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Pathology of Acute Respiratory Failure

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Cardiogenic Pulmonary Edema

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Pulmonary edema occurs when fluid moves from the capillary space into the interstitial and alveolar compartments of the lungs or when the extravascular water content of the lung is more than 4 to 5 mL/g of dry weight.[1] In cardiogenic pulmonary edema, this fluid movement takes place because the net pressure across the pulmonary microvasculature increases (*i.e.*, increased pressure edema). This form of pulmonary edema is reversible, and after the factor causing the increased intracapillary pressure is removed, the edema quickly resolves.

MECHANISMS

The theoretical approach to pulmonary edema rests on a basic understanding of the Starling forces, lymphatic drainage, and capillary and alveolar permeability.[2,3] In simplified form, there are four major Starling forces governing fluid movement: intravascular and extravascular hydrostatic pressures and intravascular and extravascular colloid osmotic pressures. Increased extravascular hydrostatic pressure causes fluid movement into vessels. Increased intravascular hydrostatic pressure, increased extravascular colloid osmotic pressure, or decreased intravascular colloid osmotic pressure moves fluid out of vessels into the interstitium and eventually into the alveolar space.

The permeability of the capillary endothelial cell influences pulmonary edema.[4,5] These cells are highly permeable to water and small molecules while having limited permeability to proteins. Alveolar epithelium, although readily permeable to water, is much less permeable to small molecules and proteins than capillary endothelium.[6,7] Changes in endothelial cell permeability are critical in the formation of pulmonary edema. Oxygen radical formation may be the actual mechanism through which permeability regulation is achieved.[8]

Lymphatic drainage affects fluid balance in the lung. Obliteration, distortion, or obstruction of lymphatic vessels promotes the formation of pulmonary edema. Congestive heart failure best illustrates the interplay of fluid movement. An increase in hydrostatic pressure in capillaries results in fluid movement into the interstitial spaces. As this occurs, there is stretching and widening of the endothelial cellular junctions, with increased permeability to plasma molecules and fluid. This increases the interstitial colloid pressures, resulting in even larger amounts of outward fluid movement. As fluid accumulates in the interstitial space, lymphatic drainage increases; when interstitial fluid exceeds maximum lymph drainage, the interstitial hydrostatic pressure breaks alveolar cell junctions, allowing fluid into the alveolar spaces.

Alterations in one or more of the Starling forces, capillary permeability, or lymphatic return occur in many disease states, particularly those with a component of heart or lung failure. Table 13-1 presents the major causes of pulmonary edema, including mechanisms of production and precipitating events.

CAUSES

Increased Capillary Pressure

Cardiogenic pulmonary edema occurs when left atrial pressure increases, causing the capillary hydrostatic pressure to rise. An increase of left atrial pressure occurs in left heart failure due to any cause, more frequently in severe mitral valve disease, especially mitral stenosis, or in rare disorders, such as left atrial myxoma occluding the mitral valve orifice. Although noncardiogenic causes, such as pulmonary venoocclusive disease, fibrosing mediastinitis, and a variety of mediastinal masses can produce increased pressure pulmonary edema, these causes are rare. When increased pressure pulmonary edema occurs in hospitalized patients with normal cardiac function, it is due to overexpansion of the vascular space by excessive intravenous fluid therapy, particularly in those with compromised renal function.

Hydrostatic forces move fluid out of the capillary into the interstitial space first (Figs. 13-1 and 13-2) and from there to the perivascular and peribronchial interstitial tissues, forming thin sheaths around pulmonary arteries, veins, bronchi, and interlobular septa (Fig. 13-3). These structures contain lymphatics that the alveoli do not; after the fluid reaches the perivascular and peri-

