Pathology of Pulmonary Disease, edited by Mario J. Saldana.
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Acute Pulmonary Thromboembolism and Other Forms of Pulmonary Embolization

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Acute pulmonary thromboembolism is a main cause of morbidity and mortality. It can be associated with profound physiologic alterations, protean clinical manifestations, and a vast display of pathologic lesions, both gross and microscopic. Other embolic phenomena that acutely alter pulmonary hemodynamics have been included for the sake of completion and include fat embolism, air embolism, and amniotic fluid embolism.

ACUTE PULMONARY THROMBOEMBOLISM

Definition and Predisposing Factors

The most common type of pulmonary embolism is thromboembolic.[1–12] Thromboemboli may develop anywhere in the systemic venous system; they commonly occur in disease states that slow peripheral venous return, particularly in the lower extremities. The latter situation may be due to congestive heart failure, decreased venous blood return due to trauma, fractures, or immobilization. Increased circulating blood platelets, alterations in normal clotting mechanisms, and the use of certain drugs are also important causes of thrombosis. The best known association is with estrogen in birth control pills. The risk of thrombosis with oral contraceptives increases dramatically if oral contraceptives are combined with smoking and increasing maternal age.[3] Estrogens, when used to treat carcinoma or to decrease lactation, also increase the risk of thrombosis and pulmonary thromboembolism.[1,3] Other conditions predisposing to pulmonary thromboembolism are hereditary and involve deficiencies of protein C, protein S, or antithrombin III, factors that normally keep clotting mechanisms in check by opposing the effects of the coagulation cascade.[1,3,5,8]

Sources of Emboli

The most frequent site of venous thrombosis is in the veins of the legs, including calf, femoral, and iliac veins.[3,5] The initial site for the development of a thrombus is usually the venous valves. Approximately 33% of lower extremity thrombi are bilateral, and the overall incidence increases with age. Situations especially prone to decreased venous return from the lower extremities include fractures, especially of femoral and pelvic bones,[10] and surgery, especially prostatectomy.[1,3] Shock, myocardial infarction, and other conditions in which the legs are immobilized also increase the risk of thromboembolism.

Thrombi may also develop in the pelvic veins, especially during pregnancy and the postpartum period. Other specific sites include the internal jugular vein and superior vena cava in association with sepsis and intravascular catheters, the right atrium in the presence of atrial fibrillation, and the umbilical veins of neonates when catheters are present.

When thrombi at any of these locations dislodge, they pass freely through the draining venous system and become trapped in the pulmonary vasculature. The size of the embolus obviously determines whether it becomes trapped in a major pulmonary artery, in precapillaries, or in intermediate vessels. Because the greatest proportion of pulmonary blood flow is to the lower lobes, it is not surprising that the majority of pulmonary emboli occur at

this location, more often on the right side. Fragmentation of a large thromboembolus frequently results in multiple pulmonary emboli.

Clinical Features

The clinical presentation of pulmonary embolism depends on the size of the thromboembolus and the severity of the resulting vascular occlusion. The majority of pulmonary emboli are asymptomatic or mildly symptomatic. Echocardiography is useful for diagnosis,[2] even though the pulmonary angiogram may appear normal.

When sudden massive occlusion of the major pulmonary arteries occurs there is a profound decrease in cardiac output by as much as 75% or more. At the same time, right ventricular pressure increases and the mortality rate is extremely high; death occurs within 1 hour of the occlusion in 34%, within 24 hours in another 39%, and in 2 to 5 days in the remaining 27%.[11] If the patient survives, it is because clot lysis with complete resolution took place as early as 2 to 3 weeks; by 4 months after a major embolic event, 60% of the thromboemboli have totally resolved.[11]

Pathologic Features

Autopsy findings in acute or sudden death from pulmonary embolism usually show thromboemboli in the major pulmonary arteries (Color Fig. 18-1). The laminated clots are of various ages and usually large. Some may have a saddle-shaped configuration resulting in occlusion of both right and left main pulmonary arteries. Thromboemboli also may occlude a single main pulmonary artery or its branches, completely obliterating their lumens. They are blunt-ended and may be Y-shaped, if that is the shape of the parent vessel. However, they do not extend into adjacent branches as smoothly as tapering postmortem clots do. Also, premortem thromboemboli are firmer and have elements mixed together in a laminated form known as lines of Zahn; the latter, however, are more distinct in arterial rather than in venous thrombi. Venous thrombi also differ from postmortem clots, which are soft and have two distinct components: the cellular elements, which resemble currant jelly or cranberry sauce, and the fluid elements, which resemble chicken fat (see Chap. 19).

