

INVITED REVIEW SERIES: PLEURAL DISEASES

The management of pleural space infections

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Abstract: Pleural infection is responsible for significant morbidity and mortality worldwide, and its clinical management is challenging. The diagnosis of empyema and tuberculous pleurisy may be difficult, and these conditions may be confused with other causes of exudative pleural effusions. Complicated parapneumonic effusion or empyema may present with 'atypical' clinical features; delays in diagnosis are common and may contribute to the high mortality of these infections. Pleural aspiration is the key diagnostic step; pleural fluid that is purulent or that has a pH < 7.2, or organisms on Gram stain or culture, is an indication for formal intercostal drainage. In order to achieve a definitive diagnosis of tuberculous pleurisy, *Mycobacterium tuberculosis* must be isolated in the culture of pleural fluid, pleural tissue or sputum; demonstration of granulomas in pleural tissue is also suggestive of tuberculosis. The use of pleural fluid biochemical markers, such as adenosine deaminase, in the diagnosis of tuberculous pleurisy varies among clinicians; the diagnostic value of such markers is affected by the background prevalence of tuberculosis and the likelihood of an alternative diagnosis. Uncertainties also remain regarding the treatment of pleural infection. Treatment of complicated parapneumonic effusion and empyema involves prolonged courses of antibiotics and attention to the patient's nutritional state. The role of intrapleural fibrinolytics and the optimal timing of surgical intervention are unknown. The lack of clear predictors of clinical outcome in empyema contributes to the difficulty in treating this condition. The pharmacological treatment of tuberculous pleurisy is the same as for pulmonary tuberculosis; the precise role of steroids in the treatment of tuberculous pleurisy remains uncertain.

Key words: empyema, parapneumonic effusion, tuberculosis.

INTRODUCTION

This review discusses the clinical aspects of pleural infection, focusing on the presentation and management of complicated parapneumonic effusion, empyema, and tuberculous pleural effusion.

Pleural infection is a common problem worldwide and is responsible for significant morbidity and mortality. In the USA there are approximately 60 000 cases of empyema annually;¹ as many as 40% of these patients will require major surgical procedures for drainage,² and the mortality rate of empyema approaches 20%.² The optimal treatment of empyema is unknown and there is considerable variation in management among clinicians.^{2,3} Delays in the diag-

nosis and treatment of empyema are common and may contribute to morbidity and mortality.^{3–6} Recent evidence-based guidelines in the UK and US have addressed these issues.⁷

Tuberculous pleural effusion is a significant problem in both developing and developed countries. The diagnosis may not be suspected because of its non-specific clinical presentation, and uncertainties remain regarding the optimal investigation of tuberculous pleurisy. Confirmation of the diagnosis may be difficult, in part because of the relatively low pleural bacterial load in most cases of tuberculosis.

PARAPNEUMONIC EFFUSION AND EMPYEMA

Definitions

The development of a pleural effusion is a common complication of pneumonia, occurring in up

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to 57% of cases.¹ The majority of these effusions are clear, sterile exudates that frequently resolve with antibiotics alone and do not require drainage ('simple parapneumonic effusion'). In some cases this initial effusion may progress to a 'complicated parapneumonic effusion', which is characterized by fibrin deposition; the fluid is infected, although organisms are not usually isolated and the fluid is not yet purulent, and typically has a pH < 7.2, glucose < 35 mg/dL and LDH > 1000 IU/L.⁸⁻¹¹ This stage is not thought to resolve without drainage of the effusion.¹¹ Persistent pleural infection may eventually result in the accumulation of pus in the pleural space ('empyema'). A more complicated classification scheme for pleural infection has been proposed.¹²

Epidemiology

Complicated parapneumonic effusion and empyema are more common in the elderly⁴ and in childhood.¹³ Risk factors for their development include diabetes mellitus, alcohol abuse, gastro-oesophageal reflux, rheumatoid arthritis, chronic lung disease and intravenous drug abuse.^{2,14-16} Anaerobic infection is associated particularly with aspiration and poor dental hygiene.² Empyema occurs commonly however, in the absence of any identifiable risk factors.²

Empyema may develop as a complication of pneumonia, or may follow surgery, trauma or iatrogenic procedures.¹⁷⁻¹⁹ Empyema may also occur as a 'primary' infection, without evidence of parenchymal lung infection. Pleural infection may rarely develop following bronchial obstruction from a tumour or foreign body.

