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32

Chronic Interstitial Pneumonias With Specific Histologic Features

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As noted in Chapter 31, most patients with chronic interstitial lung disease show a nonspecific histopathologic pattern designated as usual interstitial pneumonia (UIP). Less frequently, a specific pattern of desquamative interstitial pneumonia (DIP) may be seen. As with UIP, DIP may be either idiopathic or associated with identifiable etiologies. Other forms of interstitial pneumonia with specific histologic features have been designated giant cell interstitial pneumonia (GIP) and lymphoid interstitial pneumonia (LIP); these forms have some interesting etiologic associations (see Giant Cell Interstitial Pneumonia and Lymphocytic Interstitial Pneumonia).

As in the case of UIP, end-stage fibrosis and honeycombing can occur in DIP, GIP, and LIP. In addition, there are other entities with specific histologic features entering into the differential diagnosis of chronic interstitial lung disease; these also will be discussed (Display 32-1).

DESQUAMATIVE INTERSTITIAL PNEUMONIA

Like UIP, DIP usually occurs as an idiopathic disease, but it may sometimes be associated with a specific etiology. Some authors consider idiopathic DIP and idiopathic UIP to be, respectively, the early cellular stage and the late fibrotic stage of the same disease, idiopathic interstitial pulmonary fibrosis (IPF). According to this interpretation, many cases of DIP gradually evolve into a UIP pattern and eventually honeycomb lung. This concept is based on several observations:

- The average age for patients with idiopathic DIP is younger than that for patients with idiopathic UIP.
- Apparently, mixed patterns of DIP and UIP are found in some biopsy specimens.
- In those cases in which idiopathic DIP progresses and becomes more fibrotic, it is more difficult to distinguish it from UIP.
- An end-stage, nonspecific honeycomb lung is reached in progressive cases of DIP, at which point the two diseases can no longer be distinguished.[1–5]

However, studies have shown that idiopathic DIP and idiopathic UIP are associated with very different prognoses and responses to therapy.[6–11] Not all cases of idiopathic DIP show progression, and biopsy specimens years after the initial diagnosis may show no significant progression to fibrosis. Therefore, there is practical value in separating the two diseases.

Idiopathic DIP also shares certain clinical and radiographic features with idiopathic UIP, although the latter progresses more rapidly and, therefore, shows more advanced fibrosis for the same duration of disease. Patients with DIP present with insidious onset of cough and shortness of breath. As many as 90% of them have a smoking history of greater than 10 pack years, but the relationship, if any, has not been elucidated.

A wide variety of chest x-ray findings, similar to those seen in UIP, is seen in DIP, including reduced lung volumes and small irregular interstitial densities. Chest x-ray changes tend to be more frequent and severe in UIP. Patients with DIP are more likely to present with a normal chest x-ray film than are patients with UIP (22.5% *versus* 7.6%, respectively), and honeycombing is more likely to be present on initial chest x-ray films in patients with UIP than in those with DIP (49.1% *versus* 12.5%, respectively). Although DIP and UIP affect similar age ranges, the average age of

DISPLAY 32-1. CHRONIC INTERSTITIAL PNEUMONIAS AND OTHER INFILTRATIVE PROCESSES WITH SPECIFIC HISTOLOGIC FEATURES

Pneumonias

Desquamative interstitial pneumonia
Giant cell interstitial pneumonia
Lymphoid interstitial pneumonia (see Chaps. 45 and 55)

Other Infiltrative Processes

Pulmonary eosinophilic granuloma
Pulmonary lymphangioleiomyomatosis
Tuberous sclerosis
Pulmonary alveolar microlithiasis
Pulmonary amyloidosis
Extrinsic allergic alveolitis (see Chap. 65)
Sarcoidosis (see Chap. 66)
Idiopathic hemosiderosis (see Chaps. 9 and 11)
Lymphangitic carcinomatosis (see Chap. 22 and 59)

onset is nearly a decade earlier for DIP than for UIP (42.3 years *versus* 50.9 years, respectively).[9]

Average survival is 12.2 years for DIP *versus* 5.6 years for UIP. DIP is less likely to relentlessly progress to honeycomb lung than is UIP. Patients with DIP may spontaneously improve (21.9%) and even fully recover and are much more likely to improve with steroid therapy than are those with UIP (61.5% *versus* 11.5%, respectively).[9] When fibrosis is already advanced, there is no difference in response to therapy between DIP and UIP.[1,3,4] Late relapse of DIP after therapeutic remission can occur and has been documented by lung biopsy in two patients at 7 and 12 years after initial diagnosis. The biopsy specimens in both cases failed to show progression of the disease when compared with the initial biopsy specimens, and both patients had second complete remissions with therapy.[10] A single report of an acute form of DIP[12] and another report of a localized form of DIP[13] have been published.

Grossly, the lungs in DIP are consolidated and noncrepitant, with the presence of fibrosis and honeycombing depending on the individual patient (Fig. 32-1). There is relative uniformity of the histopathologic changes throughout, in contrast to the variable and random scarring of UIP. Most of the air spaces are filled with monotonous collections of macrophages containing fine brownish cytoplasmic granules that are periodic acid-Schiff (PAS)–positive and diastase-resistant (Color Figs. 32-1 and 32-2). This pigment has been reported to be absent in patients with DIP who do not smoke. In addition, the macrophages contain granules of iron pigment that are much finer than the typical coarse granules of hemosiderin. Necrosis, hyaline membranes, foamy macrophages, and intraalveolar fibrosis are not observed. The alveolar septa have a comparatively mild infiltrate of lymphocytes with an appreciable number of plasma cells and eosinophils.

Unlike UIP, there is in DIP a general preservation of the alveolar architecture (Fig. 32-2). Usually there is only minimal to moderate interstitial fibrosis, except for those cases that progress to honeycombing after many years (Fig. 32-3). The alveolar septa are lined by prominent rounded hyperplastic type II pneumocytes. The original belief that the cells filling the alveolar spaces were desquamated type II pneumocytes was the basis for the name

FIGURE 32-1. The lung of a middle-aged woman, who had desquamative interstitial pneumonia for 15 years and died of acute myelogenous leukemia, shows patchy areas of alveolar consolidation but no significant fibrosis or honeycombing. (Contributed by the editor.)

"desquamative interstitial pneumonia".[6] However, ultrastructural studies have since confirmed that the majority of such cells are macrophages.[14,15]

On occasion the DIP pattern is associated with an identifiable etiology, particularly inhalation of inorganic dusts (Display 32-2).[15–19] Significant asbestos exposure, which typically produces a UIP pattern of fibrosis, may, rarely, cause a DIP pattern.[15]

LESIONS THAT MIMIC DESQUAMATIVE INTERSTITIAL PNEUMONIA

A localized reaction that mimics the histopathology of DIP may sometimes be seen in the parenchyma surrounding space-occupying lesions of the lung and is referred to as a DIP-like reaction or a pseudo-DIP reaction.[20] This focal reaction is nonspecific and has no significance except that it should not be overdiagnosed as DIP (see Display 32-2). Collections of macrophages around nonspecific scars or in the cysts of honeycomb lungs should also not be overinterpreted in the absence of diagnostic features of DIP. DIP should have the diffuse, uniform pattern previously described.

