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Rare Infiltrative Lung Diseases: A Challenge for Clinicians

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Key Words
Rare diffuse infiltrative lung diseases · Alveolar proteinosis · Acute eosinophilic pneumonia · Inherited lipidoses · Pulmonary amyloidosis

Abstract
Rare diffuse infiltrative lung diseases are a challenge for clinicians, radiologists, and pathologists for at least three reasons: (a) their low incidence and prevalence hamper the acquisition of expertise and frequently the diagnosis is delayed; (b) therapeutic actions are mainly empirical and based on steroid use, and (c) pathogenetic events are difficult to explain and only recently new therapeutic measures taking advantage of innovative genetic and/or immunopathogenetic studies have been suggested. In this review rare diffuse lung disorders are briefly discussed (pulmonary alveolar proteinosis, inherited lipidoses, acute eosinophilic pneumonia, amyloidosis, pulmonary ossification, pulmonary alveolar microlithiasis). The list is obviously not exhaustive and arbitrarily chosen. The intent is, however, to emphasize that in this difficult field multidisciplinary expertise and the knowledge of the most recent pathogenetic mechanisms have the main role in diagnosis and treatment.

Previous articles in this series: 1. Zompatori M, Bnà C, Poletti V, Spaggiari E, Ormitti F, Calabrò E, Tognini G, Sverzellati N: Diagnostic imaging of diffuse infiltrative disease of the lung. *Respiration* 2004;71:4–19. 2. Poletti V, Chilosi M, Olivieri D: Diagnostic invasive procedures in diffuse infiltrative lung diseases. *Respiration* 2004;71:107–119. 3. Chetta A, Marangio E, Olivieri D: Pulmonary function testing in interstitial lung diseases. *Respiration* 2004;71:209–213. 4. Camus P, Fanton A, Bonniaud P, Camus C, Foucher P: Interstitial lung disease induced by drugs and radiation. *Respiration* 2004;71:301–326.

Introduction

Rare infiltrative lung diseases are a challenge for clinicians, radiologists and lung pathologists for at least three reasons [1–4]: (a) their low incidence and prevalence hamper the acquisition of expertise and frequently the diagnosis is delayed; (b) therapeutic actions are mainly empirical and based on steroid use, and (c) pathogenetic events are difficult to explain and only recently new therapeutic measures taking advantage of innovative genetic and/or immunopathogenetic studies have been suggested.

In this article the clinical, pathologic and radiographic patterns of rare parenchymal lung disorders are concisely reported and the more recent pathogenetic advances are briefly described.

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Pulmonary Alveolar Proteinosis

This disorder is characterized by abundant accumulation of phospholipids and proteinaceous material in the alveoli and distal airways. The intra-alveolar material mainly represents pulmonary surfactant phospholipids and protein components. The disease was first described by Rosen et al. [5] in 1958. It can be primary (idiopathic) or secondary, associated with pulmonary infections, malignancies (lymphoma, leukemia), inhalation exposure (silica, metal dusts and chemicals), neutropenia observed after chemotherapy for hematologic neoplasms, and HIV infection. A congenital form of alveolar proteinosis occurs in full-term newborns. It is an autosomal recessive disorder and involves mutations in the SP-B or SP-C genes. Infants with this disease die within the first year of life despite maximal medical therapy. Alveolar proteinosis has also been reported in patients with lysinuric protein intolerance. The secondary forms are much rarer than the primary ones. Form the morphologic point of view the alveoli are filled with a characteristic acellular, finely granular material that stains with periodic acid-Schiff (PAS) and is diastase-negative. The interstitial structures are free of inflammatory infiltrates. Type II pneumocytes may be hyperplastic. Electron microscopy reveals that the intra-alveolar material consists predominantly of unusual tubular, myelin-like, multilamellated structures, which resemble the tubular myelin found in normal lungs but lack the intersecting membranes of normal tubular myelin. Components that represent cell debris are also present. Lamellar bodies as those seen in normal lungs are only minor components [6].

Biochemical analysis of bronchoalveolar lavage (BAL) fluid has revealed that the content of total phospholipids is increased with a relative decrease in phosphatidylcholine and phosphatidylglycerol, and a relative increase in sphingomyelin and phosphatidylinositol [7, 8].

The concentrations of surfactant protein A, B and D are also increased. The relative abundance of surfactant protein A isoforms is different from that in normal BAL and varies markedly from patient to patient, suggesting heterogeneity in the severity of the condition at the level of the structure of the surfactant proteins [9, 11].