If old emboli are only partly resolved, organized fibrosis may partly or totally occlude the arterial lumen (Fig. 18-1); also, the thromboembolus may become incorporated into the vascular wall. At a later stage, intimal bands or webs may be the only remaining findings (Fig. 18-2). Occasionally, hypertensive vascular changes supervene (see Chap. 22).[13]

When a necropsy is performed in a case of pulmonary thromboembolism, the maneuver of milking the lower extremities, or dissecting the main veins of the legs, thighs, and pelvis, frequently reveals additional thrombi and their likely source.

THROMBOSIS OF MAJOR PULMONARY ARTERIES

Pulmonary thrombosis occurs, but only rarely. The conditions under which it occurs are also likely to favor embolism; therefore, it is often difficult to distinguish whether an intravascular clot is thrombotic or embolic in origin. Thrombosis of pulmonary arteries, like pulmonary embolism, usually occurs in states of decreased blood flow, vascular damage, or altered coagulation mechanisms. Vascular damage to pulmonary arteries may result from trauma, from complications of a pulmonary artery aneurysm (Color Fig. 18-2; Figs. 18-3 and 18-4), or from primary lung disease (*e.g.*, tuberculosis, emphysema, pneumoconiosis; Fig. 18-5).[3,12]

Decreased blood flow most commonly occurs in chronic congestive heart failure. Clinically, these patients have increasing dyspnea, syncope, fatigue, and rapidly progressing right heart failure. The clinical features can resemble those seen in patients with chronic pulmonary hypertension. Pertinent laboratory data include a decrease of end-tidal partial carbon dioxide pressure to levels below arterial partial CO_2 pressure. Angiographic studies outline the obstruction sites in the involved pulmonary arteries.

Grossly, the pulmonary artery involved by thrombosis has smooth, polypoid masses of laminated antemortem thrombus that project into the main divisions of the pulmonary artery. This type of thrombus usually attaches snugly to the endothelial surface

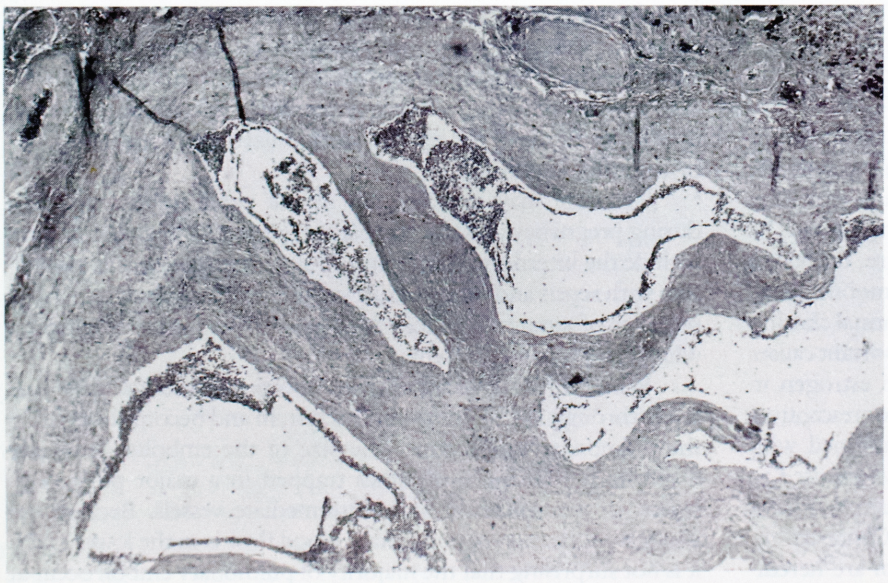

FIGURE 18-1. Recanalized pulmonary thromboembolus. A thromboembolus that occluded a large pulmonary artery was recanalized and now divides the main lumen into several channels. Fibroelastic tissues, which comprise the grossly visible bands and webs, separate the channels. (H & E stain; low magnification.)