Bacteriology

The bacteriology of empyema is extremely varied, and there are significant differences between the organisms responsible for community- and hospital-acquired infection. The provisional report of a recent large UK study (Medical Research Council/British Thoracic Society Multicentre Intrapleural Streptokinase Trial (MIST)) has characterized the bacteriology of 300 patients with complicated parapneumonic effusion and empyema.¹⁸ The commonest causes of community-acquired pleural infection in this series were *Streptococcus milleri* (28%), *Streptococcus pneumoniae* (14%), and *Staphylococci* (12%), and sometimes associated anaerobes (19%). Other less common organisms responsible for community-acquired infection include other *Streptococci*, *Enterobacteria*, *Haemophilus influenzae*, *Pseudomonas* spp., tuberculosis, and *Nocardia*. Cases of hospital-acquired infection (following pneumonia, surgery, trauma or pleural procedures) in the same series were most commonly caused by methicillin-resistant *Staphylococcus aureus* (MRSA) (27% of cases), other *Staphylococci* (22%), *Enterobacteria* (20%) or *Enterococcus* (12%).¹⁸

Clinical features

The clinical presentation of complicated parapneumonic effusion and empyema is similar to that of pneumonia; patients typically, but not universally, experience fever, sputum production, chest pain, and breathlessness. Anaerobic empyema may present less acutely, often with weight loss and without fever.²⁰ A diagnosis of pleural infection should be considered particularly in cases of 'slow to respond' pneumonia, pleural effusion with fever, or in high-risk groups with non-specific symptoms such as weight loss. In rare cases infected pleural fluid may spontaneously discharge through the chest wall ('empyema necessitans') or into the lung, leading to a bronchopleural fistula.²¹

Unusual features in the history may suggest an underlying cause for the infection. Atypical chest pain, vomiting, or oesophageal instrumentation raise the possibility of oesophageal rupture, and appropriate imaging investigations should be considered.⁷ The history of a recent sore throat may point to the rare condition Lemierre's syndrome; acute oropharyngeal infection, frequently with *Fusobacterium* species, leads to septic thrombophlebitis of the internal jugular vein and subsequent metastatic infection, particularly involving the lungs and pleura.²² Demonstration of thrombophlebitis of the internal jugular vein by CT or ultrasound provides support for this diagnosis.

Investigations and diagnosis

Diagnostic pleural aspiration

Diagnostic pleural aspiration is essential if pleural infection is suspected. Aspiration may be difficult to perform safely in heavily loculated collections, and ultrasound guidance may be required. The pleural fluid appearance should be noted, and a sample sent for Gram's stain and culture. In non-purulent effusions, pleural fluid pH should be measured using a heparinized syringe and blood gas machine. Further pleural fluid analysis may be considered in cases of diagnostic difficulty (differential cell count, cytology, amylase, glucose and LDH). Culture of infected pleural fluid is negative in around 40% of cases;^{4,18} diagnostic rates may be increased by additionally analysing samples in 'blood culture' bottles.²³

The finding of frankly purulent pleural fluid and/or the presence of organisms on pleural fluid Gram stain or culture is diagnostic of complicated parapneumonic effusion or empyema, and necessitates formal drainage of the infected pleural space. Pleural fluid with pH < 7.2, in the appropriate clinical setting, is highly suggestive of empyema and is also an indication for chest tube drainage.¹¹ However, infection may occur with a normal pleural fluid pH,⁴ and rarely an elevated pH, for example in *Proteus mirabilis* infection.^{24,25} Other pleural fluid parameters such as reduced glucose (< 35 mg/dL) or elevated LDH (> 1000 IU/L) may support the diagnosis of pleural

infection, although these are less diagnostically useful than pleural fluid pH.⁸⁻¹¹

Blood cultures

Routine blood cultures in patients with suspected pleural infection are recommended; although they are positive in only 12% of cases of empyema, in these cases they are frequently the only positive microbiology result.¹⁸

Imaging

The CXR in pleural infection usually shows a pleural effusion, often with loculation and air-fluid levels; less commonly, empyema may be manifest as a rounded subpleural opacity, mimicking the appearance of lung cancer or mesothelioma. A lateral CXR may detect small volumes of pleural fluid that are not visible on the postero-anterior view.⁹

Ultrasound scanning typically shows a homogeneous echogenic effusion,²⁶ and is useful in guiding pleural aspiration in patients with small or loculated effusions.^{27,28} Very small effusions (< 10 mm maximal thickness on ultrasound) probably do not require aspiration and can be observed.

