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# 75

# Pathology of the Pleura

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Diseases of the pleural surfaces and pleural cavity comprise a heterogeneous group of reactive, infectious, and neoplastic processes that may draw upon expertise in several areas of pathology: surgical pathology (*e.g.*, biopsies, resections), cytopathology (*e.g.*, cells in effusions), microbiology (*e.g.*, pleural culture), and clinical chemistry (*e.g.*, molecular constituents of pleural fluid). The integration of such data often clarifies the cause of the pleural disease.[1,2]

In this chapter, the histology of the normal pleura will be briefly reviewed, followed by a discussion of the different causes of pleural space enlargement. The histology of pleural abnormalities and the resultant morphologic differential diagnosis also will be covered. Because Chapters 3, 36, and 57 are devoted to cytology, asbestosis, and mesothelioma, respectively, these topics will be reviewed only briefly.

## *NORMAL STRUCTURE*

The pleura is a thin, grossly smooth and glistening serous membrane that lines the inner surfaces of the chest wall and diaphragm (*i.e.*, parietal pleura) and completely invests the lungs, extending into their interlobar fissures (*i.e.*, visceral pleura). The parietal pleura can be subdivided into four anatomic regions: costal, mediastinal, diaphragmatic, and cervical (*i.e.*, apical pleura). The left and right pleural cavities are completely separated.[1,2]

Although the pleural membrane in routine stains appears histologically simple, being composed of a single row of flattened to cuboidal mesothelial cells with a nondescript underlying fibrovascular connective tissue zone (Fig. 75-1), five distinct layers can be observed by elastic tissue stain.[3] The first layer is the mesothelial cell layer. Deep to the mesothelial cells is a loose connective tissue zone that rests on a prominent external elastic lamina (Fig. 75-2). Beneath the external elastic lamina is an interstitial zone, rich in capillaries and lymphatics. The final layer is the internal elastic lamina, which often appears interrupted or discontinuous but adheres tightly to the underlying pulmonary parenchyma, diaphragm, and chest wall.

## *DEVELOPMENTAL AND FUNCTIONAL ASPECTS*

The pleura develops from the extraembryonic coelom; the parietal pleura is derived from the somatopleura, and the visceral pleura from the splanchnopleura.[3] Both layers are lined by mesothelial cells that lie on a continuous basement membrane. Mesothelial cells are connected by tight and gap junctions and desmosomes and have surface microvilli that are more numerous on the visceral layer and toward the base of the lung; they are coated with a glycocalyx with strong affinity for acid mucopolysaccharides. This slippery surface protects from frictional damage. Mesothelial cells have pinocytotic vesicles and vacuoles and are capable of phagocytosis.[3,4] Cytoplasmic tonofilaments, representing cytokeratin, are abundant. A thin submesothelial layer of connective tissue covers a well-developed network of fibers that forms the external elastic lamina. This is separated from the internal elastic lamina by the interstitial layer, which contains lymphatics and blood vessels, and is continuous with the interlobular connective tissue.[3]

The existence of stomata between the pleural space and lymphatics in the parietal pleura has been confirmed; these stomata are marked by aggregates of macrophages and specialized mesothelial cells, referred to as Kampmeier foci. They are not found on the visceral pleura. In the caudal portion of the parietal pleura, the mesothelial and lymphatic endothelial cells are in direct apposition, without an intervening basement membrane. Here, the stomata provide a direct connection between the pleural cavity and the underlying lymphatics, allowing absorption of particles up to 10 μm in diameter.[4] Pleural fluid is normally produced mainly through the parietal pleura and is absorbed by the visceral pleura.[4]

Subserosal cells have the ultrastructural features of fibroblasts and express vimentin but not cytokeratin; differentiation of these

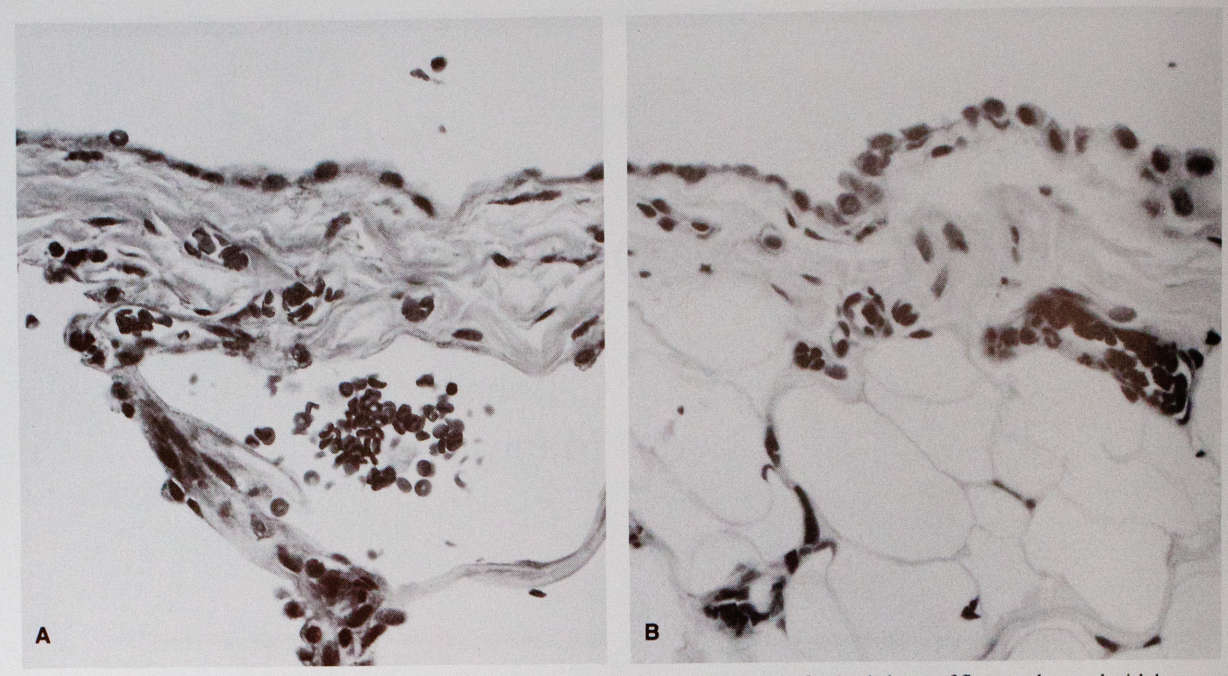


**FIGURE 75-1.** (**A**) The visceral pleura and (**B**) the parietal pleura consist of a single layer of flattened-to-cuboidal mesothelial cells that rest on a nondescript-appearing fibrovascular connective tissue zone. (H & E stain; intermediate magnifications.)

cells involves the acquisition of cytokeratin.[4] Regeneration after damage is generally complete by 8 to 10 days.[3]

## SIGNS AND SYMPTOMS OF PLEURAL DISEASE

The pleural space is normally a potential space with the visceral and parietal layers in direct apposition and separated by a thin fluid layer.[3–5] The creation of a discernible pleural space due to the accumulation of fluid (*i.e.*, effusion), air (*i.e.*, pneumothorax), or pleural thickening indicates disease and may be accompanied by the development of symptoms such as chest pain, dry nonproductive cough, or dyspnea.[1,2]

The parietal pleura contains pain fibers; therefore, the presence of pleural pain accompanied by an effusion indicates pleurisy. The pain is usually referred to the affected area. However, pain can radiate to the abdomen or shoulder, indicating diaphragmatic involvement.