The pathogenesis is not definitely proven. As surfactant and surfactant-like material are abundantly present, a derangement in the normal pathway of surfactant secretion, metabolism and reuse or degradation seems likely. Physiologically, surfactant and its corresponding apoproteins are synthesized and released in the form of lamellar bodies by alveolar type II cells. Most of the secreted surfactant is recycled and taken up by the type II cells again, probably mediated by receptors for surfactant apoprotein A on type II cells. The remainder is cleared either through phagocytosis and degradation by macrophages or to a lesser degree via lymphatics or the airways mucociliary apparatus. In alveolar proteinosis, there may be either increased surfactant production which is not eliminated sufficiently by defective alveolar macrophages, or an interruption of surfactant reuptake by type II cells. The alveolar macrophages show several secondary functional defects, such as reduced mobility, impaired adherence and chemotaxis, reduced phagocytosis, and a decreased ability to kill ingested microorganisms [12]. This functional impairment may contribute to the increased risk of pulmonary infections in patients with alveolar proteinosis. Recently, animal models of alveolar proteinosis and human data have suggested a role for granulocyte-macrophage colony-stimulating factor (GM-CSF) in the pathogenesis. GM-CSF seems essential for normal surfactant clearance by activating alveolar macrophages and increasing their rate of surfactant catabolism [12]. Mice lacking GM-CSF or the GM-CSF receptor develop a pulmonary abnormality that resembles human alveolar proteinosis [13, 14]. Local pulmonary epithelial cell expression of GM-CSF, bone marrow transplantation [15] or aerosolized GM-CSF inhalation corrects alveolar proteinosis in GM-CSF-deficient mice [13]. In congenital alveolar proteinosis a defect in the GM-CSF receptor expression has been observed [16]. In adult alveolar proteinosis, such a receptor defect was, however, not observed [17]. Furthermore, other studies showed increased serum and BAL GM-CSF levels and normal GM-CSF production by blood monocytes and alveolar macrophages in adult alveolar proteinosis and a normal response of alveolar macrophages to GM-CSF in terms of tumor necrosis factor production. These data would rather exclude a lack of GM-CSF production as an etiological factor. An immunologic explanation for these observations was revealed by the fact that BAL fluid and serum from patients with idiopathic alveolar proteinosis carry a factor that inhibits GM-CSF and is postulated to be an autoantibody [18, 19]. Some adult patients with idiopathic alveolar proteinosis improved with administration of GM-CSF [18, 20, 21]. Taken together, these observations suggest that adult idiopathic alveolar proteinosis is a heterogeneous disease that may be caused in some patients by a decreased functional availability of GM-CSF due to GM-CSF-blocking activity.

The disease occurs predominantly in men with a male: female ratio of about 3:1. The true prevalence is unknown

with current understanding based on fewer than 500 reported cases [5, 9, 10, 22–25]. The peak age of onset is between 30 and 50 years but infants and children may also be affected. Familial occurrence is rare but has been reported. There is an increased incidence in smokers. The main presenting complaints are slowly increasing dyspnea on exertion (80%) and cough (60%). Less common symptoms (20–30%) include fever, weight loss, fatigue, chest pain and hemoptysis. Physical examination is usually inconclusive; inspiratory crackles are heard in a minority of patients and clubbing occurs in 30–50%. Less frequent findings include cyanosis and evidence of cor pulmonale. The chest radiograph may be distinctive, showing diffuse bilateral symmetrical alveolar infiltrates with air bronchograms. The shadowing may be cloudy and butterfly- or batwing-like [26], as a result of the more prominent involvement of the perihilar regions. Less commonly, unilateral infiltrates or a reticulonodular pattern may by seen. Lymphadenopathy and pleural lesions are rare. Kerley B lines are absent initially but may develop later. The high-resolution CT (HRCT) shows airspace filling in variable and patchy distribution. The distinctive features are: ground-glass opacification sharply demarcated from normal lung, creating a 'geographical' pattern; intra- and interlobular septal thickening, often in polygonal shapes, called 'crazy paving', and large areas of consolidation with air bronchograms surrounded by ground-glass opacification [26].

Lung function tests characteristically show a restrictive pattern and a reduced diffusing capacity. Hypoxemia at rest is present in about one third and during exercise in more than one half of the patients. An increase in the shunt fraction while breathing 100% oxygen is seen in almost all patients. Laboratory markers show a nonspecific increase of serum lactate dehydrogenase in most patients, which declines after therapeutic lavage or spontaneous resolution; its isoenzyme pattern is normal. Elevation of serum carcinoembryonic antigen and other tumor markers has been seen and proposed as a marker of disease activity. Serum levels of surfactant protein A and D can also be increased but this is not specific for the disease, since high levels are also seen in patients with idiopathic pulmonary fibrosis. Serum levels of KL-6, a mucin-like glycoprotein, have been recognized to be extremely high in alveolar proteinosis, higher than those in patients with other interstitial lung disease. Serological diagnosis of alveolar proteinosis by demonstration of autoantibodies against GM-CSF is not yet a routine procedure, but may become available in the future [27]. The diagnosis of alveolar proteinosis should be considered in a patient with chronic insidiously developing dyspnea, a 'butterfly' pattern of acinar shadowing on the chest radiograph and characteristic findings on HRCT (geographical distribution of a 'crazy paving' pattern) along with elevated serum lactate dehydrogenase and an increased shunt fraction.

