunodeficiency since lymph is not removed from the body.

In traumatic chylothorax, the defect in the thoracic duct often closes spontaneously. The volume of fluid drainage (more or less than *c.*400 ml/day) seems to predict the likelihood of such resolution. Thoracoscopic talc pleurodesis is often effective when conservative therapy fails. Embolization of the thoracic duct from the abdomen is nowadays the therapy of choice if the expertise is available.

Surgical intervention involves thoracic duct ligation at VATS or thoracotomy. The site of the leak may be identified preoperatively by lymphangiography as mentioned earlier, and identification of the duct at surgery can be facilitated by preoperative drinking of cream. Laparoscopic ligation of the abdominal thoracic duct has also been successful.

Pseudochylothorax

Pseudochylothorax is less common than chylothorax. The fluid is turbid due to high levels of cholesterol or lecithin–globulin complexes (**Fig. 18.17.13**). Pathogenesis remains unknown, but most patients with pseudochylothorax have marked pleural thickening and a chronic pleural effusion, and it is hypothesized that inflammation increases filtration of cholesterol into pleural fluid and/or cholesterol is liberated from degenerative inflammatory red and white blood cells within the effusion. The thickened pleura may also inhibit the exit of cholesterol from the pleural space.

Pseudochylothorax is most frequently attributable to tuberculous (54%) or rheumatoid (10%) pleurisy. The clinical picture is of a stable chronic effusion, although in some cases the effusion gradually enlarges with time.

Haemothorax

Haemothorax is blood in the pleural space, defined as a pleural fluid haematocrit of more than 50% that of blood. A heavily bloodstained pleural effusion often has a haematocrit of under 5%, hence a haematocrit should be performed whenever haemothorax is suspected.

Traumatic haemothorax

Clinical features and diagnosis

Traumatic haemothorax should be suspected following any chest trauma, whether penetrating or not. It often develops in the first few days after trauma, is not detectable on 25% of presentation chest radiographs (occult haemothorax, which can be demonstrated by CT), and in patients with multiple or displaced rib fractures late haemothorax may occur up to a week after presentation (delayed haemothorax). Thoracic CT identifies all cases, and bedside ultrasonography has similar diagnostic sensitivity. The condition is a potential surgical emergency and should be managed by a thoracic/trauma surgeon.

Management

Traumatic haemothorax is treated with an immediate large-bore chest tube (≥28 F) for blood evacuation, which also allows quantification of continued bleeding. Blood lost from haemothorax can be autotransfused if necessary, and early effective evacuation of haemothorax may decrease the frequency of empyema and late thoracic contraction due to pleural scarring ('fibrothorax').

About 20% of patients with haemothorax require surgical intervention for suspected cardiac tamponade, vascular injury, pleural contamination, debridement of devitalized tissue, chest wounds, major bronchial air leaks, or continued pleural haemorrhage. Posttraumatic haemothorax was managed exclusively by thoracotomy, but advances in VATS have made this minimally invasive technique the procedure of choice in many centres, with thoracotomy reserved for massive haemorrhage or patients with haemodynamic instability. There are no precise criteria for the amount of pleural bleeding that should mandate surgery, and each case must be managed on its merits, but surgical intervention is likely to be required if bleeding is more than 200 ml/h for 4 hours and shows no signs of slowing, or the initial drainage exceeds 1500 ml following tube thoracostomy.

Complications

The four main pleural complications of traumatic haemothorax are the retention of clotted blood in the pleural space, pleural infection, pleural effusion, and fibrothorax. Most patients with small to moderate amounts of clotted blood remaining in their pleural space have no residual pleural abnormalities even if no intervention is undertaken, but evacuation is recommended if the volume of retained haemothorax is greater than 300 ml. In a randomized trial, VATS was more effective than thoracostomy tube drainage, reducing the duration of hospital stay and chest tube drainage. If the volume of clotted blood is more than 900 ml or there is an associated diaphragmatic injury, thoracotomy is the best choice.

Intrapleural administration of fibrinolytic agents to improve clot drainage may be safe in haemothorax, but there have been no comparative studies to confirm these agents are efficacious and safe in this setting.

The administration of prophylactic antibiotics (cefazolin) before tube thoracostomy in traumatic haemothoraces reduces the incidence of pleural infection in randomized trials. Empyema occurs in 1–4% of cases and should be suspected in the febrile patient. Its treatment is similar to that of other pleural infections.

Iatrogenic haemothorax

The incidence of iatrogenic haemothorax is highest after cardiac or thoracic surgery, or perforation of a central vein or artery by a percutaneous catheter. An occasional haemothorax results from pleural procedures (e.g. thoracentesis, pleural biopsy, chest tube insertion; see Fig. 18.17.15), and percutaneous lung aspiration or biopsy. Rarely, it is associated with endoscopic oesophageal variceal therapy, liver biopsy, cardiopulmonary resuscitation, and translumbar aortography. Management is similar to that of traumatic haemothorax.

Nontraumatic haemothorax

Nontraumatic haemothoraces are uncommon, but most frequently follow malignant pleural disease or anticoagulation (particularly for pulmonary embolism). Rarer causes include abnormal blood vessels (subpleural arteriovenous malformations, Osler–Weber–Rendu disease, aneurysm of the aorta or pulmonary artery, aortic dissection, patent ductus arteriosus, coarctation of the aorta), bleeding disorders (haemophilia, severe thrombocytopenia), the use of intrapleural fibrinolytics, spontaneous pneumothorax, bronchopulmonary sequestration, thoracic endometriosis, chickenpox pneumonia, costal exostoses, and intrathoracic extramedullary haematopoiesis. Rarely, neurofibromatosis can cause haemothorax from aneurysmal changes in large arteries or from dysplastic changes in small vessels. Also, other neoplastic processes such as metastatic angiosarcoma to the lung can result in haemothorax.

Blood can accumulate in the pleural space from abdominal pathology (e.g. rupture of a splenic artery aneurysm through the diaphragm, pancreatic pseudocysts, and rupture of hepatocellular carcinoma).

The cause of some spontaneous haemothoraces remains unknown despite thoracotomy, although rupture of pleural adhesions has been reported in some cases.

Benign asbestos-related pleural diseases

Asbestos is a family of hydrated silicate fibres subdivided into curly (serpentine) and needle-like (amphibole) types. Chrysotile (white asbestos) is the main serpentine form; amphiboles include crocidolite (blue asbestos), amosite (brown asbestos), anthophyllite, tremolite, and actinolite. Most benign asbestos-related pleural diseases are due to occupational exposure, although environmental exposure causes disease in some high-prevalence asbestos areas such as central and south-east Turkey, north-west Greece, and Finland. The benign asbestos pleural diseases comprise of pleural plaques, benign asbestos pleurisy, diffuse pleural thickening, and rounded atelectasis.

Pathogenesis

The pathogenesis of benign asbestos-induced pleural disease is poorly understood. The route by which asbestos fibres transfer to the pleura after inhalation is unclear. Fibre burden studies have shown higher fibre numbers in lymph nodes and pleural plaques than in lung parenchyma, and it is likely that at least some fibres are cleared from the lung parenchyma to the lymph nodes and pleura through lymphatic spread. Amphiboles fibres in particular are associated with 'black spots' of anthracotic deposits near lymphatic vessels.

