of PCIS are usually self-limited, but recurrences are frequent. Recurrent episodes become progressively more resistant to treatment with nonsteroidal anti-inflammatory agents but usually respond to corticosteroid therapy.

The management of pleural effusions occurring after abdominal surgery depends on the size of the effusions. If the effusion is small, no diagnostic or therapeutic interventions are warranted. If the effusion is more than minimal, a diagnostic thoracentesis should be performed to rule out pleural infection. If the effusion develops more than 72 h after surgery, pulmonary embolism and subphrenic abscess should be considered.

The natural history of a pleural effusion after liver transplantation is to increase in size during the first 3 postoperative days and then gradually resolve over several weeks to months. Pleural effusions that increase in size after the first 3 days are likely associated with subdiaphragmatic pathology such as hematoma, biloma, or abscess and, accordingly, such patients should be evaluated for subdiaphragmatic pathology. If the patient becomes short of breath from the effusion, a therapeutic thoracentesis should be performed. One report suggested that pleural effusions that occur after liver transplantation can be largely prevented if a fibrin sealant is sprayed on the undersurface of the diaphragm around the insertion of the liver ligaments at the time of transplantation.

Immediately postlung transplantation, pleural effusions are usually not evident because patients have a chest tube. The mean output of pleural fluid is approximately 400 ml per day on day 1 and decreases gradually to 200 ml per day on day 4. The pleural fluid on day 1 is a bloody neutrophil-predominant exudate. Patients who develop complications post-lung transplantation are also likely to have a pleural effusion. Pleural effusions occur in more than 50% of patients who develop acute rejection, chronic rejection, pulmonary infection, and lymphoproliferative disease. Treatment of early pleural effusions with lung transplantation consists of continuation of the tube thoracostomy. Management of late pleural effusions is dependent on the underlying complication causing the effusions.

See also: Pleural Effusions: Overview; Pleural Fluid, Transudate and Exudate; Pleural Fluid Analysis, Thoracentesis, Biopsy, and Chest Tube. Surgery: Transplantation.

Further Reading


Pleural Fibrosis

J T Huggins and S A Sahn, Medical University of South Carolina, Charleston, SC, USA

© 2006 Elsevier Ltd. All rights reserved.

Abstract

The response of the mesothelial cell and basement membrane to injury is vital in determining whether there is normal healing or pleural fibrosis. The formation of a fibrinous intrapleural matrix
is critical to the development of pleural fibrosis. This matrix is the result of disordered fibrin turnover, whereby fibrin formation is upregulated and fibrin dissolution is downregulated. Transforming growth factor beta and tumor necrosis factor alpha are important cytokines that facilitate formation of the fibrin matrix. A complete understanding of the pathogenesis of pleural fibrosis and why dysfunctional pleural space remodeling occurs in some and not in others remains unknown.

Clinically significant pleural fibrosis requires involvement of the visceral pleura, while isolated parietal pleural fibrosis does not cause restriction or respiratory impairment. The vast majority of diseases causing visceral pleural fibrosis include asbestos-associated diffuse pleural thickening, coronary bypass graft surgery, tuberculous pleurisy, rheumatoid pleurisy, uremic pleurisy, hemothorax, radiation, and empyema.

Systemic and intrapleural corticosteroids administered during the initial presentation of rheumatoid pleurisy anecdotaly may have decreased the incidence of pleural fibrosis. Several randomized control trials of corticosteroids in tuberculous pleurisy have not shown efficacy in reducing residual pleural fibrosis. Decortication is effective in treating symptomatic patients regardless of the cause of pleural fibrosis as long as chronicity has been documented and significant underlying parenchymal disease has been excluded.

