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Mixed Interstitial and Intraalveolar Processes

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Several entities in pulmonary pathology are characterized by an intraalveolar as well as an interstitial component. These disorders may pose diagnostic problems, and the pathologist should be aware of their clinical and radiologic features. Radiographically, fluffy alveolar infiltrates, frequently bilateral, are a prominent feature, and these may be superimposed on a background of fine reticulonodular interstitial shadows. This group of diseases includes bronchiolitis obliterans organizing pneumonia (BOOP), endogenous lipoid pneumonia (ELP), pulmonary alveolar proteinosis (PAP), and pulmonary interstitial disease associated with gastroesophageal reflux (GER) in children. Their etiology and pathogenesis remain obscure, although some intriguing observations have been made. Nonetheless, a correct diagnosis is important because treatment strategies differ in each instance. In this chapter, we will discuss the specific clinical and pathologic features of each of the above disorders and point out their distinction from one another and from other entities with which they may be confused.

BRONCHIOLITIS OBLITERANS ORGANIZING PNEUMONIA

BOOP was first described as a clinical entity with characteristic radiographic and pathologic features by Epler and colleagues in 1985,[1] but the first instances of this disease were already noted by Lange in 1901.[2] Since the report by Epler and associates in 1985, a number of studies have appeared in the literature. An international congress devoted to BOOP was held in Kyoto, Japan, in 1990.[3] The same disorder is referred to in the British literature as "cryptogenic organizing pneumonitis."[3]

BOOP occurs in both men and women 20 to 70 years of age and is often preceded by a flulike illness. Cough and dyspnea are frequent complaints, with a relatively rapid onset of illness and short duration of symptoms; however, some patients experience a more insidious onset and symptoms that resemble chronic interstitial lung diseases. Fever is common, and fine end-expiratory rales are often heard upon pulmonary auscultation. There is no relationship with cigarette smoking. Chest radiographs usually show bilateral patchy infiltrates, a finding confirmed by computed tomography (CT). High-resolution CT may show in addition bronchial wall thickening and dilatation. Pulmonary function tests show restrictive changes with normal diffusing capacity.

Bronchoalveolar lavage fluid analysis shows a lymphocytosis with a decreased CD_4:CD_8 ratio often associated with an increased percentage of neutrophils and eosinophils.[3] In some patients, BOOP is associated with a collagen-vascular disorder such as systemic lupus erythematosus, Behçet disease, Sjögren syndrome, polymyalgia rheumatica, polymyositis, or dermatomyositis. Treatment for BOOP consists of systemic corticosteroids, which often produce prompt resolution of fever and infiltrates. The prognosis appears to be worse for those patients with a concomitant collagen-vascular disorder.[1]

Pathologically, BOOP is characterized by granulation tissue plugs (*i.e.*, Masson bodies), located within the lumen of small airways and extending into alveolar ducts and alveoli.[1,3,4] These consist of rounded balls of myxomatous connective tissue that form intraluminal polyps within bronchioles and air spaces (Fig. 33-1). Within alveolar ducts, these connective tissue polyps may display a branching pattern (Fig. 33-2). Inflammatory cells, including neutrophils, lymphocytes, and plasma cells, are sometimes seen at the center of the intraluminal myxoid polyps. At low magnification, BOOP appears as a patchy consolidation with adjacent areas of nearly normal lung parenchyma (Fig. 33-3). Other features include intraalveolar foamy macrophages, fibrinous exudates, and an interstitial mononuclear cell infiltrate of variable

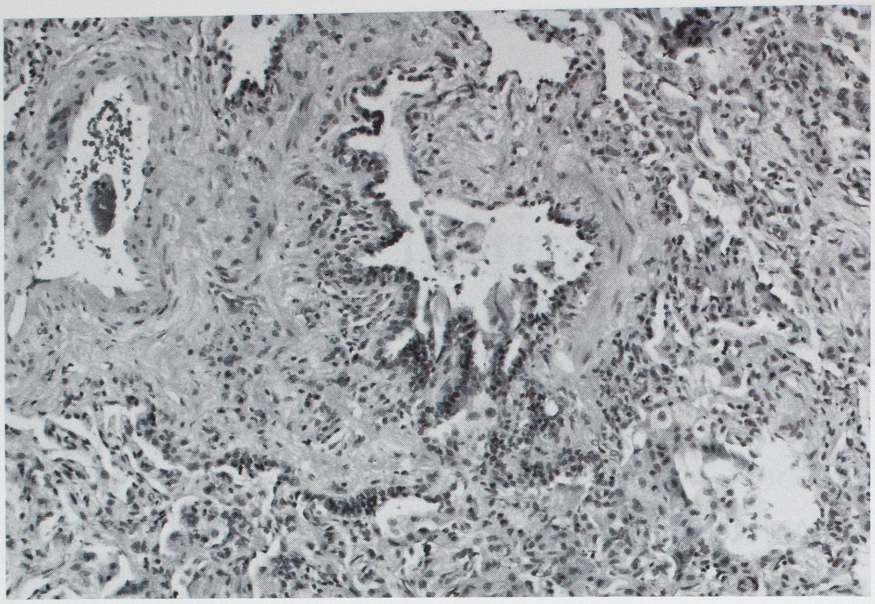

FIGURE 33-1. In bronchiolitis obliterans organizing pneumonia, the bronchiolar lumen is partially obstructed by a plug of young, edematous granulation tissue projecting into the lumen in a polypoid fashion. (H & E stain; low magnification.)

density.[3] Honeycombing and extensive interstitial fibrosis are not usual features of BOOP; the histologic features are similar in patients with or without an accompanying collagen-vascular disorder.

A variety of disorders may be associated with the BOOP pattern described above. Infectious disorders must always be considered in the differential diagnosis, including viral, *Mycoplasma*, bacterial, fungal, and *Pneumocystis* infections. Organizing diffuse alveolar damage may also show features overlapping with those of BOOP. A histologic picture of BOOP may also be observed distal to obstruction or in association with aspiration pneumonia. It can also be focally observed in biopsy specimens from patients with hypersensitivity pneumonitis and chronic eosinophilic pneumonia. In addition, drug reactions or exposures to toxic fumes or gases may result in a histologic picture of BOOP. Focally, diffuse panbronchiolitis and Wegener granulomatosis may show a similar pattern. Finally, features of BOOP may be seen in individuals who have undergone bone marrow, lung, or heart-lung transplantation.[3,4] Thus, a diagnosis of idiopathic BOOP should be made only after a careful consideration of the histologic features in combination with the clinical information and radiographic findings.

Whereas BOOP is typically associated with intraluminal myxoid polyps of granulation tissue, some disorders from which BOOP must be distinguished are associated with constrictive bronchiolitis. The latter consists of mucosal, submucosal, and peribronchiolar inflammatory infiltrates that progress to collagenous fibrosis with partial or total obliteration of the bronchiolar lumen (Figs. 33-4 and 33-5). Constrictive bronchiolitis is usually associated with obstructive changes on pulmonary function tests.