Fibre toxicity may be related to a number of factors, including fibre length and diameter, chemical properties such as iron content and surface charge, and durability. Long, thin fibres (e.g. crocidolite) are especially carcinogenic and clear more slowly from the lung, although the exact relationship of different fibre types to benign and malignant pleural diseases is still debated. The iron content of asbestos bodies (Fig. 18.17.16) may influence reactive oxygen species generation, causing pleuropulmonary toxicity. Carbon nanotubes, which have even higher length:width ratio than crocidolite asbestos, have recently been shown to cause significant mesothelial abnormalities in preclinical models.

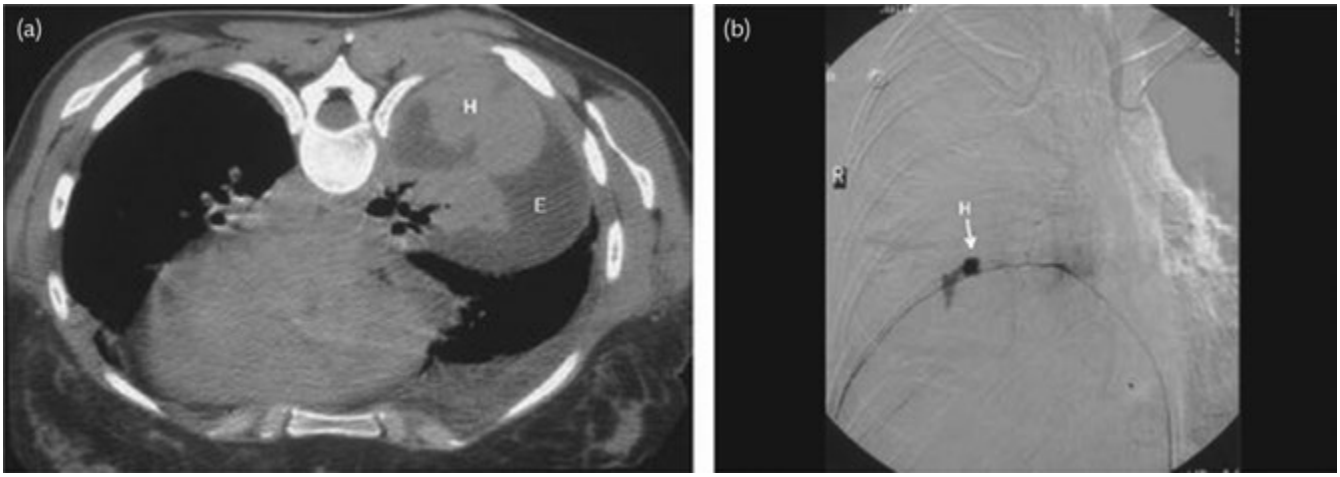

Fig. 18.17.15 Haemothorax due to laceration of an intercostal artery during chest drain insertion. The CT (a) shows acute haemorrhage (H) into a pleural effusion that was already present (E). The angiogram (b) shows acute haemorrhage (H) from intercostal artery, which was halted by intercostal embolization.

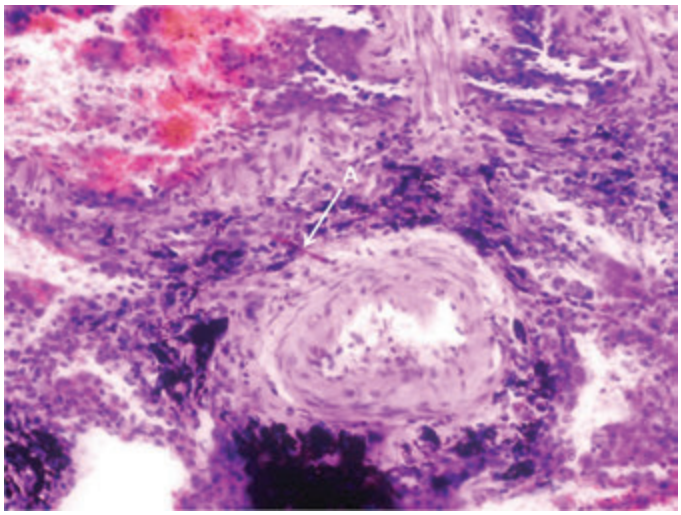

Fig. 18.17.16 An asbestos body where an asbestos fibre (A, arrowed) has become encased in iron-rich material.

A primary mechanism of asbestos fibre-induced injury is pleural inflammation. Fibres induce intrapleural IL-8 production from pleural mesothelial cells which causes a neutrophil influx that precedes the development of pleural plaques. A prolonged macrophage influx follows, probably due to monocyte chemoattractant protein-1 (MCP-1), TNFα, or IL-1β production. The mechanisms that cause pleural fibrosis and plaque formation following this inflammation are not clearly understood.

Clinical manifestations

Benign asbestos-related pleural plaques

Circumscribed pleural plaques are the most common manifestation of asbestos exposure and comprise discrete areas of white or yellow thickening on the parietal pleura with a raised 'beaded' edge visible at thoracoscopy (Fig. 18.17.17). They are frequently bilateral and occur particularly on the posterolateral chest wall between the fifth and eighth ribs overlying the internal rib surfaces. They also occur on the dome of the diaphragm and over the mediastinal pleura. Histologically they are acellular, with a 'basket-weave' pattern of hyalinized collagen strands, covered by a single layer of normal mesothelial cells on the pleural surface (Fig. 18.17.17).

Pleural plaques typically develop 20–30 years after asbestos exposure. They affect up to 50% of exposed workers, with incidence relating to exposure dose, although the extent of plaques within an individual case is not dose related. They are often calcified and can be easily identified on chest radiographs and CT. In fact, a calcified plaque on the diaphragm is highly suggestive of prior asbestos exposure, provided there is no previous history of surgery or trauma. Patients with pleural plaques are typically asymptomatic. Pleural plaques do not have any potential for malignant transformation and clinical management consists of patient reassurance. However, their presence indicates significant asbestos exposure and its inherent risk for mesothelioma.

Benign asbestos pleural effusion

This is a diagnosis of exclusion when an exudative and often blood-stained, effusion occurs in a patient with asbestos exposure (which can be within the preceding 10 years) and no other cause is found after full investigation, including pleural histology, and at least a 2-year follow-up (to exclude malignancy). The effusion is most commonly unilateral and, in few instances, associated with fever and pleuritic chest pain. The risk of benign asbestos effusion is dose dependant with respect to asbestos exposure but can occasionally occur after minimal exposure. It usually persists for several months and resolves completely. However, it could precede the development of diffuse pleural thickening, leaving behind blunting of the costophrenic angle, or recur on the ipsilateral, or contralateral side.