TABLE 13-1
Pathogenesis of Pulmonary Edema

Cause	Initiating Event
Increased capillary hydrostatic pressure	Fluid overload, mitral stenosis, myocardial infarction, atrial myxoma, venoocclusive disease, fibrous mediastinitis, mediastinal tumors and masses
Increased capillary permeability	Adult respiratory distress syndrome, circulating or inhaled toxins, oxygen toxicity, irradiation
Lymphatic insufficiency	Metastatic carcinoma with lymphangitic spread, silicosis
Decreased colloid osmotic pressure	Hypoproteinemia, overtransfusion of crystalloids
Decreased interstitial pressure	Hyperinflation, pneumothorax, rapid removal of pleural effusion
Unknown	Heroin, high altitude, neurogenic event

bronchial interstitium, some moves through the lymphatics, and the rest expands through the loose interstitial tissue. The lymphatic vessels actively pump the lymph toward the bronchial and hilar lymph nodes and through the thoracic duct into the superior vena cava.

If excessive amounts of fluid escape from the capillaries, two factors limit the flow. First, a fall in the colloid osmotic pressure of the interstitial fluid occurs because of protein dilution. Although this is an attempt to limit further flow, it is ineffective if capillary permeability increases greatly. Second, a rise in hydrostatic pressure in the interstitial space reduces the net filtration pressure and tends to reduce fluid movement out of the capillaries.

The formation of pulmonary edema takes place in two stages. In the first stage, interstitial edema, characterized by engorgement of the perivascular and peribronchial interstitial tissue (*i.e.*, cuffing) occurs. The lymphatics are widened, and lymph flow increases. There is also some widening of the interstitium of the alveolar walls. At this stage, there is little effect on pulmonary function although some radiologic changes may occur. This stage of pulmonary edema may be difficult to recognize.

The second stage is alveolar edema (Color Fig. 13-1), the stage in which fluid moves from the interstitial compartment into the alveoli. As a result of surface tension forces, the edematous alveoli shrink, preventing adequate ventilation, and hypoxemia is inevitable. When edema fluid moves into the small and large airways, the patient coughs it up as abundant frothy sputum. In patients with congestive heart failure, the edema fluid is pink because of the erythrocytes in it.

The mechanisms of the transition from interstitial to alveolar edema are not fully understood. The lymphatics probably become overloaded, and the pressure in the interstitial space increases so much that fluid spills over into the alveoli. The permeability of the alveolar epithelium increases, which accounts for the protein and erythrocytes in the alveolar fluid.

Increased Capillary Permeability

An increase in capillary permeability results in intraalveolar accumulation of fluid and proteins (*e.g.*, fibrinogen), including hyaline membranes (Color Fig. 13-2). This is usually the result of shock, circulating and inhaled toxins, oxygen toxicity, or radiation injury to the lung, which are all factors leading to acute respiratory distress syndrome (ARDS) of the adult and its pathologic counterpart, diffuse alveolar damage. A complete discussion of this subject is provided in Chapters 14 and 15.

Lymphatic Insufficiency

Because the lymphatics clear protein from the interstitial space, lymphatic obstruction can increase interstitial protein concentration. In animals, partial ligation of pulmonary lymphatics