Introduction

Pleural fibrosis can result from a vast array of inflammatory processes, including dust exposure (asbestos), immunologic disease (rheumatoid pleurisy), infection (bacterial empyema, tuberculous pleurisy), improperly drained hemothorax, radiation, malignancy, post-coronary artery bypass surgery (post-CABG), and uremic pleurisy. The response of the mesothelial cell to injury and its ability with the underlying basement membrane to maintain integrity is crucial in determining whether there is normal or dysfunctional healing (pleural fibrosis).

Trapped lung and fibrothorax are two unique and rare clinical entities that can be a consequence of pleural fibrosis. Trapped lung presents as a chronic, unilateral, pleural effusion that is the result of a remote inflammatory process. It is characterized by the inability of the lung to expand and fill the thoracic cavity due to a restrictive, fibrous visceral pleural peel. The resultant negative pressurepleural space becomes filled with low-protein pleural fluid that persists due to the hydrostatic disequilibrium. A prerequisite for the development of a trapped lung is remote pleural inflammation or hemothorax. The pleural effusion must persist long enough to allow fibrous tissue to develop on the visceral pleura while the pleural surfaces remain separated.

Fibrothorax represents the most severe form of pleural fibrosis. This term is reserved for an intense fibrotic response of the visceral pleura leading to fusion of both the visceral and parietal membranes. As a result, there is contracture of the involved hemithorax and reduced mobility of the lung and thoracic cage due to progressive pleural fibrosis and symphysis of the pleural membranes. As the fibrothorax matures, the intercostal spaces narrow, the size of the ipsilateral hemithorax diminishes, and the mediastinum is displaced ipsilateral.

Pleural fibrosis becomes clinically important when it involves the visceral pleural surface. Isolated parietal pleural fibrosis, as with asbestos-related pleural plaques, does not result in respiratory symptoms or clinically relevant decrements in lung function. In contrast, the development of visceral pleural fibrosis can lead to lung entrapment resulting in dyspnea and, in some patients, respiratory failure.

Etiology

Asbestos

Pleural fibrosis is the most common radiographic finding among those exposed to asbestos. The two forms of asbestos-induced pleural fibrosis are parietal pleural plaques and diffuse pleural thickening. The development of pleural fibrosis is dependent on the duration and cumulative dose of asbestos exposure. Pleural plaques, localized fibrous lesions of the parietal pleura, are the most common manifestation of asbestos exposure. Because of their parietal pleural location, they are not typically associated with respiratory symptoms or pulmonary impairment. Dyspnea or restrictive physiology implies asbestosis, even with a normal chest radiograph, or an alternative diagnosis. Pleural plaques appear on average 20–30 years after initial exposure to asbestos, with the incidence varying with asbestos fiber type and duration of exposure.

The term diffuse pleural thickening is often used interchangeably with two different presentations: (1) diffuse thickening involving the majority of the pleura leading to encasement of the lung; and (2) limited thickening involving at least one-fourth of the visceral pleura. Diffuse pleural thickening primarily involves the visceral pleura, is usually unilateral, and commonly involves the costophrenic recess. Diffuse pleural thickening is thought to be the sequela of an asbestos-related exudative pleural effusion. It could also be the result of repeated bouts of asbestos-related pleurisy whereby a fibrinous scaffold is laid down, matures, and organizes into dense collagenous tissue. Pleural adhesions and fusion of the visceral and parietal pleura commonly occur with diffuse pleural thickening.

Rheumatoid Pleurisy

Pathological studies have demonstrated that pleural effusion and pleural fibrosis occur in 50% of patients
with rheumatoid arthritis. The degree of pleural fibrosis ranges from small fibrous plaques to extensive fibrosis of the pleura. Those with a protracted course of rheumatoid pleurisy may develop significant pleural fibrosis and trapped lung.

**Tuberculous Pleurisy**

Tuberculous pleurisy is the most frequent extrapulmonary manifestation of tuberculosis. Residual pleural thickening is the most common sequela following pleural tuberculosis, and has been reported in 20–50% of cases.