Contrast-enhanced CT scanning may support the diagnosis of pleural infection and enable visualization of the distribution of fluid, position of chest drains and presence of loculations. Pleural contrast-enhancement and increased attenuation of extrapleural subcostal fat occur in association with pleural infection.²⁹⁻³¹ An absence of pleural thickening on CT is unusual in empyema and is more suggestive of simple parapneumonic effusion.²⁹ Computed tomography may also identify a proximal endobronchial obstructing lesion.

Differential diagnosis

The diagnosis of pleural infection can be difficult, particularly in cases of negative pleural fluid Gram stain and culture. The 'classical' clinical features of fever accompanied by pleural effusion are non-specific; other causes include malignancy (including mesothelioma), tuberculosis, pulmonary embolic disease, rheumatoid pleuritis, oesophageal rupture, pancreatitis, and lupus pleuritis. In cases of anaerobic empyema presenting solely with weight loss, the diagnosis is often not suspected. The findings of a low pleural fluid pH and glucose are not specific to empyema; other important causes include rheumatoid pleuritis, malignant pleural effusion, tuberculous pleural effusion, oesophageal rupture and lupus pleuritis.³²

Treatment

Antibiotics

All patients with pleural infection should be treated with antibiotics. Intravenous antibiotics are recom-

mended as initial therapy. The choice of antibiotic should be based on the results of blood and pleural fluid cultures and sensitivities. Anaerobes are difficult to culture and often coexist with aerobic organisms, and so additional empirical anaerobic cover should be considered. In cases where the culture results are unknown or negative, the choice of antibiotic should be guided by local hospital prescribing guidelines and the location of the acquisition of the infection. Community-acquired empyema requires antibiotic cover for community pathogens and anaerobes; choices include a second generation cephalosporin (e.g. cefuroxime) or intravenous aminopenicillin, plus therapy for anaerobic infection (e.g. metronidazole or clindamycin).⁷ For subjects allergic to both penicillin and cephalosporins, combinations such as ciprofloxacin and clindamycin may be effective. In hospital-acquired empyema, treatment for both Gram-positive and Gram-negative aerobic organisms as well as anaerobes is needed and the highly antibiotic-resistant characteristics of the bacteria in these cases need to be considered. Options include carbapenems, antipseudomonal penicillins, or third generation cephalosporins (e.g. ceftazidime) with metronidazole.^{7,33} In our unit, current initial therapy for patients with culture-negative hospital-acquired empyema is vancomycin (to treat MRSA) and meropenem (which has a broad spectrum of activity including anaerobic efficacy). Aminoglycosides should be avoided because they penetrate the pleural space poorly and have a weaker action in acidic surroundings.^{33,34}

A change to oral antibiotics may be considered following clinical improvement and resolution of fever. Typical choices of oral antibiotic in culture-negative cases include oral aminopenicillin with a beta lactamase inhibitor or ciprofloxacin and clindamycin. The optimal duration of antibiotic treatment is unclear, although it is likely to be at least 3 weeks.⁷ Measurement of inflammatory markers such as serum C-reactive protein, in addition to clinical assessment, provides a useful guide to treatment response.

Chest tube drainage

Indications for chest tube drainage are the aspiration of frankly purulent or turbid pleural fluid,^{11,12} the identification of organisms on pleural fluid Gram stain or culture,^{11,12} or a pleural fluid pH < 7.2 in the clinical setting of a pneumonic illness.¹¹ Drainage may also be considered for symptomatic relief in very large parapneumonic effusions. Insertion of the chest tube should ideally be carried out under ultrasound or CT guidance, as effusions are frequently loculated. The ideal chest tube size remains unclear and has not been addressed in randomized trials. Small bore (12-14 French) drains are easier to insert, more comfortable, and adequate for the drainage of infected pleural collections in most cases.³⁵⁻³⁷ We recommend applying suction (20 cmH₂O) and flushing regularly (e.g. 30 mL normal saline every 6 h) to prevent the occlusion of small drains. The optimal duration of drainage is unknown; drain removal may be considered when the output falls to less than 150 mL daily

for 2 days in the setting of clinical and radiographic improvement.