Dyspnea is usually related to a reduction in lung volume due to the presence of a large effusion or pneumothorax. However, the depressed respiration cannot be solely accounted for by the size of the effusion, suggesting participation of additional factors such as intrinsic lung disease. The etiology of the dry cough is not clear, but it is probably related to pleural inflammation.

## PLEURAL EFFUSIONS

Evaluation of the pleural fluid is useful to formulate an initial differential diagnosis and direct further diagnostic or therapeutic maneuvers.[1,2,6,7] The initial question usually posed is whether the effusion is a transudate or an exudate. The traditional point of separation is a protein concentration of 3 g/dL. However, Light and colleagues have proposed more sensitive parameters that can be employed.[6] Display 75-1 lists the major causes of pleural effusion in decreasing order of incidence.[1]

### *Transudates*

Pleural transudates should be clearly separated from exudates (Table 75-1). A transudate is a straw-colored, nonviscous, odorless serous effusion. The effusion is usually clear but may be blood-

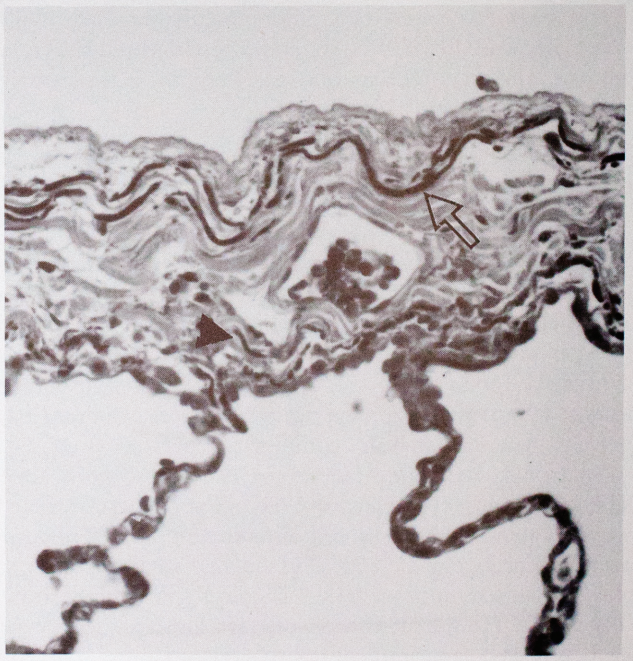

**FIGURE 75-2.** An elastic-stained section of the visceral pleura reveals a well-developed external elastic lamina (*open arrow*) and a discontinuous internal elastic lamina (*closed arrow*) that bracket the capillary and lymphatic containment zone. (Intermediate magnification.)

**DISPLAY 75-1. CAUSES OF PLEURAL EFFUSION IN DECREASING ORDER OF INCIDENCE**

Congestive heart failure
Bacterial pneumonia
Malignant neoplasms
Pulmonary embolus
Viral pneumonia
Cirrhosis
Gastrointestinal disease
Collagen-vascular disease
Tuberculosis
Asbestos
Mesothelioma

*From Light RW, ed. Pleural diseases. Philadelphia: Lea and Febiger, 1983:1.*

**DISPLAY 75-2. CAUSES OF PLEURAL TRANSUDATE**

**Most Common Causes**
Congestive heart failure
Nephrotic syndrome
Cirrhosis
Pulmonary embolus

**Other Causes**
Constrictive pericarditis
Sarcoidosis
Meigs syndrome
Dressler syndrome
Mediastinal tumor
Myxedema
Peritoneal dialysis

tinged; it is low in protein and cellular elements.[3–5] It develops when the intravascular colloid oncotic pressure is low or when the capillary hydrostatic pressure is high enough to favor accumulation of fluid in the pleural space.[3,6] The fluid will accumulate until the hydrostatic or oncotic forces achieve equilibrium. Hypoproteinemic states and congestive heart failure are the most common causes of pleural transudates. Because the pleural membranes themselves are not responsible for this process, once a transudative effusion is recognized, attention should be addressed to the underlying systemic factors promoting formation of the effusion (Display 75-2). A transudative effusion does not totally exclude the presence of a neoplastic or infective process but does reduce the likelihood that pleural fluid or biopsy will provide the definitive answer.

## *Exudates*

Exudative pleural effusions contain high levels of protein and, usually, cellular elements. An exudate results from increased vascular permeability secondary to disease intrinsic to the pleural membranes. There are numerous pleural and systemic diseases that may be responsible for an exudate. The characteristics of the exudate, results of pleural fluid cytology or pleural biopsy, and clinical information, require correlation to define the disease process responsible. There are four basic types of exudates: serous, which produces hydrothorax; bloody, which produces hemothorax; purulent, which produces pyothorax; and chylous, which produces chylothorax. The nonserous nature of an exudate is particularly useful to focus the attention on several possibilities.

**TABLE 75-1**
Separation of Transudate From Exudate

| | Transudate | Exudate |
|---|---|---|
| Protein concentration (g/dL) | <3 | >3 |
| Pleural protein to serum protein ratio | <0.5 | >0.5 |
| Pleural fluid LDH level (IU/L) | <200 | >200 |
| Pleural LDH to serum LDH ratio | <0.6 | >0.6 |
| Specific gravity | <1.015 | >1.015 |

*LDH, lactic dehydrogenase.*
*From Light RW, MacGregor MI, Luchsinger PC, et al. Pleura effusions: the diagnostic separation of transudates and exudates. Ann Intern Med 1972;77:507.*

## *Hemothorax*

Hemothorax results from hemorrhage into the pleural cavity. Although small quantities of red blood cells (*i.e.*, 5000–6000 cells/mm) can impart a reddish tint to an effusion, hemothorax is defined by a hematocrit at least 50% of that of the peripheral blood.[1] The blood in the pleural space is usually evacuated to avoid several possible complications, such as infection, effusion enlargement, or fibrothorax. The etiology of hemothorax includes blunt chest trauma and penetrating chest injuries (Fig. 75-3), iatrogenic causes (*e.g.*, bleeding diathesis), neoplasms (*e.g.*, mesothelioma, carcinoma), and pulmonary infarcts. In patients with no predisposing events in whom pulmonary embolus is excluded, pleural biopsy and cytology are necessary to rule out a neoplastic cause.