DISPLAY 32-2. IDENTIFIABLE ETIOLOGIES OF DESQUAMATIVE INTERSTITIAL PNEUMONIA (DIP) AND CONDITIONS ASSOCIATED WITH DIP-LIKE REACTIONS

DIP	DIP-Like Reactions
Nitrofurantoin	Eosinophilic granuloma
Aluminum	Respiratory bronchiolitis/interstitial lung disease
Asbestos	
Talc	Tuberculosis granuloma
Hard metals	Rheumatoid nodule
Wood dust	Malignant tumor
Silica	Intrapulmonary lymph node
Silicates	Nonspecific scars
	Hamartoma

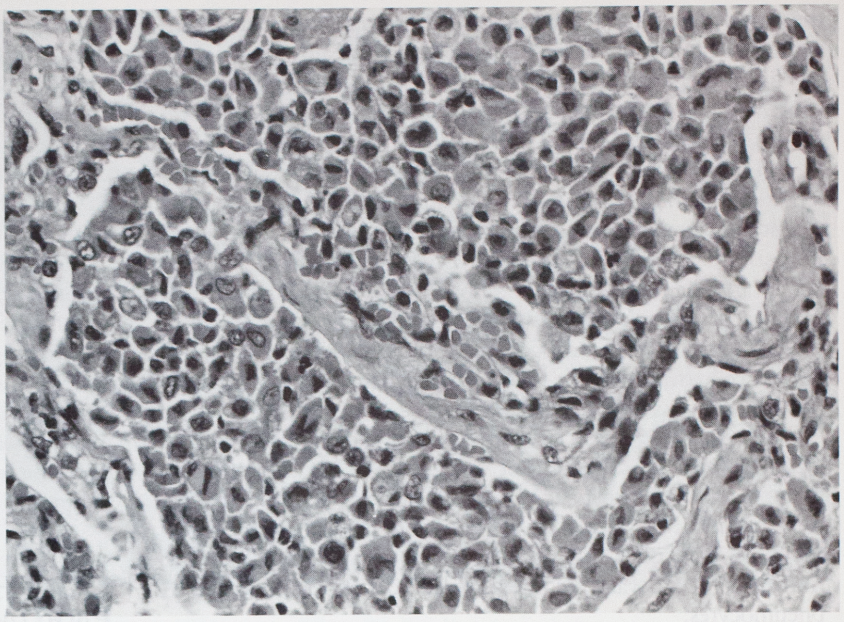

FIGURE 32-2. In desquamative interstitial pneumonia, alveoli are uniformly filled with abundant macrophages. One alveolar septum appears mildly fibrotic. (H & E stain; intermediate magnification.)

Respiratory bronchiolitis is an incidental finding in the membranous and respiratory bronchioles of many smokers in which there is minimal peribronchiolar fibrosis associated with intraluminal and intraalveolar macrophages containing fine brown pigment (see Chap. 30).[21] In some patients, the histopathologic findings may be more pronounced, suggesting DIP, and may be associated with relatively mild clinical, radiographic, and functional changes compatible with IPF.[22] Yousem and colleagues have referred to this as respiratory bronchiolitis–associated interstitial lung disease (RBILD).[23] RBILD differs from DIP in that in the former the findings are patchy and mild, bronchiolocentric, and nonuniform compared with the diffuse, widespread, and uniform findings in DIP. Furthermore, RBILD does not progress to end-stage fibrosis and improves with cessation of smoking.

Before making a diagnosis of DIP by biopsy, it is important to know if the clinical and radiologic findings are consistent with this disease. Because of the risk of overinterpreting a DIP-like reaction, diagnosis of DIP probably should not be made by transbronchial biopsy.[11]

GIANT CELL INTERSTITIAL PNEUMONIA

GIP is a very rare and histopathologically distinctive form of chronic interstitial pneumonia that is characterized by insidious onset of shortness of breath and cough, chest x-ray findings that vary from normal to more typical bilateral reticulonodular densities, restrictive changes on pulmonary function studies, and the potential for progression to end-stage fibrosis.[6,8,24]

Almost all cases of GIP are associated with exposure to hard metal, a diamond-hard alloy of tungsten carbide, cobalt titanium, and tantalum, with a number of industrial uses. Most patients are diamond polishers or are involved in the grinding of hard metal or

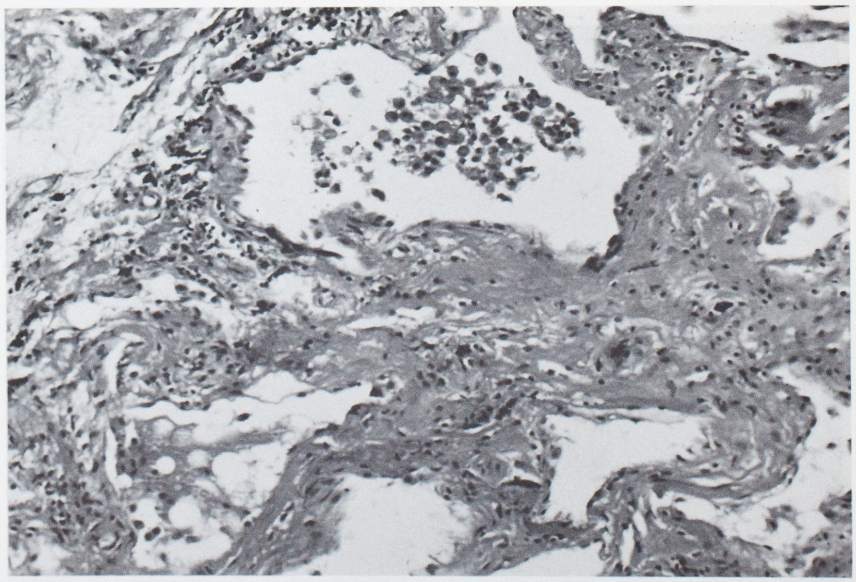

FIGURE 32-3. Desquamative interstitial pneumonia (DIP) progressing to interstitial fibrosis. There is marked thickening of the alveolar septa by fibromuscular tissue. One alveolus contains residual DIP. A prior biopsy specimen showed typical findings of DIP. (H & E stain, low magnification; contributed by the editor.)

the production of hard metal tools.[24–27] Animal studies and observations in human workers indicate that the cobalt component is the likeliest etiologic agent, although the solubility of cobalt in proteinaceous fluids makes its detection in tissue samples difficult.[28,29] In a few cases, GIP is apparently idiopathic.[30,31]

Histopathologically, there is a patchy pattern of variable interstitial inflammation and fibrosis reminiscent of UIP with areas of intense lymphoplasmacytic interstitial infiltrates and active fibrosis intermixed with areas of normal parenchyma and honeycombing. The interstitial inflammation may also contain lymphoid aggregates, neutrophils, and eosinophils. The air spaces contain numerous macrophages and abundant large multinucleated cells that resemble foreign-body giant cells and that are derived from macrophages (Fig. 32-4).

The giant cells may contain anthracosilicotic pigment and typically exhibit cannibalism of smaller cells with one to several lymphocytes or macrophages within their cytoplasm. Although some authors refer to this incorporation of cells as phagocytosis, the intact state of the cells suggests instead emperiopolesis. The fibrotic air space walls are lined by cuboidal hyperplastic type II pneumocytes.

Multinucleated giant cells derived from the lining type II pneumocyte may be attached to the air space walls, sometimes by a narrow neck in a polypoid fashion, or occasionally detached into the air spaces. These epithelial giant cells are smaller and less abundant than the macrophage-derived giant cells.

Bronchioles may show bronchiolitis obliterans with obstruction by intraluminal granulation tissue and scarring.[27] Honeycombing with its typical histopathologic findings may be present. Despite the prominence of giant cells, granulomas are not a feature of this disease. Avoidance of additional hard metal exposure early in the disease and possibly steroid therapy may result in arrest of the disease or even improvement.[24]

A patient with occupational exposure to hard metal who developed advanced pulmonary fibrosis as a result of GIP underwent single lung transplant at my institution. This patient subsequently developed abundant multinucleated giant cells on bronchoalveolar lavage from the transplanted lung, and biopsy showed multinucleated giant calls primarily lining alveolar septa. Although these giant cells did not exhibit cannibalism and metals could not be demonstrated, the patient subsequently developed diffuse interstitial lung disease, suggesting that the patient was manifesting a GIP reaction in the transplanted lung. Perhaps soluble metals originating from the native lung or immunologic factors in association with the original GIP reaction had triggered the process in the transplanted lung. If so, the usefulness of single lung transplant as a treatment for GIP is questionable.

The differential diagnosis of GIP includes giant cell pneumonia due to measles and other viruses, specifically respiratory syncytial virus and parainfluenza virus (Fig. 32-5).[6,8,27,32,33] Viral-related giant cell pneumonias can be differentiated from GIP by the presence of viral inclusions, the occurrence of an acute viral illness, and the younger age of most patients (see Chap. 42). Hard metal exposure may also produce UIP or DIP patterns of pulmonary disease. Hard metal pneumoconiosis is further discussed in Chapters 17 and 37.