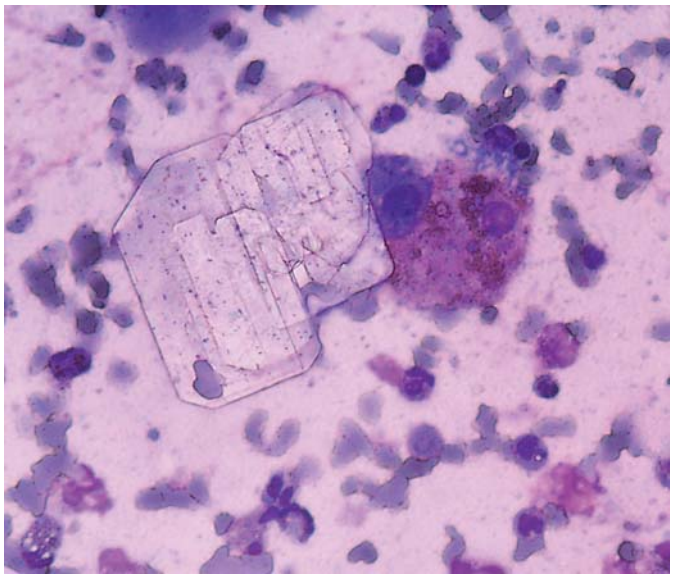

Fig. 1. BAL in a patient with secondary pulmonary alveolar proteinosis (lysinuric protein intolerance). A cholesterol crystal is evident. May-Grünwald-Giemsa. ×400.

The diagnosis is usually established by BAL, obviating the need for transbronchial or open biopsy in many instances. On gross examination, the BAL fluid has a characteristic milky appearance. On light microscopy the striking features are: acellular globules that are basophilic on May-Grünwald-Giemsa and positive with PAS staining; few and foamy macrophages, and large amounts of cell debris showing weak PAS staining. In cases associated with protein intolerance and lysinuria cholesterol crystals may be prominent (pers. experience) (fig. 1). Electron microscopy is not usually required to establish the diagnosis but if performed shows that the BAL sediment consists of characteristic myelin-like multilamellated structures and lamellar bodies.

Spontaneous remission occurs in up to one third of patients. Treatment is indicated when respiratory symptoms impair the quality of life or when lung function deteriorates. The treatment of choice is whole-lung lavage, which is almost always effective. Treatment with GM-CSF still has to be considered experimental. Anecdotal reports show responses to this therapy in some but not all

Table 1. Molecular genetics of Gaucher, Niemann-Pick, and Fabry diseases

Disease	Chromosome assignment	Molecular characteristics
Gaucher	1q21	cDNA, functional and pseudogenomic sequences, >200 mutant alleles known
Niemann-Pick		
Types A and B	11p15.1 to p15.4	cDNA , entire genomic sequence, >30 mutant alleles known
Type C	18q11-q12 region	cDNA, entire genomic sequence, >100 mutant alleles known
Fabry	Xq22.1	cDNA, entire genomic sequences, >200 mutant alleles known

patients. Whole-lung lavage is safe when performed by an experienced team and under continuous monitoring of oxygen saturation, blood pressure, electrocardiography and lavage fluid balance. The more severely affected lung is lavaged first. The severity of respiratory impairment may be estimated by CT scan or by lung perfusion scanning. The second lung may be lavaged 3–7 days later. The procedure is performed under general anesthesia. The patient is intubated with a double-lumen endotracheal tube (e.g. Carlens tube). After 15 min ventilation of both lungs with 100% oxygen to wash out the nitrogen, one lung is lavaged with isotonic saline at 37°C. The volume used for each filling is 500–1,000 ml. The lung is then allowed to drain by gravity. This filling and drainage is repeated until the effluent is virtually clear which may require 10–40 liters.

The prognosis has improved considerably with the introduction of therapeutic lavage. Although there are no established response criteria for therapeutic lavage, significant clinical, physiologic, and radiologic improvements were claimed following the first therapeutic lavage in 84% of the evaluable published cases [6, 12, 24, 25, 28–32]. In the literature cases, the interval between the diagnosis of pulmonary alveolar proteinosis and the first application of therapeutic whole-lung lavage ranged from 0 (immediate lavage) to 210 months with a median of 2 months. The majority of patients who underwent lavage did so within 12 months of diagnosis (79%), but there was a continuing increase in the proportion of patients having received such therapy. In the era when lavage was available after 1964, the likelihood of a patient with pulmonary alveolar proteinosis remaining free from therapeutic lavage was only 37% at 5 years [25]. In 55 instances of reported response to lavage, there was information provided on the duration of the benefit.