## *Pyothorax*

A purulent pleural effusion or empyema is usually a parapneumonic complication of a bacterial pulmonary infection, or results from infection following a penetrating chest injury. It can be associated with hemothorax or pneumothorax, or it can be a therapeutic complication of thoracotomy, thoracocentesis, or endoscopy. Although empyemas are rich in neutrophils, the minimum number required is not established, nor is the requirement for a positive culture. Although either aerobic or anaerobic organisms, or both, may be cultured, empyema is most common with necrotizing anaerobic pneumonias, and a large percentage of cases will have more than one organism cultured (see Chap. 39).[1,2]

Empyemas that are inadequately treated or poorly responsive to treatment may show evolution from an initial exudative phase rich in fibrin, neutrophils, and organisms though an organization phase with granulation tissue formation (Figs. 75-4 and 75-5). Loculation, adhesion formation, or even fibrothorax may develop. Less often, a fistulous pleurocutaneous or pleurobronchial complication may occur.

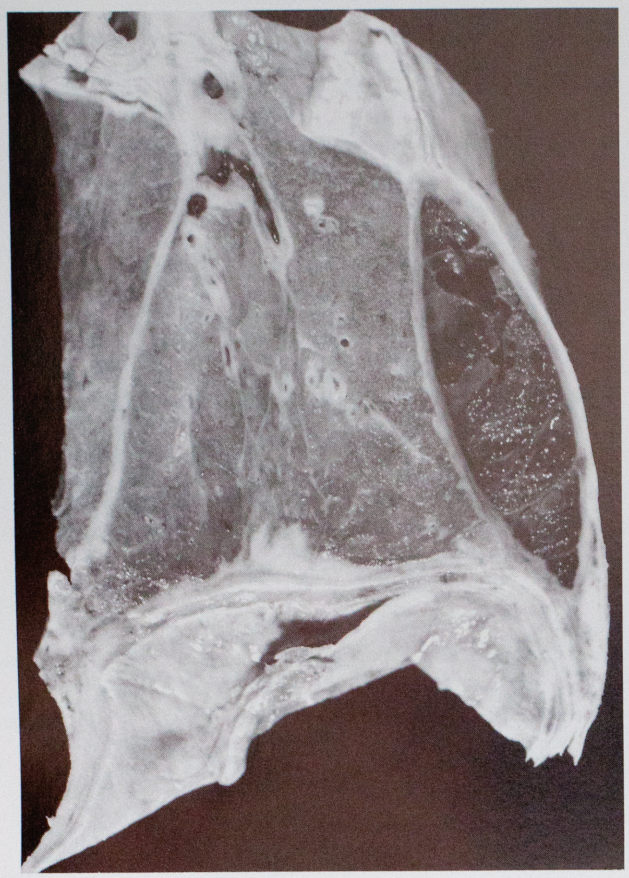

**FIGURE 75-3.** Gross postmortem appearance of the lung in a patient who had been in a car accident and had sustained numerous rib fractures and hemothorax. (Contributed by the editor.)

### *Chylothorax*

Chylothorax is an odorless, milky effusion rich in triglycerides (>110 mg/dL) of intestinal chylomicron origin.[8,9] Trauma is the second most common cause, and often develops as a delayed complication of cardiovascular or esophageal surgery (Display 75-3). Histologic diagnosis is useful in adult nontraumatic causes because neoplasia is likely. In this context, cytologic evaluation of the effusion in conjunction with pleural biopsy provides a greater diagnostic yield than either study alone.[10,11]

Chylothorax presenting in a neonate focuses the attention on developmental anomalies.[8,9] Lung biopsy will often be performed to see if congenital pulmonary lymphangiectasia (CPL; see Miscellaneous) is present.[12,13] As indicated in Display 75-3, ectasia of pleural lymphatics may have several other causes. It is particularly important to exclude cardiovascular etiologies because they require a radically different therapy.[8,9,12,13]

## *PNEUMOTHORAX*

Pneumothorax is the accumulation of air within the pleural space following an abnormal communication with the outside or with a hollow viscus; it is usually the result of rupture of an emphysematous bleb in the lung (Fig. 75-6; Display 75-4).

The air leak may close with gradual resorption (*i.e.*, closed pneumothorax) or remain open with air freely moving in and out of the pleural cavity (*i.e.*, open pneumothorax). Alternatively, air

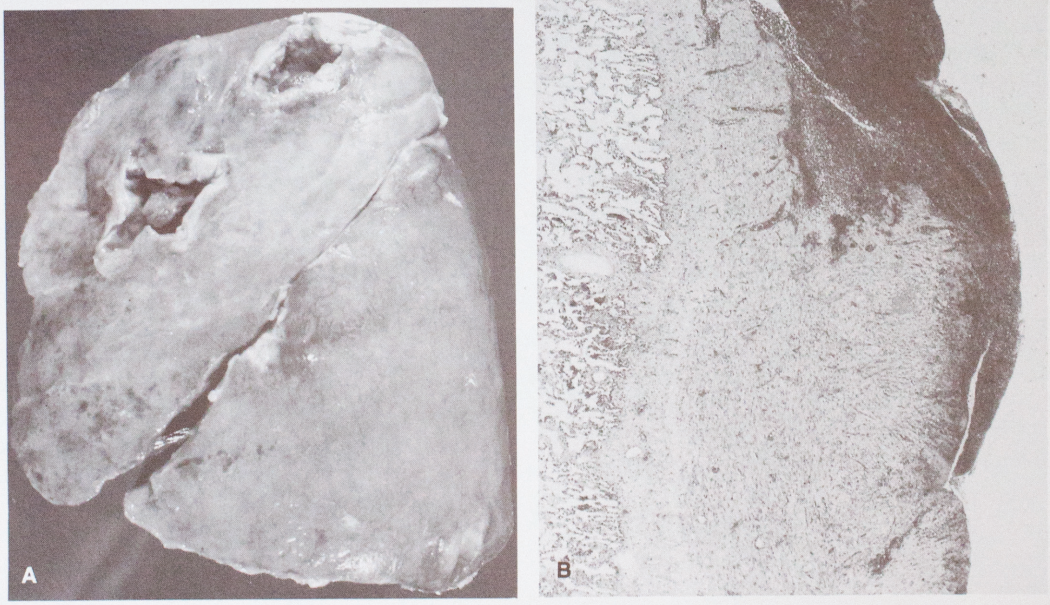


**FIGURE 75-4.** (**A**) Lungs of a child who died following complications of staphylococcal pneumonia with empyema after an episode of near-drowning. (**B**) Pleurectomy in a patient with empyema complicating a bacterial pneumonia shows hemorrhage and a thick layer of inflamed granulation tissue. (H & E stains; low magnifications.)