LYMPHOCYTIC INTERSTITIAL PNEUMONIA

LIP shares with other chronic interstitial pneumonias the clinical features of progressive shortness of breath and cough, variable radiographic findings that most typically consist of bilateral diffuse reticulonodular infiltrates, restrictive defect on pulmonary function tests, and the potential for progression to fibrosis. Unlike the other chronic interstitial pneumonias, systemic symptoms such as weight loss, fever, and lymphadenopathy are typically present. Dysproteinemia, either hypergammaglobulinemia or hypogammaglobulinemia, is often present. LIP also has a number of intriguing associations, including disorders of immunity and oncogenic retroviruses.[6,8,34–41]

Histopathologically, LIP is characterized by an intense polymorphous infiltrate that involves the interstitium diffusely (Fig. 32-6). The infiltrate is composed of mature lymphocytes admixed with plasma cells and histiocytes, although in a few cases the infiltrates may consist mainly of plasma cells.[34] These infiltrates are polyclonal by immunohistochemistry.[41] Additional features that

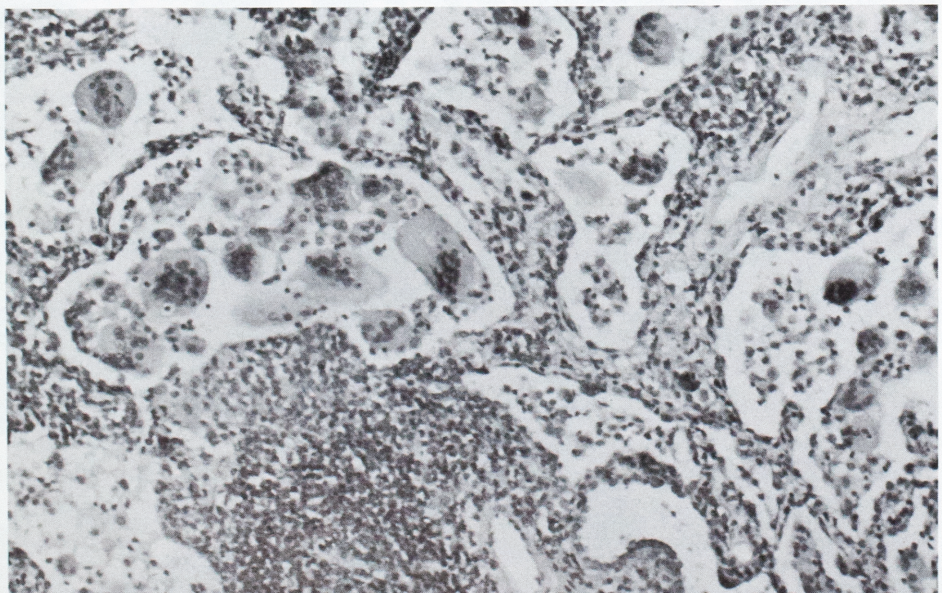

FIGURE 32-4. Giant cell interstitial pneumonia produces intraalveolar multinucleated giant cells, interstitial

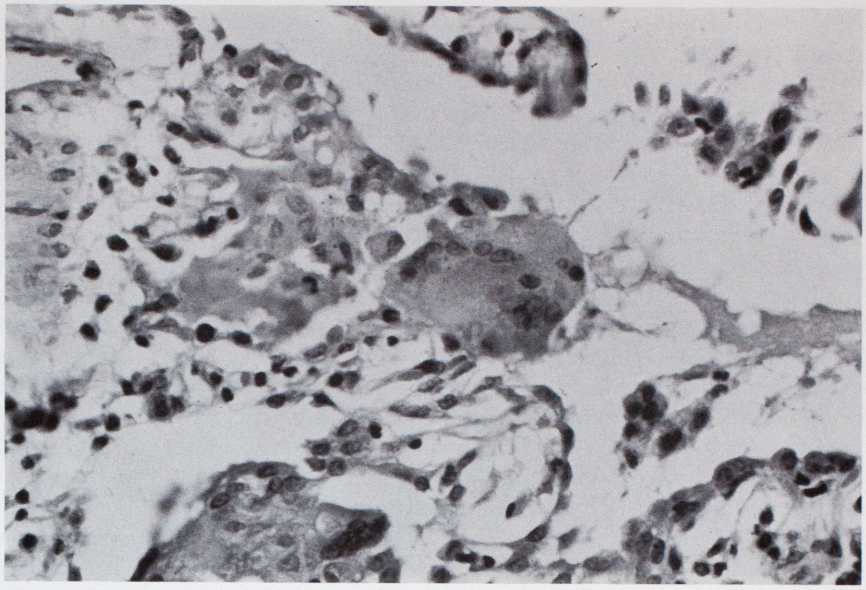

FIGURE 32-5. Giant cell interstitial pneumonia is present in an 8-year-old boy with a clinical picture of viral pneumonia. (H & E stain; intermediate magnification; contributed by the editor.)

may sometimes be present include germinal centers, amyloid, rare granulomas, interstitial fibrosis, and honeycombing.

A number of observations suggest that LIP may be a lymphoproliferative disorder associated with disordered immunity, perhaps with a pathogenetic role for specific viruses associated with other lymphoproliferative disorders. It is likely that many cases of LIP are indolent, low-grade, well-differentiated lymphomas from the beginning or are premalignant lymphoproliferative disorders that can eventually progress to lymphoma. LIP has been associated with autoimmune diseases such as Sjogren syndrome,[36] chronic active hepatitis,[37] and autoimmune hemolytic anemia,[35] and with graft-*versus*-host disease in bone marrow transplant patients.[38]

LIP has emerged as a feature of pulmonary involvement in the acquired immunodeficiency syndrome (AIDS) due to the human immunodeficiency virus (HIV) in adults and especially in children.[38,41] Studies have demonstrated seropositivity for human T-cell lymphotropic virus type I (HTLV-1) in five of six patients with LIP.[39] Epstein-Barr virus (EBV) genome was detected in lung biopsy specimens from 9 of 14 patients with LIP by *in situ* hybridization.[40] The HIV, HTLV-1, and EBV viruses are all associated with various lymphoproliferative disorders and lymphomas, as well as altered immunity, and their association with LIP is probably not coincidental. LIP is further discussed in this book in relation to AIDS and lymphoma (Chaps. 45 and 55).

EOSINOPHILIC GRANULOMA

Pulmonary eosinophilic granuloma (PEG) is a form of interstitial lung disease characterized by scattered nodular proliferations of Langerhans cells, a type of mononuclear phagocyte, which result in multifocal scars and which, in some cases, progress to honeycomb lung. The origin of this disease is unknown, and whether it is a neoplastic or non-neoplastic proliferation has not yet been established. Despite the name, eosinophils are not the main proliferating cells within the characteristic nodules and may even

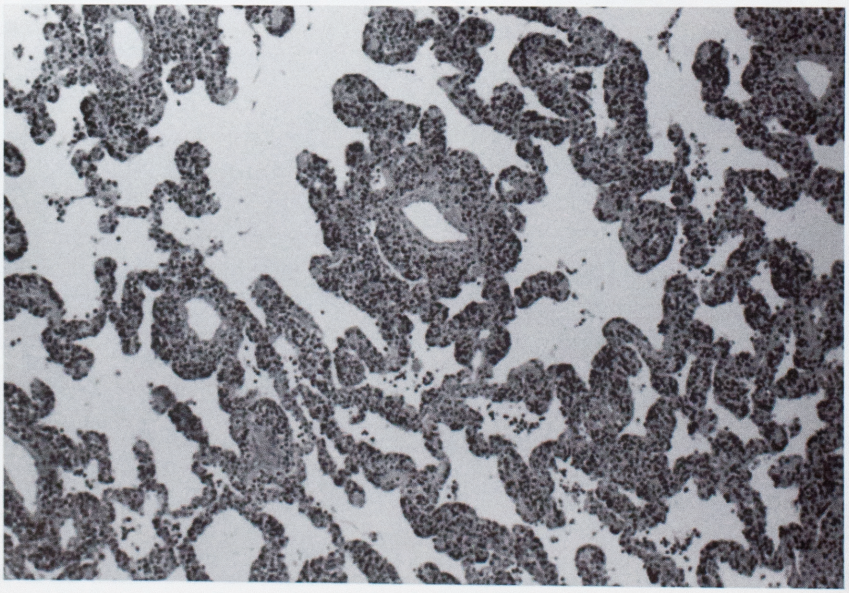

FIGURE 32-6. Lymphocytic interstitial pneumonia is characterized by an intense polymorphous lymphocytic infiltrate. (H & E stain; low magnification.)

be sparse. This disease is part of the primary pulmonary histiocytosis-X syndrome.[42,43]

Patients with PEG may have active disease for weeks to many years. Often the disease will remit spontaneously or with steroid therapy. In one large series of 60 patients, 55% remained asymptomatic from the outset or experienced complete remission.[42] Another 37% had stable or improved residual symptomatic, radiographic, or functional changes. As noted above, some patients progress to significant pulmonary fibrosis and end-stage honeycomb lung. In the aforementioned series, 8% had progression of their illness with one death due to PEG.