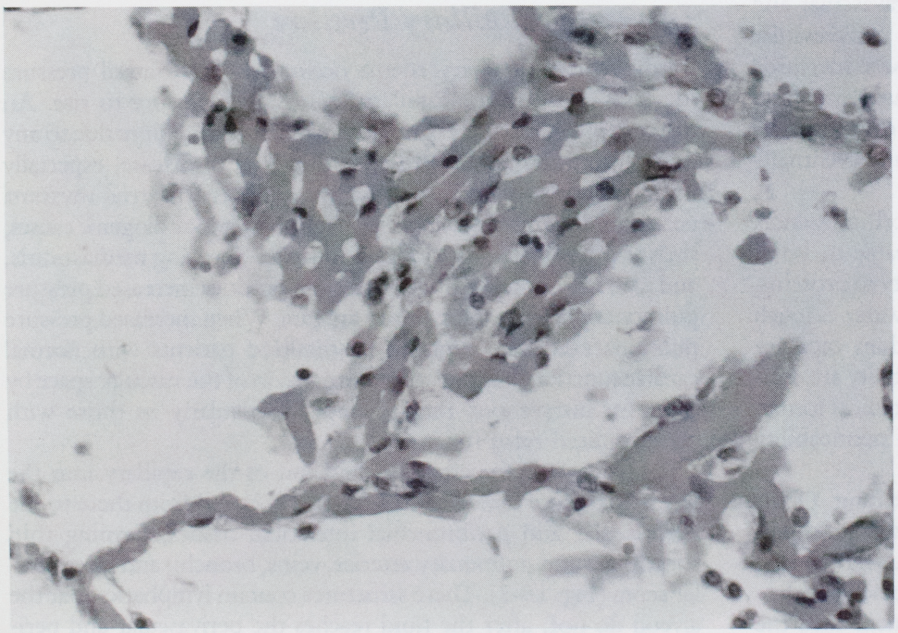

FIGURE 13-1. On-face section through an alveolar wall of a normal lung shows a congested capillary network. The clear spaces are interstitium with no evidence of edema fluid. (H & E stain; low magnification; contributed by the editor.)

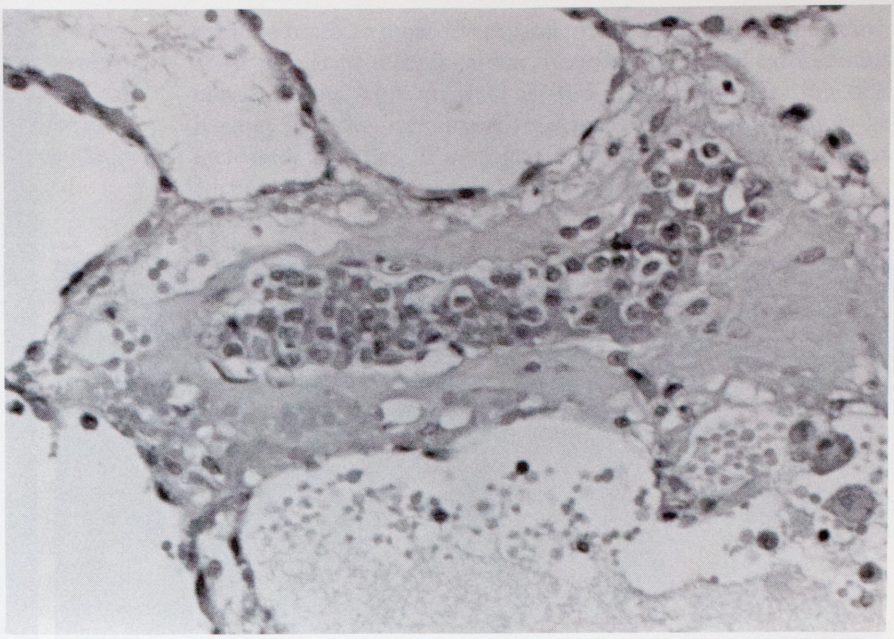

FIGURE 13-2. In interstitial pulmonary edema, the fluid distends the interstitial space surrounding a small pulmonary vessel. Edema fluid is not in the adjacent alveoli. (H & E stain; intermediate magnification; contributed by the editor.)

resulted in marked pulmonary edema when left atrial pressure increased. Patients with silicosis develop pulmonary edema with raised left atrial pressure because silicotic nodules partially obstruct the lymphatics. The lymphatics protect against edema by removing fluid and protein from the interstitial space, and interference with lymphatic structure or function is an important predisposing factor in the development of pulmonary edema (Fig. 13-4).

Decreased Interstitial Pressure

In some conditions, the pressure gradient across the microvascular endothelium increases as the interstitial pressure diminishes. For example, acute atelectasis may occur with pulmonary edema; this is called the drowned lung syndrome. The collapse of a lobe decreases interstitial pressure, and the pressure drop across the microvasculature increases. However, when acute atelectasis is produced in animals, it is difficult to show an actual increased amount of extravascular fluid in the lung. However, convincing cases of acute pulmonary edema occur with rapid reexpansion of a lung or lobe after hydrothorax or pneumothorax. This type of edema usually clears rapidly after full lung expansion.