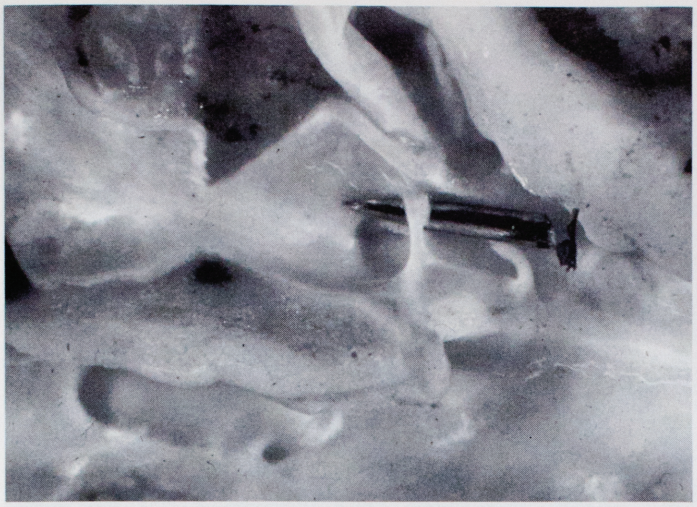

FIGURE 18-2. A pulmonary web consists of a Y-shaped band that attaches to the pulmonary artery intima at three sites to form an organized thromboembolus.

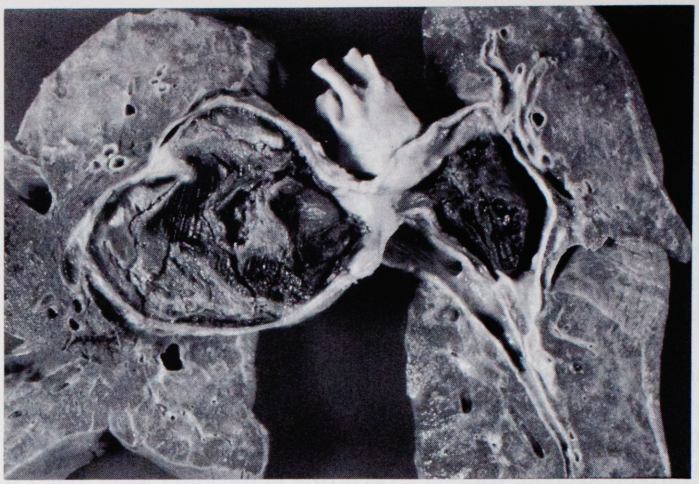

FIGURE 18-4. An adolescent with Eisenmenger complex developed extreme pulmonary hypertension and bilateral aneurysms of the main pulmonary arteries; the latter are completely occluded by laminated thrombi. (Contributed by the editor.)

of the vessel involved and does not coil upon itself as emboli do (see Fig. 18-5).

Thrombosis of small pulmonary arteries usually occurs when pulmonary blood flow decreases greatly. This situation occurs in congenital heart diseases (*e.g.*, uncorrected tetralogy of Fallot, pulmonic stenosis, tricuspid stenosis, neonatal sepsis, sickle cell anemia; see Chap. 25).[14–16] Pulmonary thrombosis occurs in 70% to 90% of untreated cases of tetralogy of Fallot; less frequently, thrombosis occurs in pulmonary veins and results in dilation and proliferation of bronchial arteries. The occurrence of such pulmonary thrombosis is more frequent in patients having hemoglobin levels greater than 20 g/dL.

Pulmonary thrombosis may occur in concert with pulmonary venous thrombosis. When both arteries and veins have obliterative thrombi, infarction of the lung may occur. On rare occasions, systemic emboli may be a consequence of pulmonary venous thrombi.

Microscopically, organized thromboemboli have varied appearances depending on their age. Differing amounts of fibroblastic tissue replace the organized thrombus and result in eccentrically placed plaques or polypoid masses attached to the vessel vall. As organization continues, the masses may recanalize. Sevral channels are present, often in a longitudinal direction, separated by narrow septae of fibroelastic tissue, and they bridge the lumen proximal to distal to the occlusion.