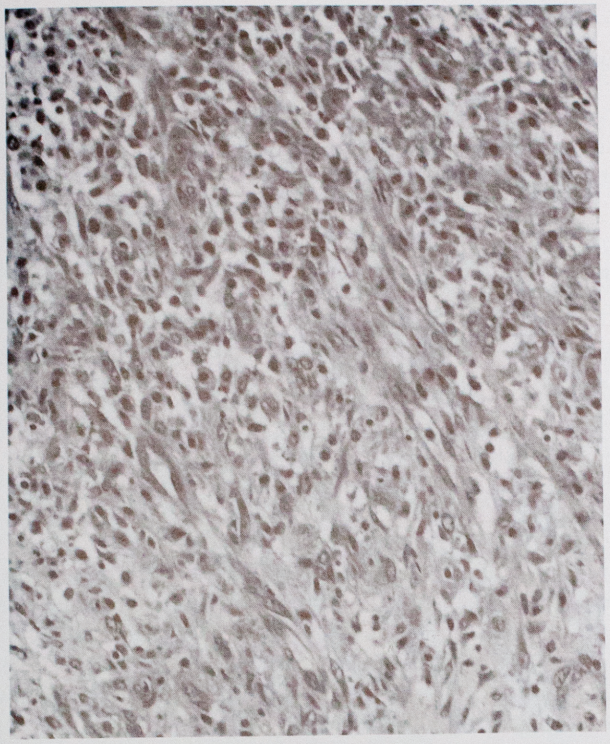

**FIGURE 75-5.** Granulation tissue is seen in specimen with empyema (Figure 75-4*B*). (H & E stain; low magnification.)

may enter the pleural space without leaving (*i.e.*, tension pneumothorax) because of a valvelike effect of tissue at the orifice. This results in a progressive increase in the pneumothorax respiratory compromise, and mediastinal shift.

There is usually intrinsic pulmonary disease visible on chest x-ray films or apparent histologically in resected tissue as a bleb developing in the context of chronic obstructive pulmonary disease (COPD) or chronic infection.[14–18] Even in spontaneous or idiopathic pneumothorax of adults, which can develop in otherwise healthy young adults, resected tissue is not normal.[14,15] Apical bleb formation can often be implicated by the presence of nonspecific changes similar to those encountered in COPD and chronic infection. Mesothelial hyperplasia, pleural fibrosis, emphysematous changes, and a mixed-cell inflammatory infiltration are usual findings.[14,15] A subgroup of patients with pneumothorax, approximately 40%, will show a distinctive lesion known as reactive eosinophilic pleuritis (see Fibrinoinflammatory Processes).[16,17]

## CYTOLOGY OF PLEURAL DISEASE

The cytologic findings of a pleural effusion can provide useful diagnostic information. The most significant finding is the presence of neoplastic cells of a primary or metastatic tumor. Chapters 3 and 4 contain discussions of the pertinent cytologic clinical and histologic features, respectively.[1,3,7] The presence of non-neoplastic inflammatory cells can also be a guide to the diagnostic possibilities and necessity for microbiologic studies or further clinical information (Display 75-5).

**DISPLAY 75-3. CLASSIFICATION AND MAJOR ETIOLOGIES OF CHYLOTHORAX**

- Congenital
  - Malformations of thoracic duct
  - Pulmonary lymphangiectasia
    - Primary
    - Secondary to congenital heart disease
    - Part of systemic lymphangiectasia
- Traumatic
  - Thoracic surgery
  - Penetrating injury
  - Violent coughing and vomiting
- Nontraumatic
  - Malignant neoplasm
  - Lymphangioleiomyomatosis
  - Parasitic infections
  - Tuberculosis
- Idiopathic

## HISTOLOGY OF PLEURAL DISEASE

It is not surprising that because the pleural membranes are simple in their histology, consisting of fibrovascular tissue, lymphatics, and mesothelial cells, the pleura has a limited range of response to injury. The histologic expression of pleural diseases can be grouped into four general categories: fibrinoinflammatory processes, fi-

**FIGURE 75-6.** Gross appearance of a totally collapsed lung in a young-adult patient with pneumothorax of unknown cause. (Contributed by the editor.)

**DISPLAY 75-4. CAUSES OF PNEUMOTHORAX**

**Parietal Origin**

Penetrating chest wall injury
Fractured rib penetrating skin and pleura

**Visceral Origin**

Chronic obstructive pulmonary disease (*i.e.*, emphysema, chronic bronchitis)
Chronic infections (*i.e.*, bronchiectasis, cystic fibrosis, tuberculosis)
Neonatal respiratory distress syndrome
Mechanical ventilation
Idiopathic pneumothorax of young adults

**Rare Causes**

Eosinophilic granuloma
Lymphangioleiomyomatosis
Endometriosis
Pneumoconiosis

brosing processes, neoplastic processes, and miscellaneous processes. The first three of these are not mutually exclusive, because fibrosing disorders are usually preceded by an exudative fibrinoinflammatory phase and may accompany neoplastic pleural involvement.

Pleural tissue for histologic diagnosis is either derived from percutaneous pleural biopsies or included with a portion of resected lung. In biopsies, only the parietal pleura is usually sampled, unless the pleural space has been obliterated. In several large series of pleural biopsies, tuberculosis and malignancy have been the most common diagnoses established by biopsy.[10,11,18–20]

**DISPLAY 75-5. CELLULAR COMPOSITION OF PLEURAL EXUDATES (PERCENTAGE OF CELLS)**

**Lymphocytic Exudates (>50%)**

Tuberculosis
Malignancy
Connective tissue diseases

**Neutrophilic Exudates (>50%)**

Empyema
Pulmonary embolus
Subphrenic abscess
Tuberculosis, early in disease
Pancreatitis
Malignancy

**Eosinophilic Exudates (>10%)**

Pneumothorax
Hemothorax
Eosinophilic granuloma
Drug reaction
Parasites
Fungi
Collagen-vascular disease
Pulmonary embolus

## *FIBRINOINFLAMMATORY PROCESSES*

A variety of systemic, infectious, and iatrogenic diseases can result in an inflammatory or fibrinous pleuritis (*e.g.*, infections, hemothorax, uremia, connective tissue diseases, radiation, drug reaction, vasculitis).[3,5,21]

### *Fibrinous Pleuritis*

Fibrinous pleuritis is invariably accompanied by an exudative effusion. The pleura is thick and edematous with the deposition of a layer of fibrin over the pleural surface.[3,5,21] It is associated with a variable loss of mesothelial cells or reactive mesothelial changes (Fig. 75-7). If the fibrinous exudate does not resolve, it will ultimately provoke fibroblast proliferation and capillary ingrowth characteristic of granulation tissue, which may culminate in pleural fibrosis. The reactive mesothelial cells in fibrinous pleuritis and reactive fibroblasts in active granulation tissue need to be distinguished from neoplastic alterations, a distinction that can be difficult in small biopsy specimens.