Both men and women are affected, and the average age at diagnosis is in the fourth decade. A majority of patients are smokers or former smokers,[42] but the relationship of smoking to PEG has not been clearly elucidated. An increase in chemotactic factors for monocytes and fibroblasts secondary to pulmonary neuroendocrine cell hyperplasia caused by cigarette smoking has been postulated.[44]

Patients may occasionally be asymptomatic at presentation, but most have shortness of breath, cough, or chest pain. Systemic symptoms, including malaise, weight loss, and fever, occur in one third of patients. Patients may present with pneumothorax, which occurs in 6% to 20% of patients.[42,43] Chest x-ray findings are variable, but classic features include bilateral, symmetric, predominantly upper lobe reticulonodular infiltrates with sparing of the costophrenic angles. The radiographic nodules are classically stellate, reflecting their pathologic appearance. Cavitation and honeycombing may be seen in 10% to 15% of patients.[43] Rarely, PEG presents as a solitary nodule on x-ray films.[45] Function study abnormalities are variable and may include obstructive and restrictive defects. Abnormal gas exchange is found in most patients.

Histopathologically, the multifocal parenchymal nodules of PEG progress from very cellular lesions (Fig. 32-7) to residual focal scars. Lesions in various stages of development are often present in the same biopsy specimen. Typical nodules vary in size from 1 mm to 1.5 cm. The earliest lesions, frequently found in the walls of bronchioles, consist of interstitial collections of Langerhans cells mixed with varying numbers of eosinophils, lymphocytes, fibroblasts, and giant cells (Fig. 32-8). The precise mixture of cells typically varies from one cellular lesion to the next, and mitoses may be present. Over time, the cellular lesions grow in size, may be cavitary (Figs. 32-9 and 32-10), and develop central scarring. This produces the most classic lesion of PEG, which consists of a stellate nodule with a central scar and cellular arms.

Eventually, the fibrosis advances outward, replacing the cellular constituents until only a residual scar remains. In those cases in which the disease progresses, the multiplying nodules become confluent, eventually producing extensive honeycombing that is most prominent in the upper lobes (see Fig. 32-10).

The lesions of PEG may produce a significant focal pseudo-DIP reaction that should not be misinterpreted as DIP.[20] The residual focal scars of PEG may need to be differentiated from UIP or focal subpleural honeycombing associated with pneumothorax and reactive eosinophilic pleuritis.[46,47]

If there is uncertainty about the diagnosis of PEG, positive identification of the Langerhans cells may be of great assistance. The Langerhans cells in the lungs are dendritic mononuclear cells similar to those in the skin and have a characteristic appearance with convoluted nuclei, pale cytoplasm, and indistinct cell borders.[43] However, they may be difficult to distinguish from alveolar macrophages, particularly when admixed with other cells. These cells are positive for S-100 protein by immunohistochemistry (Color Fig. 32-3)[48,49]; they can also be positively identified by the presence of Birbeck granules on electron microscopy (Fig. 32-11). S-100 immunostaining has the advantages over electron microscopy of greater sampling area, lesser expense, and faster turnaround results.

The mere presence of a few Langerhans cells on S-100 immunostaining may not be sufficient for the diagnosis. Langerhans cells are present in the normal lung in a variety of pathologic conditions, including UIP, that enter into the differential diagnosis of PEG.[49] In addition, as lesions of PEG become less cellular and more fibrotic, there are fewer and fewer Langerhans cells. Webber found 75 S-100–positive cells per 20 high-power fields in active or resolving PEG lesions and fewer than 35 in other lesions and in completely scarred PEG.[48] Thus, evaluation for Langerhans cells by S-100 immunostaining must take into account the overall

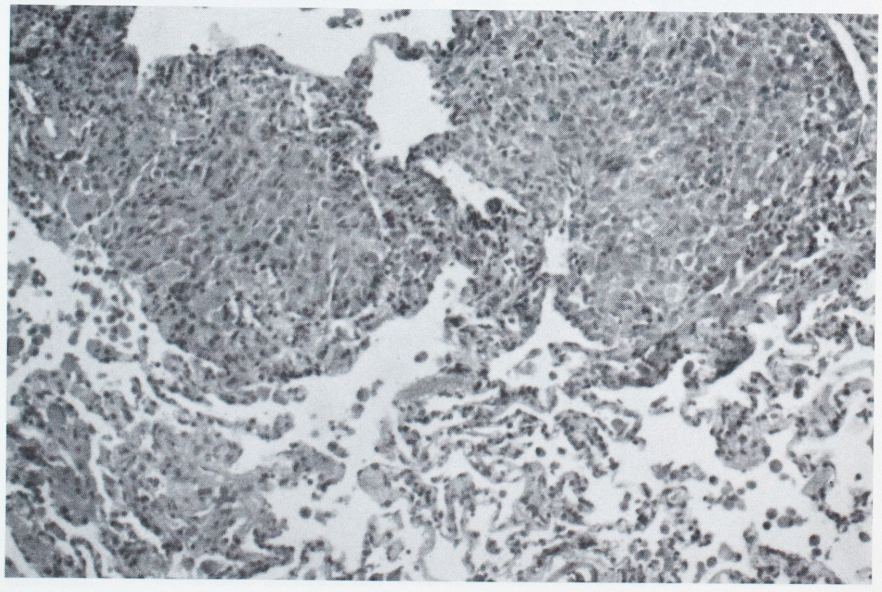

FIGURE 32-7. Well-circumscribed nodular interstitial infiltrates are present in a patient with eosinophilic granuloma. (H & E stain; low magnification; courtesy of J. Stead, M.D., Morgantown, WV.)

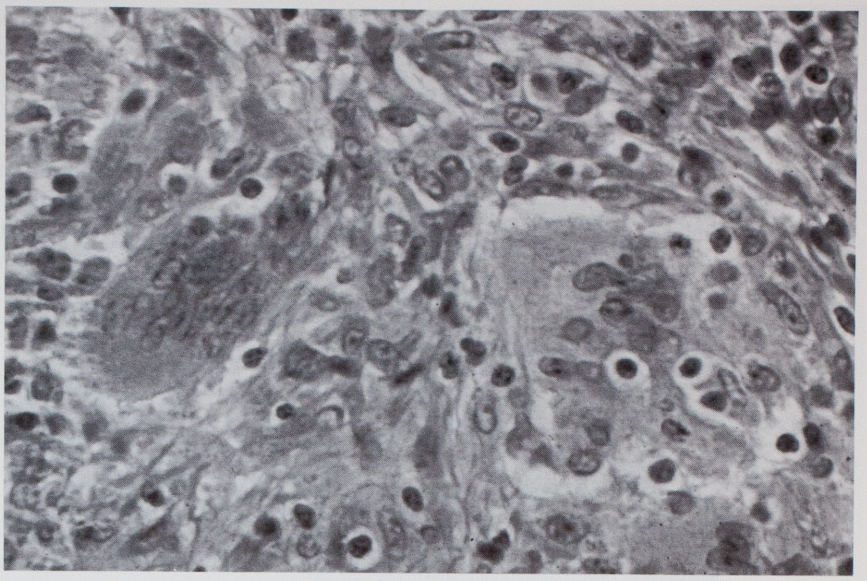

FIGURE 32-8. Eosinophilic granuloma with prominent giant cells. (H & E stain; intermediate magnification; contributed by the editor.)

cellularity of the lesion as well as the number of S-100–positive histiocytes present.