In small pulmonary arteries, concentric intimal fibroelastosis may occur. This change, also present in chronic pulmonary hypertension, may be residua of small, organized thrombi. These vessels

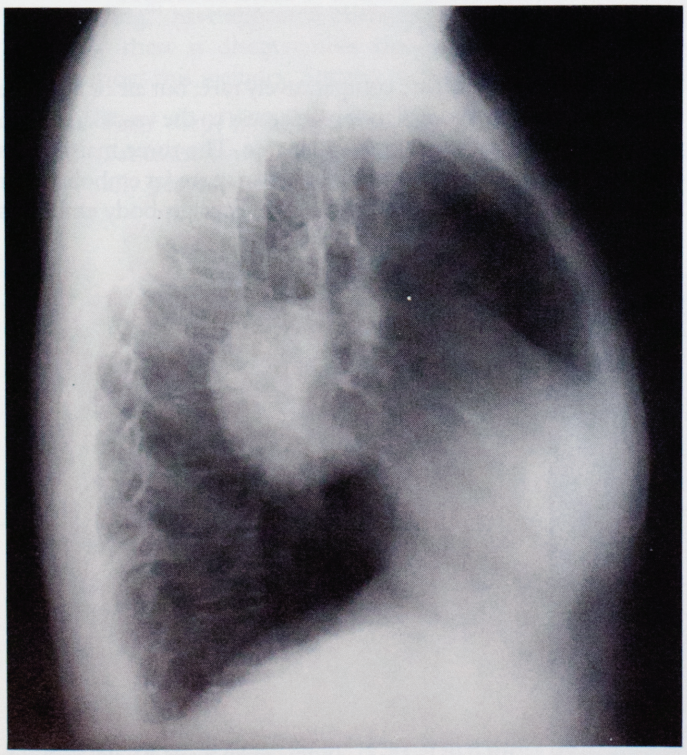

FIGURE 18-3. This patient presented with a lesion that was radiologically interpreted as a mediastinal tumor (see Color Fig. 18-2). (Contributed by the editor.)

FIGURE 18-5. A gross specimen from a patient who had chronic obstructive pulmonary disease, pulmonary hypertension, and thrombosis of the major pulmonary arteries. (Contributed by the editor.)

would also show atrophy of the media at the site of the lesion (see Chap. 25).

PULMONARY INFARCTS

The lung and liver are the only two major organs with a dual blood supply; because the lung receives its blood supply from both pulmonary and bronchial arteries, infarcts of pulmonary parenchyma are quite rare.[1,3,12] Patients at high risk for infarction are those in low-flow states usually associated with primary respiratory or cardiac disease. Most infarcts occur in patients older than 40 years of age and occur with equal frequency in men and women; they are often multiple.

The distribution of infarcts in the lungs is similar to that of thromboemboli, with 75% occurring in the lower lobes, often at the costophrenic angles. Typically, infarcts are pyramidal or wedge shaped, with their broad base on the pleural surface.

Radiographic studies may aid in the diagnosis. Within 12 to 24 hours of onset, the chest x-ray may show a blurred shadow that later becomes a pleural-based, wedge-shaped opacity. This correlates with the gross findings at autopsy (Fig. 18-6). The thromboembolus that caused the infarct usually can be found by serially sectioning the pulmonary vessels supplying the region of infarct. Microscopically, hemorrhage and edema are present in the early stages of the infarct from bronchial arterial collateral flow. If sufficient, the latter may prevent progression of the infarct. Eventually, alveolar capillaries rupture, resulting in blood and edema fluid leaking into the alveoli. At this time, the infarct will appear red. Intraalveolar blood, edema, and fibrin will elicit an inflammatory macrophage response that gives a pale appearance to the involved region. Digested old blood appears in hemosiderin-laden macrophages. As the infarct continues to develop, complete necrosis will occur, leaving only cellular outlines with a ghost-town appearance of the pulmonary parenchyma (Fig. 18-7).

Organization with scar formation will be the final resolution of most infarcts. This process may require a year or more. Scar size may be small and may not adequately reflect infarct size or volume of lost lung tissue. At the margin of scars, bronchiolar or alveolar epithelial proliferation is present. The neoplastic potential of this proliferation as a scar carcinoma is not entirely clear (Fig. 18-8; see Chap. 31).