Decreased Colloid Osmotic Pressure

An acute reduction in colloid osmotic pressure from 25 to 15 mm Hg produces pulmonary edema at modestly elevated capillary hydrostatic pressures. Patients with reduced plasma protein concentrations even without overt left heart failure may develop edema with modest fluid overload. Such situations may occur with hypoalbuminemia associated with liver and renal disease and possibly in starvation. The colloid osmotic pressure also decreases after overtransfusion of crystalloids, a possible cause of ARDS (see Chap. 14).

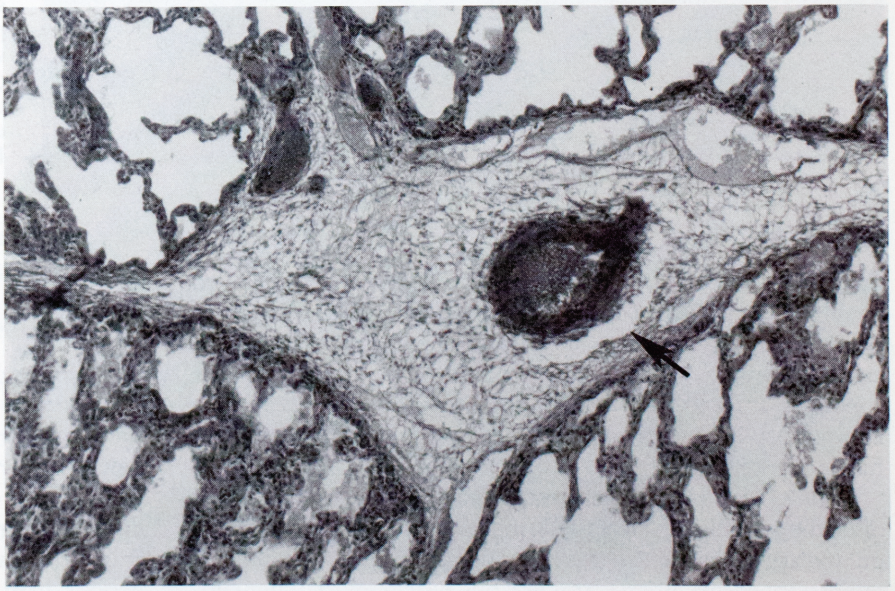

FIGURE 13-3. In perivascular pulmonary edema in the interlobular septum, there is expansion of the loose interstitial tissue surrounding a small muscular artery, probably bronchial, caused by the edema fluid. Some fluid moves through the lymphatic channels in the interstitium, resulting in dilation of the perivascular lymphatic channels (*arrow*). (H & E stain; low magnification.)