In cases of parapneumonic effusions where there is no indication for drainage, the patient should be treated with antibiotics and monitored closely. If their clinical condition fails to improve or deteriorates, the effusion should be re-sampled and formal chest drainage considered. A minority of patients with a pleural fluid pH > 7.2 will fail medical management with tube drainage and require surgery.⁴

The role of therapeutic thoracentesis as an alternative to formal chest drain placement in complicated parapneumonic effusion and early empyema is unknown. Use of serial thoracentesis may avoid the complications of chest drainage and perhaps allow outpatient management of select cases.³⁸ Daily therapeutic thoracentesis has been demonstrated to be as effective as formal drainage in a rabbit model of empyema.³⁸ Successful treatment of empyema with therapeutic thoracentesis and antibiotics alone has been documented,^{2,39} but thoracentesis has not yet been compared to formal drainage in randomized controlled trials.

Intrapleural fibrinolytics

Infected pleural fluid often becomes loculated and resistant to drainage with a single chest tube. Intrapleural administration of a fibrinolytic agent may facilitate fluid drainage by dissolving fibrous adhesions, and the successful use of intrapleural fibrinolytics such as streptokinase and urokinase has been documented in many observational studies.^{19,40-46} Only a small number of randomized controlled trials have addressed this issue, however, and these have been inadequately powered to assess effects on mortality or the need for surgery.⁴⁷⁻⁴⁹ On the basis of current evidence, the role of intrapleural fibrinolytics in the management of complicated parapneumonic effusion and empyema has to remain inconclusive. The results of the Medical Research Council/British Thoracic Society Multicentre Intrapleural Streptokinase Trial (MIST) are expected to resolve this issue.

Another intrapleural agent that may facilitate catheter drainage of empyema is deoxyribonuclease (DNase), which acts by reducing the viscosity of pus. Liquefaction of pus from experimental and human empyema has been demonstrated following incubation with streptodornase (streptococcal DNase) or with human recombinant DNase.^{50,51} Successful use of intrapleural human recombinant DNase in the treatment of empyema following failure of streptokinase has been described in a single case report.⁵² Use of intrapleural DNase has not yet however, been evaluated in a randomized, controlled manner.

Nutritional support

Malnutrition is common in the setting of empyema and is associated with a poor prognosis.^{2,53} Provision of nutritional support is an essential component of the treatment of suppurative lung disease; many patients

require supplementary nasogastric feeding, and parenteral nutrition may sometimes be indicated.

Surgery

A number of different surgical approaches are available to treat empyema. Thoracotomy and decortication is the most traditional operation and involves the removal of fibrinous and infected tissue from the pleural space, a major surgical procedure.⁵⁴ A similar procedure may also be performed through a smaller incision (mini-thoracotomy). Video-assisted thoracoscopic surgery (VATS) allows the breakdown of adhesions and drainage of any residual collection, and is increasingly used in the management of empyema.⁵⁵⁻⁶² It is frequently unsuccessful in chronic empyema with a very thickened visceral pleura, and conversion to open thoracotomy may be required. Finally, rib resection and open thoracic drainage involves the resection of segments of several ribs adjacent to the empyema and insertion of large bore drains into the cavity. This relatively minor procedure can be performed under local anaesthesia, but results in an open chest wound for a period of around 6 months.⁵⁴ Open drainage is useful in patients who are unable to tolerate general anaesthesia and are unfit for decortication.

The optimal timing of surgery for empyema is unknown. In the majority of cases, patients are managed initially with antibiotics and tube drainage and only referred for consideration of surgery if these measures fail. Although a role for earlier surgical intervention has been suggested,^{3,58} there is a lack of randomized controlled data to support this at present. A single, small prospective study compared the early use of VATS with intrapleural streptokinase and continued chest drainage in the management of empyema;⁶³ the need for surgery was decided on day three of treatment. Surgery resulted in shorter drainage periods and hospital stays, but the failure rate in the control group was unusually high and the need for surgery was decided in an unblinded fashion.⁶³ There is a need to replicate the results of this study in a much larger group.

A further difficulty is that it is not currently possible to predict those patients with a poor prognosis who may benefit from earlier surgical intervention. A study of 85 patients treated in a consistent manner with antibiotics, drainage and intrapleural streptokinase failed to identify any clinically useful predictors of outcome.⁴ In particular, visceral pleural peel thickness, pleural biochemistry and clinical features were unhelpful in predicting the requirement for surgery.⁴

In the absence of any clear data to guide the timing of surgery, our recommendation is to consider surgical intervention if there is evidence of continuing sepsis and a significant residual pleural collection after 7 days of treatment with tube drainage and antibiotics.