The cellular composition of the accompanying pleural inflammatory infiltrate can be quite variable. A lymphocytic predominance is common but nonspecific. A neutrophilic infiltrate may reflect infection or be part of the granulation tissue response. The presence of eosinophils or granulomas, however, may be diagnostically useful. Granulomatous pleuritis can elicit a differential diagnosis of mycobacterial infection, sarcoidosis, rheumatoid arthritis, foreign-body reaction, or fungal infection.

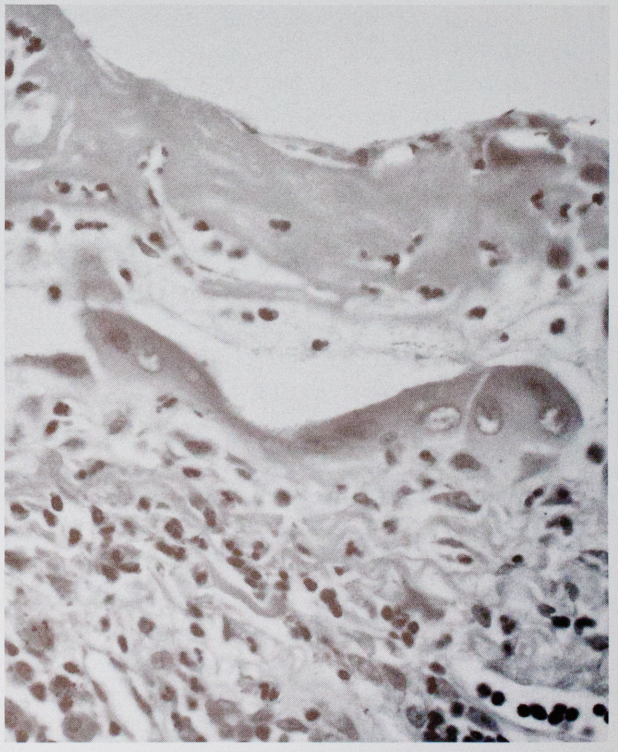

**FIGURE 75-7.** Fibrinous pleuritis with large reactive mesothelial cells embedded within a layer of fibrin. (H & E stain; intermediate magnification.)

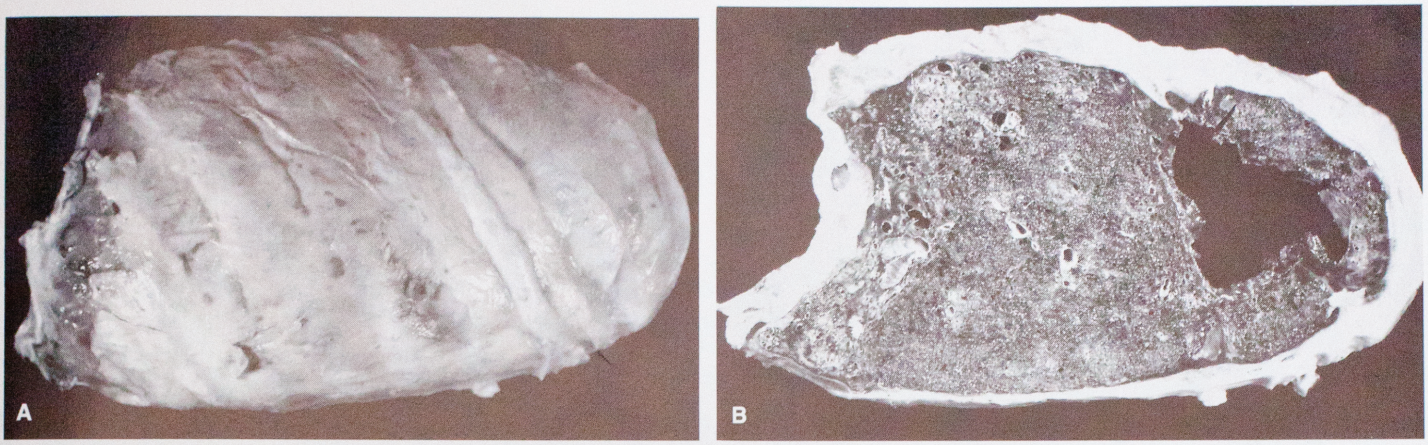


**FIGURE 75-8.** Tuberculous pleuritis. (**A**) External appearance of the left lung in a patient with coal worker's pneumoconiosis. (**B**) A sagittal section of the lung reveals a cavitary lesion of progressive massive fibrosis and extensive pleural tuberculosis. (Contributed by the editor.)

### *Tuberculosis Pleuritis*

Tuberculosis pleuritis accounts for 95% of cases of pleural granulomas regardless of whether caseation or acid-fast organisms are present (Fig. 75-8).[1,2] It can be the initial manifestation of tuberculosis and therefore can be present without obvious pulmonary parenchymal involvement. Pleural biopsy is an effective approach to the diagnosis of suspected tuberculosis (Fig. 75-9). It provides material for culture and reveals granulomas in 60% to 80% of cases.

### *Granulomatous Pleuritis*

Granulomatous pleuritis will occasionally have other etiologies.[21] In 1% to 5% of cases of sarcoidosis or rheumatoid arthritis, pleural involvement develops, occasionally accompanied by granulomas or actual rheumatoid nodules, respectively.[21,22] In contrast to tuberculosis patients, there are usually obvious pulmonary parenchymal lesions and lymph node enlargement in sarcoid or obvious arthritis, and subcutaneous nodules in rheumatoid arthritis, and this assists in the biopsy interpretation. Pleural involvement is rare in fungal disease; however, special stains for both fungi and acid-fast organisms are always warranted in the histologic evaluation of granulomas.