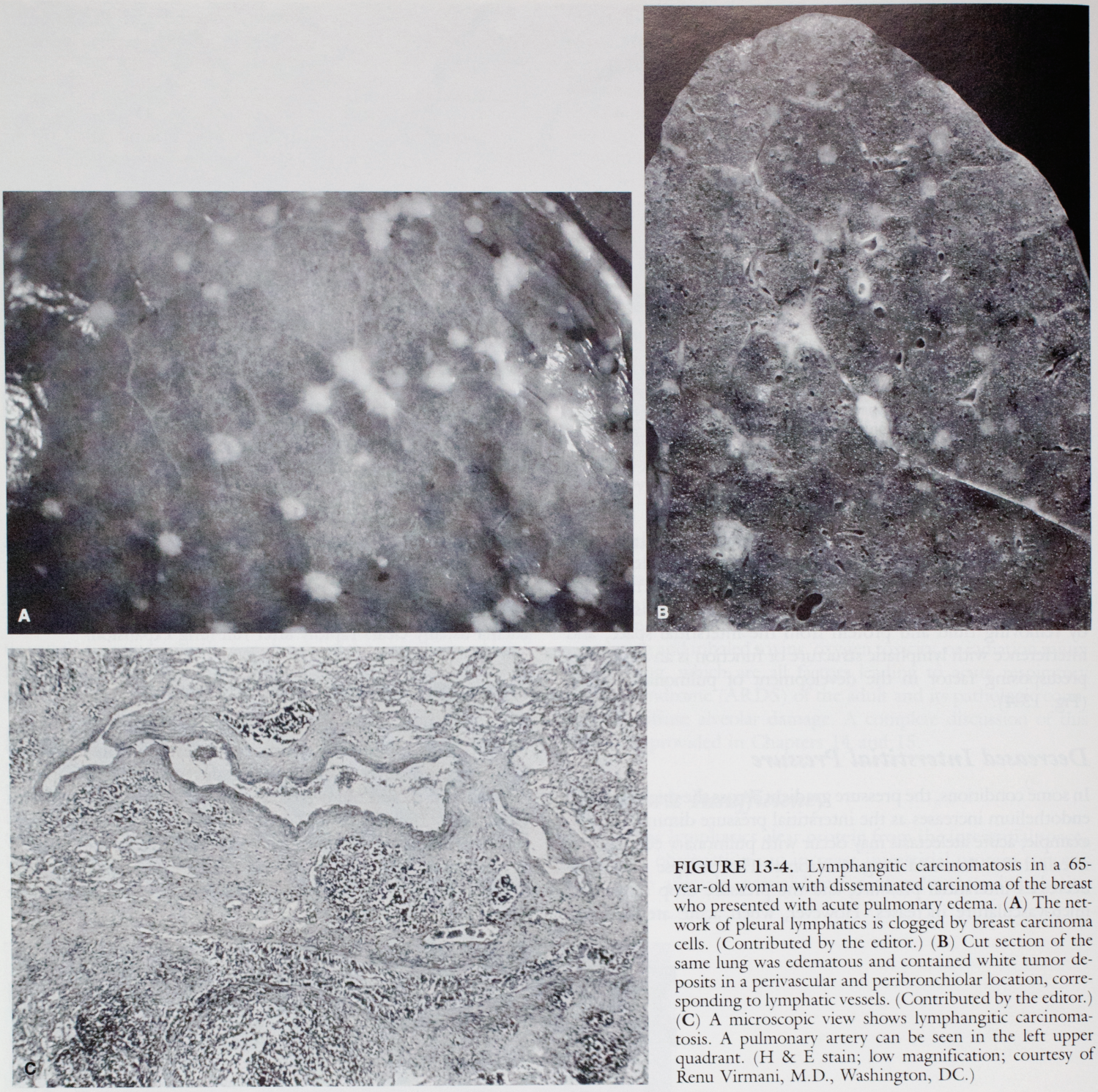

FIGURE 13-4. Lymphangitic carcinomatosis in a 65-year-old woman with disseminated carcinoma of the breast who presented with acute pulmonary edema. (**A**) The network of pleural lymphatics is clogged by breast carcinoma cells. (Contributed by the editor.) (**B**) Cut section of the same lung was edematous and contained white tumor deposits in a perivascular and peribronchiolar location, corresponding to lymphatic vessels. (Contributed by the editor.) (**C**) A microscopic view shows lymphangitic carcinomatosis. A pulmonary artery can be seen in the left upper quadrant. (H & E stain; low magnification; courtesy of Renu Virmani, M.D., Washington, DC.)

Miscellaneous Causes

Pulmonary edema can occur during many seemingly unrelated conditions for which the mechanisms are unknown. These include eclampsia, cardioversion, cardiopulmonary bypass, pulmonary embolism, and pulmonary venoocclusive disease. Edema in these conditions is partially caused by increased hydrostatic pressure or increased capillary permeability, but the precise mechanisms await future investigation.

Three additional clinical settings producing pulmonary edema of unknown pathogenesis include high-altitude pulmonary edema, pulmonary edema associated with heroin use, and neurogenic pulmonary edema after central nervous system injury. High-altitude pulmonary edema and neurogenic pulmonary edema merit separate discussion.