Difficulties in management

In a number of cases, patients fail to improve despite initial treatment with antibiotics and chest tube

drainage. In situations where chest drainage ceases despite a residual pleural collection, the drain should be flushed with normal saline and examined to exclude a kink at the skin insertion site. The microbiology results should be reviewed to ensure the use of appropriate antibiotics, and alternative diagnoses such as tuberculosis, malignancy, or oesophageal rupture may be considered. A contrast-enhanced CT scan of the chest is useful in patients with features of ongoing sepsis, and allows assessment of the residual collection and the position of drain(s). Surgical intervention may be considered at this point. A particular management difficulty arises with patients who fail to improve with medical treatment, but who are unfit for a general anaesthetic. Insertion of further image-guided chest drains into loculated effusions and the use of intrapleural fibrinolytics may be beneficial in such cases. A final option is surgical rib resection and open drainage under local anaesthesia.

Future developments

A number of uncertainties remain regarding the optimal management of complicated parapneumonic effusion and empyema. Current evidence regarding the use of intrapleural fibrinolytics is inconclusive, and intrapleural DNase has yet to be studied in large trials. The precise role of VATS is unclear, and further trials examining its role in the early treatment of empyema are required. A method of outcome prediction would be helpful in identifying those patients with a poor prognosis, and those who may benefit from early consideration of surgery. There may also be groups of patients with a good prognosis who could be potentially managed with a conservative outpatient regime, such as with a small-bore catheter (e.g. PleuRx) and oral antibiotics, resulting in significant healthcare cost savings.

TUBERCULOUS PLEURAL EFFUSION

Tuberculous pleural effusion develops from a delayed hypersensitivity reaction to mycobacteria in the pleural space following rupture of a subpleural caseous focus.⁶⁴ The frequency of pleural effusion as a manifestation of tuberculosis varies worldwide, from 5% of tuberculosis cases in the USA,⁶⁵ to 23% of cases in Spain,⁶⁶ and 31% of cases in sub-Saharan Africa.⁶⁷ In areas with a high prevalence of tuberculosis, tuberculous pleurisy typically occurs during primary infection and tends to affect younger individuals. In regions where tuberculosis is less common, pleurisy is becoming increasingly recognized as a manifestation of disease reactivation, and is affecting older patients.⁶⁸ Pleural infection may be a more common manifestation of tuberculosis in patients coinfecting with HIV,⁶⁹ although this has not been found in all studies.^{67,70}

Clinical features

Patients may be asymptomatic, or present with constitutional symptoms such as weight loss, chest pain,

and fever. Tuberculous effusions are typically small to moderate in volume, although they can be massive.

Investigations and diagnosis

Tuberculin skin tests are of limited use in the investigation of tuberculous pleurisy; they are positive in only two-thirds of cases,⁷¹ and are even less sensitive in HIV-infected patients.⁷² The findings on initial pleural fluid analysis in tuberculous pleurisy are non-specific. The pleural fluid is usually a serous exudate, with protein levels often greater than 5 g/dL, and lactate dehydrogenase levels greater than 500 IU/L.⁷¹ Pleural fluid glucose and pH values are lowered in around 20% of patients.^{71,73} A predominance of pleural fluid lymphocytes is a typical finding,⁷¹ although a neutrophilia may be seen early in the course of disease.⁷³ Pleural fluid mesothelial cells are scarce.⁷⁴

In order to achieve a definitive diagnosis of tuberculous pleurisy, *Mycobacterium tuberculosis* must be isolated in the culture of pleural fluid, pleural tissue or sputum; the demonstration of granulomas in pleural tissue is also suggestive of tuberculosis.⁶⁶ Studies of these procedures have reported variable results; sensitivities range from 10 to 47% for pleural fluid culture,^{71,75–77} 39–84% for pleural biopsy histology,^{71,75–77} and 56–82% for pleural biopsy culture.^{71,76} Culture of pleural biopsy specimens for mycobacteria in addition to histological studies increases the diagnostic yield when compared to histology alone.⁷¹ Thoracoscopic pleural biopsies have a reported sensitivity of 98% for the diagnosis of tuberculosis.⁷⁸