Disorders leading to constrictive bronchiolitis include infections (*e.g.*, *Mycoplasma* species; viruses, especially adenovirus), exposure to toxic fumes and gases, drug reactions (*e.g.*, penicillamine), and exposure to certain mineral dusts. It may also be seen as a complication of bronchiectasis, diffuse alveolar damage, inflammatory bowel disease, or collagen-vascular disorders, especially rheumatoid arthritis. Diffuse panbronchiolitis may progress

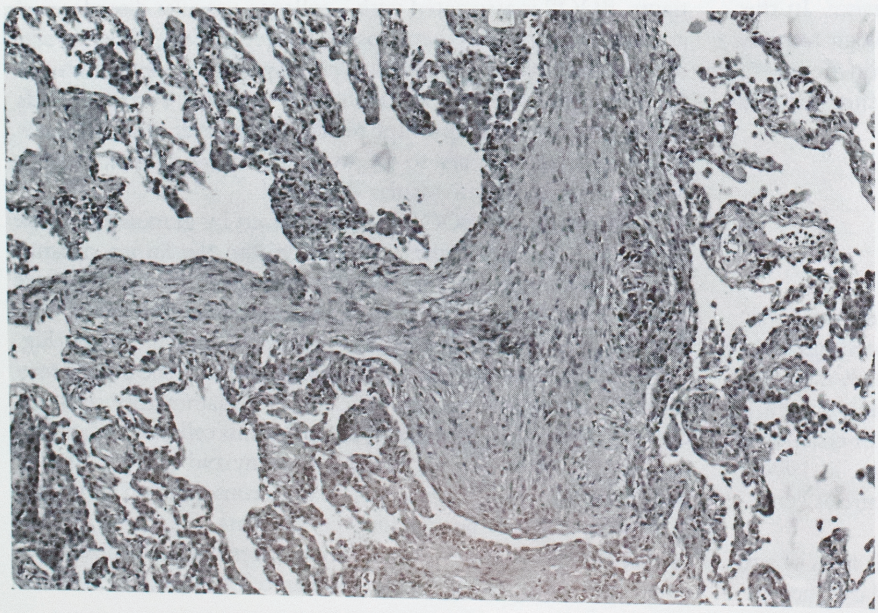

FIGURE 33-2. In bronchiolitis obliterans organizing pneumonia, a branching plug of granulation tissue fills the lumen of an alveolar duct. (H & E stain; low magnification.)

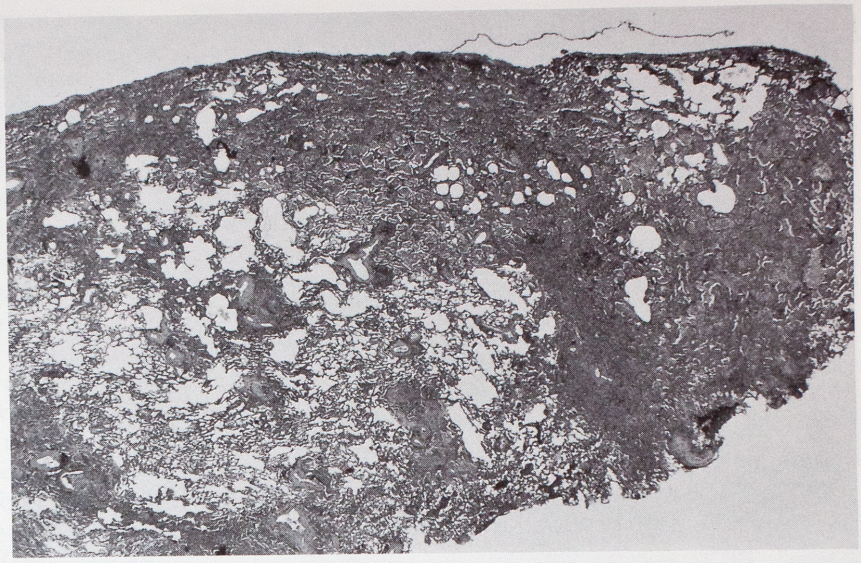

FIGURE 33-3. A low-power view in a patient with bronchiolitis obliterans organizing pneumonia shows consolidated areas adjacent to near-normal lung parenchyma. The patient developed pulmonary disease following long-term treatment with Furadantin (H & E stain; panoramic view.)

to constrictive bronchiolitis, and constrictive bronchiolitis may also be observed focally in patients with hypersensitivity pneumonitis. Finally, constrictive bronchiolitis occurs as a late complication of bone marrow, lung, or heart-lung transplantation (see Chaps. 30 and 71).[4]

BOOP is most likely to be confused clinically and pathologically with idiopathic pulmonary fibrosis (*i.e.*, usual interstitial pneumonia; see Chap. 31).[1,5] The latter usually presents with insidious onset of dyspnea and radiologic interstitial markings with peripheral and basilar accentuation, in contrast to the more abrupt onset and bilateral patchy, fluffy infiltrates of BOOP. Histologically, usual interstitial pneumonia shows areas of interstitial inflammation and fibrosis of varying ages, whereas the connective tissue plugs in BOOP all appear to be about the same age. Although some intraalveolar rounded balls of myxomatous connective tissue (*i.e.*, Masson bodies) may also be seen in usual interstitial pneumonia, they are never the dominant feature as in BOOP. There is also some overlap in the histologic features of hypersensitivity pneumonitis and BOOP, as noted above (see Chap. 65).

The presence of giant cells and minute incomplete or ill-formed granulomas is useful for distinguishing hypersensitivity pneumonitis from BOOP.[4] Chronic eosinophilic pneumonia may have histologic features in some areas that are indistinguishable from those of BOOP (see Chap. 64). The finding of numerous eosinophils with eosinophilic abscesses and clinical features of asthma and peripheral eosinophilia favors the diagnosis of chronic eosinophilic pneumonia. Clinical and pathologic features that distinguish BOOP from these three disorders are summarized in Table 33-1. BOOP must not be confused with the respiratory bronchiolitis and focal interstitial fibrosis seen in some heavy smokers (see Chap. 30).[6]

The etiology and pathogenesis of idiopathic BOOP are unknown. Ultrastructural studies have demonstrated extensive epithelial damage involving peribronchiolar alveolar septa, resulting in denudation of epithelial basement membranes and complex infoldings of the denuded membrane into alveolar septa.[7] These findings suggest that BOOP may result from acute epithelial injury. The development of experimental models of bronchiolitis

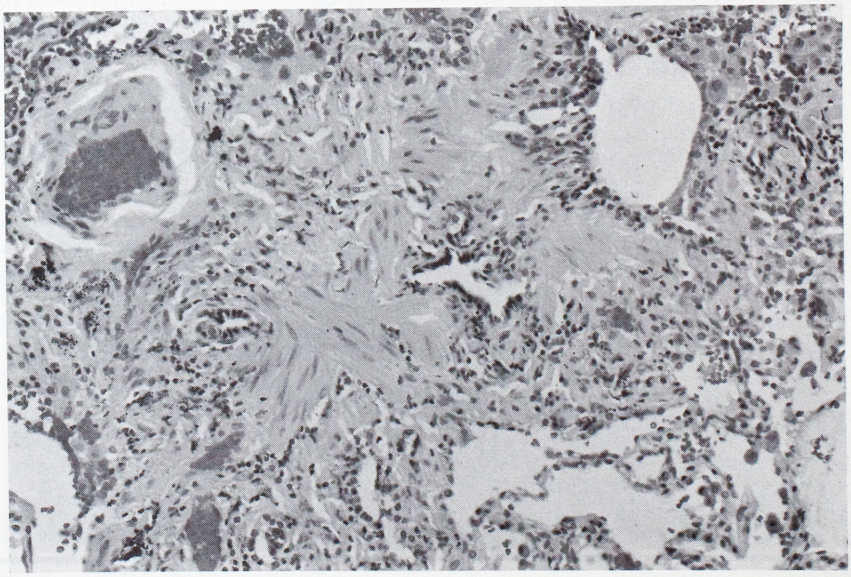

FIGURE 33-4. In constrictive bronchiolitis occurring secondary to pulmonary ammonia burn, a bronchiole is distorted with narrowing and partial obliteration of the lumen by dense connective tissue and scattered chronic inflammatory cells. (H & E stain; low magnification.)