HIGH-ALTITUDE PULMONARY EDEMA

Perhaps the greatest mystery in the study of pulmonary edema is high-altitude pulmonary edema. Although extensively studied, the mechanism remains obscure. Because most studies have shown pulmonary arterial hypertension due to hypoxic vasoconstriction with normal or nearly normal pulmonary wedge pressure, it is difficult to implicate left ventricular failure. Similarly, studies of animals breathing low concentrations of oxygen for extended periods have not resulted in the development of pulmonary

edema, and hypoxia by itself is insufficient to explain this phenomenon. Other investigators have suggested that the edema is due to rupture of arterial walls proximal to the hypoxia-constricted pulmonary arteriolar segments. However, no single mechanism satisfactorily explains the pathogenesis of high-altitude pulmonary edema (see Chaps. 14 and 24).

NEUROGENIC PULMONARY EDEMA

Neurogenic pulmonary edema occurs in patients with head injuries or intracerebral hemorrhage and who have massive sympathetic discharges. It may also be produced experimentally by injecting fibrin into the fourth ventricle. Systemic hypertension and left ventricular failure are not essential factors; one study demonstrated the development of pulmonary edema with normal left atrial pressure. The nature of the escape of fluid and protein into the alveoli suggests that, at least in the early stages, the edema is caused by markedly increased pulmonary vascular pressure. Documented cases suggest that increased left atrial pressures occur but do not remain elevated for a long time. It has also been suggested that capillary endothelial cell pores become stretched during these brief elevations of pulmonary capillary hypertension. Pulmonary edema may occur after this stretched-pore phenomenon.

Other factors may play a role in the development of pulmonary edema. For example, in ARDS, granulocyte aggregation in the pulmonary microcirculation may be a factor related to edema formation.[9,10] However, the exact roles of intravascular colloid osmotic pressure and interstitial pressure are unclear (see Chap. 14).

CLINICAL FEATURES

The clinical features of pulmonary edema depend on its degree and cause. Symptoms range from exertional dyspnea to dyspnea at rest with or without orthopnea and paroxysmal nocturnal dyspnea. If the edema is mild, the patients frequently have a dry cough. With increasing edema, the sputum becomes frothy and blood tinged. Auscultatory changes of the lungs include crackles at the bases to rhonchi with decreasing or absent breath sounds. In the early stages of edema, the physician hears fine inspiratory crepitations at the lung bases; in more severe cases, musical rhonchi may be heard. If the primary disease is cardiac, heart murmurs and extra sounds may be heard. Most patients are too ill for pulmonary function testing; however, the airway resistances have been shown to be increased, and there is a progressive decrease in gas exchange as edema increases due to filling of the interstitium and alveoli. An increase in pulmonary vascular resistance may develop secondarily to hypoxic vasoconstriction.

The chest radiograph often shows an enlarged heart and prominent pulmonary vessels. Interstitial edema causes Kerley B lines; these are short, linear, horizontal markings originating near the pleural surface in the lower lobes. Severely edematous interlobular septa are responsible for these linear markings. In more severe stages of edema, blotchy shadowing appears and radiates from the hilar regions, giving a bat-wing or butterfly appearance. This distribution may be related to the perivascular and peribronchial cuffing by fluid that occurs around the large vessels in the hilar region.

PATHOLOGIC FEATURES

The most important histologic features of acute pulmonary edema are depicted in Figures 13-2 and 13-3 and in Color Figure 13-1. The lungs in acute pulmonary edema, regardless of its cause, are heavy and exude frothy fluid when pressure is applied to the cut surface, particularly in the lower lobes. Although the fluid is frequently watery in appearance, it is well preserved in formalin-fixed, hematoxylin and eosin–stained sections (see Color Fig. 13-1). In other cases, the edema fluid has a fluffy or granular character, depending on the content of protein (Fig. 13-5); in still other cases, the edema fluid may appear distinctly fibrinous and contain inflammatory cells (Fig. 13-6).