Diffuse, benign asbestos-induced pleural thickening

Diffuse pleural thickening consists of extensive fibrosis of the visceral pleura, with areas of adhesion with the parietal pleura and

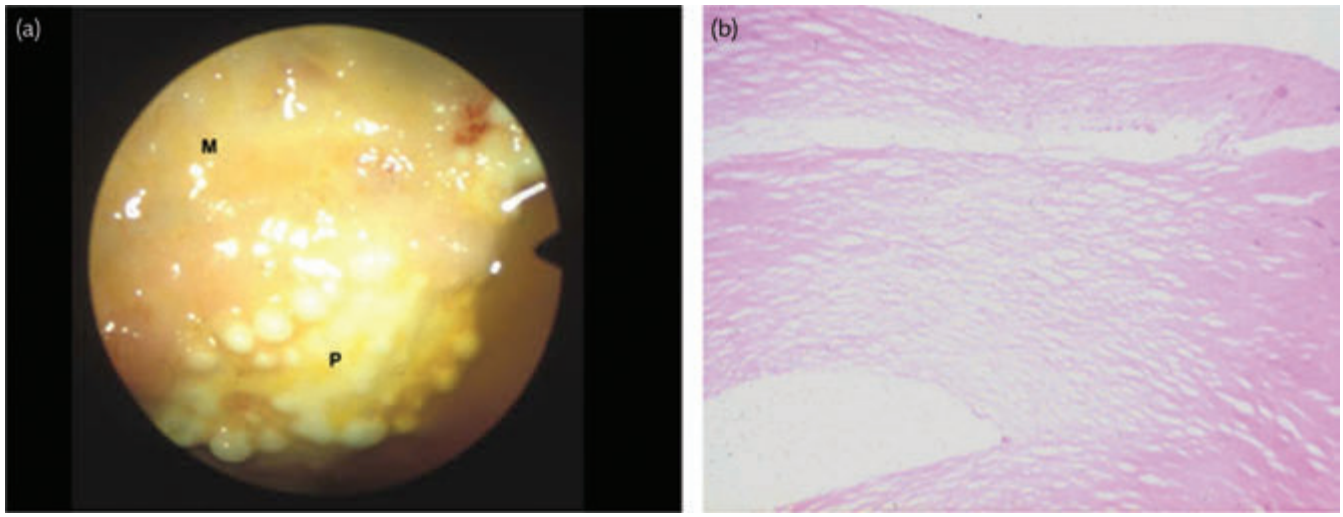

Fig. 18.17.17 (a) A pleural plaque (marked P) seen at local anaesthetic thoracoscopy. The raised 'beaded' edge of the plaque is clearly seen. Malignant pleural mesothelioma is also present in this case, with tumour tissue seen infiltrating superiorly to the plaque (marked m). Fig. (b) shows the typical histological appearance of benign pleural plaque.

consequent obliteration of the pleural space. It is arbitrarily defined as a more than 3 mm thick pleura extending more than 8 cm craniocaudally and 5 cm laterally on the thoracic CT. Unlike pleural plaques, the margins of the fibrosis are usually tapered. It frequently involves the costophrenic angles, apices, and interlobar fissures. Diffuse fibrosis often follows benign asbestos-related pleural effusion.

Diffuse pleural thickening may be asymptomatic or cause breathlessness. Chest pain, when present, should raise concerns and a thorough investigation should be performed for malignant pleural mesothelioma (see Chapter 18.19.3). Pleural thickening is usually slowly progressive and may cause significant lung function impairment, especially if the costophrenic angle is involved. Treatment is largely supportive. Hypercapnoeic ventilatory failure can (rarely) develop. Surgical decortication is generally ineffective in providing clinical or functional improvement.

Rounded atelectasis

Rounded atelectasis (also known as rolled atelectasis, folded lung, pleuroma, Blesovsky syndrome, or shrinking pleuritis with atelectasis) develops as contracting visceral pleural fibrosis rolls and ensnares the underlying lung. This results in the distinctive radiological appearance of a rounded or oval pleural-based mass 2.5–5 cm in diameter, with bands of contracted and atelectatic lung radiating out in a whirling fashion (known as 'comet tails') on chest radiograph or thoracic CT (Fig. 18.17.18).

Although asbestos exposure is the most likely cause, other pleural processes may manifest as rounded atelectasis (e.g. trauma, coronary artery surgery, lymphangioleiomyomatosis, tuberculosis, silicosis, histoplasmosis, use of pergolide, Dressler's syndrome). Rounded atelectasis, which can be multiple and bilateral, is typically asymptomatic and stable or only slowly progressive. It can be confounded, however, with lung cancer or mesothelioma. Specific therapy is rarely required. Serious complications such as obstructive pneumonia and local pulmonary artery thrombosis are rare. Surgical decortication often results in reduced lung volumes and is not generally recommended.

Pneumothorax

Pneumothorax is air in the pleural cavity, between the lung and the chest wall. Pneumothoraces can be subclassified into *spontaneous* where there was no preceding insult or an obvious precipitant to the lung, or *traumatic* following direct or indirect injury to the chest. Iatrogenic pneumothoraces occur following injury to the lung during diagnostic or therapeutic procedures.

Pathophysiology

During normal tidal breathing the pleural pressure is continuously negative with respect to alveolar/atmospheric pressure. When a communication develops between the pleural space and the lung (or outside atmosphere via a chest wall injury), then air flows into the pleural space until this negative pressure equilibrates or the airways in the collapsing lung occlude to prevent further alveolar gas escape via the airway. This 'air trapping' occurs earlier in patients with chronic obstructive pulmonary disease (COPD). The removal of negative pleural pressure also causes the chest wall to 'spring out' due to loss of the recoil pressure across the chest wall (by about 8% of vital capacity), hence the overall volume of the hemithorax increases.

Primary spontaneous pneumothorax

Incidence

Incidence is higher in men with a reported rate of 18–28/100 000 per annum and in women 1.2–6/100 000 per annum. Emergency hospital admissions from primary spontaneous pneumothorax (PSP) can be as high as 11.1/100 000.