PULMONARY LYMPHANGIOLEIOMYOMATOSIS

Pulmonary lymphangioleiomyomatosis (PLAM) is a unique, rare, and progressive interstitial lung disease of unknown etiology that enters into the differential diagnosis of chronic interstitial lung disease and honeycomb lung. This disease occurs almost exclusively in women of childbearing age, although rare reports of PLAM in men exist.[50] The lesions consist of hyperplasia of atypical smooth muscle cells in a lymphangitic distribution. Lymphatics in the mediastinum or abdomen may also share in the smooth muscle proliferation.[51–54]

PLAM typically presents as progressive shortness of breath, cough, intermittent hemoptysis, and recurrent pneumothorax and pleural effusions, often chylous, in premenopausal women. Pleural effusions occur in 79% of patients; approximately 30% of such effusions are chylous in nature. Chest x-ray films may occasionally be normal initially, but they typically show features of both obstructive and restrictive disease with hyperdistention and reticulonodular densities greatest at the base. With progression, the chest x-ray shows cysts in a honeycomb manner. Function studies also show a relatively unique combination of obstructive and restrictive findings with increased total lung capacity and decreased diffusing capacity.

Grossly, the lungs in PLAM show cystlike air spaces with firm, thickened walls. Histopathologically, the lungs show diffuse, proliferating, immature smooth muscle surrounding dilated lymphatic spaces and multiple emphysematous spaces of various size, partly encircled by thickened walls of proliferating, immature smooth muscle (Fig. 32-12). Subpleural blebs, focal hemorrhage, and hemosiderin-laden macrophages are also seen. The proliferating smooth muscle initially follows the pulmonary lymphatics

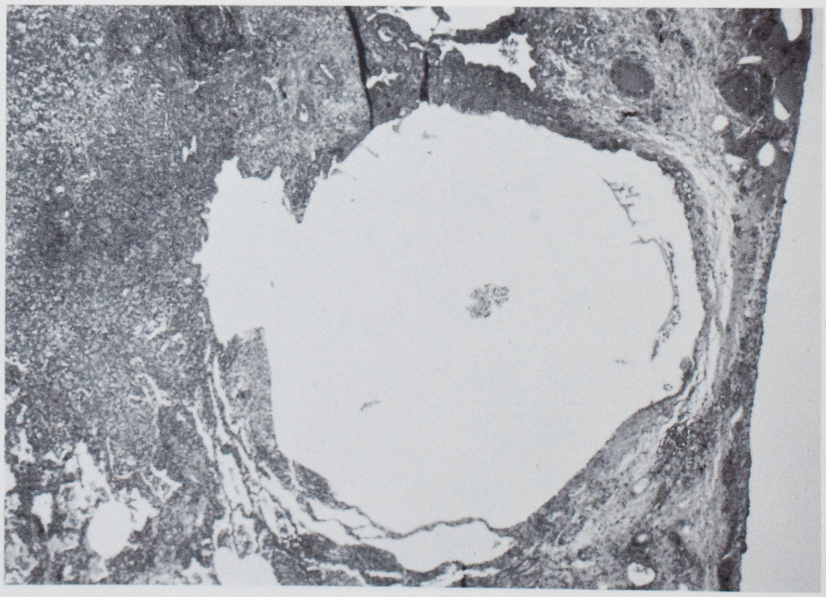

FIGURE 32-9. Lung biopsy specimen from a 21-year-old man who had spontaneous pneumothorax in 1950. A subpleural cyst is adjacent to dense histiocyte infiltrates characteristic of eosinophilic granuloma. The case predates the original description of pulmonary eosinophilic granuloma. (H & E stain; low magnification; contributed by the editor.)

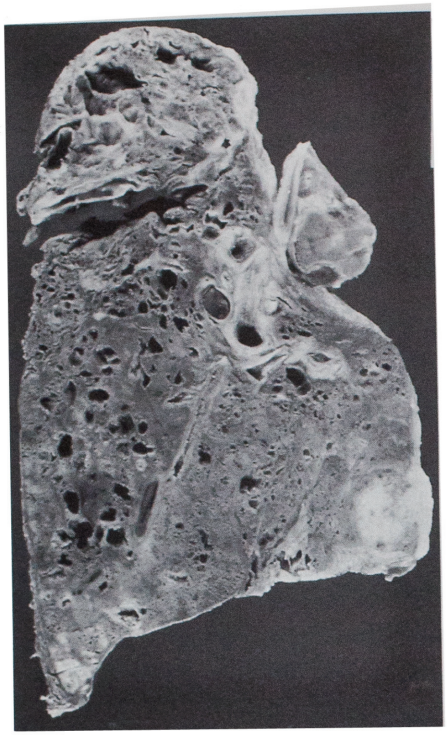

FIGURE 32-10. Honeycomb lung is present in the patient depicted in Figure 32-9. Twenty years after the biopsy specimen in Figure 32-9 was taken, the patient presented with a picture of diabetes insipidus and metastatic colonic carcinoma in the right lower lobe. He died shortly afterward from a pulmonary embolus. (Contributed by the editor.)

in the bronchovascular bundles, interlobular septa, and pleura but eventually involves extensive areas of parenchyma (Figs. 32-13 and 32-14).

The presence of abundant immature smooth muscle should distinguish PLAM from other entities that it may resemble, such as emphysema, focal subpleural honeycombing, or proliferating smooth muscle in a scar. The atypical smooth muscle cells of PLAM are plump and immature in contrast to the mature smooth muscle cells seen in a scar, but they lack the features of malignancy seen in a leiomyosarcoma. The smooth muscle cells can be highlighted by trichrome stain or by immunostaining for actin or desmin to demonstrate their abundance in an equivocal emphysematous lesion.

Obstruction of various structures by the proliferating smooth muscle probably explains many of the findings in PLAM.[52] Airway obstruction leads to increased lung volumes, emphysema, and pneumothorax. Blood vessel obstruction leads to hemorrhage, collections of hemosiderin-laden macrophages, and hemoptysis. Lymphatic obstruction leads to chylothorax.

Patients with PLAM usually succumb to progressive respiratory failure within 10 years of diagnosis.[51] Attempts to treat PLAM with surgery, radiation, and chemotherapy have been unsuccessful.[55,56] The occurrence of PLAM in women of childbearing age, its exacerbation with pregnancy,[57,58] and the apparent periodicity of symptoms in conjunction with the menstrual cycle in some patients[58,59] have led to the suspicion that PLAM is influenced by sex hormones. Furthermore, estrogen and progesterone receptors have been demonstrated in the immature smooth muscle of PLAM by both biochemical and immunohistochemical techniques.[53,58,60,61] Various hormonal therapies based on these observations have been attempted. A metanalysis of cases in the literature has shown that improvement or stabilization of the disease can be achieved with oophorectomy (in five of seven reported patients), oophorectomy plus progesterone (two of two patients), or progesterone alone (five of nine patients).[55] Success depends on instituting therapy early in the course of the disease. Lung transplant is an option for those patients who do not respond or who have advanced disease.

TUBEROUS SCLEROSIS

Tuberous sclerosis is a disease characterized by central nervous system lesions, mental retardation, and sebaceous adenomas of skin; fewer than 1% of these patients have pulmonary lesions. The latter produce clinical, radiographic, and functional findings similar to those of PLAM. Histologically, the pulmonary lesions in tuberous sclerosis closely resemble those in PLAM and lead to progressive respiratory failure as well. Also, those patients with tuberous sclerosis who develop pulmonary lesions do tend to be women of childbearing age. These observations have led some

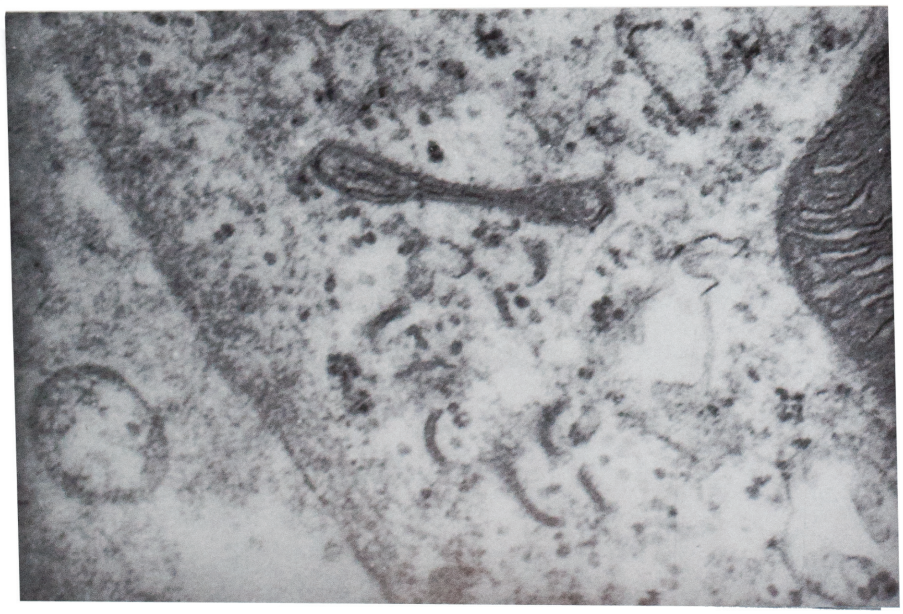

FIGURE 32-11. An intracytoplasmic Birbeck granule is present in a patient with eosinophilic granuloma of the lung. (Original magnification × 5000; contributed by the editor.)