The median duration of clinical benefit from lavage was 15 months with less than 20% of those patients followed beyond 3 years remaining free of recurrent pulmonary alveolar proteinosis manifestations. Comparing the demographic and disease-related features of patients who did or did not respond to therapeutic lavage, there were no differences seen in gender, region of origin, duration of symptoms, smoking status, and time from diagnosis to lavage. When response rates to lavage were calculated within cohorts for age at diagnosis (20 years or less, 21–39 years, and 40 years or more), a significant difference was observed: 58, 84 and 90%, respectively [25]. In four series totaling 64 patients there were no deaths related to alveolar proteinosis after 10–15 years' experience with whole-lung lavage. Improvement may be long-lasting: 25–50% of patients achieve permanent remission after one lavage. In the others the procedure has to be repeated at intervals of 6–24 months. Alveolar proteinosis may be complicated by infections such as nocardiosis, cryptococcosis, mucormycosis and others. In the era of therapeutic lavage these complications are rare. There have been single reports of progressive interstitial pulmonary fibrosis developing in patients previously affected by alveolar proteinosis. Lung transplantation may be an option for these patients, although recurrence of disease has recently been reported in 1 patient following double lung transplantation.

Inherited Lipidoses

The underlying defect in the inherited lipidoses is the accumulation of metabolites, including the glycolipids and sphingomyelin. The glycosphingolipids, which have a major structural function in many cells, are formed by the addition of various carbohydrates to a backbone of ceramide, an acylated sphingosine. In table 1 the molecular genetics of Gaucher, Niemann-Pick, and Fabry diseases are depicted.

Gaucher disease is characterized by the deposition of glucosylceramide in cells of the macrophage-monocyte system. It was first described by Gaucher in 1882 and the storage of glucocerebroside was first recognized by Epstein in 1924. There are three clinical subtypes that are delineated by the absence or presence and progression of neurological involvement: type I or the adult, nonneuronopathic form; type II or the infantile or acute neuronopathic form, and type III or the juvenile or Norrbotten form. All three subtypes are inherited as autosomal recessive traits and result from the deficient activity of the lysosomal hydrolase acid β-glucosidase. The pathologic disease hallmark is the presence of the Gaucher cell in the macrophage-monocyte system, particularly in the bone marrow. These cells, which are 20–100 μm in diameter, have a characteristic wrinkled-paper appearance resulting from intracytoplasmic substrate deposition and stain positively with PAS.

Four distinct patterns of pulmonary involvement by Gaucher cells have been described: intracapillary, patchy interstitial infiltrates in a lymphatic distribution, massive interstitial thickening of alveolar septa, and intra-alveolar infiltrates. Pulmonary involvement may be part of the broad spectrum of clinical expression among patients with type I disease. It is clinically evident in less than 5% of patients [33]. Dyspnea, diffuse and/or patchy lung infiltrates, restrictive impairment and low single breath CO diffusing capacity represent the clinical disease profile. About 10% of patients, although with normal physical examination and chest radiographs and with normal or nearly normal pulmonary function tests, may experience limitations in physical exertion and are easily fatigued. L444P homozygotes appear at major risk for developing pulmonary disease, even at earlier ages [34]. Pulmonary hypertension, strongly associated with splenectomy and female gender, may occur in subjects with non-N370S acid β-glucosidase (GBA) gene mutation, positive family history, and ACE I gene polymorphism [35].

Replacement therapy with recombinant acid β-glucosidase has improved the pulmonary status; substrate reduction therapy (the greatest experience has been with miglustat) is now an alternative in patients in whom the first option is not suitable [36].

Niemann-Pick disease types A and B result from deficient acid sphingomyelinase activity. In type C, the genetic defect involves the defective transport of cholesterol from the lysosome to the cytosol. Two different genes causing the altered cholesterol transport in type C disease were recently identified, permitting more precise diagnosis, carrier detection, and prenatal diagnosis in affected families. Pulmonary involvement is due to widespread infiltration of both alveoli and interstitium by sea-blue histiocytes [37].

Clinically lung involvement in type B disease is chronic with a dry cough and exertional dyspnea, mild restrictive impairment and minimal alteration of the diffusing capacity for carbon monoxide. In type C disease lung involvement may be pronounced, leading to early death caused by respiratory failure [38].

Fabry disease is an X-linked inborn error of glycosphingolipid catabolism, which results from a deficiency of lysosomal galactosidase activity. This results in an abnormal accumulation of the glycosphingolipid ceramide trihexoside in vascular smooth muscle throughout the body, particularly in vessels of the skin, kidneys, heart, pulmonary vascular system, and neurological system. Pulmonary involvement has occasionally been reported: diffuse alveolar hemorrhage associated with renal failure or, more frequently, airflow obstruction due to the presence of typical lamellar inclusion bodies within ciliated bronchial epithelial cells [39, 40]. Previously a universally fatal disease, the recent development of human recombinant α-galactosidase A, has been shown to reverse the clinical manifestations of the disease [41].