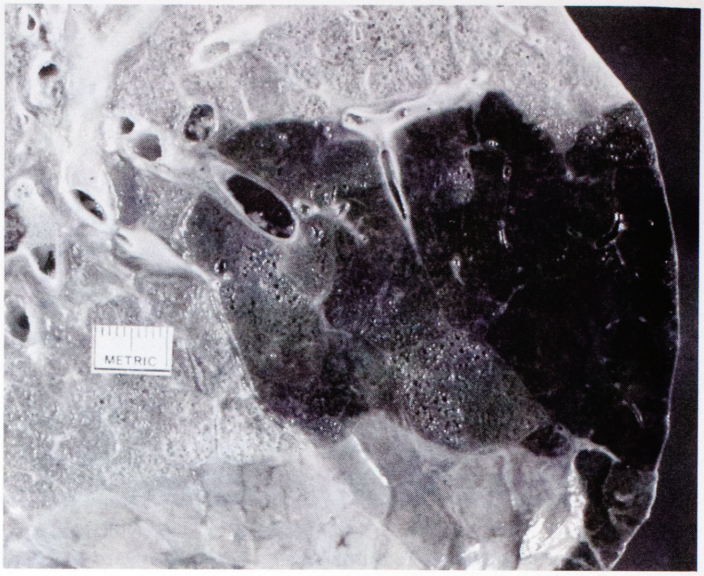

FIGURE 18-6. The wedge-shaped, dark, hemorrhagic zone extending to the pleural surface is a pulmonary infarct. At the apex of the infarct is an artery occluded by a thromboembolus.

A complication of pulmonary infarction is infection with resultant lung abscess. This occurs in about 2% to 3% of cases.[17,18] The sources of organisms include septic emboli, sepsis in the blood circulating through the lung, and infection spreading from adjacent lung tissue (Color Fig. 18-3).

NONTHROMBOTIC PULMONARY EMBOLIZATION

Nonthrombotic emboli are comparatively rare, but air or any type of tissue or foreign material may gain access to the vascular system and lodge in the pulmonary vascular tree. The three main forms that may give rise to respiratory insufficiency are fat embolism, air embolism, and amniotic fluid embolism. Foreign-body emboli as

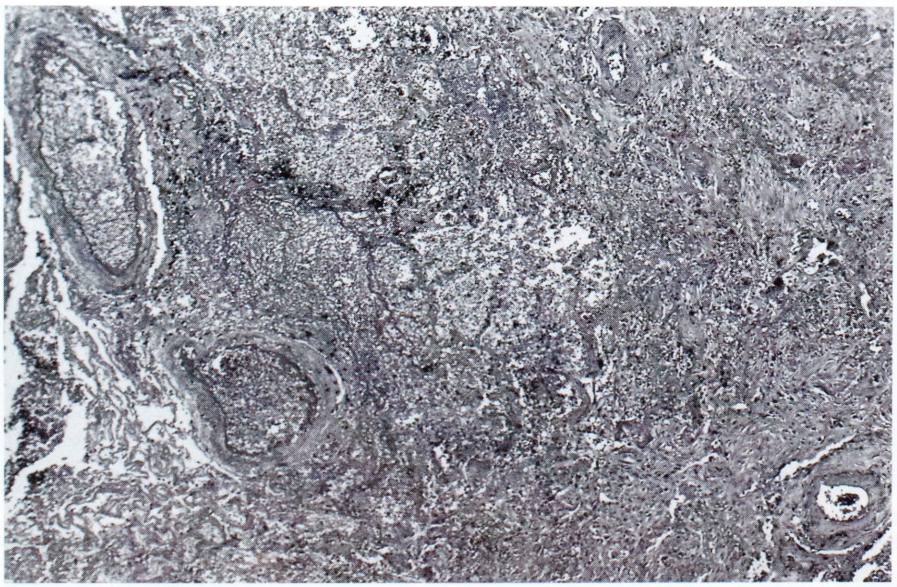

FIGURE 18-7. In this pulmonary infarct, both diffuse pulmonary edema and intraalveolar hemorrhage are present. Many alveolar septa are necrotic, resulting in a ghostlike appearance. (H & E stain; low magnification.)