Chronic passive congestion is a term that applies predominantly to chronic passive congestion of the lungs secondary to cardiac failure, because other causes of edema, such as high altitude or heroin use, occur as acute episodes. Other mechanisms, particularly those causing lymphatic insufficiency, may act chronically. In long-standing chronic passive congestion, the lungs have a rusty

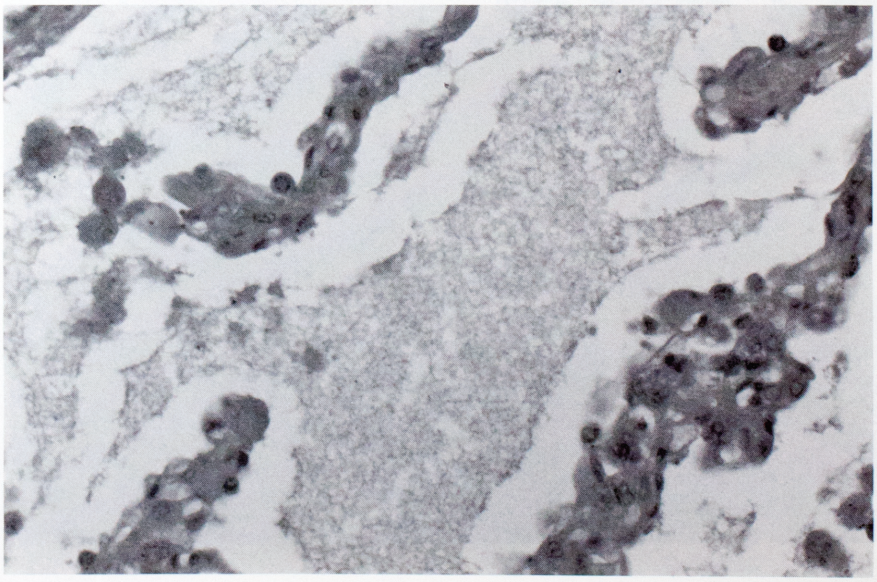

FIGURE 13-5. Fine, granular edema fluid is present in the alveoli, and the pulmonary capillaries are congested. (H & E stain; intermediate magnification.)

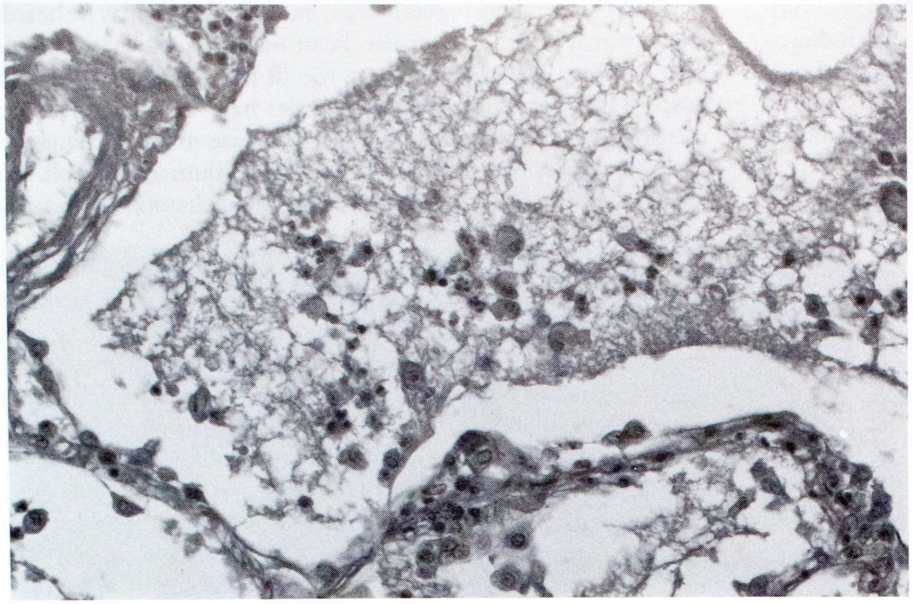

FIGURE 13-6. Fibrinous pulmonary edema fluid in the alveolar space has fibrin strands intermixed with the fluid, and some leukocytes are seen. This form of pulmonary edema frequently occurs in the acute, early phases of an infectious process, such as pneumococcal pneumonia. (H & E stain; intermediate magnification.)