The presence of a predominance of eosinophils can elicit a differential diagnosis of reactive eosinophilic pleuritis secondary to pneumothorax, eosinophilic granulomas, Hodgkin disease, parasitic infection, or vasculitis (*i.e.,* Wegener granulomatosis and Churg-Strauss syndrome).

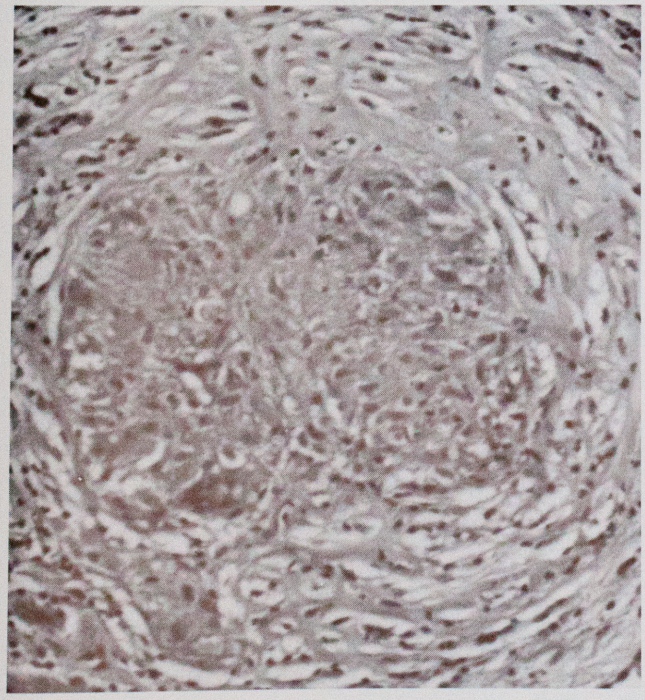

**FIGURE 75-9.** Tuberculous pleural granuloma is seen in a pleural biopsy specimen. (H & E stain; low magnification.)

### *Reactive Eosinophilic Pleuritis*

Reactive eosinophilic pleuritis (REP) is the most common cause of pleural eosinophilia. It is a nonspecific pleural response to air and develops following pneumothorax in 40% of cases.[15–17] It is characterized by a dense infiltrate of eosinophils and histiocytes within a thickened pleura (Fig. 75-10). Early lesions have fibrin and granulation tissue; older lesions demonstrate less inflammation and more fibrosis. To exclude the underlying diseases listed previously, nodular lung lesions should be absent, and the cytologic features of the processes require careful evaluation for Langerhans cells in eosinophilic granuloma, atypical cells of Hodgkin disease, organisms, and so forth. This is particularly important because pneumothorax with REP can develop as a complication of several other disorders, especially eosinophilic granuloma.[15–17]

## *PLEURAL FIBROSIS*

Pleural fibrosis is a common histologic abnormality. It is usually a reflection of a prior fibrinous or inflammatory pleuritis that has progressed to fibrosis. Evidence of a prior inflammatory process may remain, or the history or presence of associated pulmonary disease may assist in establishing its etiology. Causes of pleural fibrosis include organization of a fibrinoinflammatory process, intrinsic lung disease (*e.g.*, COPD, usual interstitial pneumonia),

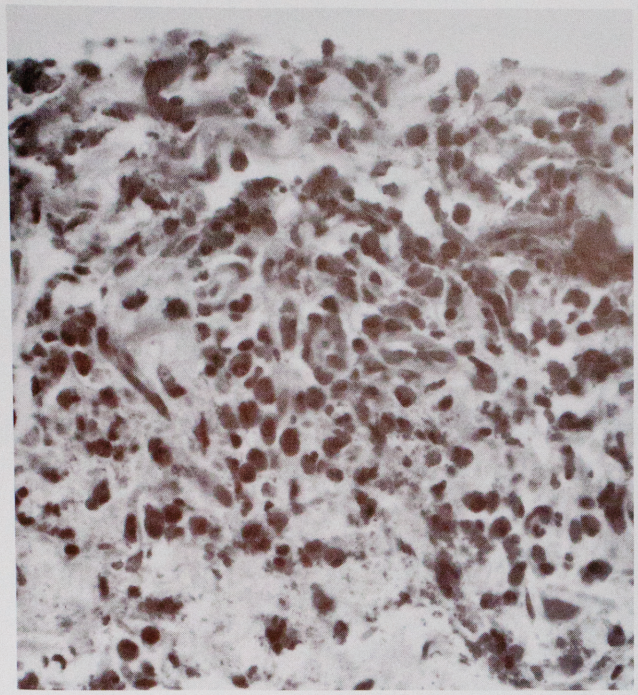

**FIGURE 75-10.** Reactive eosinophilic pleuritis occurred as a result of pneumothorax in a patient with emphysema. Most of the inflammatory cells are eosinophils. (H & E stain; intermediate magnification.)

asbestos-related plaques and diffuse pleural fibrosis, and tumor desmoplasia.

The organization of pleural exudates or fibrinoinflammatory pleuritis may culminate in several patterns of pleural fibrosis, which may evoke certain etiologic possibilities or clinical concerns. Such patterns include localized fibrosis with adhesion, hyalin plaque, and rounded atelectasis. Widespread fibrosis includes diffuse fibrosis, such as that seen in asbestos-exposed individuals, and fibrothorax.

### *Rounded Atelectasis*

Rounded atelectasis (*i.e.*, folded lung, shrinking pleuritis with lobar atelectasis) is a localized patch of lung distorted by pleural fibrosis, which produces a radiographic opacity that can resemble a peripheral lung mass and suggest a neoplastic process.[23,24] It is characterized by a thick folded or wrinkled pleura whose reexpansion is restricted by a thick layer of fibrous tissue. The adjacent lung is distorted and may be normal or show interstitial fibrosis. Some patients have a history of asbestos exposure with recurrent effusions.

### *Pleural Plaques*

Pleural plaques are circumscribed smooth, firm, gray-white, lustrous lesions (Color Figs. 75-1 and 75-2). They are rare on the visceral pleura. They are usually located on the lower parietal or diaphragmatic pleura and, particularly when bilateral, are associated with an asbestos exposure. Histologically, they are composed of hypocellular dense lamellae of collagen. The overlying mesothelial cells are flattened or more often denuded. Frequently, calcification is encountered. Vascular structures and inflammation are absent in the plaque but may be noted at its periphery (Fig. 75-11). Asbestos bodies are not usually identified unless digestion procedures are employed (see Chap. 36).[25]

### *Diffuse Fibrosis*

Diffuse fibrosis may affect the visceral pleura, parietal pleura, or both, and may obliterate the pleural cavity (*i.e.*, fibrothorax). The former may follow organization of chronic effusions in asbestos-associated pleural disease or may follow organization of a long-standing fibrinoinflammatory process, especially those of an infectious etiology. Histologically, the fibrosis is nonspecific. When it is bilateral and involves the lower portion of the lung or forms a diffuse thin layer of visceral fibrosis, again an asbestos exposure history should be sought (see Chap. 36). Biopsy and cytology are usually performed because diffuse pleural mesothelioma and metastatic carcinoma can also simulate diffuse pleural fibrosis.