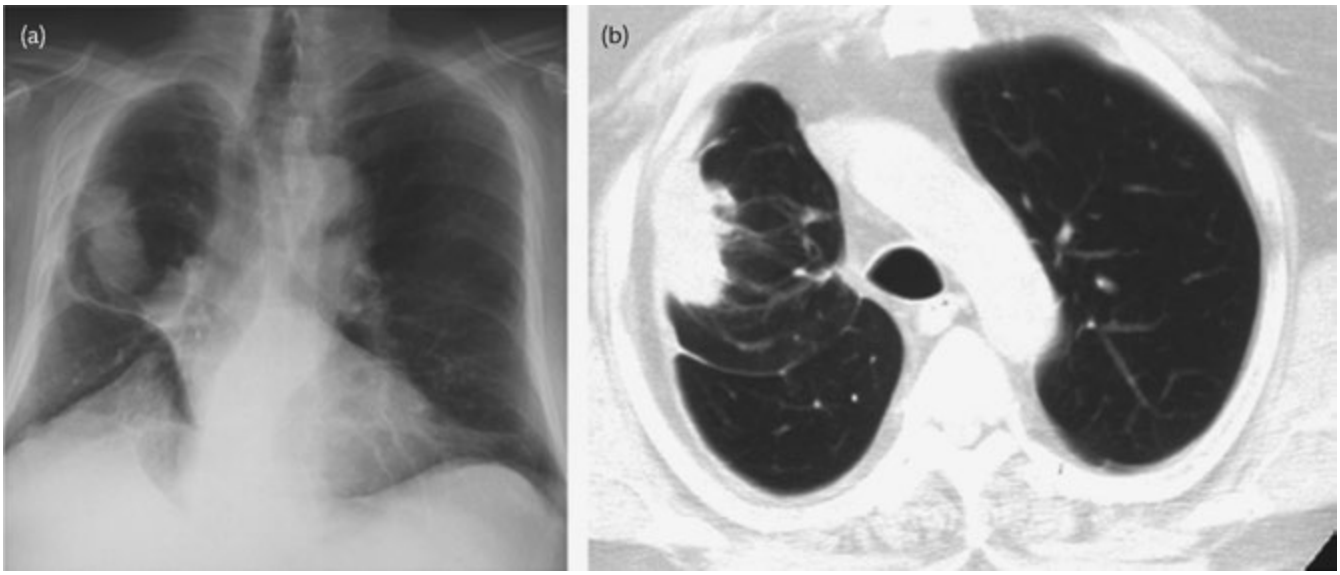

Fig. 18.17.18 (a) Chest radiograph and (b) CT showing 'rounded atelectasis' where visceral pleural fibrosis has contracted to enfold the underlying lung. Characteristic 'comet tails' are seen in the lung parenchyma.

Aetiology

Although PSP is said to be in a healthy lung with no apparent respiratory disease, macroscopic appearances of the lung suggest otherwise. Apical subpleural blebs or emphysema like changes are present in 75–100% of cases of PSP, on thoracoscopic visualization of the pleura and on high resolution CT scanning of the chest. These areas represent weakness of the pleura prone to rupture and air leak from the lung to the pleural space. It is unclear whether it is a rupture of a bleb or an air leak from the tissue surrounding the bleb, due to anatomical abnormality that causes the air leak, as blebs are seen inflated during thoracoscopy. The development of blebs and emphysema like changes are due to a variety of causes including distal airway inflammation, hereditary disposition, and connective tissue abnormalities.

Smoking is a major risk factor for PSP with a lifetime risk of 12% in smokers compared to 0.1% in nonsmokers. Eighty percent of PSPs are in smokers and a dose-response relationship exists in both men and women. Similarly, cannabis smoking is associated with emphysema like changes that predispose users to an increased risk of PSP.

Tall stature and low body mass index are also associated with higher risk of pneumothorax. A tall thin body habitus leads to an increased pressure gradient between the apex and the base of the lung, pleural pressure falls by 0.20 cmH_2O/cm of vertical chest height, resulting in an increased alveolar distending pressure at the apex.

Primary spontaneous pneumothorax has a genetic component in some cases; Marfan syndrome, tuberous sclerosis, α-1 antitrypsin deficiency, homocystinuria, and Birt-Hogg-Dubé syndrome and other mutations of the Folliculin gene (*FLCN*) all showing an increased risk of PSP. Birt-Hogg-Dubé syndrome is a rare autosomal dominant condition that predisposes to cystic lung disease and hence pneumothorax. Up to 5% of patients with PSP may have underlying Birt-Hogg-Dubé syndrome. The frequency of PSP is highest in patients with Marfan syndrome, with reported rates between 4 and 11%, higher in those with chest deformity.

Clinical features

The peak age of presentation for primary pneumothorax is in the early 20s; the incidence is much lower beyond the age of 40. Predominant symptoms are chest pain and dyspnoea, with up to 64% of patients reporting both symptoms at presentation. Chest pain tends to be of acute onset and localized to the side of the pneumothorax. Occasionally patients may not have any symptoms at all.

Physical examination is unremarkable in most the cases. A slight to moderate tachycardia, reduced expansion of the affected side, and a hyperresonant percussion note may be found in large pneumothoraces. Rarely a 'crunching' noise known as the Hamman's sign may be heard, this is a noise caused by collections of pleural air being pushed against the chest wall due to the cardiac impulse.

Tension Pneumothorax

Tension pneumothorax is a rare but important variant of pneumothorax where a 'flap valve' mechanism at the visceral pleural surface results in the development of increasing positive pressure in the pleural space. It is an important diagnosis not to be missed in mechanically ventilated patients with rapidly increasing respiratory distress. Tension pneumothorax causes progressive mediastinal shift away from the side of the pneumothorax, and ultimately impedes venous return to the heart—causing hypotension, shock, and collapse.

The diagnosis of tension pneumothorax is based on the clinical features of a large pneumothorax with mediastinal shift away from the affected side, cardiovascular compromise, and severe progressive dyspnoea. The pulse rate can exceed 140 beats/min, and hypotension, cyanosis, or pulseless electrical activity may occur. On examination the side of the chest affected is enlarged, moves less during the respiratory cycle, and the trachea and apex beat may be shifted towards the contralateral side. Tactile fremitus is absent, the percussion note is hyperresonant, and the breath sounds are absent or reduced on the affected side. The liver may be shifted inferiorly with a right-sided pneumothorax.

Chest radiographic demonstration of modest deviation of the mediastinum away from the site of pneumothorax and depression of diaphragm ipsilateral to the pneumothorax are not, in the absence of the characteristic clinical features, sufficient to diagnose a tension pneumothorax. These changes are common features of an uncomplicated pneumothorax (up to 20%) and are due to expansion of the thoracic cavity following the loss of elastic lung recoil pressure.

The treatment of tension pneumothorax requires urgent thoracic decompression, followed by chest tube placement (see Chapter 30.2).

Diagnosis of an uncomplicated pneumothorax

Chest radiography has been the choice of imaging for the diagnosis of a pneumothorax (**Fig. 18.17.19**); presence of a 'lung edge'—a pleural line—and absence of lung markings beyond the pleural line supports the diagnosis. Further radiology with Computed tomography (CT) is rarely needed. Bedside point-of-care ultrasound is a quick and portable mode of imaging that can also be used to diagnose a pneumothorax although the signs seen are subtle and only those who are confident should be using this modality for the diagnosis. When the lung sliding and the comet tail sign are both present the diagnosis of a pneumothorax can be ruled out. Presence of only one of the signs is not strong enough to exclude the diagnosis on its own. When in doubt, a chest radiograph should be performed.

About 15% of radiographs showing a primary pneumothorax also show a small pleural effusion causing a fluid level. This pleural fluid is usually eosinophilic on cytology. Rarely, spontaneous pneumothorax causes brisk pleural bleeding from a torn pleural adhesion, with urgent surgery often required to stop this.

Estimating the size of a pneumothorax is a contentious issue. The actual size of the pneumothorax is less important than the associated symptoms, as managemessnt decisions rely largely on the severity of the breathlessness. Various methods have been postulated on how to accurately estimate the size of a pneumothorax, one of the most widely used methods assume that the volumes of the lung and the hemithorax are roughly proportional to the cube of their diameters. Estimating the size of a pneumothorax therefore requires the measurement of the horizontal diameter of the lung and chest wall and the use of the formula: % pneumothorax volume = 100% × [1 – (lung diameter^3/hemithorax diameter^3)].