**Coronary Artery Bypass Surgery**

Left-sided exudative pleural effusions following CABG are common. The incidence of pleural effusions is higher with internal mammary artery grafts than with saphenous vein grafts. The natural history of these chronic effusions is gradual resolution. However, in a subgroup of patients, effusions may persist for months following CABG. Pleural biopsy specimens from patients undergoing thoracoscopy for persistent post-CABG effusions show an intense lymphocytic pleuritis within the first few months following surgery. With time, there is a reduction in the cellular inflammation and an increase in pleural fibrosis leading to the development of a trapped lung. The true incidence of trapped lung following CABG is unknown. However, due to the vast number of these surgical procedures performed each year, CABG is the most common cause of trapped lung encountered today.

**Fibrosing Uremic Pleuritis**

Fibrinous pleuritis has been found in 20% of uremic patients at autopsy. Spontaneous resolution of uremic pleurisy typically occurs in 4–6 weeks leaving clinically unimportant pleural thickening in most patients. In rare cases, the pleural fluid becomes gelatinous and a thick fibrous pleural peel develops (Figure 1).

**Hemothorax**

Diffuse pleural thickening producing a fibrothorax is a late complication of a hemothorax. Fortunately, this complication occurs in less than 1% of patients even if residual blood is not removed from the pleural space. Fibrothorax appears to be more common with a hemothorax or when pleural space infection complicates management.

**Cryptogenic Fibrosing Pleuritis**

This disease entity was originally described in four patients who developed progressive bilateral pleural fibrosis following exudative pleural effusions. An extensive evaluation failed to reveal an attributable cause of the pleural fibrosis; hence the term, bilateral cryptogenic fibrosing pleuritis. All four cases plus two of our cases were HLA-B44 positive suggesting a genetic link with this disease.

**Trapped Lung and Fibrothorax**

Conditions most often associated with trapped lung are complicated parapneumonic effusion, empyema, and postcardiac surgery, especially with internal mammary artery grafting. Other conditions associated with trapped lung include uremic pleuritis, rheumatoid pleuritis, tuberculous pleurisy, and a complicated hemothorax.

The causes of fibrothorax are similar to those that cause trapped lung. The primary causes of fibrothorax include hemothorax, bacterial empyema, and tuberculous empyema. Uremia and rheumatoid pleurisy have also been associated with fibrothorax.

**Pathology**

Pleuritis with pleural effusion frequently develops in a wide variety of disorders with most of the pleural changes regressing spontaneously without intervention. How these pleural changes regress is not completely understood.

The histology of asbestos-pleural plaques reveals a hypocellular lesion comprised of dense collagen
bundles arranged in a ‘basket-weave’ configuration. Rarely, mild inflammation may be observed; however, the mesothelial cell layer overlying the plaque appears normal.

Noninvasive ways of grading pleural thickening by computed tomography have been proposed by Copley and co-workers. Quantification of pleural fibrosis by their method has been correlated to the severity of physiologic impairment.

**Clinical Features**

Standard chest radiographs are the most common diagnostic modality used to detect focal and diffuse pleural fibrosis. Asbestos-pleural plaques appear as well-demarcated lesions along the midlateral chest wall (Figure 2). The costophrenic angles and apices are typically spared. Plaques may also be found over the dome of the diaphragm and on the pericardium. Occasionally, it may be difficult to distinguish plaques from muscle or extrapleural fat. Computed tomography can differentiate plaques from extrapleural fat causing an increased radiographic density.

The radiographic appearance of diffuse pleural thickening associated with asbestos is a smooth, uninterrupted pleural density extending over at least one-fourth of the chest wall. The posterior and posteromedial pleura overlying the lower lobes are more commonly involved. Nodularity and pleural thickening greater than 1 cm are radiographic signs suggestive of malignant mesothelioma or pleural metastasis.

For nonasbestos-related diffuse pleural thickening, the radiograph can provide helpful clues as to the underlying etiology. For example, in patients with chronic tuberculous empyema, unilateral parietal and visceral calcifications and remote parenchymal disease is often seen.