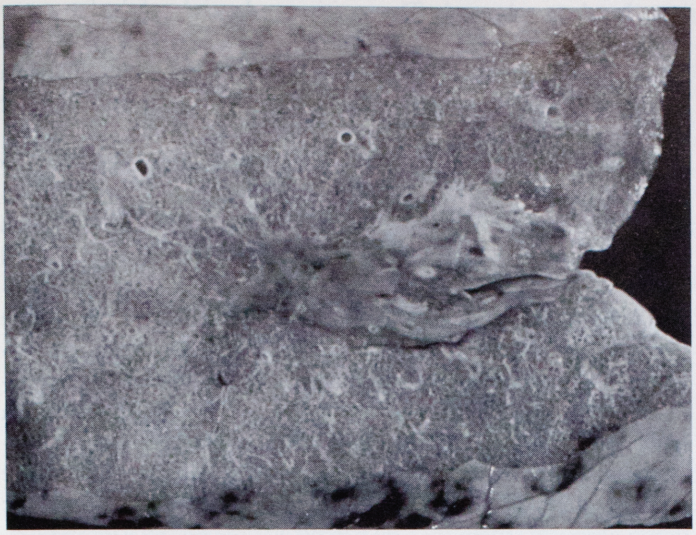

FIGURE 18-8. A peripheral, indented scar is present in the right lower lobe of the lung in a man who recovered from a large pulmonary infarction. There is secondary anthracotic staining of the scar but no histologic evidence of scar-associated malignancy was found. (Contributed by the editor.)

well as a variety of tissue emboli to the lungs are discussed in Chapter 22.

Fat Emboli

At autopsy, the presence of fat emboli in the lungs is a common finding in patients dying soon after traumatic injury.[19] They also occur after bone fractures, soft tissue injury, and surgical operations. Reports of fat embolism after liposuction[20] and intravenous lipid feeding[21] have appeared. Although everyone accepts fat emboli,[22–24] there is disagreement among pathologists regarding what entities this includes. Spencer defines three distinct entities:

1. Fatty tissue embolism with emboli of intact fat cells
2. Fat embolism with emboli of fat released from cells usually because of trauma
3. Traumatic lipemia in which there are alterations in the finely particulate fat of chylomicrons and serum lipoproteins during hemorrhage, burns, cold injury, and diabetes.[12]

Both fat and fatty tissue emboli are associated with accidents[3,11,22] or surgical trauma; the incidence is 35% to 88% after accidental trauma and 100% after surgical trauma. There is an apparent increase in detection with increased survival time after injury and increased age of the patient. Fat emboli occur after injury to bone (especially marrow), subcutaneous fat, and fatty liver, and in association with such states as acute pancreatitis, osteomyelitis, diabetes, burns, and steroid use.

The clinical picture ranges from no symptoms to shock and death. It depends on the extent of emboli and the associated injuries or disease state. If the patient dies, gross autopsy findings will include a firm, solid state of the lungs secondary to hemorrhage and edema. Fat particles are seen against the endothelium of the pulmonary arteries. Microscopically, there is fatty tissue within the microvasculature. These cells, as well as fat particles released from tissue, are best demonstrated with oil red O fat stain in frozen sections (Fig. 18-9).

Air Emboli

Air embolism occurs when air rapidly passes into the vascular system.[3,12] It happens in a variety of clinical settings:

- head and neck surgery and other head and neck diagnostic procedures
- trauma to the great veins
- intrauterine and intravaginal injection of soap solutions or intravaginal manipulation with resulting air penetration into lacerations of cervical and placental veins
- injection of therapeutic and diagnostic solutions into places such as the nasal sinuses or urinary bladder
- inadvertent air injection during intravenous infusion or during changes of intravenous tubing
- therapeutic insufflation of fallopian tubes
- air introduced into the lung during pneumothorax
- hyperbaric decompression