Management

Treatment of pneumothorax aims to drain the pleural cavity of air to relieve the symptoms and prevent recurrence. Detailed guidelines are in place from the British Thoracic Society and American College

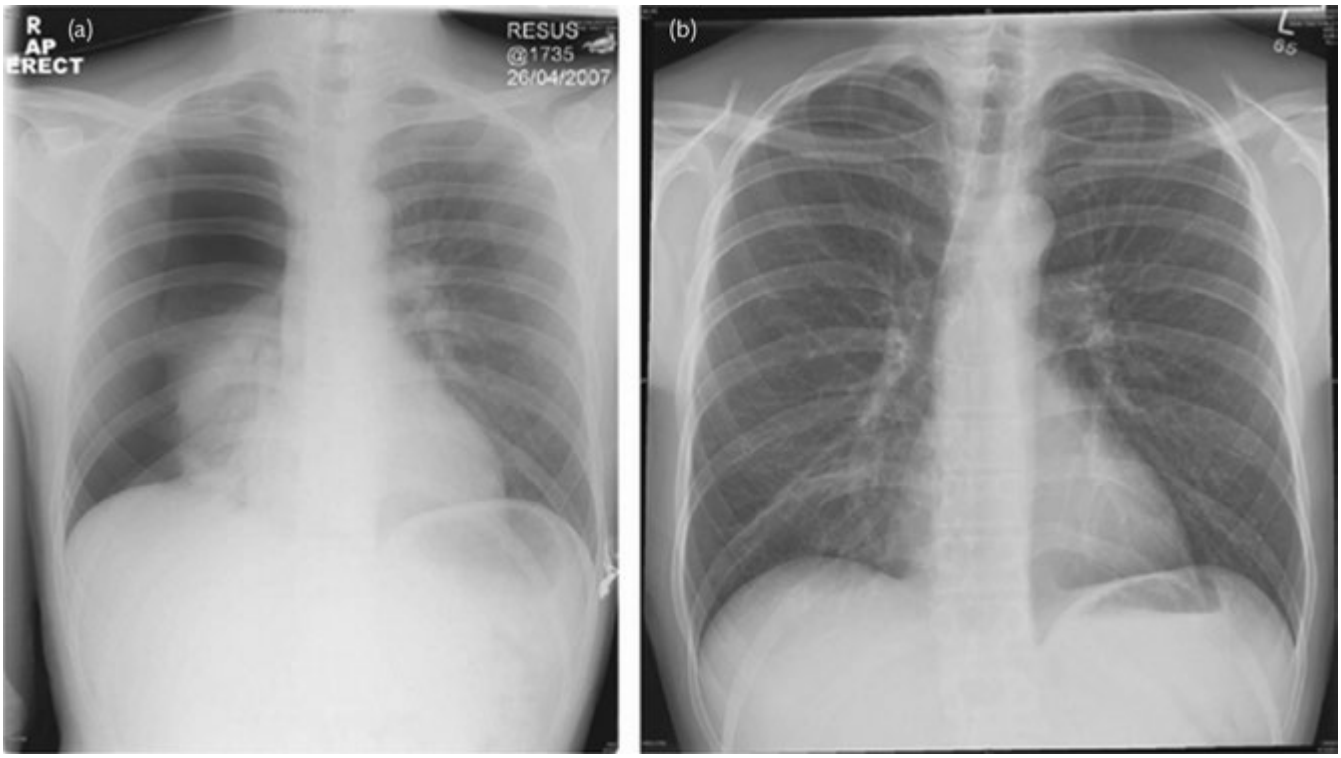

Fig. 18.17.19 Chest radiographs showing a primary spontaneous pneumothorax before (a) and after (b) successful pleural aspiration.

of Chest Physicians that may aid clinicians in the management of pneumothorax.

A small pneumothorax with few symptoms can be conservatively managed provided the air leak has ceased. Air will be reabsorbed at 2% per day. This process can be expedited by supplemental oxygen. High flow oxygen will increase the capillary partial pressure of oxygen and decrease the partial pressure of nitrogen, resulting in a much higher net gradient for absorption of gas, compared to breathing normal room air. Alternatively, air can be aspirated percutaneously using a small catheter (cannula) inserted in the second intercostal space in the mid-clavicular line or fourth or fifth intercostal space anterior to mid-axillary line. A purpose built aspiration kit, or a fluid giving set connected to a stopcock, is attached to the catheter and air is manually aspirated with a 60 ml syringe. If more than 4 litres of air is aspirated, an ongoing air leak is likely and an intercostal chest drain should be inserted. Similarly, in cases where aspiration has failed or is inappropriate, a chest tube is indicated.

When a pneumothorax is loculated, imaging with CT or ultrasound can help in localizing the safest site for aspiration or insertion of chest drain.

Ambulatory management of pneumothorax with a Heimlich valve device (one way valve connected to the end of a chest drain) has been the subject of several publications in recent years. This is an attractive management strategy in that it allows the patient more freedom to mobilize and potentially be discharged from hospital, letting the lung re-expand in its own time. However, there are no high quality studies to support this method over traditional management strategies, although a randomized controlled study examining this question is due to start soon in the United Kingdom.

The role of thoracic suction in persistent air leaks is still widely debated. There is a paucity of evidence to suggest the use of thoracic suction accelerates lung re-inflation, hence its routine use cannot be supported, although it may have a role in selected cases.

VATS surgery with pleurectomy or talc poudrage appears a highly effective treatment for those with persistent air leaks, but optimum timing of surgery is still unknown.

Prognosis and prevention of recurrence

The risk of recurrence of pneumothorax where some form of pleurodesis has not been attempted is approximately 30%, range of 16–52%, regardless of conservative management, aspiration, or chest tube insertion. Following one recurrence the risk of further recurrence is up to 50% per year therefore surgical management is indicated after a second event. Tall thin stature and continued smoking are other factors that influence pneumothorax. There is no relationship between the number of apical blebs on CT or the macroscopic appearance of lung at surgery, and the risk of recurrence. Surgery is indicated for professionals in high-risk occupations such as divers and pilots, following a first pneumothorax.

The surgical management of pneumothorax aims to reduce recurrence by resection of visible blebs or bullae and performing pleurodesis either by pleurectomy, pleural abrasion, and/or instillation of a sclerosing agent. The surgical approach can be either through VATS or thoracotomy. Recurrence rates following surgery are less than 5% in most series. Instillation of pleurodesing agents via chest tube is less likely to be successful and is not advocated in patients who are fit enough to proceed with surgery.

Iatrogenic pneumothorax

Iatrogenic pneumothorax is the most common cause of a pneumothorax in the developed world, with an incidence increasing in parallel to the increase in invasive procedures. Interventions such as

thoracentesis, percutaneous and transbronchial biopsies, central venous catheter insertion, and assisted mechanical ventilation are all high-risk procedures for pneumothorax. The incidence of iatrogenic pneumothorax with thoracentesis has been reported as high as 6.0%, with up to a third of these requiring chest tube drainage for management. Transthoracic needle biopsy of parenchymal lesions has a risk of up to 24%, with the rates being highest in patients with COPD and lesions deep within the lung.