Because of their parietal pleural location, asbestos-pleural plaques are not typically associated with respiratory symptoms. Dyspnea or restrictive physiology implies asbestosis, even with a normal chest radiograph, or an alternative diagnosis. In contrast, diffuse pleural thickening regardless of etiology can cause dyspnea of varying severity to overt respiratory failure. Restriction on pulmonary function testing is often noted.

The diagnosis of trapped lung requires documentation of chronicity and the absence of malignancy or active pleural inflammation. The pleural fluid resulting from a trapped lung has lactate dehydrogenase and total protein values in the transudative range. Findings that suggest a trapped lung are an initial negative mean pleural liquid pressure, increased pleural space elastance (a change of >25 cmH₂O pressure after removing 1 l of pleural fluid), failure of lung expansion after thoracentesis or tube drainage, and the demonstration of a visceral pleural peel on an air-contrast chest computed tomography. Trapped lung is confirmed when the lung expands to the chest wall following decortication.

**Pathogenesis**

Pleuritis with pleural effusions develops in patients with a number of diseases. The majority of these pleural insults regress, either spontaneously or with medications, without the need for pleural space drainage. How pleural inflammation resolves in some and pleural fibrosis develops in others remains unclear. In experimental models of pleuritis, the mesothelial cells proliferate and become reactive in response to injury. These mesothelial cell changes appear to assist in the removal of fibrin and inflammatory debris and in repair of the pleural surface. The degree of mesothelial cell and basement membrane injury and regeneration are pivotal in determining if pleural fibrosis occurs.

In the normal pleural space, a matrix does not exist. For pleural fibrosis to develop, a matrix must form to allow the fibrotic process to continue. This matrix is a product of plasma coagulation substrates that are released into the pleural space by the inflammatory response. Tissue factor is the major procoagulant that initiates matrix formation. Tissue factor, released from mesothelial cells, fibroblasts, and macrophages, acts upon other procoagulant...
substrates, resulting in the conversion of fibrinogen to fibrin, which is pivotal to the creation of the matrix. Tissue factor pathway inhibitor (TFPI), an inhibitor of tissue factor, is also elaborated by mesothelial cells and lung fibroblasts in response to injury. The balance between tissue factor and TFPI is important in the production and persistence of pleural fibrosis. When intrapleural generation of tissue factor exceeds the formation of TFPI, the procoagulant state that exists favors fibrin formation. Concomitantly, fibrinolysis is downregulated by the increased expression of plasminogen activator inhibitor-1 (PAI-1), allowing for the formation of the fibrin matrix. Therefore, the pathogenesis of pleural fibrosis can be considered a disorder of fibrin turnover.

An early response to mesothelial cell injury is the elaboration of chemokines, which facilitate phagocytic cell migration intrapleurally. Vascular endothelial growth factor (VEGF) is one of the chemokines that is upregulated in malignancy, empyema, and tuberculous pleurisy. VEGF not only promotes angiogenesis but is also responsible for increasing vascular permeability, which allows for the efflux of procoagulant fluid intrapleurally.

Both cellular and extracellular proteins are responsible for perpetuating pleural inflammation. One of these protein mediators is hyaluronan, which emulates the inflammatory process by attracting mononuclear cells and malignant cells in pleural metastases. Type I and IV collagen and fibronectin released by mesothelial cells may also participate in sustaining inflammation through recruitment of inflammatory cells and maintenance of vascular permeability.

The mesothelial cells not only are vital in initiating inflammation but also in regulating the duration of the inflammatory response. Apoptosis of inflammatory cells is inhibited by granulocyte-macrophage colony-stimulating factor (GM-CSF), which is elaborated by mesothelial cells. GM-CSF will also inhibit programmed cell death of neutrophils, monocytes, and lymphocytes during pleural space inflammation. The inflammation may resolve ‘normally’ with an intact mesothelium without fibrosis/remodeling; however, pleural space remodeling may occur. How pleural space remodeling occurs remains unknown, although some insight into this process has been made with the talc pleurodesis model.