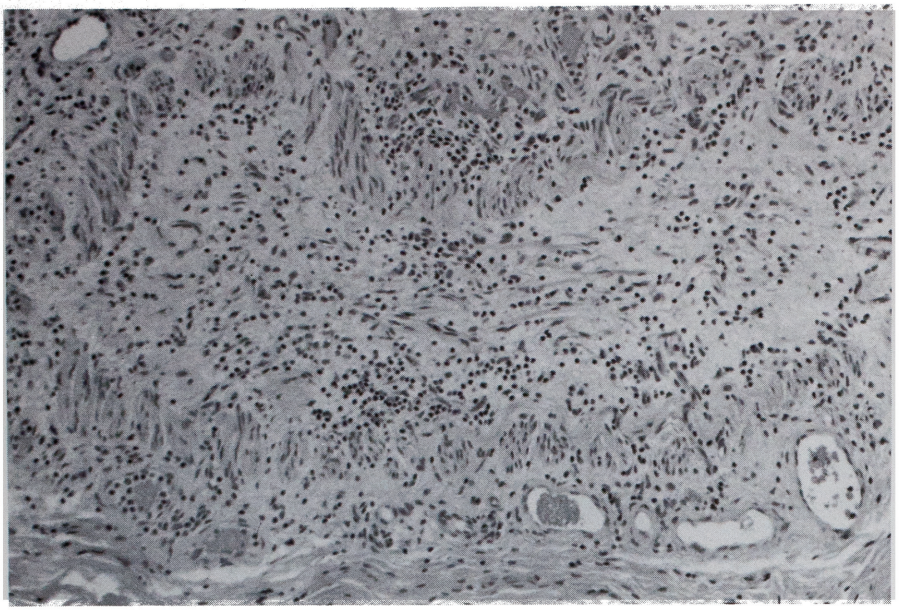

FIGURE 33-5. In constrictive bronchiolitis occurring secondary to adenovirus infection, the bronchiolar lumen is completely obliterated by dense connective tissue and scattered chronic inflammatory cells. The bronchiolar smooth muscle is apparent at the periphery, but bronchiolar epithelium has been totally destroyed in this cross section. (H & E stain; low magnification.)

obliterans and pneumonia may help to further elucidate the pathogenesis of BOOP and related disorders.[8]

ENDOGENOUS LIPOID PNEUMONIA

Lipoid pneumonia is classified into the exogenous and endogenous varieties.[9] The exogenous form is associated with aspiration of oily substances, such as mineral oil, petroleum jelly–based products, some radiographic contrast media (*e.g.*, Dionosil, Lipiodol, Hytrast), and oily mists (see Chap. 37).[10] In contrast, lipid in ELP derives from the breakdown of cell membranes or lipoprotein secretions such as surfactant.

Most cases of ELP occur as the result of localized pulmonary lesions. However, in some instances ELP may present as more diffuse disease with no discernible etiology.[9] Because of the consolidation of air spaces and associated interstitial fibrotic changes with long-standing disease, chest radiographs may show a mixed

TABLE 33-1
Clinical and Pathologic Comparison of Bronchiolitis Obliterans Organizing Pneumonia (BOOP), Idiopathic Pulmonary Fibrosis/Usual Interstitial Pneumonia (IPF/UIP), Chronic Eosinophilic Pneumonia (CEP), and Hypersensitivity Pneumonitis/Extrinsic Allergic Alveolitis (HP/EAA)

BOOP	IPF/UIP	CEP	HP/EAA
CLINICAL PRESENTATION			
Abrupt onset with flulike febrile illness, cough, and dyspnea	Insidious onset of dyspnea; nonproductive cough	Dyspnea associated with asthma; peripheral eosinophilia	Febrile illness with cough, dyspnea, often associated with exposure to organic dusts
RADIOGRAPHIC APPEARANCE			
Bilateral patchy infiltrates	Increased interstitial markings with a peripheral and basilar accentuation	Bilateral patchy infiltrates	Reticulonodular infiltrates with basilar predominance
CHARACTERISTIC HISTOLOGIC FEATURES			
Young edematous connective tissue plugs within bronchioles, alveoli, and alveolar ducts; patchy distribution and of same age	Interstitial fibrosis and inflammation in patchy distribution and of variable age; often associated with honeycomb changes	Intraalveolar infiltrates of eosinophils and macrophages, sometimes with eosinophilic abscesses; mild interstitial thickening	Interstitial infiltrates of lymphocytes with small granulomas and giant cells; bronchiolocentric pattern; honeycomb changes may be seen in advanced cases
RESPONSE TO STEROIDS			
Excellent; prognosis worse in patients with concomitant collagen-vascular disorder	Variable, often poor	Excellent	Excellent; patient also responds to removal from offending antigen when recognized

interstitial and alveolar pattern. The pathologic features of and the various conditions associated with ELP are reviewed in Display 33-1.

ELP is sometimes referred to as cholesterol pneumonia or golden pneumonia. The latter term derives from the characteristic golden yellow appearance of the involved areas of the lung on gross inspection (Color Fig. 33-1). This gross appearance is indistinguishable from that of exogenous lipoid pneumonia. Microscopically, the characteristic feature is the marked intraalveolar and interstitial accumulation of lipid-laden, foamy histiocytes (Fig. 33-6).

The lipid in ELP is finely divided, and this distinguishes it from the large, variably sized vacuoles of exogenous lipoid pneumonia. Focally, cholesterol clefts may be observed, and in some patients these may be prominent and associated with a marked giant cell reaction (see Pulmonary Interstitial Disease and Gastroesophageal Reflux in Children). In advanced cases, there may be interstitial fibrosis with prominent type II cell hyperplasia (Fig. 33-7). Ultrastructurally, the lipid in ELP takes the form of multilamellated structures (MS) consisting of concentric whorls of lipid membranes (see Pulmonary Interstitial Disease and Gastroesophageal Reflux in Children).[11]

In most patients, ELP occurs distal to areas of obstruction,[12] especially distal to bronchi obstructed by neoplasms or foreign bodies. Another cause of bronchial obstruction leading to ELP is bronchial stenosis secondary to surgery, irradiation, or laser therapy.[10] Obstruction of smaller airways, such as bronchiolitis obliterans,[13] may also be associated with ELP (see Bronchiolitis Obliterans Organizing Pneumonia).