Hermansky-Pudlak Syndrome

It is a rare autosomal recessive disorder manifested by oculocutaneous albinism, a bleeding tendency, and in some cases ceroid-lipofuscin-lysosomal storage disease. The storage pool defect arises from defects in formation or trafficking of lysosomes and related organelles, including melanosomes and platelet dense granules. The molecular basis for Hermansky-Pudlak syndrome (HPS) is complex and heterogeneous, involving different genetic loci. HPS-causing mutations have been identified in several human genes [42]. One of these genes encodes for the beta-3A subunit of AP-3, a protein complex that mediates signal-dependent trafficking of integral membrane proteins to lysosomes and related organelles. Other genes are now identified causing HPS in humans (HPS1, 3, 4, 5, 6). The HPS1, 3, 4, 5 and 6 proteins all have unknown functions [43–46].

HPS1, HPS3 and HPS4 products are part of a stable protein complex named biogenesis of lysosome-related organelle complex (BLOC-2). HPS5 and HPS6 also interact and form BLOC-2. Linkage analysis of Puerto Rico families mapped the *HPS1* gene to chromosome 10q23. The *HPS1* gene has 20 exons, and it encodes a protein

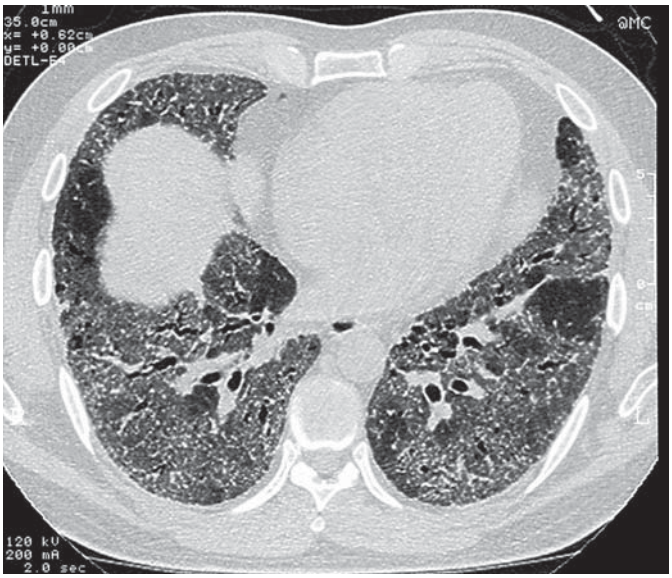

Fig. 2. HPS. HRCT scan at the lung basis. Interlobular and intralobular reticular lines with architectural derangement.

with 700 amino acids and a molecular mass of 79.3 kDa. Albinism in HPS is tyrosinase positive. The bleeding diathesis varies from mild to severe. Some subjects develop a granulomatous colitis that is similar to that seen in Crohn's disease, and renal and cardiac failure may occur. Pulmonary involvement manifests as interstitial lung disease with a nonproductive cough, progressive dyspnea, and ventilatory impairment. The mean age of onset of pulmonary symptoms is about 35 years and there is no gender predominance. HRCT features are septal thickening, ground-glass opacification and honeycomb lung changes ranging from mild to severe [47] (fig. 2). The histological pattern is closer to that of nonspecific interstitial pneumonia, cellular and fibrosing (fig. 3). In the advanced cases honeycomb changes are evident. An increased number of ceroid-filled histiocytes (PAS-positive cells) in the airspaces and interstitium represents the hallmark of the disease. These histiocytes may also be identified in BAL fluid. Markedly vacuolated type II pneumocytes may also be present. Constrictive bronchiolitis and type two cells hyperplasia/dysplasia has been documented in a minority of cases [48] (fig. 4). Pirfenidone (800 mg t.i.d.) appears to slow the progression of pulmonary fibrosis [49].