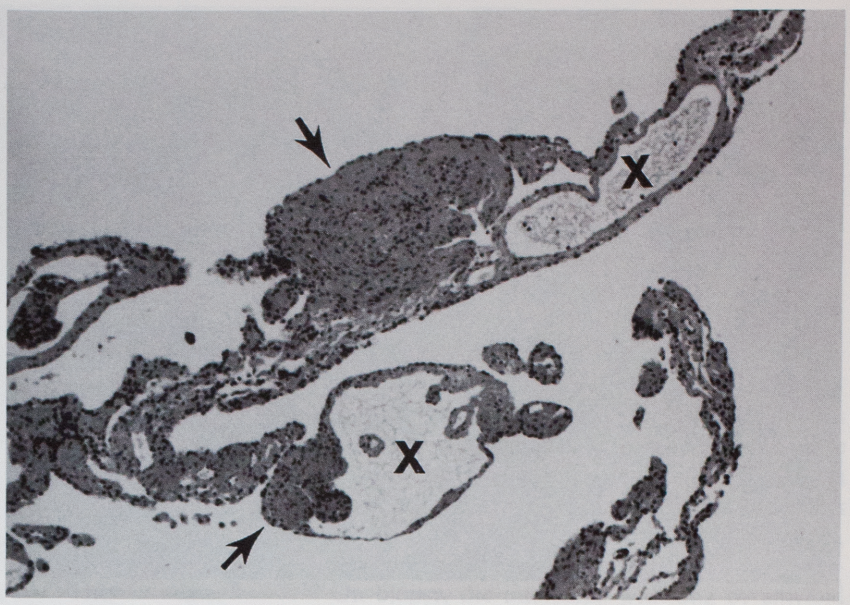

FIGURE 32-12. Pulmonary lymphangioleiomyomatosis shows dilated lymphatics (X) associated with proliferating immature smooth muscle (*arrows*). (H & E stain; low magnification.)

authors to consider PLAM a *forme fruste* of tuberous sclerosis. However, this view is controversial, and the relationship between these two diseases remains yet to be elucidated.[50,59,62]

PULMONARY ALVEOLAR MICROLITHIASIS

Pulmonary alveolar microlithiasis (PAM) is a rare, slowly progressive lung disease of unknown etiology characterized by widespread intraalveolar microcalcifications referred to as calcospherites in patients with normal serum calcium levels.[63–68] In advanced cases, interstitial fibrosis and restrictive lung disease are present. Fewer than 160 cases have been reported in the literature.[68] In about one half of the reported cases of PAM there is a familial occurrence.[66–69] Patients range in age from newborn to 80 years old, with a mean age of 35 years at diagnosis. In Japan, this disorder peaks at 4 to 9 years of age.[65] There is no gender predominance.

Most patients, 70% in one series of 26 patients, are asymptomatic at presentation.[67] In those presenting with symptoms, cough is the most frequent complaint, and microliths may sometimes be coughed up. Some patients go for years without symptoms despite abnormalities on radiographic and pulmonary function studies, and at least one patient has been followed for more than 15 years without the development of symptoms.[67]

Progression of the disease is very slow, and the clinical course remained stable in seven of eight patients with a mean follow-up of 12.5 years in one study.[67] Two patients have been reported to be stable, both clinically and radiographically, for 28 years and 35 years, respectively. However, when the disease does progress, patients develop dyspnea and sometimes hemoptysis.[67] Spontaneous pneumothorax has been reported. As the disease becomes more severe, clubbing, cyanosis, and progressive cor pulmonale may occur.

The chest x-ray findings of PAM are very characteristic and virtually diagnostic. Fine, sandlike microcalcifications are diffusely

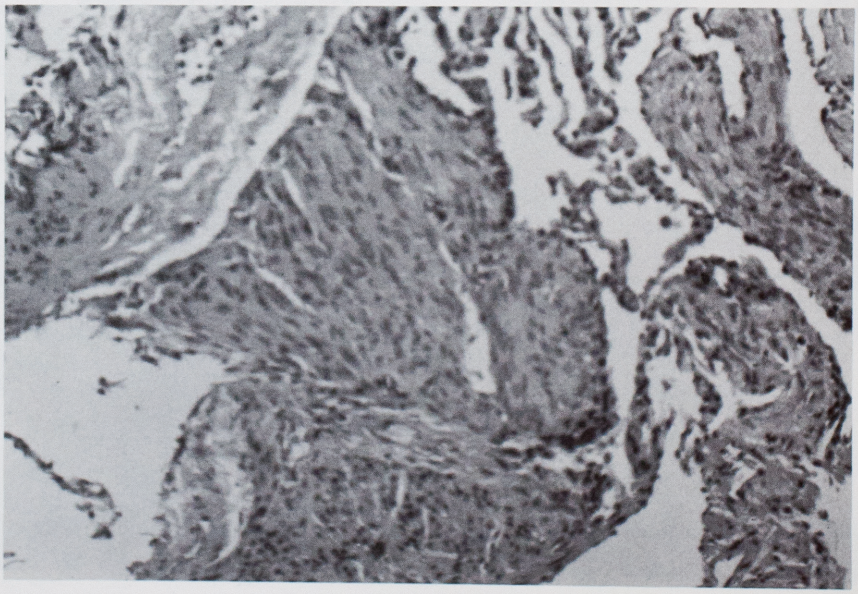

FIGURE 32-13. Dense interstitial muscular proliferation is present in a patient with lymphangioleiomyomatosis diagnosed by fiberoptic bronchoscopy. (H & E stain; low magnification; contributed by the editor.)

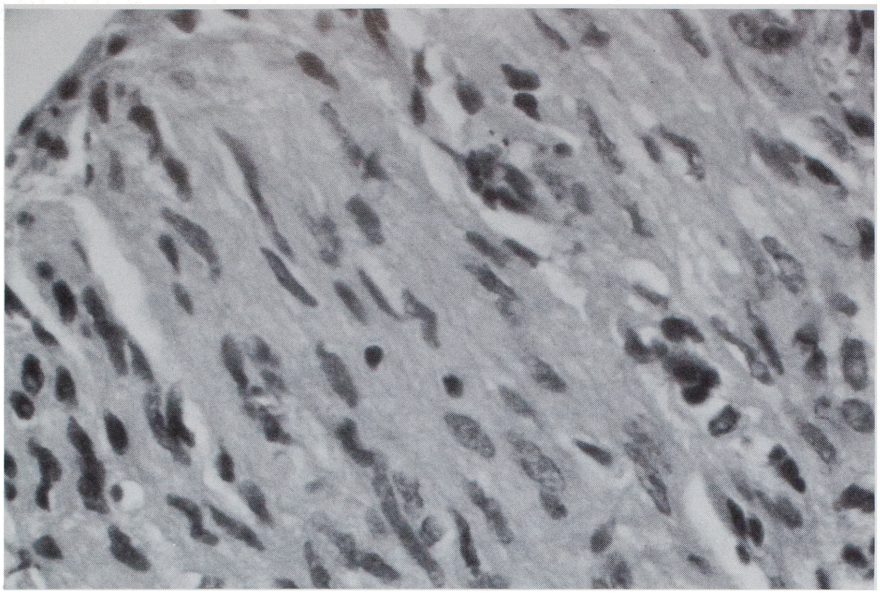

FIGURE 32-14. Higher magnification of Figure 32-13 shows prominent smooth muscle bundles in the pulmonary interstitium. (H & E stain; intermediate magnification; contributed by the editor.)

scattered throughout both lungs with a higher density at the lung bases and with obliteration of the heart borders and diaphragm. This appearance is often referred to as sandstorm lung. Small bullae are often present in the apexes. A black pleural line is present as a zone of translucence along the parietal pleura and has been proposed to be an illusion caused by the contrast between the density of the sandstorm lung on one side of the pleura and the ribs on the other. According to one study, high-resolution CT has shown that the black line consists of a ribbon of 5- to 10-mm thin-walled cysts immediately beneath the parietal pleura.[68]

Pulmonary function tests are typically normal in the early stages. About 30% of patients have abnormal function studies, usually mild, and changes apparently depend on the presence of interstitial fibrosis. Function studies show a restrictive pattern with decreased total lung capacity, decreased vital capacity, decreased diffusing capacity for carbon monoxide, and normal ratio of residual volume to total lung capacity.[67]

Grossly, the lungs in PAM have a hard, gritty cut surface that may resemble sandpaper, and a saw may sometimes be required to cut the lung. When the lung tissue is sectioned, numerous calcospherites, ranging in size from 0.01 mm to 2.8 mm, spill out. Apical bullae, subpleural blebs, or pleural adhesions may be present.