Risk of barotrauma in mechanically ventilated patients on ICU can range from 2.9–4%. Rapid clinical deterioration in a mechanically ventilated patient should alert the clinicians to the possibility of a tension pneumothorax. Barotrauma and associated risk of pneumothorax is partly dependant on the underlying lung condition, patients with acute respiratory distress syndrome, COPD, and *Pneumocystis jirovecii* pneumonia are at highest risk.

Management

The diagnosis is established by appropriate clinical suspicion in a high-risk patient, combined with a chest radiograph. Treatment differs from spontaneous pneumothorax in that recurrence prevention is not needed as the underlying lung is normal, hence air evacuation is the sole aim of treatment. If the patient has few/no symptoms, is not artificially ventilated, and the pneumothorax is small, simple observation with the administration of supplemental oxygen is appropriate. Simple aspiration or chest tube drainage is appropriate if the patient has significant symptoms or the pneumothorax is large.

The patient with a pneumothorax secondary to assisted mechanical ventilation should always receive chest tube drainage to avoid the development of a tension pneumothorax due to the positive inspiratory pressures generated by the ventilator driving air into the pleural space. Sometimes this mechanism produces an air leak so large that a high percentage of the total inspired volume exits via the chest tube. This usually still provides effective ventilation, as the drained gases have a similar CO_2 content to exhaled air.

Secondary spontaneous pneumothorax

Secondary spontaneous pneumothorax is associated with underlying lung disease. Epidemiological data has shown a pneumothorax incidence rate for the over 55 age group in the order of 32.4/100 000/year for men and 10.9/100 000/year for women in the United Kingdom, with peak incidence of secondary spontaneous pneumothorax within the age range 60–65 years. With poor pulmonary reserve and other comorbidities in this group of patients, a secondary pneumothorax tends to be symptomatic, require immediate treatment, and carries a high mortality rate.

Aetiology

COPD is by far the commonest cause of secondary pneumothorax, and risk of pneumothorax increases with increasing severity of the disease. Other diseases associated with secondary pneumothoraces are pulmonary fibrosis, tuberculosis, *Pneumocystis jirovecii* pneumonia, cystic fibrosis, and other rare cystic lung diseases such as lymphangioleiomyomatosis and Langerhans cell histiocytosis.

Clinical features

Symptoms are more pronounced than with primary spontaneous pneumothorax. Almost all patients will have dyspnoea. Any patient with COPD and with worsening dyspnoea, particularly in association with chest pain should be suspected of pneumothorax. Examination is unremarkable except for the finding of low oxygen saturations and low partial pressures of oxygen on arterial blood gas. A chest radiograph would help establishing the diagnosis but one must be cautious in distinguishing a large air containing bulla from a pneumothorax. The visceral pleural line in a pneumothorax is convex towards the lateral chest wall whereas the apparent pleural line in a bulla is concave towards the lateral chest wall. Where there is doubt between a pneumothorax and a large bulla a chest CT should be performed to help distinguish prior to any pleural intervention (**Fig. 18.17.20**). Attempted insertion of a chest tube into a bulla, with formation of a bronchopleural fistula, could have disastrous consequences for a patient who may already be compromised from their underlying disease.

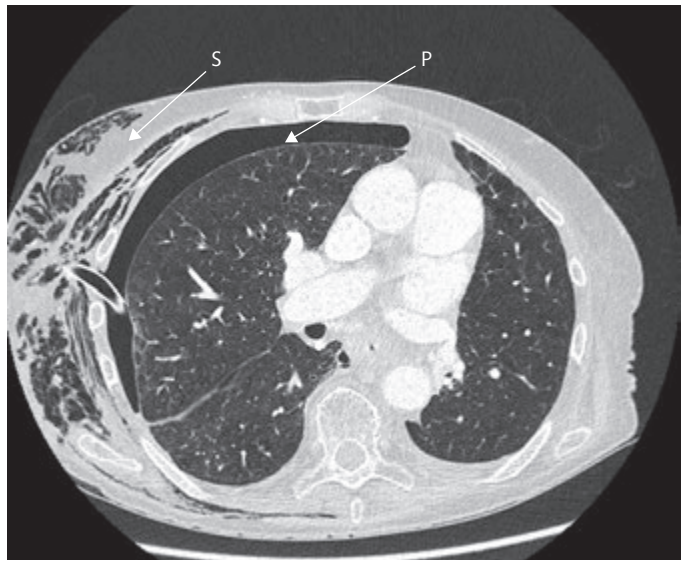

Fig. 18.17.20 CT showing a secondary pneumothorax (P) with subcutaneous air (S) (surgical emphysema). A chest tube is seen entering the chest cavity from in between the ribs.

Management

Secondary pneumothoraces are less likely than primary pneumothoraces to be tolerated or resolve spontaneously. Prompt treatment and effective recurrence prevention are therefore higher priorities in secondary than in primary pneumothorax as patients are more symptomatic, have an appreciable mortality before treatment, and a higher recurrence rate (45% over 3–5 years). Aspiration is less likely to be successful in this cohort of patients. Chest tube insertion often leads to a rapid improvement in symptoms. Those with ongoing air leak for more than 48 hours should be discussed with thoracic surgeons.

The prognosis after tube drainage is worse than in primary pneumothorax. The median duration of drainage for a secondary pneumothorax due to COPD is 5 days, compared with 1 day for primary pneumothorax, and about 20% of patients with secondary pneumothorax have a prolonged air leak lasting for more than 7 days. Bronchoscopically placed endobronchial valves to manage prolonged air leaks, have shown promising results in small case series. Similarly, anecdotal evidence support the use Heimlich valves

in an ambulatory setting to manage secondary pneumothoraces but large randomized controlled trials (RCTs) to support their use is yet to come.

Prevention

Surgical pleurodesis should be the treatment of choice where possible. Recurrence rate following surgery is generally low (1–3%). For patients not fit for surgery chemical pleurodesis via chest tube using talc or doxycycline is appropriate but has a higher recurrence rate around 20%.

Traumatic pneumothorax

The incidence of a pneumothorax after blunt trauma depends on the severity of the injury, but is high and exceeds 35% in some series. With penetrating chest trauma the mechanism of pneumothorax is simply air entry through the wound or via the visceral pleura from injury to the lung. With nonpenetrating trauma a pneumothorax may develop if the visceral pleura is lacerated by a rib fracture or dislocation, but in most cases there are no associated rib fractures and it is thought that sudden chest compression increases alveolar pressures and causes alveolar rupture. Air then enters the interstitial space and dissects towards either the visceral pleura or the mediastinum, with a pneumothorax developing when the visceral or mediastinal pleura ruptures and allows air to enter the pleural space.

Diagnosis and management

The diagnosis is made by chest radiograph or CT, with 40% of pneumothoraces demonstrated on the initial chest radiograph being clinically unexpected. Thoracic ultrasonography, performed at the bedside, is also a sensitive diagnostic technique, but is inaccurate in subjects with COPD.

Most traumatic pneumothoraces are treated with chest tube drainage, although an occult or small pneumothorax can be managed conservatively if assisted ventilation is not needed. After chest tube drainage, the lung usually expands within 24 h.