## *PLEURAL NEOPLASIA*

Neoplastic diseases of the pleura include several primary thoracic neoplasms and tumors metastatic to the pleura.[26–28] Although the

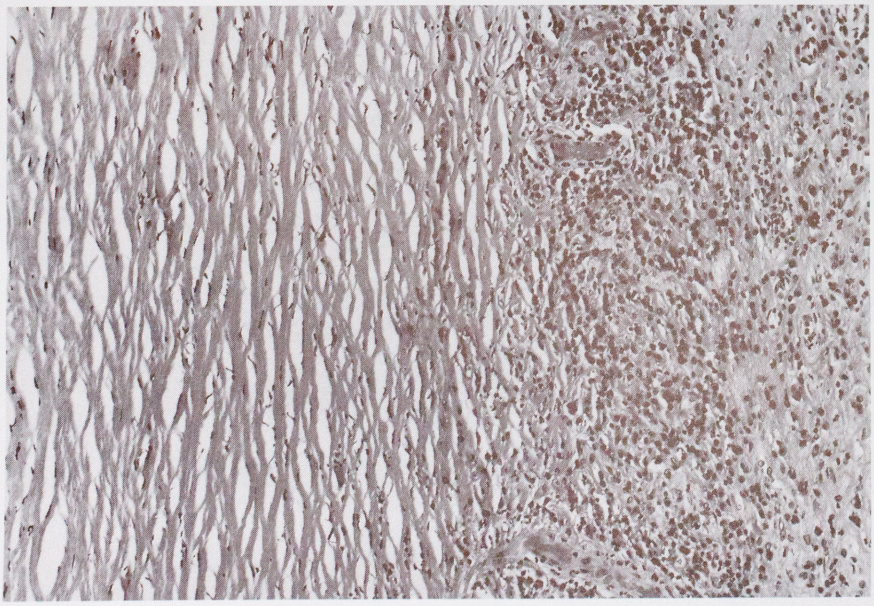

**FIGURE 75-11.** A histologic section of a pleural plaque in an asbestos-exposed individual shows the characteristic basket-weave fibrosis. Inflammation is present immediately beneath the plaque (*right*). (H & E stain; low magnification.)

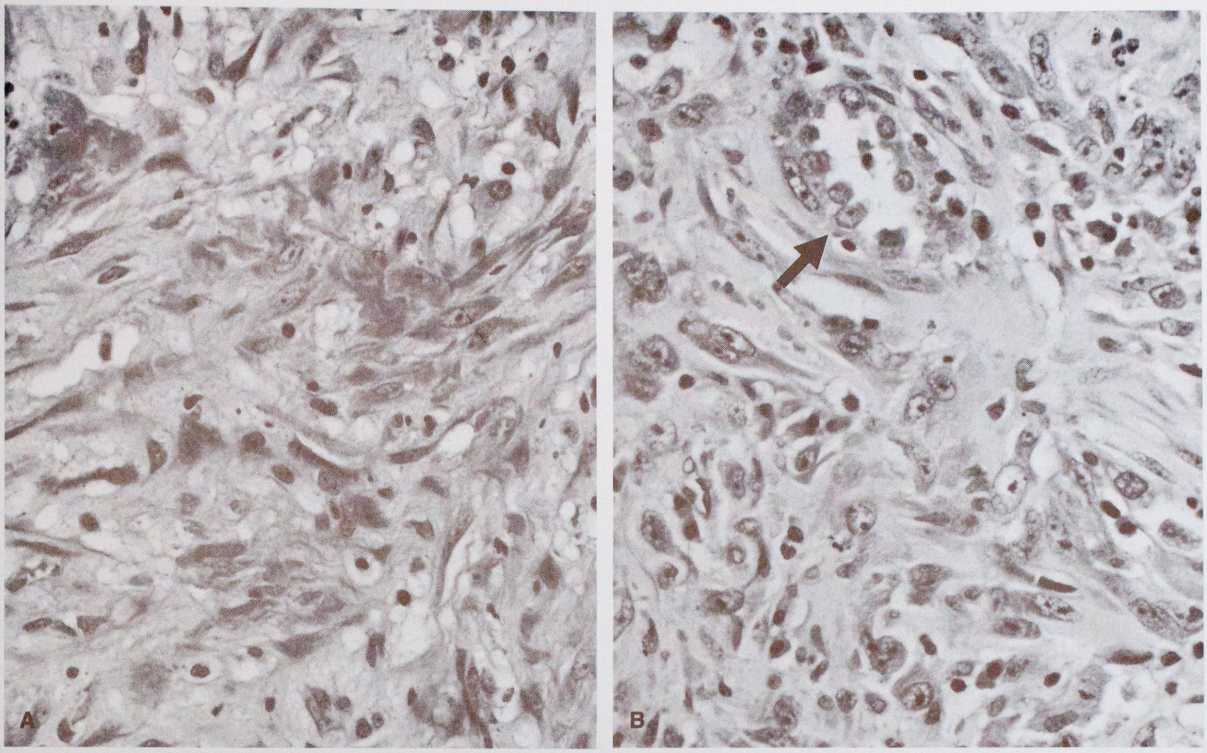


**FIGURE 75-12.** A histologic comparison of (**A**) pleural fibroplasia and (**B**) pleural malignant mesothelioma. The nuclear features in **B** and the presence of rudimentary gland formation (*arrow*) assist in ruling out a reactive process. (H & E stain; intermediate magnification.)

number of neoplasms is limited, their histology is diverse, and substantial morphologic overlap occurs between neoplasms and reactive processes of mesothelium and its stroma.[26–32]

From a morphologic perspective, pleural neoplasias can be divided into those with an epithelial cell phenotype and those with a mesenchymal or spindle cell phenotype. The initial and most crucial problem is discriminating between reactive mesothelial proliferation and stromal fibroplasia from neoplastic proliferation.[29,33] Reliance must be placed on cytologic features such as nuclear pleomorphism, nuclear hyperchromatism, and mitotic activity, as illustrated in Figure 75-12 (see Chap. 57).