Recent interest has focused on biochemical markers in pleural fluid, which may assist the early diagnosis of tuberculous pleurisy.⁶⁶ Measurement of pleural fluid adenosine deaminase (ADA) has received the most interest. Pleural fluid ADA levels are high in pleural tuberculosis, although a raised value is non-specific and may occur in other conditions such as empyema and malignancy.⁷⁹ Analysis of ADA should be interpreted in the context of the local prevalence of tuberculosis. In regions with a high prevalence of tuberculosis, the sensitivity and specificity of an elevated ADA value are high, particularly in young patients (<35 years) in whom empyema has been excluded; empirical anti-tuberculous treatment without resort to pleural biopsy may be considered in such cases.⁸⁰ A raised ADA level is less helpful in older patients because of the increased likelihood of alternative diagnoses such as malignancy,⁶⁶ and further, definitive investigation is recommended. In countries where the prevalence of tuberculosis is low, false-positive ADA measurements are more likely and the test is less useful for confirming the diagnosis of tuberculosis; the finding of a persistently low ADA value may still be useful, however, as it makes tuberculosis an unlikely diagnosis.⁸¹ A possible disadvantage of ADA measurement is that a lack of drug sensitivity information may lead to inadequate treatment of drug-resistant tuberculosis.

Routine clinical use of other pleural fluid markers of tuberculosis such as γ -interferon, lysozyme, and the polymerase chain reaction to detect mycobacte-

rial DNA is restricted by their high cost and/or reduced sensitivity.⁶⁶

Sputum culture for acid-fast bacilli has previously been considered to be an insensitive test for the diagnosis of pleural tuberculosis, particularly in the absence of parenchymal lesions on the chest radiograph.^{71,82} A recent study of 84 patients with tuberculous pleural effusions in a Brazilian centre, however, has demonstrated a high yield of mycobacterial culture from single induced sputum specimens; cultures were positive from induced sputum in 52% of cases overall, and in 55% of patients with normal lung parenchyma on CXR.⁸³ Analysis of induced sputum may therefore play a useful role in the diagnosis of pleural tuberculosis in patients from high-incidence countries. This finding also raises the possibility that pleural tuberculosis may be more contagious than previously appreciated.⁸³

Treatment

Without treatment, tuberculous pleural effusions typically resolve spontaneously over a period of several months. However, patients should receive treatment, as 65% of untreated patients develop active pulmonary tuberculosis within 5 years.⁸⁴ Drug treatment of tuberculous pleurisy is the same as for pulmonary tuberculosis. The role of steroids in the treatment of tuberculous pleurisy remains uncertain; steroids may hasten both the resolution of clinical symptoms and the absorption of pleural fluid,⁸⁵ although this has not been noted in all studies.⁸⁶ Further studies are required to clarify the effect of steroids on mortality or lung function following treatment.⁸⁷

Paradoxical increases in effusion size are relatively common during effective treatment, and therapeutic thoracentesis is often required for symptomatic relief.⁸⁸ The development of new pulmonary nodules during treatment is also documented, and these lesions appear to resolve without changes in treatment.⁸⁹ Residual pleural thickening is observed in 50% of patients 1 year after the start of treatment,⁹⁰ and is not prevented by the use of steroids⁸⁵ or by formal drainage of the effusion.⁹¹ Functional sequelae, however, appear to be infrequent and mild.⁹²

TUBERCULOUS EMPYEMA

Tuberculous empyema is considerably rarer than tuberculous pleural effusion, and differs in that the pleural space is infected with a high mycobacterial load. Chronic, asymptomatic pleural infection may be followed by a presentation with empyema necessitans or a bronchopleural fistula, or by symptoms of weight loss, fever, and night sweats.⁹³ The pleural fluid is purulent and smear-positive for acid-fast bacilli.⁹³ CT imaging typically demonstrates a thickened, calcified pleural rind and loculated pleural effusion;⁹⁴ an associated extrapleural mass is suggestive of empyema necessitans. Treatment involves formal drainage of the pleural space in addition to anti-tuberculous chemotherapy.⁹⁵ Difficulty re-expanding the trapped

lung is a common problem, and surgery is challenging.⁹³ Concerns have also been raised about the development of drug resistance due to poor antibiotic penetration into the pleural cavity.⁹⁵ Chronic tuberculous empyema may be associated with the development of pleural malignancy, particularly non-Hodgkin's lymphoma.⁹³

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