Traumatic pneumothorax is occasionally the presenting feature of rupture of the trachea or a major bronchus (usually after anterior or lateral fracture of some of the first three ribs). Most of these patients also have haemoptysis. Bronchoscopy should be performed when this diagnosis is suspected, with rapid surgical repair of any defect identified.

Traumatic rupture of the oesophagus is another uncommon but important differential diagnosis presenting as pneumothorax (Boerhaave syndrome). Hydropneumothorax is usual in this situation. The measurement of pleural fluid amylase (due to the entry of amylase rich saliva into the pleural space) reliably identifies this problem.

Catamenial pneumothorax

Catamenial pneumothorax is a rare condition, defined as spontaneous, recurrent pneumothoraces occurring in women of child bearing age, in synchrony with menses. They are often right-sided, but left-sided and bilateral (not necessarily simultaneous) cases can occur.

The aetiology of catamenial pneumothorax is obscure, but there are several hypotheses. Migration and deposition of endometrial tissue which undergoes cyclical necrosis and sloughing, leading to diaphragmatic and visceral pleural defects, is the most popular. Transvaginal air entry which travels into the thorax via diaphragmatic pores is another theory. Diaphragmatic pores, nodules, or spots on the diaphragm and pleurae are characteristic intraoperative findings of catamenial pneumothorax.

Medical treatment with hormonal therapy (GnRH analogue) for endometriosis is effective in approximately half the patients. VATS or open thoracic surgery allows inspection of the diaphragm and pleura, repair of diaphragmatic defects, and mechanical pleurodesis. This has a higher failure rate than when employed for primary spontaneous pneumothorax, and postoperative use of hormonal control should be considered.

Other issues

Air travel after pneumothorax

Air travel per se does not increase the risk of a pneumothorax, but the consequences of a pneumothorax during air travel maybe serious. Air travel should be delayed until after definitive treatment of pneumothorax and complete lung expansion has been confirmed radiographically. Consensus on optimum time for travel after a pneumothorax varies, 2 weeks from complete radiographic resolution is generally the accepted rule, although there is no robust evidence to support this.

Re-expansion pulmonary oedema

Unilateral pulmonary oedema (re-expansion pulmonary oedema) occurs when the lung is rapidly reinflated after a period of collapse (usually at least several days) due to a pneumothorax or pleural effusion (Fig 18.17.21). The phenomenon is uncommon and only very rarely fatal, and its clinical frequency is far lower than the frequency with which it is discussed. There were three cases in the Veterans Administration cooperative study of more than 500 spontaneous pneumothoraces.

Aetiology

The alveolar oedema fluid has a high protein content, hence it is due to increased capillary leakiness rather than increased hydrostatic pressure. Possible mechanisms include damage caused by mechanical stresses applied to the lung during re-expansion, or ischaemia/reperfusion injury due to oxygen free radicals. Oxygen-scavenging compounds such as dimethylthiourea, catalase, or superoxide dismutase partially inhibit neutrophilic infiltration of re-expansion pulmonary oedema, but do not substantially decrease the amount of oedema itself. In experimental animals, re-expansion oedema only occurs if the lung has been collapsed for several days and is re-expanded rapidly: this fits the clinical picture where the pneumothorax or effusion has usually been present for more than 3 days.

Clinical features

Re-expansion and oedema causes coughing and chest tightness during or immediately after lung re-expansion. Symptoms may progress for 12–24 h, with chest radiographs showing ipsilateral pulmonary oedema that may rarely progress to involved contralateral lung. If the patient survives the first 48 h, recovery is usually complete. Treatment is supportive, with administration of supplemental oxygen, diuretics, intubation, and mechanical ventilation if needed.

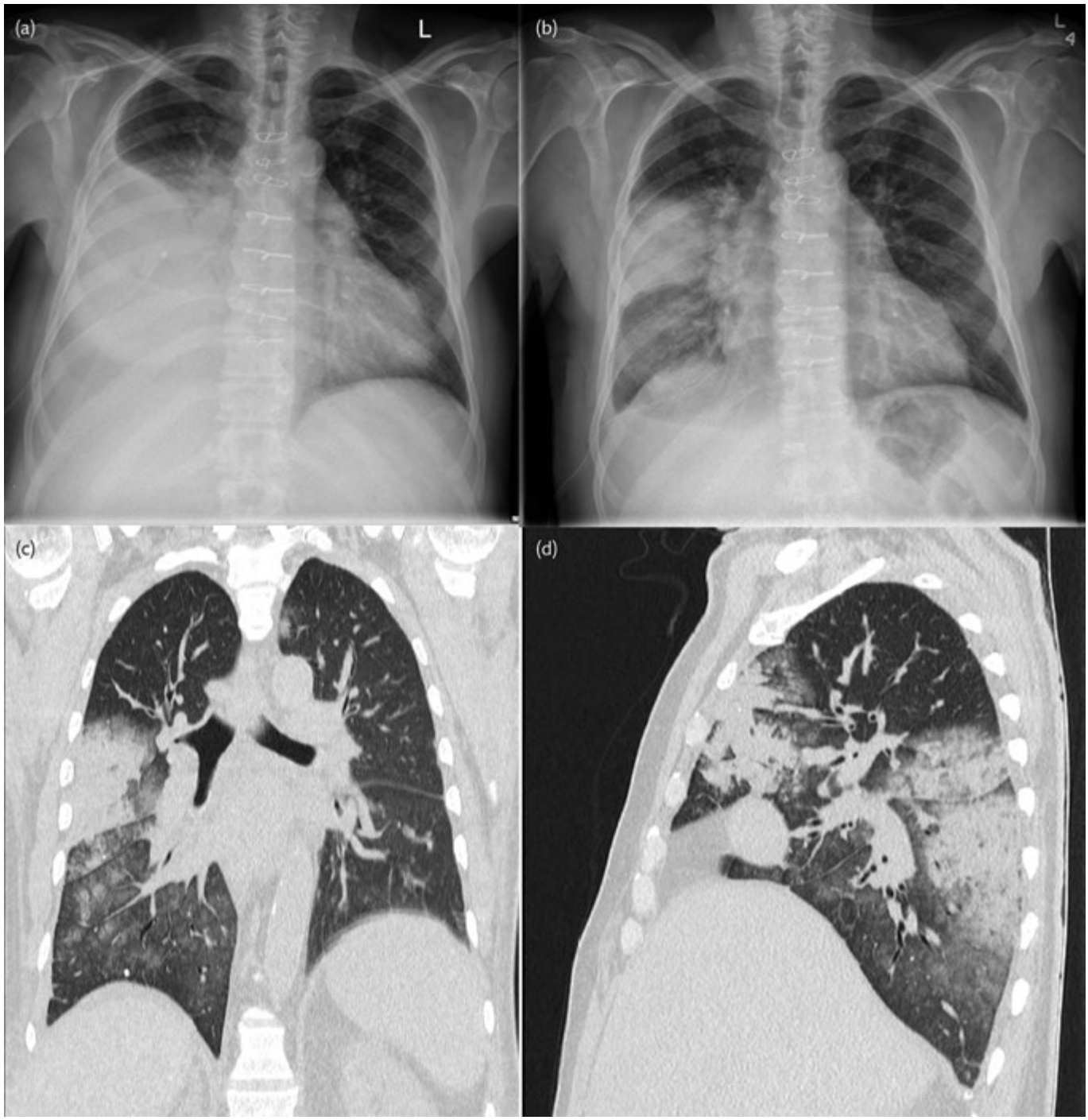

Fig. 18.17.21 A chest X-ray of a large right-sided pleural effusion with a chest drain *in situ* is shown in figure (a). Second chest X-ray following controlled drainage of 5 litres of fluid, showing air space shadowing (b). Coronal (c) and sagittal (d) CT images confirming pulmonary oedema. All changes resolved with conservative management.