ELP may also be observed adjacent to malignant neoplasms in which there is no identifiable obstruction, and adjacent to pulmonary abscesses. Organizing pneumonia is commonly associated with focal areas of ELP. Foamy histiocytes may also be observed in areas of pulmonary hemorrhage from the breakdown of erythrocytes. Drug toxicity may be associated with the accumulation of foamy histiocytes within alveoli and the pulmonary interstitium, particularly the antiarrhythmia agent amiodarone.[10,14] In some instances, ELP occurs with no discernible etiology; such cases are deemed idiopathic. A likely source of lipid in some instances of ELP is increased cell turnover. Alternatively, decreased lipid removal from the air spaces, as may occur with obstruction, or inhibition of lipid breakdown, as occurs with amiodarone toxicity, may be a contributing factor.

DISPLAY 33-1. CONDITIONS ASSOCIATED WITH ENDOGENOUS LIPOID PNEUMONIA

Bronchial obstruction by tumor or foreign body
Bronchial stenosis secondary to surgery, radiation, or laser therapy
Bronchiolitis obliterans
Endogenous lipoid pneumonia adjacent to pulmonary abscesses
Organizing pneumonia
Organizing hematomas or intraalveolar hemorrhages
Drug toxicity (*e.g.*, amiodarone)
Gastroesophageal reflux
Idiopathic endogenous lipoid (*i.e.*, cholesterol) pneumonia

PULMONARY ALVEOLAR PROTEINOSIS

PAP was originally described by Rosen and colleagues in 1958.[15] This is an uncommon condition occurring primarily in individuals 20 to 50 years of age. However, rare cases have been described in childhood and infancy.[16] PAP occurs about three times as often in males as in females. This disease presents clinically with insidious onset of dyspnea and cough associated with bilateral, patchy airspace disease on chest radiographs. The cough is usually nonproductive, although some patients may produce sputum containing fragments of gelatinous material. Other symptoms occurring less commonly include fatigue, weight loss, chest pain, and repeated febrile episodes. Hypoxemia is present and increases with exercise, and pulmonary function tests usually show mild restrictive changes. In some patients, the disease progresses to diffuse pulmonary fibrosis with increased interstitial markings on chest roentgenograms and respiratory failure.

Grossly, the lung parenchyma contains multiple ill-defined, firm, gray-yellow areas of consolidation (Fig. 33-8). Histologi-

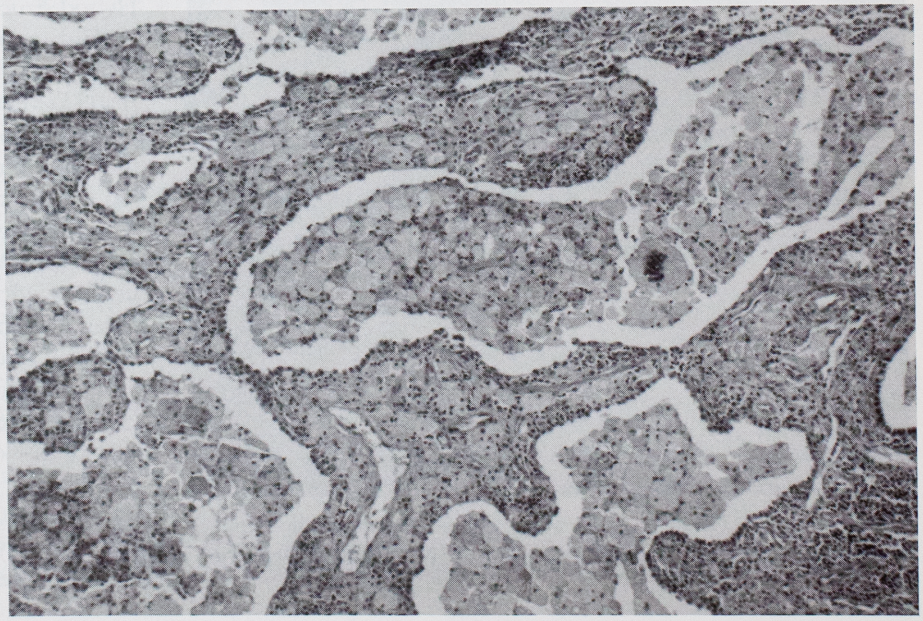

FIGURE 33-6. In endogenous lipoid pneumonia, the alveoli are filled with foamy, lipid-laden macrophages. The alveolar septa are thickened. (H & E stain; low magnification.)

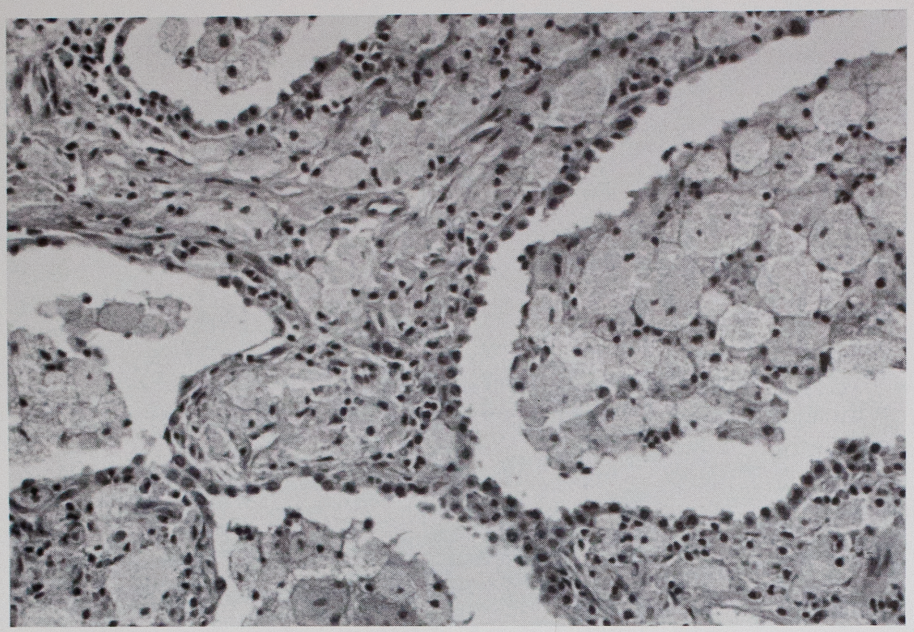

FIGURE 33-7. In endogenous lipoid pneumonia, detail of foamy histiocytes shows both their intraalveolar and interstitial location. Hyperplastic alveolar type II pneumocytes can also be seen lining the thickened alveolar septa. (H & E stain; intermediate magnification.)

cally, there is massive accumulation of finely granular, proteinaceous acellular material within alveoli, alveolar ducts, and bronchioles. This material is strongly periodic acid-Schiff (PAS)–positive and diastase-resistant (Fig. 33-9) and does not stain with alcian blue, which distinguishes it from mucus. In frozen sections, this acellular material is strongly oil red O– and Sudan black–positive, indicating a high lipid content.[17] Immunohistochemical studies have shown that this amorphous material also contains abundant surfactant apoprotein.[18]

Type II pneumocyte hyperplasia is frequently observed, and along the periphery of involved areas, foamy macrophages that are directly apposed to the acellular debris may be seen. Another feature is the presence of cholesterol clefts within the amorphous intraalveolar material, including cholesterol granulomas (CG) in some instances. In advanced cases, diffuse interstitial fibrosis with prominent type II cell hyperplasia is observed, and in these instances, focal collections of the characteristic intraalveolar acellular proteinaceous debris may be difficult to find (Fig. 33-10).