orange-brown color (*i.e.*, brown induration) on gross inspection (Color Fig. 13-3*A*). The location of this staining may be more centriacinar and centrilobular, leaving the periphery of the secondary lobule unstained and resembling leopard spots. The lung can be dry, firm, and somewhat contracted. Acute edema, evidenced by frothy fluid, is not typically a part of uncomplicated chronic passive congestion unless a new acute event has supervened. Microscopically, interstitial thickening consists of dilated capillaries and fine fibrosis. Intraalveolar macrophages stain heavily for iron in their cytoplasm (Color Fig. 13-3*B*, *C*).[11]

Metaplastic ossification sometimes occurs with chronic passive congestion, particularly in chronic mitral stenosis.[12] Typically, the patient presents with calcific densities on chest x-ray films and a history of mitral stenosis. On gross examination, the changes consist of tiny bony fragments that are 2 to 3 mm in diameter. Microscopically, intraalveolar bone is seen (Fig. 13-7). The pathogenesis of this phenomenon is thought to be dystrophic ossification occurring on an organized intraalveolar exudate.

In chronic passive congestion, the lung has an interesting protective defense mechanism. The increased venous pressure causes arterial hypertension, which decreases the blood flow into the lung and prevents flooding of the capillary bed. Hypertensive vascular changes consist of intimal fibrous thickening and medial hypertrophy of small pulmonary muscular arteries and arterioles. Chronic passive congestive changes also develop outside the lung in a retrograde venous hypertensive fashion, particularly in the liver and spleen. In time, both organs develop fibrosis in the zones of greatest venous pressure.

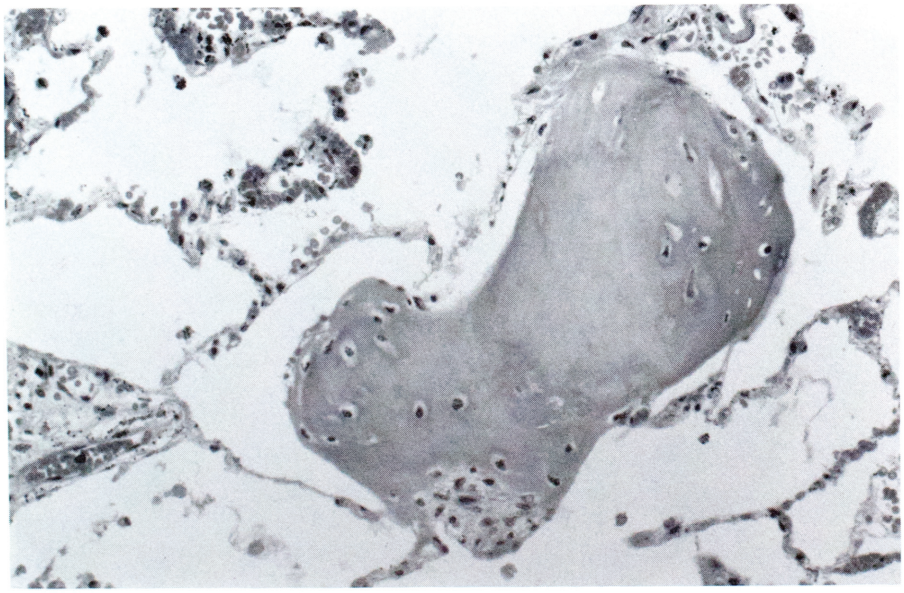

FIGURE 13-7. In this case of metaplastic ossification in chronic, passive congestion, a large, irregular nodule of well-formed bone occupies the alveolar tissue. (H & E stain; intermediate magnification.)

Acknowledgment

The illustrations in this chapter are courtesy of the Averill A. Liebow Pulmonary Pathology Collection, Department of Pathology, UCSD School of Medicine, La Jolla, California.

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