Histopathologically, two thirds of the alveoli are filled and sometimes distended by the calcospherites, which have an appearance superficially similar to that of corpora amylacea, commonly encountered by the pathologist (Color Fig. 32-4; Fig. 32-15). They are light blue to purple and roughly round, with laminations or concentric circles like an onionskin. They do not adhere to the alveolar walls and are strongly PAS-positive.

Analysis has shown that the microliths are composed of calcium phosphate and may have small amounts of calcium carbonate, silica, magnesium, and iron. Calcospherites also have been reported in bronchial walls and the interstitium. In early cases, the alveoli are typically normal, but in advanced cases, diffuse interstitial fibrosis is present.[67]

The etiology of PAM is unknown. It is thought that the calcium phosphate is deposited around an alveolar cellular exu-

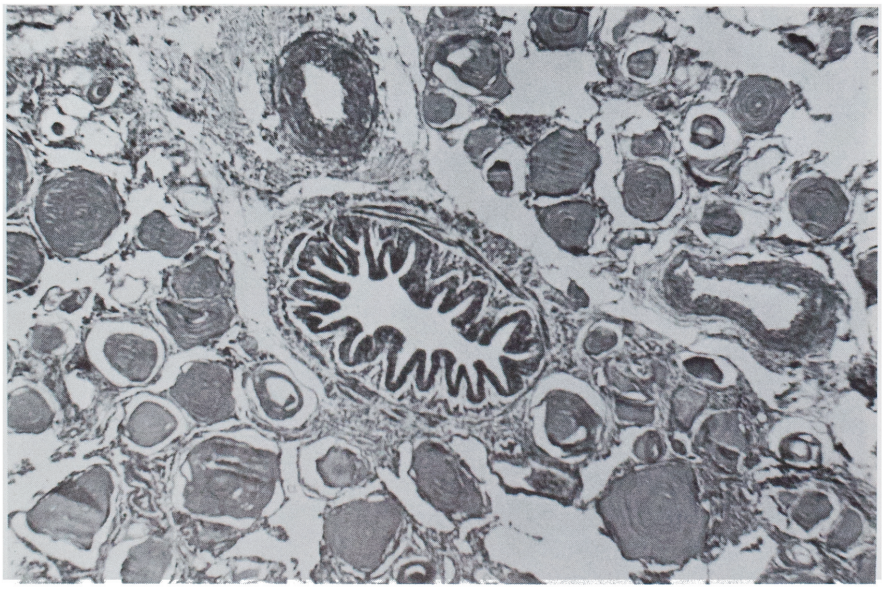

FIGURE 32-15. Characteristic microscopic picture of pulmonary alveolar microlithiasis. (H & E stain; low magnification; contributed by J. Stead, M.D., Morgantown, WV.)

date. A wide variety of associated conditions has led to some hypotheses about the origin of this entity. Unproven theories of pathogenesis have proposed an inborn error of metabolism,[69,70] an immune response to inflammatory processes that produce an intraalveolar proteinaceous exudate,[63] and mineralization of desquamated epithelial cells.[64] There is no treatment for this condition.

Other forms of intraalveolar bodies and pulmonary calcification may enter into the differential diagnosis of PAM, and these are mentioned for completeness. Corpora amylacea are roughly round, pink, laminated, PAS-positive bodies (Color Fig. 32-5) that are an incidental finding in alveoli in adult lungs, occurring in about 3.8% of autopsies.[71] These bodies somewhat resemble the calcospherites of PAM but are considerably less abundant and generally do not contain calcium. They vary in size from 30 to 200 μm. The etiology of corpora amylacea is unknown, but their incidence appears to increase with age.[71] They are sometimes surrounded by macrophages and may represent concretions around inhaled particles.

Blue bodies are single or multiple, laminated, and blue-gray, and they range in size from 15 to 40 μm (Color Fig. 32-6).[72] They are composed of calcium carbonate, iron, and mucopolysaccharide and therefore are positive by von Kossa, Prussian blue, and PAS stains. These bodies are seen in association with macrophages and giant cells in DIP, in UIP, near lung cancers, and in other pulmonary diseases. They are thought to represent products of macrophage metabolism.

Schaumann or conchoidal bodies are laminated 25- to 200-μm bodies found in the cytoplasm of epithelioid histiocytes or giant cells or extruded from these cells in granulomas (Color Fig. 32-7).[73] They are composed of mucopolysaccharide, calcium, and iron and are typically associated with calcium carbonate crystals. Schaumann bodies are found in 88% of patients with sarcoidosis, 62% of patients with berylliosis, and 6% of patients with tuberculosis.[73]

As in other sites throughout the body, dystrophic calcification and dystrophic ossification can occur in sites of injury and are relatively common nonspecific findings in pulmonary scarring of all types. They have little clinical significance. Metastatic calcification of alveolar septa and blood vessels may be focal or extensive. The most common setting for this finding is chronic renal failure with prolonged dialysis and secondary hyperparathyroidism (Color Fig. 32-8). Usually the metastatic calcification is an incidental finding, but it may rarely be associated with progressive dyspnea.[74,75] Diffuse pulmonary metaplastic ossification is most commonly seen in association with chronic passive congestion, particularly mitral valve stenosis (Figs. 32-16 and 32-17).[76]

PULMONARY AMYLOIDOSIS

The lung may contain amyloid as one of the multiple organs involved in systemic amyloidosis or, much less frequently, as the only organ in isolated pulmonary amyloidosis.[77–88] Typically in the systemic cases and rarely in the isolated cases, the amyloid is deposited in a diffuse alveolar-septal pattern that produces clinical, radiographic, and functional findings of interstitial lung disease.[78,79–81,84] On biopsy, the interstitial widening by amyloid deposits could conceivably be confused with interstitial fibrosis. Forms of pulmonary amyloidosis other than the diffuse alveolar-septal type will also be discussed in this section for the sake of completeness.

Diffuse alveolar-septal amyloidosis has been reported in up to 90% to 92% of patients with primary amyloidosis and up to 100% of patients with amyloidosis associated with immunocytic dyscrasias.[79] Diffuse alveolar-septal amyloidosis localized exclusively to the lungs is extremely rare.[80,85] As a manifestation of secondary amyloidosis, it is even rarer. Therefore, most of the information about diffuse alveolar-septal amyloidosis comes from cases that are a component of systemic primary amyloidosis.