FIGURE 33-8. Patchy, irregular areas of gray-tan consolidation can be seen macroscopically in an autopsy specimen from a patient with pulmonary alveolar proteinosis.

Ultrastructurally, the amorphous acellular debris within the alveolar spaces is seen to consist of MS, of which four distinct varieties have been described.[19–22] Type A MS are the most common and consist of osmiophilic lamellae showing a trilaminar structure typical of bilayer membranes and having a mean intermembranous spacing of approximately 20 nm (Fig. 33-11). Type B MS are highly ordered fused-membrane structures with a periodicity of approximately 5.5 nm that produce what is sometimes referred to as a fingerprint pattern. Type C MS have a more irregular spacing of closely packed membranes and are indistinguishable from the lamellar bodies produced and secreted by type II pneumocytes. Type D MS have a lattice structure resembling that of tubular myelin. Hybrid structures containing features of two or more of the previously described varieties of MS are sometimes observed.[21] Aggregates of amorphous material are also seen in the vicinity of MS. Types A and D MS have protein between the bilayers, whereas types B and C MS do not have significant levels of protein.[23] The ultrastructural and immunohistochemical features of the amorphous material in PAP are indicative of an origin from surfactant.

A variety of conditions has been associated with the development of PAP (Display 33-2). The inhalation of large quantities of finely divided dusts (*e.g.*, silica, aluminum) may result in the accumulation of intraalveolar amorphous debris with morphologic and tinctorial characteristics of PAP.[24,25] Dust-induced lipoproteinosis has been reproduced in experimental animal models.[26] PAP has been associated with hematologic malignancies (*e.g.*, chronic myelogenous leukemia, acute myeloblastic leukemia, acute lymphocytic leukemia, hairy cell leukemia, essential thrombocythemia, Hodgkin and non-Hodgkin lymphomas, polycythemia vera, myelofibrosis, idiopathic thrombocytopenic purpura, multiple myeloma, macroglobulinemia, myelodysplasia).[27,28]

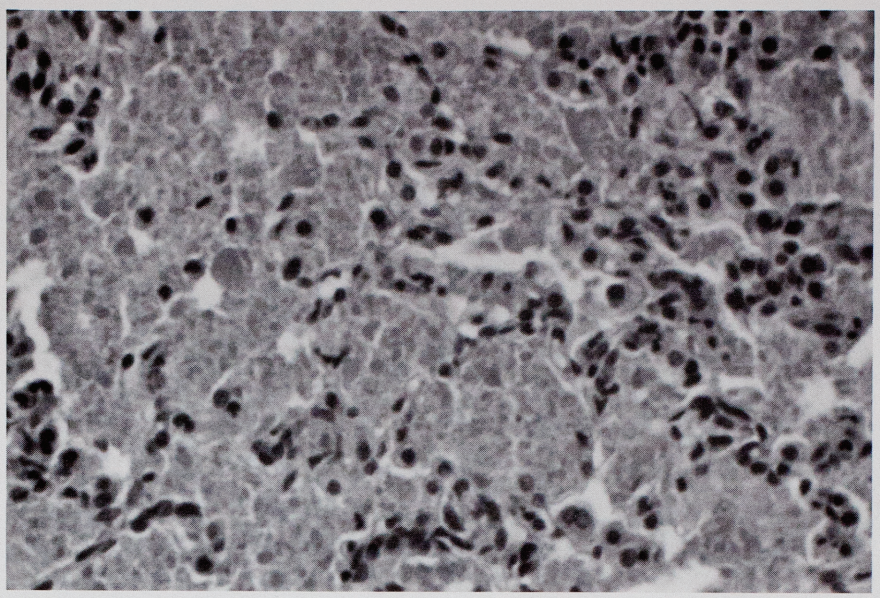

FIGURE 33-9. Periodic acid-Schiff–positive granular amorphous debris fills the alveoli in this infant with pulmonary alveolar proteinosis of unknown cause. (Intermediate magnification.)

The frequent association between PAP and opportunistic infection with organisms such as *Nocardia* species suggests that altered immunity is a predisposing factor.[28] Rare cases associated with prior mycobacterial infection have also been described.[29] *Pneumocystis carinii* pneumonia may also present with a pattern that mimics PAP.[18] A few patients with lysinuric protein intolerance have been reported who subsequently developed PAP.[30] However, in most patients with PAP, no etiologic factors can be identified.

The pathogenesis of PAP is still poorly understood. As noted above, ultrastructural and immunohistochemical features of the amorphous acellular material that accumulates within alveoli support an origin from surfactant. Abnormal accumulation of this altered surfactant material could result from either excessive production or decreased removal of surfactant. Bedrossian and colleagues proposed that the association of PAP with hematologic malignancies and opportunistic infections could be explained by a failure of clearance mechanisms, due to either deficient recruitment or intrinsic malfunction of alveolar phagocytic cells.[28] *In vitro* studies have confirmed that alveolar macrophages from patients with PAP have impaired phagocytosis and phagolysosome fusion compared with those of controls. Furthermore, cell-free fractions of lavage fluid from patients with PAP suppressed phagocytosis and phagolysosome fusion of normal control macrophages and produced alterations in macrophage morphology.[31] It is probable that a number of noxious stimuli are capable of altering the intraalveolar metabolism of pulmonary surfactant and surfactant proteins, resulting in the formation of MS that are subsequently ingested by macrophages. This in turn leads to macrophage dysfunction and demise, and their subsequent degradation creates the

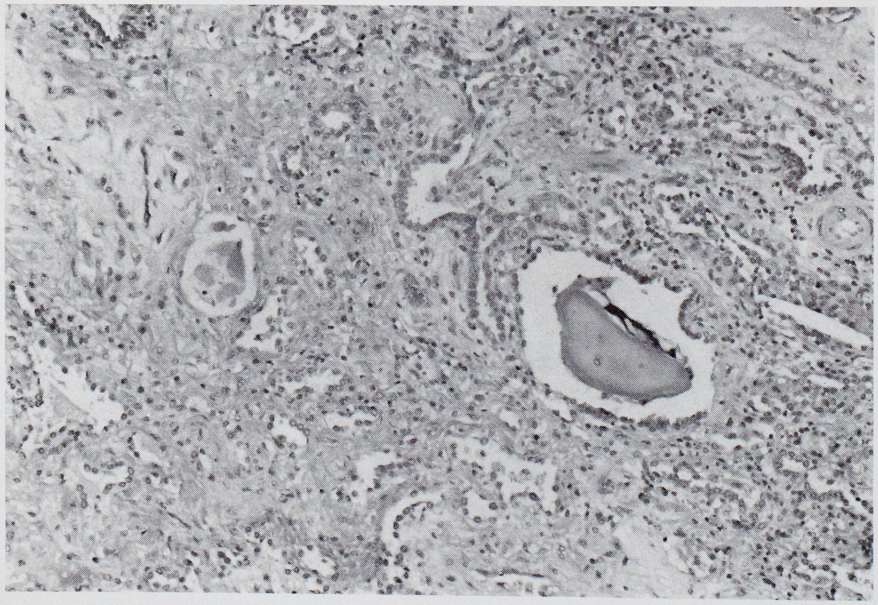

FIGURE 33-10. Lung parenchyma shows advanced fibrosis in the native lungs of a 40-year-old woman undergoing double-lung transplantation for pulmonary alveolar proteinosis. Previous biopsy specimens had shown typical features of pulmonary alveolar proteinosis, but the patient gradually became refractory to whole-lung lavage treatment and developed diffuse interstitial disease, which was identified radiographically. A few residual foci of proteinosis are still present. (H & E stain; low magnification.)