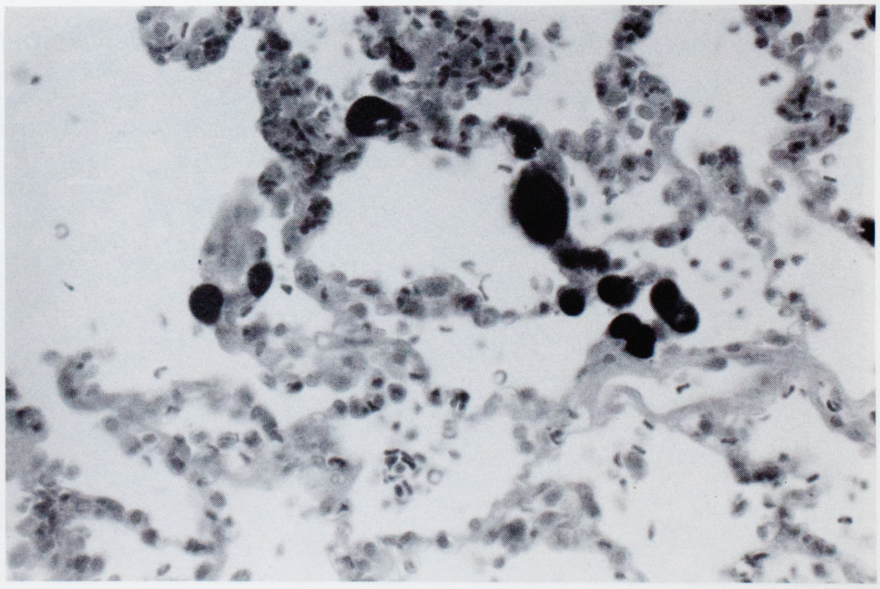

FIGURE 18-9. A frozen section of lung tissue shows scattered fat emboli in distended capillaries. The fat droplets are stained darkly. (Oil red O stain; intermediate magnification.)

- forced positive-pressure ventilation for treating the respiratory distress syndrome (*i.e.*, hyaline membrane disease) of neonates.

Within the pulmonary capillaries, the disruption of blood flow produces an increase in pressure, and blood flow ceases because air acts as a buffer to the column of blood coming its way. If only small amounts are present, the air is eventually reabsorbed, and reflow through the pulmonary capillary bed occurs. Large amounts of air will result in obstruction of pulmonary blood flow sufficient to produce a picture of shock due to increased right atrial pressure and right heart failure. Also, there will be a drop in cardiac output due to decreased venous return and acute left heart failure, causing low systemic blood pressure. Pulmonary edema and effusion also may occur secondary to regional increases in intracapillary pressure. In massive air embolism, resuscitative efforts are usually unsuccessful.

At autopsy, the most striking finding is frothy blood in the pulmonary arteries and veins. Also, the right atrium and inferior vena cava are dilated. The contracted left ventricle is empty. Pulmonary edema and pleural effusions may also be present. The major differential diagnosis to consider is clostridial sepsis with gas production. However, in clostridial sepsis, the gas is foul-smelling and is present in all cardiac chambers, other major organs, and both pulmonary and systemic vessels. In clostridial sepsis, most often air bubbles appear in the subcapsular vessels of the liver and the serosal vessels of the gastrointestinal tract, and one feels crepitations of the spleen. The hemolytic nature of clostridia also may result in dark, dirty staining of the intimal surface of the vascular system.

Amniotic Fluid Emboli

Several types of peripartum emboli may occur. The most common type of these rare forms of emboli is amniotic fluid embolism. It occurs in approximately 1 of 26,000 deliveries (0.004%), including both vaginal and cesarean section types.[25–30]

The mechanism usually involves partial detachment of the placenta followed by continued uterine contractions forcing fluid into the placental vessels. The position and weight of the fetus may contribute in forcing amniotic fluid into the vessels. Amniotic fluid may also gain access to uterine wall vessels exposed during a cesarean section or through tears in the lower uterine segment or cervix in vaginal deliveries.

Small, clinically insignificant amniotic fluid emboli probably occur in almost all deliveries. With massive amniotic fluid embolism, the patient experiences the acute onset of respiratory distress with difficulty in ventilating even if intubated. Hypoxemia and decreased cardiac output with decreased systemic pressure produces shock and often death. Experimental studies show that there are vasoconstrictive substances in the amniotic fluid that compound the obstructive effects of the fluid. If resuscitation is successful, a state of disseminated intravascular coagulation with afibrinogenemia may develop. Disseminated intravascular coagulation is probably secondary to thromboplastic substances in the amniotic fluid. Gross autopsy findings are nonspecific in amniotic fluid embolism; there may be patchy edema, atelectasis, and emphysema. The diagnosis rests on the identification of amniotic fluid contents within the pulmonary vessels.[30] These include squamous epithelial cells, lanugo hairs, fat, mucin, and bits of meconium. Most of the time, hematoxylin and eosin sections are sufficient to identify amniotic fluid emboli (Fig. 18-10). However, polarized light may assist in identifying hair. Keratin and mucin stains may aid in identifying squamous cells and meconium; the Attwood stain is particularly vivid.[26] It combines magenta purple staining of squamous cells with alcian blue staining for mucus and myxoid products.