Intrapleural instillation of talc rapidly upregulates basic fibroblast growth factor (b-FGF) in pleural fluid, while in vitro, talc stimulates b-FGF release from mesothelial cells. An inverse correlation was observed between tumor mass and b-FGF levels indicating that patients with larger tumor burdens had lower b-FGF levels and were more likely to have failed pleurodesis. Therefore, for talc pleurodesis to be successful, mesothelial cells must be intact and stimulated to produce b-FGF, which leads to pleural fibroblast proliferation and subsequent pleural fibrosis.

Another cytokine that plays a pivotal role in the development of pleural fibrosis is transforming growth factor beta (TGF-β). TGF-β, which is considered to be the most potent profibrotic cytokine, has generated recent attention for its role in promoting pleural fibrosis. Intrapleural instillation of TGF-β induces rapid pleural fibrosis in an experimental animal model. Not only is TGF-β a potent chemoattractant for fibroblasts, it also plays a role in matrix production by upregulation of collagen formation and matrix remodeling. TGF-β has been shown to inhibit plasminogen activator and stimulate plasminogen activator inhibitor secretion from pleural mesothelial cells. TGF-β appears to be an important link between disordered fibrin turnover and the development of pleural fibrosis (Figure 3).

Animal Models

Most animal models of pleural inflammation utilizing irritants are a method of investigating fibrothorax; however, there are animal models more relevant to investigating the common pathological pleural fibrotic diseases seen in humans. Asbestos-induced pleural disease and tuberculous pleuritis are two examples of diseases studied in several mammalian species that resemble human diseases.

In tuberculous pleurisy, animals are immunized to BCG several weeks prior to intrapleural instillation injection of BCG. The development of pleurisy with well-defined stages of inflammation is consistently observed. The earliest stage of pleuritis is the development of a granulocytic exudative pleural effusion, which rapidly changes to a predominance of mononuclear leukocytes. With resolution of the pleural effusion, there is a residue of pleural adhesions and fibrosis.

In a model of asbestos-induced pleural effusion, chrysotile asbestos was injected into the pleural space of rabbits. The initial response to the intrapleural asbestos fibers was a granulocytic influx with localization of asbestos fibers into granulomatosis pleural plaques. In neutropenic rabbits, a granulocytic response to asbestos fibers was absent and plaque formation did not develop. Atypical mesothelial cells invading the subpleural connective tissue was noted at 10 months.

Management and Current Therapy

Appropriate management of pleural fibrosis requires an understanding that clinically significant pleural
fibrosis requires involvement of the visceral pleura. Patients with isolated parietal pleural fibrosis, such as asbestos pleural plaques, do not develop respiratory symptoms. In contrast, visceral pleural fibrosis can lead to significant restriction, dyspnea, and respiratory failure.

The use of steroids to reduce or prevent pleural fibrosis has been limited to tuberculous and rheumatoid pleurisy. Some have advocated systemic corticosteroids in the management of tuberculous pleurisy to limit the degree of pleural inflammation and resultant pleural fibrosis. Although most agree that residual pleural thickening following tuberculous pleurisy has little or no effect on lung function, several randomized trials of corticosteroids have been performed. Based on these studies, there is insufficient evidence to support the use of corticosteroids to prevent or diminish the development of pleural fibrosis in tuberculous pleural effusions. However, systemic corticosteroids will result in more rapid resolution of the effusion and improvement in symptoms.

Those with a protracted course of rheumatoid pleurisy may develop significant pleural fibrosis and trapped lung. There are no controlled studies that have evaluated the effectiveness of corticosteroids in the management of rheumatoid pleurisy. Single case reports and small series using systemic and intrapleural corticosteroids have described variable success.