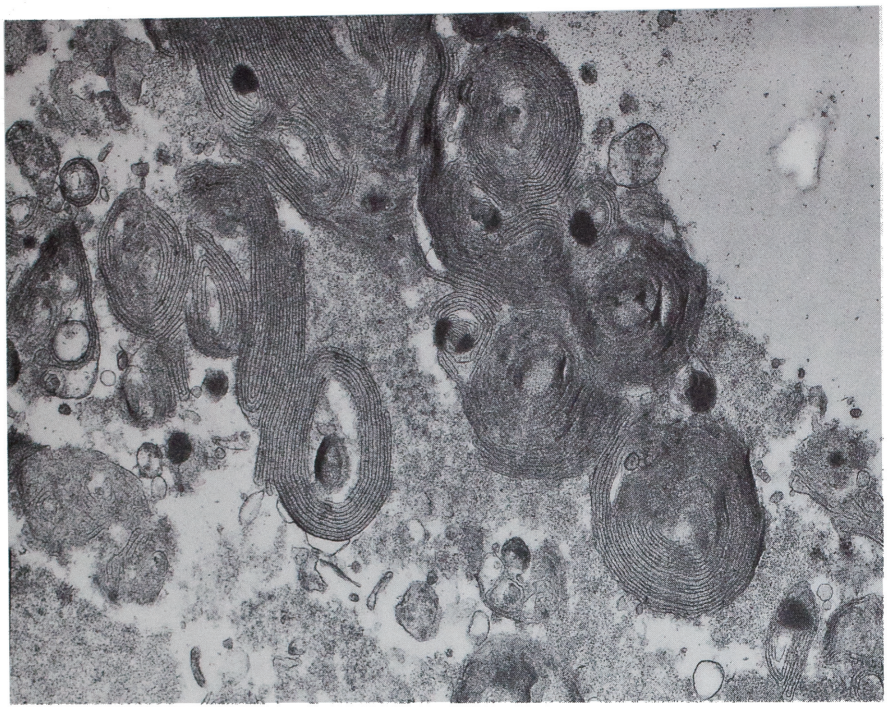

FIGURE 33-11. The ultrastructural appearance of type A multilamellated structures in pulmonary alveolar proteinosis shows the trilaminar morphology of the membrane layers with an intermembrane spacing of about 20 nm. Amorphous granular material, membrane vesicles, and dense bodies are also present. (Alveolar lavage specimen; uranyl acetate–lead citrate stain; original magnification × 5000.)

acellular debris characteristic of PAP. Removal of this acellular debris by means of whole-lung lavage often results in significant clinical improvement and is the treatment of choice.

PULMONARY INTERSTITIAL DISEASE AND GASTROESOPHAGEAL REFLUX IN CHILDREN

Several pediatric patients with diffuse interstitial lung disease and pathologic evidence of a mixed interstitial and intraalveolar process were reported by Fisher and colleagues.[32] The histologic features included a mixture of ELP, PAP, and CG within alveoli or pulmonary interstitium. Six of eight patients had clinically documented GER (Table 33-2). The association of ELP, PAP, and CG noted by Fisher and colleagues in these eight pediatric patients had previously been recognized by other investigators.[32] Verbeken and associates described three patients with features of both ELP and PAP distal to an obstructed bronchus,[33] and Haberle and colleagues noted an association between PAP and CG.[34] As noted in the previous sections, these disorders are manifestations of abnormal processing or metabolism of phospholipids and lipoproteins within the alveolar spaces. The associated tissue injury may eventually lead to pulmonary interstitial fibrosis of a diffuse nature.

These eight patients represent a diverse group from the standpoint of primary disease processes (see Table 33-2). Three patients had severe combined immunodeficiency and two had pulmonary hypertension. All eight patients exhibited a delayed growth pattern, and six of these eight had digital clubbing. Six patients had depressed appetites or anorexia, and five had anemia. Pulmonary function tests were performed in four patients. Two patients demonstrated restrictive changes, and two had both restrictive and obstructive changes; one of the latter patients had cystic fibrosis. Of note was the fact that six of these patients had GER as documented by barium swallow and Tuttle test (*i.e.*, esophageal *p*H probing). Five of these six underwent Nissen fundoplication in an attempt to control the reflux. For two patients there was no documented evidence of reflux, although tests to exclude GER had not been performed. However, one of these was the only patient with cystic fibrosis, a disorder well recognized to be associated with GER.[35–37]

The roentgenographic findings in these eight patients are summarized in Table 33-2. Five patients had generalized, diffuse, and fine nodular opacities. In one patient, nodular opacities were discrete and localized to the right lower lobe. With more severe involvement, the opacities tended to obscure the pulmonary vasculature. The patient with cystic fibrosis (patient 6) had extensive changes of bronchiectasis with areas of overinflation and atelectasis. These changes were most severe in the upper lobes. Patient 8, who was the youngest patient in the series at 4 months of age, displayed mild hazy opacities rather than discrete nodular opacities. CT was performed in one instance (patient 3) and confirmed the findings of generalized, diffuse, fine nodular opacities with peripheral accentuation.[32]

Microscopically, there was an admixture of ELP, PAP, and CG. In four of the patients (patients 1, 4, 6, and 8), ELP was the predominant pattern, whereas in two patients (patients 2 and 7), PAP predominated. In two additional patients (patients 3 and 5),

DISPLAY 33-2. CONDITIONS ASSOCIATED WITH PULMONARY ALVEOLAR PROTEINOSIS

Exposure to noxious dusts and fumes
Hematologic malignancies
Altered immune states
Mycobacterial infections
Pneumocystis carinii pneumonia
Lysinuric protein intolerance
Gastroesophageal reflux
Idiopathic pulmonary alveolar proteinosis

TABLE 33-2
Clinical and Roentgenographic Findings in Eight Patients With Endogenous Lipoid Pneumonia, Pulmonary Alveolar Proteinosis, and Cholesterol Granulomas

Patient Number	Age	Gender	Diagnosis	Gastroesophageal Reflex	Roentgenographic Findings
1	13 y	Male	Pulmonary hypertension	+	Diffuse fine nodular pulmonary opacity L > R
2	31 y	Female	Pulmonary hypertension	ND	Bilateral generalized nodular pulmonary opacity
3	4 y	Female	Lysinuric protein intolerance	+	Generalized diffuse nodular pulmonary opacity
4	3 y	Female	SCID	+	Generalized diffuse fine nodular pulmonary opacity
5	8 y	Female	SCID	+	Generalized diffuse fine nodular pulmonary opacity
6	23 y	Female	Cystic fibrosis	ND	Bronchiectasis and peribronchial cuffing, predominantly upper lobes
7	5 y	Male	SCID	+	Discrete nodular pulmonary opacity
8	4 mo	Male	Trisomy 10q; VSD	+	Generalized hazy pulmonary opacity

+, present; L > R, left greater than right; ND, no data; SCID, severe combined immunodeficiency; VSD, ventricular septal defect.