Table 2. Diagnostic criteria for AEP

Acute febrile illness usually of 1–5 days' duration
Hypoxemic respiratory failure
Diffuse alveolar or mixed alveolar-interstitial chest radiographic infiltrates
BAL fluid eosinophilia (>25%)
Absence of parasitic, fungal, or other infections
Prompt and complete response to corticosteroids
Failure to relapse after discontinuation of corticosteroids

Acute Eosinophilic Pneumonia

This is an acute febrile illness that can result in life-threatening respiratory failure. A thorough exposure history (including occupational or environmental exposure and drug intake) is mandatory. If presumptive etiologies are identified (drugs, new exposure to tobacco smoke, or herbicides) these agents should be avoided by the patient in the future [50]. It has been suggested that cigarette smoking (especially the substantial phase of smoking) is related to eosinophilic lung diseases inducing acute eosinophilic pneumonia (AEP) [51, 52]. Several case reports described the association of AEP with smoking because these patients had started smoking several days before the onset of the symptoms. Because a lymphocyte stimulation test gave a positive reaction to a cigarette extract, a challenge test was done in a patient [51]. After this, the patient had fever and hypoxemia suggesting that cigarette smoking induces AEP. The average age at presentation is about 30 years in the largest series. Symptoms at presentation consist of coughing, dyspnea and frequently acute respiratory failure, fever and chest pain. Abdominal complaints and myalgias may be the leading symptoms at the onset. The chest radiograph shows bilateral infiltrates with mixed alveolar and interstitial opacities, frequently bilateral pleural effusion and Kerley's B lines mimicking features typical of cardiogenic pulmonary edema. On HRCT scan ground-glass opacities and airspace consolidation distributed in the peribronchovascular zones are typically observed, as well as poorly defined nodules and interlobular septal thickening. Bilateral pleural effusion is an ancillary finding useful to suggest the diagnosis [50, 52]. White blood cell count at presentation usually shows increased neutrophils without eosinophilia [52]. The diagnosis of AEP can usually be made quickly and safely in most cases by examining BAL fluid (BAL fluid differential with $\geq 25\%$ eosinophils) even when the patient is already critically ill together with clinical information (ta-

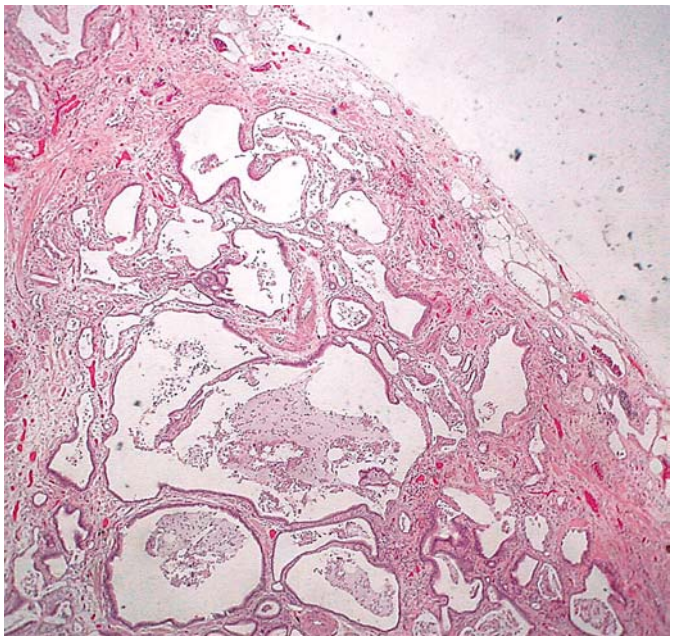

Fig. 3. Open lung biopsy in the same case. Interstitial thickening due to acellular fibrosis and honeycomb changes. The subpleural distribution typical of usual interstitial pneumonia is not observed and fibroblastic foci are absent. H&E. ×40.

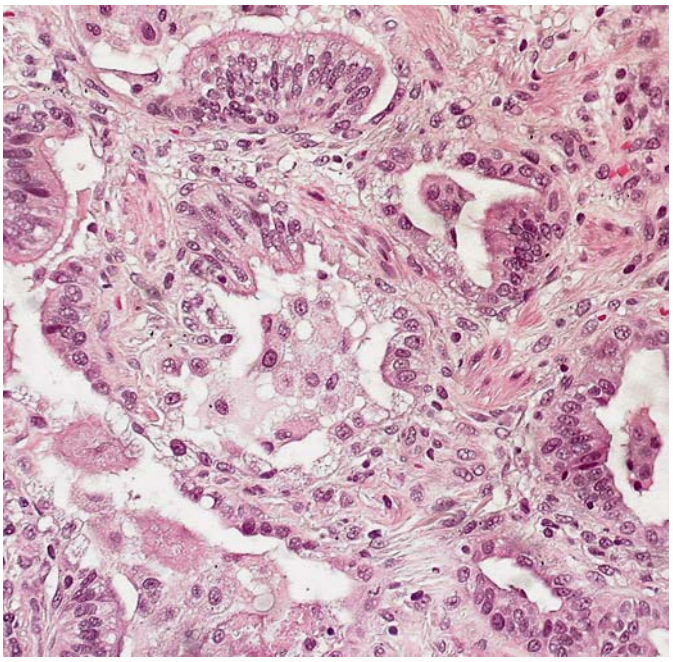

Fig. 4. Open lung biopsy in the same case. Atypical cuboidal metaplasia of the cells lining alveolar spaces. Macrovacuoles in their cytoplasm are evident. H&E. ×250.

ble 2). Moreover, lung biopsy is often not an option in acutely ill patients such as those with AEP. Furthermore, the presence of BAL fluid findings consistent with diffuse alveolar damage may strengthen the suspicion of AEP [53]. Intervention with corticosteroids results in rapid complete recovery without relapse.