Electron microscopy and immunohistochemistry are effective approaches to the subclassification of neoplasms once reactive processes have been excluded.[26–28,34] The absence of several con-

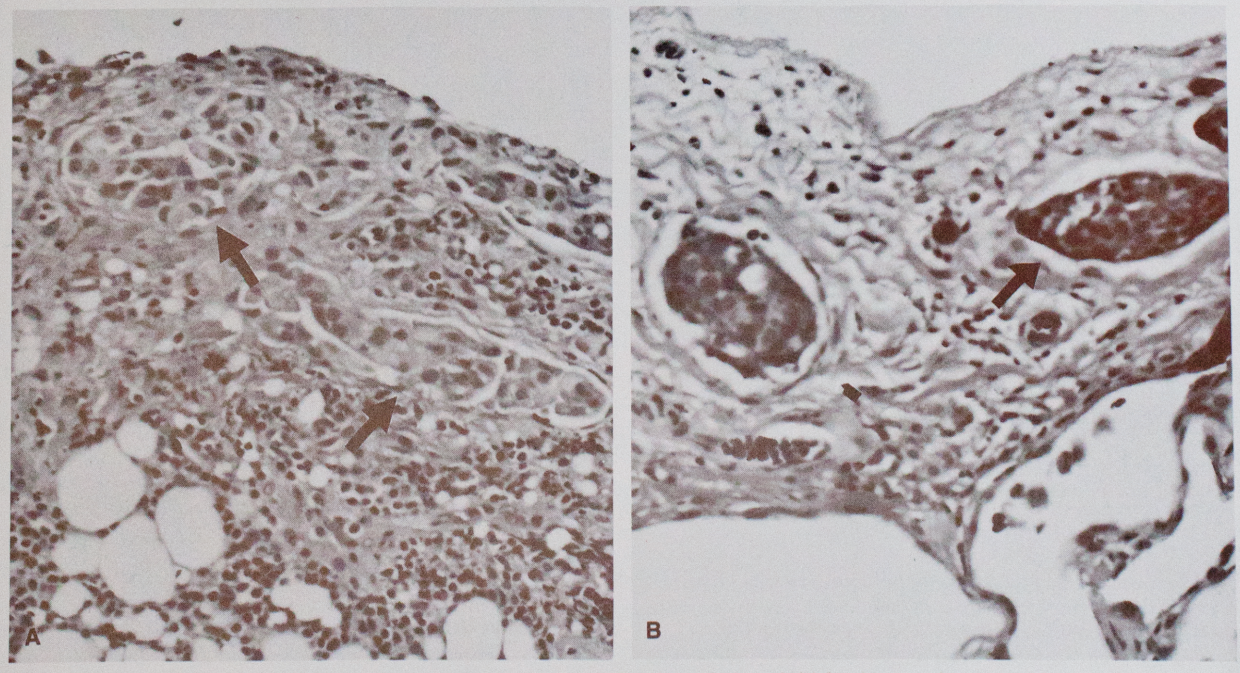


**FIGURE 75-13.** (**A**) Parietal pleural thickening and (**B**) visceral pleural thickening are the result of lymphangitic spread of breast and lung carcinoma, respectively (*arrows*). (H & E stain; low magnifications.)

stituents in mesothelioma (*e.g.*, epithelial mucin, carcinoembryonic antigen, Leu-M1, HMGF) supports the use of a panel of reactants. Even in examples of clinically typical diffuse pleural malignant mesothelioma, these ancillary studies are required because neoplastic diffuse pleural thickening can also occur in peripheral lung cancers (*i.e.*, pseudomesotheliomatous adenocarcinoma) and can result from desmoplasia associated with pleural lymphangitic spread (Fig. 75-13) of metastatic adenocarcinoma, most often from the lung, breast, ovary, and stomach.[35–37]

Pleural involvement occurs in approximately 20% of primary lung cancer and places the patient in a higher stage, T2.[38,39] Pleural involvement is defined by invasion through the internal elastic lamina, an observation that often requires elastic tissue stain.[38] This feature is biologically significant because it identifies tumors that have gained access to the rich capillary and lymphatic networks of the pleura. In addition, malignant pleural effusion can develop with further potential for dissemination.

## MISCELLANEOUS

Congenital pulmonary lymphangiectasia (CPL) is a serious, often lethal cause of neonatal acute respiratory distress.[12,13] Patients present with bilateral chylothorax within hours of birth. The lungs at thoracotomy or autopsy appear firm and bulky with a network of cysts or dilated lymphatics visible on the visceral pleura. Microscopically, large dilated subpleural, septal, and peribronchial lymphatics are present (Fig. 75-14; see Chap. 8). Systemic lymphangiectasia and lymphangiectasia secondary to cardiovascular disease will have an identical appearance.

CPL must also be morphologically distinguished from interstitial emphysema. In interstitial emphysema, the pleura itself is not involved, the spaces lack an endothelial cell lining, and there is often a foreign-body–type giant cell reaction (see Chaps. 19 and 26).[40]

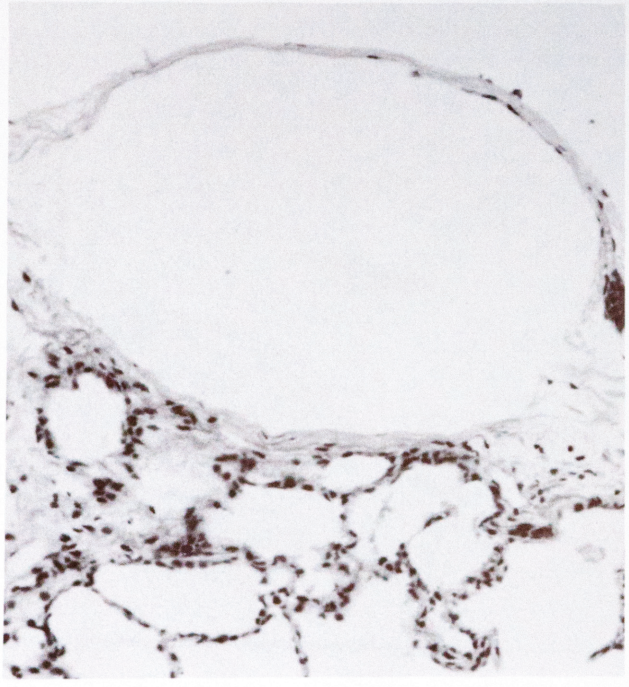

**FIGURE 75-14.** Congenital pulmonary lymphangiectasia is identified by large, dilated pleural lymphatics in a neonate who presented with chylothorax but no congenital heart disease or systemic lymphangiectasia. Septal lymphatics were also affected (not shown). (H & E stain; low magnification.)

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