The chest x-ray films of patients with diffuse alveolar-septal amyloidosis show diffuse, bilateral reticulonodular interstitial infiltrates that may be confused with pulmonary fibrosis or pulmonary congestion and edema. Patients, particularly those with localized lung involvement, frequently die of progressive respiratory insufficiency. In those patients who also have cardiac amyloidosis,

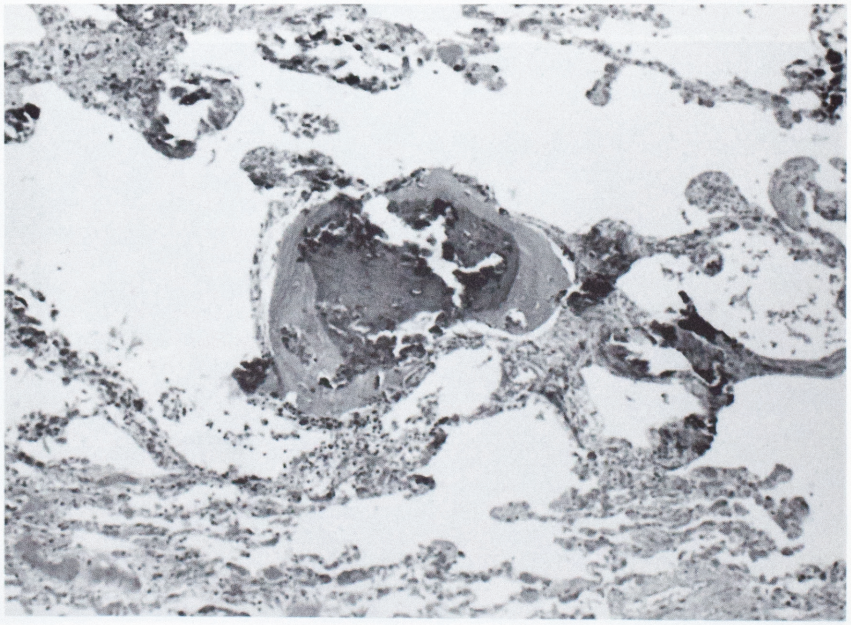

FIGURE 32-16. A focus of metaplastic ossification is present within the pulmonary interstitium. (H & E stain; low magnification.)

FIGURE 32-17. A right lower lobe shows dendritic ossification with subpleural involvement of the lung parenchyma. (Courtesy of Luis Alucrey, M.D., Miami, FL.)

congestive heart failure may contribute significantly to the symptoms and poor prognosis.[81]

Grossly, the lungs are bulky and have a diffuse, uniform rubber-sponge appearance on cut section (Fig. 32-18).[78] Microscopically, the architecture is relatively well preserved, with diffuse thickening of the alveolar septa by deposition of amorphous, eosinophilic amyloid. The interstitial amyloid deposits may be diffuse and uniform or consist of multiple small interstitial nodules. Scant infiltrates of plasma cells or giant cells may be present. The media of blood vessels also show amyloid deposits (Fig. 32-19). The pleura may also occasionally show extensive involvement,[86] and this as well as congestive heart failure due to cardiac involvement may account for the pleural effusions seen in some patients.

Nodular parenchymal lesions commonly occur as solitary or multiple incidental nodules that frequently are detected on chest x-ray films as a coin lesion and are removed to rule out cancer or granuloma. Patients with nodular parenchymal amyloidosis are usually asymptomatic but may uncommonly present with cough, dyspnea, or hemoptysis. The nodules are typically peripheral and often subpleural (Fig. 32-20). When multiple, the nodules may be unilateral or bilateral. In one series, the right lung was involved 2.5 times more often than the left, with the right lower lobe being the most frequent site of involvement. The nodules generally range in size from 0.6 to 9 cm, with an average size of about 3 cm.

On chest x-ray films, calcification is seen in 29% of the nodules and cavitation in 11%. Occasionally nodules have been observed to increase in size over time. The prognosis in these patients is excellent.[80,85] Microscopically, the nodules consist of amorphous eosinophilic amyloid and often show areas of calcification, cartilage, or bone (Color Fig. 32-9; see Fig. 32-20). Clusters of plasma cells or foreign body giant cells may be seen adjacent to or within the amyloid nodules.[85]

Tracheobronchial amyloidosis involves both the trachea and bronchi in most cases but may involve only the trachea or a bronchus. The submucosal amyloid deposits may occur as diffuse infiltrates, multiple masses, or a single mass. Most patients have symptoms and may present with dyspnea, cough, hemoptysis, hoarseness, recurrent pneumonia, or atelectasis. Chest x-ray films may show narrowing of the distal trachea or narrowing of mainstem bronchi. Chronic atelectasis is observed in 56% and hilar or mediastinal masses in 9% of patients. Prognosis is generally good.[80,85]

OTHER INTERSTITIAL LUNG DISEASES

A number of other lung diseases may enter into the differential diagnosis of interstitial lung disease (see Display 32-1). They are, in many cases, potential causes of interstitial fibrosis and honeycombing. These diseases include extrinsic allergic alveolitis (*i.e.,* hypersensitivity pneumonitis; Chap. 65), sarcoidosis (Chap. 66), various pneumoconioses (Chaps. 34 through 37), granulomatous infections (Chaps. 41, 43, and 44), and lymphangitic carcinomatosis (Chaps. 22 and 59).

FIGURE 32-18. Gross appearance of the lung in a patient with systemic amyloidosis. There is marked thickening of pulmonary septa and vessels by amyloid deposits. (Contributed by the editor.)

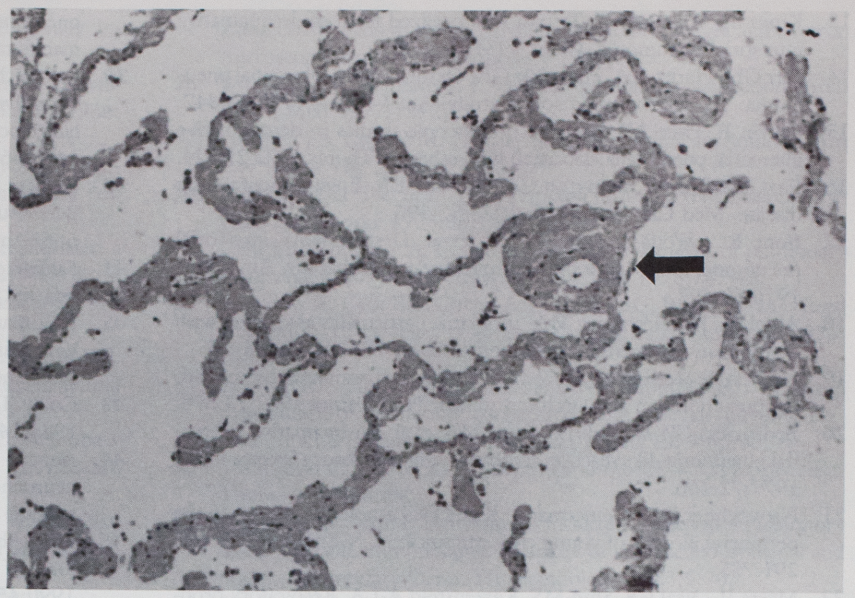

FIGURE 32-19. Diffuse alveolar-septal amyloidosis is present with thickening of the alveolar septa and blood vessel walls (*arrow*) by amyloid. (H & E stain; low magnification.)

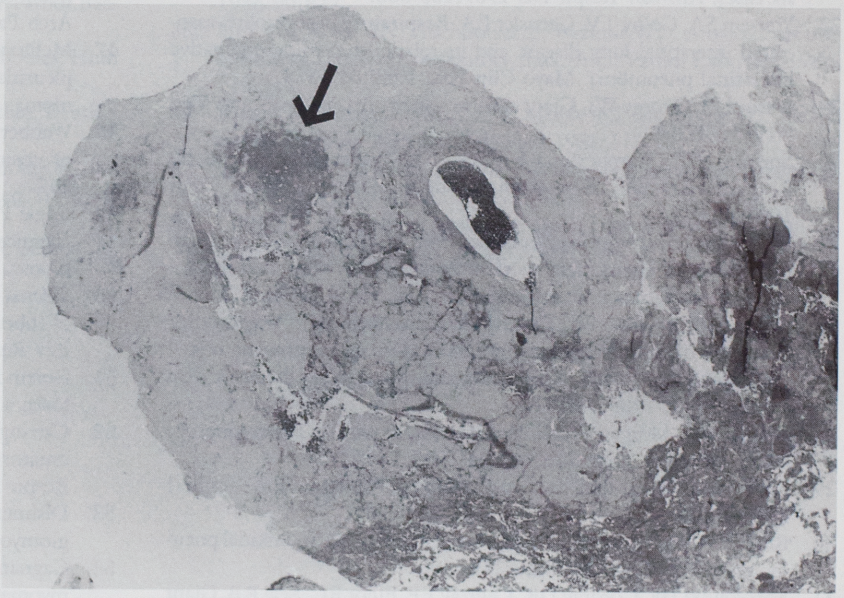

FIGURE 32-20. A solitary nodular parenchymal lesion consists of a well-circumscribed mass of amyloid with focal cartilage (*arrow*). (H & E stain; low magnification.)

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