Amyloidosis

This term stands for a heterogeneous group of diseases characterized by deposition of an insoluble β-pleated fibrillar protein in the extracellular matrix of involved tissues. A classification of the various forms of amyloid is now based on the plasma precursors involved (immunoglobulins, light and heavy chains, serum amyloid A, transthyretin, fibrinogen, β_2-microglobulin, amyloid β-protein precursor), the protein deposited in tissues and on the clinical profile with which these deposits manifest themselves (table 3).

The diverse spectrum of amyloid-related diseases is now recognized to include Alzheimer's disease, type II diabetes, and the transmissible spongiform encephalopa-

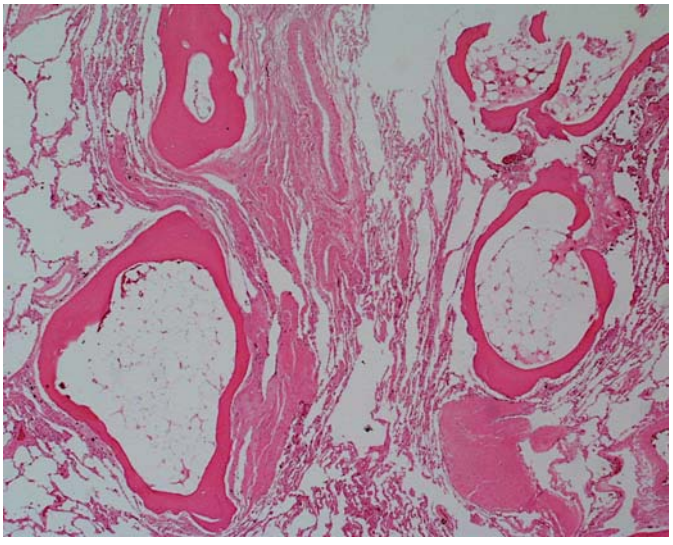

Fig. 5. Idiopathic dendritic or racemose pulmonary ossification. Open lung biopsy: foci of mature lamellar bone with fat-filled marrow spaces that protrude into the alveolar spaces. H&E. ×100.

Table 3. Nomenclature of amyloidosis

Clinical profile	Precursor	Protein
Primary or localized; myeloma or macroglobulinemia association	Immunoglobulin light or heavy chain	AL or AH
Secondary or familial Mediterranean fever	SAA	AA
Familial or senile	Transthyretin	ATTR
Familial renal amyloidosis (Ostertag)	Fibrinogen	A fibrinogen
Dialysis-associated carpal tunnel syndrome	β_2-Microglobulin	Aβ2M
Alzheimer's disease	AβPP	Aβ

AA = Secondary amyloidosis; AβPP = amyloid β-protein precursor; AH = immunoglobulin heavy chain amyloid; AL = primary amyloid; ATTR = amyloid transthyretin; SAA = serum amyloid A.

thies. Amyloidosis can be hereditary or acquired, localized or systemic, and potentially lethal or merely an incidental finding.

Respiratory Tract Amyloidosis

Amyloid localized to the respiratory tract was recognized by Lesser in 1877. Since then various classifications have been proposed based upon radiographic or bronchoscopic findings [54, 55]. Inclusion of pulmonary vascular amyloidosis as a clinical syndrome is confusing since this is a histological finding that occurs to some extent in all its systemic forms.

There have been a few reports of systemic amyloidosis affecting the lungs but fibril typing has generally been imperfect [56–58] and all studies in which the fibril protein has been sequenced identified AL type [59–61]. Prominent lung disease is not a recognized feature of hereditary amyloidosis. In most situations, therefore, respiratory amyloidosis will be of the AL type although the presence of chronic inflammatory disease or a family history or extreme old age should signal other possibilities.

Tracheobronchial Amyloidosis

Tracheobronchial amyloidosis is an uncommon diagnosis [54]. It will not be reviewed in this article limited to diffuse disorders of the lung parenchyma.