Adapted from Fisher M, Roggli V, Merten D, Mulvihill D, Spock A. Coexisting endogenous lipoid pneumonia, cholesteral granulomas, and pulmonary alveolar proteinosis in a pediatric population: a clinical, radiographic, and pathologic correlation. Pediatr Pathol 1992;12:365.

more than one biopsy specimen was available, which showed a changing pattern with time. Patient 3 had two open lung biopsies 2 years apart, followed by an autopsy 1 year after the last open biopsy. ELP predominated on the two open biopsies, whereas PAP was the predominant pattern found at autopsy. Patient 5 had two open lung biopsies 1 year apart. The first showed a pattern that was predominantly PAP, whereas in the second, ELP was the most prominent feature.

CG were a striking feature in seven of eight patients. These consisted of aggregates of empty cleftlike spaces often associated with and engulfed by foreign-body giant cells (Fig. 33-12). The CG appeared to originate within the alveoli and gradually became incorporated into the pulmonary interstitium. The incorporation process was associated with interstitial fibrosis, which was occasionally severe (Color Fig. 33-2).

Foamy macrophages were the predominant feature in the youngest patient in our study, who was 4 months old; this suggests that accumulation of these cells within the alveolar spaces is the earliest morphologic abnormality in these patients. Cholesterol clefts and fibrosis were not observed in this patient (patient 8). A predominance of ELP without fibrosis or CG was also noted in the first open biopsy specimen from patient 3, who was 1 year of age. In some instances, a transition could be observed between degenerating, PAS-positive foamy macrophages and the PAS-positive acellular debris characteristic of PAP. Indeed, all three patterns could occasionally be found in the same microscopic field (Fig. 33-13).

The origin of the cholesterol clefts was unclear, although iron-stained sections showed a close association between cholesterol clefts and hemosiderin granules in some instances. This finding suggests that erythrocytes may be one possible source for the cholesterol clefts observed.[38] Ultrastructural studies performed in three patients (patients 3, 5, and 8) showed MS (see Fig. 33-11) and lipid-laden alveolar macrophages. In seven of the eight pa-

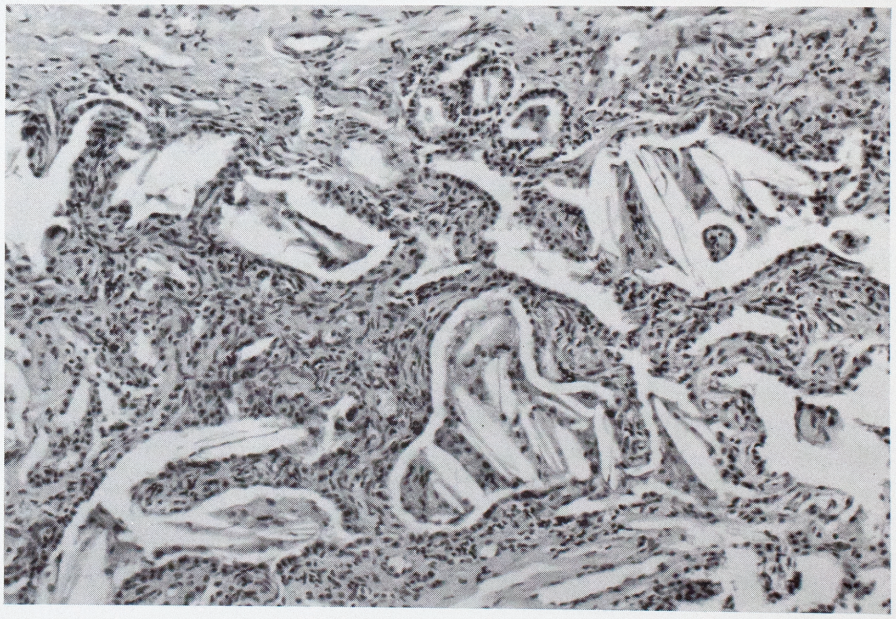

FIGURE 33-12. Cholesterol granulomas and interstitial fibrosis are present in a 13-year-old boy with pulmonary hypertension and clinically documented gastroesophageal reflux. The needle-shaped or cleftlike spaces are partially surrounded by foreign-body giant cells (see Patient 1, Table 33-2). (H & E stain; low magnification.)

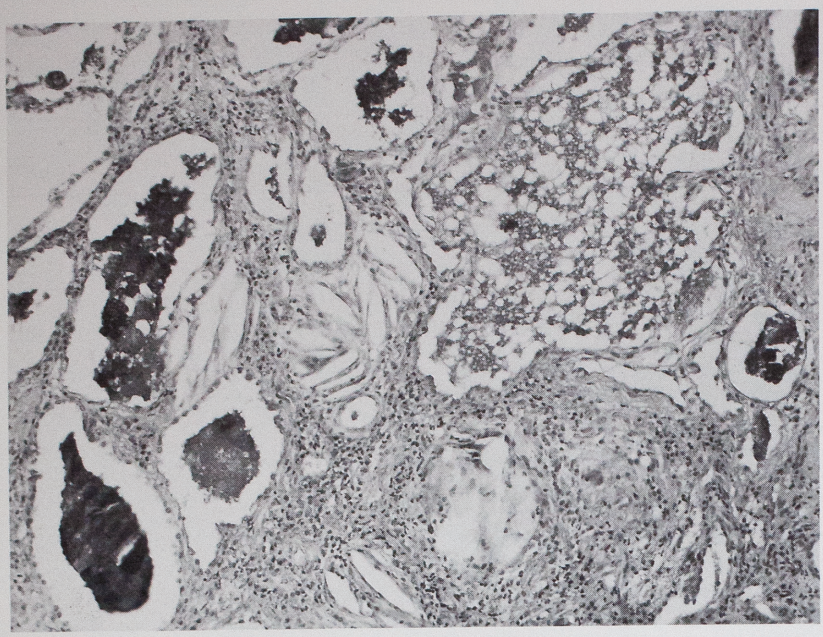

FIGURE 33-13. Periodic acid-Schiff (PAS)–positive foamy macrophages (*upper right*), cholesterol clefts (*center*), and PAS-positive acellular debris (*left*) are all present in the same microscopic field, illustrating features of endogenous lipoid pneumonia, pulmonary alveolar proteinosis, and cholesterol granulomas (see Patient 2, Table 33-2). (H & E stain; low magnification; from Fisher M, Roggli V, Merten D, Mulvihill D, Spock A. Coexisting endogenous lipoid pneumonia, cholesterol granuloma, and pulmonary alveolar proteinosis in a pediatric population: a clinical, radiographic, and pathologic correlation. Pediatr Pathol 1992;12:365.)

tients, no evidence of bronchiolar obstruction was detected histologically. The one exception was the patient with CF, who showed mucus obstruction primarily in the upper lobes and ELP and CG in the lower lobes, more so in the right than the left lobe.