Two additional pulmonary emboli associated with pregnancy are trophoblast emboli and decidual emboli (see Chap. 22).[31] Both may occur in the same settings and in the same patients in which amniotic fluid emboli occur. Trophoblast emboli also occur in patients with hydatidiform mole; these cases are more often fatal and associated with pulmonary infarcts. In surviving cases of trophoblast emboli, the trophoblastic tissue begins to degenerate within a week (Fig. 18-11; see Fig. 18-10). In decidual emboli, the decidual cells that lodge in the pulmonary arteries on very rare occasions may proliferate; this entity is recognized as deciduosis of the lung.[30]

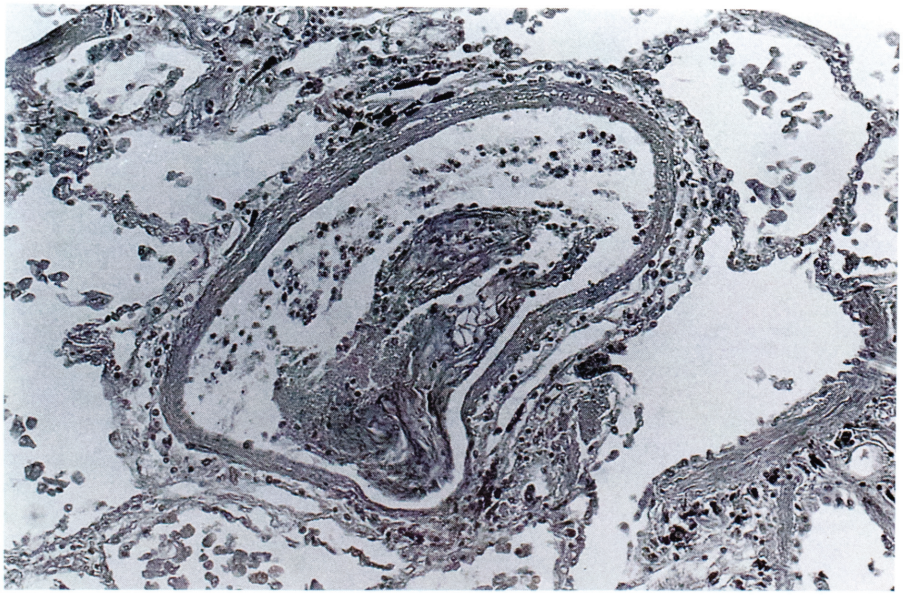

FIGURE 18-10. An amniotic fluid embolus lies in a muscular pulmonary artery. This type of embolus contains squamous cells, lanugo hairs, and mucin. (Attwood stain; low magnification.)

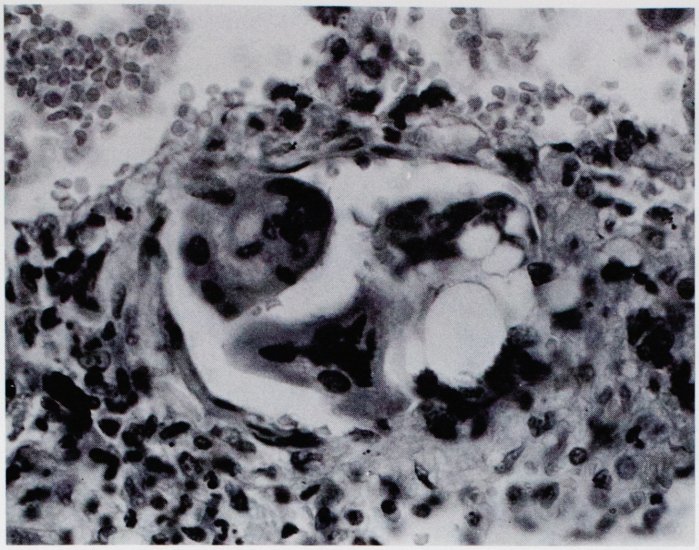

FIGURE 18-11. A multinucleated mass of trophoblasts occludes the lumen of a pulmonary artery. (H & E stain; high magnification.)

Acknowledgment

Illustrations 1, 2, 6, 7, 9, 10, and 11 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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