Decortication is an effective strategy for treating symptomatic patients regardless of cause when significant underlying parenchymal disease has been excluded. For patients with severe respiratory compromise, decortication is the only effective treatment of a trapped lung or fibrothorax. The timing of decortication is important, since pleural thickening in some patients typically resolve over several months. Therefore, only when pleural fibrosis has been stable.

Figure 3  Pathogenic model of pleural fibrosis. TGF-β, transforming growth factor beta; PAI-1, plasminogen activator inhibitor-1; TFPI, tissue factor pathway inhibitor; VEGF, vascular endothelial growth factor.
Chylothorax, Pseudochylothorax, LAM, and Yellow Nail Syndrome

I Kalomenidis, Athens University, Athens, Greece
Y C G Lee, University College London, London, UK

© 2006 Elsevier Ltd. All rights reserved.

Abstract

Chylothorax and pseudochylothorax are pleural effusions with high lipid contents. Chylothorax is a triglyceride-rich effusion caused by the disruption of the thoracic duct, most commonly by trauma or mediastinal tumors. Pseudochylothorax is a chronic, cholesterol-rich pleural effusion, usually secondary to tuberculous pleuritis. Pleural fluid lipid analysis is needed to establish the diagnoses. The initial management strategies for chylothorax include nutrition support, reduction of chyle flow, and drainage of the pleural space for symptomatic relief. If the chylothorax persists, thoracic duct embolization, surgical repair, or pleurodesis may be considered, depending on the etiology of the chylothorax. Lymphangioleiomyomatosis is a progressive cystic lung disease often complicated by recurrent chylous effusions and/or pneumothoraces. Yellow nail syndrome is a rare disorder of unknown etiology characterized by yellow nails, lymphoedema, and recurrent lymphocytic pleural effusions, which may require pleurodesis.

Chylothorax

Chylothorax, the accumulation of chyle in the pleural cavity, usually develops secondary to disruption of the thoracic duct along its intrathoracic route. The thoracic duct drains chyle (lymph-rich in chylomicrons from dietary fat) from the abdomen through the diaphragm and into the posterior mediastinum before terminating in the region of the left jugular and subclavian veins.

The thoracic duct drains approximately 21 lymphs a day, but the flow rate varies with diet and increases significantly after ingestion of fat. Chyle is rich in T lymphocytes and, typically, has an electrolyte profile similar to serum and a protein concentration higher than 3 g dl$^{-1}$. Loss of chyle can lead to immunodeficiency, dehydration, and nutritional depletion. Chyle in the pleural space seldom elicits pleural inflammation or fibrosis, and secondary infection of chylous effusion is rare.

Pathogenesis and Etiology

Chylothorax most frequently results from trauma (including surgery) or tumor infiltration of the thoracic duct (Table 1). Occasionally, chylothorax can accumulate when chylous ascites migrate through the diaphragm into the pleural space. Common causes of chylous ascites include traumatic or malignant disruption of intra-abdominal lymphatic vessels and cirrhosis.

Malignancy and trauma (including surgery) are by far the leading causes of chylothorax (Table 1). Lymphoma accounts for 75% of the chylothorax cases due to malignancy. As such, lymphoma needs to be excluded in all patients with chylothoraces in whom no other causes can be identified.

Cardiothoracic surgery, especially involving the posterior mediastinum, can lead to postoperative chylothorax (up to 4% in an esophagectomy series). Nonsurgical thoracic trauma (both penetrating and nonpenetrating) is a recognized cause of chylothorax. Lymphatic abnormalities (e.g., lymphangioleiomyomatosis and benign mediastinal disorders; Table 1) are less common etiologies. A chylothorax is termed idiopathic when no cause is found.

Chylothorax can affect people of all ages. Fetal chylothorax, although uncommon, is a recognized cause of developmental abnormalities and can be fatal. Chylothorax is also the most common type of...