PATHOGENETIC CONSIDERATIONS

The findings in the patients described previously suggest the possibility that GER can somehow result in the accumulation of lipid materials within the alveolar spaces, manifesting histologically as ELP, PAP, and CG. Studies have firmly established a relationship between chronic lung disease and GER. Malfroot and colleagues studied 38 children with unexplained pulmonary problems, including chronic wheeze, recurrent bronchitis, and recurrent pneumonia, and found that 63% had documented GER by prolonged esophageal *p*H monitoring and gastroesophageal scintiscanning.[39] Pulmonary symptoms improved with control of reflux in most of their patients. Similar percentages of GER in patients with chronic unexplained lung disease were reported by Euler and associates (65%)[40] and Hoyoux and colleagues (53%).[41] Improvement in symptoms with control of reflux was also noted in these latter studies.

The pathophysiologic mechanism by which GER mediates pulmonary disease has long been felt to be recurrent pulmonary microaspiration.[42] Experimental studies in dogs have shown that intratracheal instillation of hydrochloric acid ranging in *p*H from 1.8 to 5.9 results in a chemical pneumonitis characterized by edema, hemorrhage, and inflammation.[43] Furthermore, GER-induced lung disease could result in a vicious cycle, because respiratory disorders can in turn aggravate GER through positive abdominal pressure during coughing or wheezing and negative intrathoracic pressure as seen in stridor.[42] Clinical studies have also shown that the occurrence of lipid-laden alveolar macrophages in bronchoalveolar lavage fluid correlates well with the presence of GER in patients with parenchymal lung disease.[44–46]

There is still a question regarding the mechanism by which microaspiration of gastric acid results in the accumulation of lipid within alveoli. The infrequent occurrence of large lipid droplets indicative of exogenous lipoid pneumonia and the absence of food particles suggest that repeated microaspirations of gastric acid while the patient is asleep are a major contributory factor. As shown in Displays 33-1 and 33-2, a wide variety of disorders and noxious stimuli can result in the intraalveolar accumulation of phospholipids and lipoproteins, as manifested morphologically by ELP and PAP. The synthesis, secretion, degradation, and reuptake of surfactant and surfactant apoproteins are complex and subject to a number of regulatory controls.[47,48] The removal of 10% to 30% of intraalveolar surfactant per hour is needed to maintain a steady state with production.[48] It is conceivable that repeated microaspirations could alter surfactant apoproteins or perhaps the ratio of apoprotein to phospholipid content, resulting in defective tubular myelin.[19] The turnover and metabolism of pulmonary surfactant could in turn be altered, resulting in the accumulation of MS within the alveolar spaces.

Phagocytosis of these MS would result in the accumulation of foamy macrophages within the alveolar spaces, the characteristic feature of ELP. This could also account for the finding of lipid-laden alveolar macrophages in bronchoalveolar lavage fluid from patients with GER and aspiration.[44–46] Excessive lipid burden in turn results in macrophage dysfunction and eventual disintegration.

Experimental models of PAP have shown that the onset of the condition is preceded by the accumulation of lipid-laden alveolar macrophages that subsequently degenerate, leaving the amorphous intraalveolar debris characteristic of this disorder.[26,49,50] This early phase of PAP is morphologically similar to ELP. X-ray diffraction studies of the acicular clefts in CG have shown them to be composed primarily of the palmitic ester of cholesterol, a finding consistent with the ultimate derivation of CG from degraded surfactant.[38] The intraalveolar CG may become incorporated into the pulmonary interstitium through a process similar to that known to exist in many interstitial lung disorders.[51,52]

An interesting association with important implications for intraalveolar accumulation of lipoproteins is the relationship between lysinuric protein intolerance and PAP.[30] This is a rare autosomal recessive disorder with only 80 patients known in the world literature. The condition is characterized by the abnormal transport of the cationic amino acids lysine, arginine, and or-

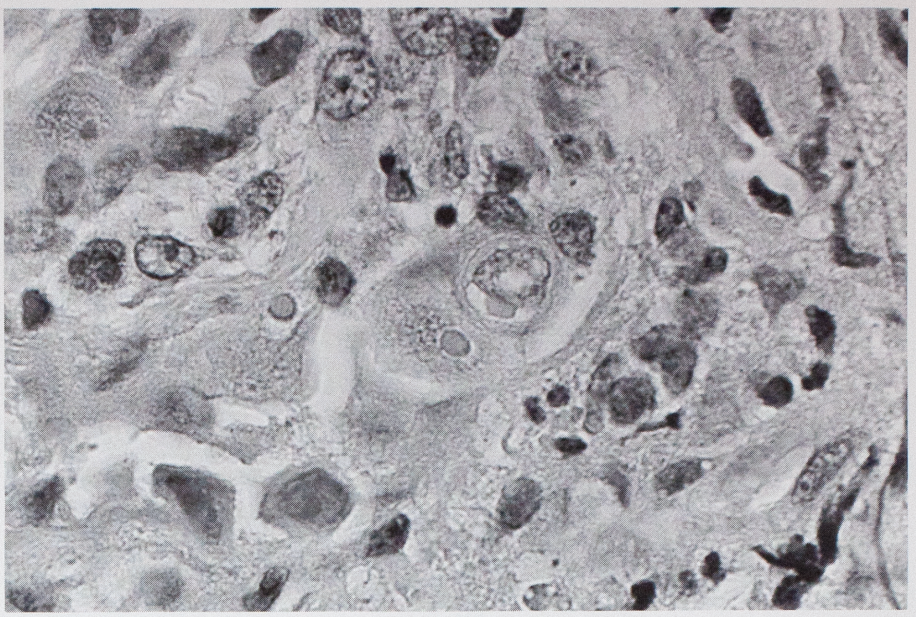

FIGURE 33-14. Eosinophilic cytoplasmic inclusions of respiratory syncytial virus are present within hyperplastic alveolar type II pneumocytes in this infant with severe combined immunodeficiency. (H & E stain; high magnification; courtesy of T.V. Colby, M.D., Rochester, MN.)

nithine in the membranes of the kidney tubule, intestine, cultured fibroblasts, and possibly the hepatocyte. These patients develop severe nausea and vomiting, failure to thrive, and, in some instances, an interstitial pneumonia that histologically resembles PAP. The patient reported by Fisher and colleagues (see Table 33-2, patient 3) had two open lung biopsies at ages 1 and 3 years that predominately showed ELP, whereas postmortem findings 1 year after the last open biopsy showed predominately PAP and interstitial fibrosis.[32] Patients with lysinuric protein intolerance have been shown to have abnormal cationic amino acids within the alveolus, and Simell proposes that abnormal transport of these amino acids by the respiratory epithelium may be the mechanism leading to the accumulation of lipoproteinaceous debris within the alveolus.[30]

It should be noted that in pediatric patients with the PAP-ELP-CG complex described by Fisher and colleagues, mechanisms other than GER and microaspiration may be operative with regard to the intraalveolar accumulation of lipid debris.[32] For example, Colby and associates described a PAP-like picture in an infant with severe combined immunodeficiency and infection of the lower respiratory tract with respiratory syncytial virus.[53] In this patient, alveoli were filled with amorphous, granular eosinophilic debris and disintegrating neutrophils. Prominent spherical eosinophilic cytoplasmic inclusions were present in many alveolar type II cells (Fig. 33-14). More information is therefore necessary to understand the precise mechanisms leading to these disorders of intraalveolar accumulation of phospholipids and lipoproteins, and to perhaps devise appropriate treatments or preventative measures.

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