Prevention

The risk of re-expansion oedema is probably reduced if lung inflation is gentle, hence a chest tube for pneumothorax should be attached to an underwater seal drainage without suction to allow gradual lung re-expansion. During drainage of a pleural effusion, the procedure should be terminated if the patient develops chest tightness or persistent coughing. Arbitrary maximal volumes for a single thoracentesis are often suggested to reduce the risk of re-expansion oedema, but there is no direct evidence to substantiate this strategy.

Acknowledgements

We acknowledge Robert Davies, Fergus Gleeson, Fraser Brims, and Jose Porcel who produced earlier versions of the chapter in this book's previous editions.

FURTHER READING

The pleura

Hooper C, Lee YCG, Maskell N (2010). Investigation of a unilateral pleural effusion in adults: British Thoracic Society pleural disease guideline 2010. *Thorax*, **65**, ii4–ii7.

Leung AN, Muller NL, Miller RR (1990). CT in differential diagnosis of diffuse pleural disease. *AJR Am J Roentgenol*, **154**, 3–92.

Light RW, Gary Lee YC (eds). (2016). *Textbook of pleural diseases* (3rd edn). CRC Press, Florida.

Light RW, *et al*. (1972). Pleural effusions: the diagnostic separation of transudates and exudates. *Ann Intern Med*, **77**, 507–13.

Maskell NA, Gleeson FV, Davies RJO (2003). Standard pleural biopsy versus CT-guided cutting-needle biopsy for diagnosis of malignant disease in pleural effusions: a randomised controlled trial. *Lancet*, **361**, 1326–30.

Pleural effusion

Arnold D, *et al*. (2015). Pleural fluid adenosine deaminase (Pfada) in the diagnosis of tuberculous effusions in a low incidence population. *PloS One*, DOI: 10.1371/journal.pone.0113047.

Heffner JE, Highland K, Brown LK (2003). A meta-analysis derivation of continuous likelihood ratios for diagnosing pleural fluid exudates. *Am J Respir Crit Care Med*, **1679**, 1591–9.

Matsuie S, *et al*. (2012). Respiratory involvement in IgG4 related Mikulicz's disease. *Modern Rheumatology*, **22**, 31–9.

Menzies S, *et al*. (2011). Blood culture bottle culture of pleural fluid in pleural infection. *Thorax*, **66**, 658–62.

Pyogenic pleural infection

Colice GL, *et al*. (2000). Medical and surgical treatment of parapneumonic effusions: an evidence-based guideline. *Chest*, **118**, 4–71.

Davies H, Davies R, Davies C (2010). Management of pleural infection in adults: British Thoracic Society pleural disease guidelines. *Thorax*, **65**, ii41–ii53.

Heffner JE, *et al*. (1995). Pleural fluid chemical analysis in parapneumonic effusions. A meta-analysis. *Am J Respir Crit Care Med*, **151**, 1700–8.

Maskell NA, *et al*. (2005). UK controlled trial of intrapleural streptokinase for pleural infection. *N Engl J Med*, **352**, 865–74.

Maskell NA, *et al*. (2006). The bacteriology of pleural infection by genetic and standard methods and its mortality significance. *Am J Respir Crit Care Med*, **174**, 817–23.

Rahman N, Kahan B, Miller R (2014). A clinical score (RAPID) to identify those at risk for poor outcome at presentation with pleural infection. *Chest*, **145**, 848–55.

Rahman N, Maskell N, West A (2011). Intrapleural use of tissue plasminogen activator and DNase in pleural infection. *NEJM*, **365**, 518–26.

Tuberculous pleural effusion and empyema

Cohen L, Light R (2015). Tuberculous pleural effusion. *Turkish Thoracic Journal*, **16**, 1–9.

Diacon AH, *et al*. (2003). Diagnostic tools in tuberculous pleurisy: a direct comparative study. *Eur Respir J*, **22**, 589–91.

Gopi A, *et al*. (2007). Diagnosis and treatment of tuberculous pleural effusion in 2006. *Chest*, **131**, 880–9.

Chylothorax and pseudochylothorax

Gruber-Rouh T, Naguib N, Lehnert T (2014). Direct lymphangiography as treatment option of lymphatic leakage: indications, outcomes and role in patient's management. *Eur J Radiol*, **83**, 2167–71.

Light RW, Lee YCG (2005). Pneumothorax, chylothorax, hemothorax and fibrothorax. In: Murray J, *et al*. (eds) *Textbook of respiratory diseases*, 4th edition, pp. 1961–88. W B Saunders, Philadelphia.

Haemothorax

Broderick SR, *et al*. (2013). Hemothorax. Etiology, diagnosis, and management. *Thorac Surg Clin*, **23**, 89–96.

Maxwell RA, *et al*. (2004). Use of presumptive antibiotics following tube thoracostomy for traumatic hemopneumothorax in the prevention of empyema and pneumonia—a multi-center trial. *J Trauma*, **57**, 742–8.

Benign asbestos-induced pleural disease

King C, *et al*. (2011). Benign asbestos-related pleural disease. *Dis Month*, **57**, 27–39.

Pneumothorax

Barker A, *et al*. (2006). Recurrence rates of video-assisted thoracoscopic versus open surgery in the prevention of recurrent pneumothoraces: a systematic review of randomised and non-randomised trials. *Lancet*, **370**, 329–35.

Bintcliffe O, *et al*. (2015). Spontaneous pneumothorax: time to rethink management. *Lancet Respir Med*, **3**, 578–88.

Gupta D, Hansell A, Nichols T (2010). Epidemiology of pneumothorax in England. *Thorax*, **55**, 666–71.

MacDuff A, Arnold A, Harvey J (2010). Management of spontaneous pneumothorax: British Thoracic Society pleural disease guidelines 2010. *Thorax*, **65** supplement 2, ii8–ii31.

Noppen M, Baumann M (2003). Pathogenesis and treatment of primary spontaneous pneumothorax: an overview. *Respiration*, **70**, 431–8.

Noppen M, *et al*. (2002). Manual aspiration versus chest tube drainage in first episodes of primary spontaneous pneumothorax: a multicenter, prospective, randomized pilot study. *Am J Respir Crit Care Med*, **165**, 1240–4.

Tschopp JM, *et al*. (2015). ERS taskforce statement: diagnosis and treatment of primary spontaneous pneumothorax. *Eur Respir J*, **46**, 321–35.

Visouli *et al*. Catamenial pneumothorax. *J Thorac Dis*, **4**, 17–31.