Parenchymal Amyloidosis

Amyloid involving the lung parenchyma is the most frequently diagnosed respiratory amyloidosis syndrome. Amyloid nodules in the lung parenchyma are usually an incidental finding that needs to be distinguished from neoplasia. They are usually peripheral and subpleural, occur more frequently in the lower lobes, may be bilateral, and range in diameter from 0.4 to 15 cm. They grow slowly and frequently cavitate or calcify [62–64]. Larger nodules can occasionally produce space-occupying effects. Diffuse alveolar septal amyloid is the least common form of isolated pulmonary amyloidosis and only a few cases have been reported [65]. Patients have dyspnea and a cough but rarely hemoptysis. Radiographically reticular and reticulonodular infiltrates of varying severity are detected. CT scan findings are small nodules, patchy ground-glass opacities or alveolar opacification, thickening of the interlobular septa and irregular linear opacities. Honeycomb lung may occur later. Foci of calcification in the nodules have also been observed. Pleural effusion may be present and occasionally dominate the clinical course. Multiple cysts and calcification probably resulting from fragile alveolar walls as a consequence of amyloid deposition both on alveolar walls and around capillaries have been described [66, 67].

Autopsy series have confirmed that diffuse parenchymal amyloid deposition is a common histological findings in systemic amyloidosis [68]. Clinical involvement is rare but can be confused with pulmonary edema and/or fibrosis. Respiratory function tests may, but not always do, reveal a restrictive defect with impaired gas exchange, but it can be difficult to determine the relative contribution to symptoms of pulmonary versus cardiac amyloid which frequently coexist [56]. Pulmonary involvement is not a major contributor to death in systemic amyloidosis [68] and the median survival of patients with clinically overt lung deposition is about 16 months, similar to that for systemic amyloidosis in general [54]. The lymphatic system is frequently affected in systemic amyloidosis although predominant lymph node deposition is unusual [69, 70]. Hilar or mediastinal adenopathy is rarely associ-

ated with localized pulmonary amyloidosis [71] and its discovery should prompt a search for a systemic etiology. Amyloid lymphadenopathy can also represent localized AL deposition in association with solitary or multifocal B cell lymphomas. Pulmonary hypertension due to pulmonary artery occlusive involvement by amyloid deposits has been described [54]. The diagnosis of amyloidosis usually requires histological confirmation, and Congo red staining that produces green birefringence under crossed polarized light remains the gold standard [72]. Most tissue specimens, ranging from needle biopsies to open surgical resections, can be studied for amyloid although small biopsy specimens are open to significant sampling error. Positive histology results for amyloid must be followed up by immunohistochemical analysis to determine the fibril type [73]. Radiolabelled serum amyloid P component may help to localize specifically amyloid deposits in vivo; it is more sensitive for solid viscera such as the liver, kidneys and spleen [65, 74]. Intense fluorodeoxyglucose activity on positron emission tomography has been described in amyloidosis [75].

Once the diagnosis is clear, nodular parenchymal amyloidosis rarely requires intervention [55]. In contrast, diffuse parenchymal amyloidosis is usually a systemic phenomenon with a poor prognosis [56]. Treatment with corticosteroids or irradiation does not influence its course [63]. However, assuming that amyloid deposits are of AL type chemotherapy to suppress the underlying plasma cell dyscrasia has to be considered [54, 76].

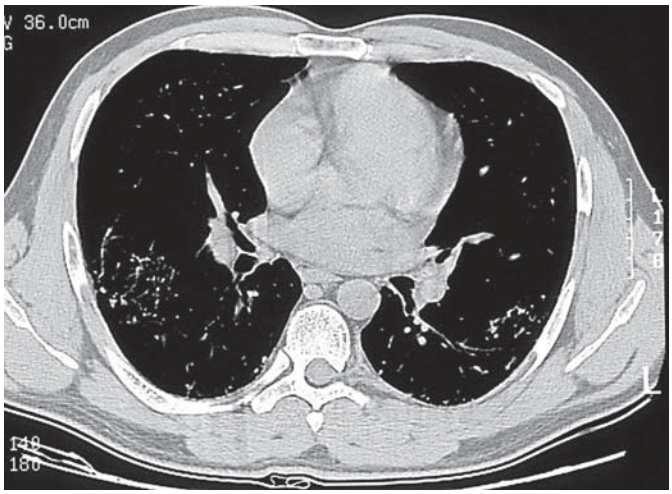

Fig. 6. Idiopathic dendritic or racemose pulmonary ossification. HRCT scan at the lung basis. Irregular lines with bone density in both lower lobes.

Pulmonary Ossification

Pulmonary calcification and ossification are relatively rare and often asymptomatic. Several predisposing conditions are associated with pulmonary parenchymal calcification with or without ossification. These include hypercalcemia, hyperphosphatemia, alkalosis, and lung injury in the presence or absence of conditions that result in angiogenesis and increased pulmonary blood flow causing elevated vessel wall shear stress. The clinical states associated with pulmonary calcification include other underlying pulmonary diseases such as interstitial fibrosis, recurrent bronchopneumonia, amyloidosis, or pulmonary edema (particularly with mitral stenosis), but also hyperparathyroidism, chronic renal failure, hemodialysis, orthotopic liver transplantation, granulomatous infection, infection by DNA viruses or parasites. It most commonly affects the lower lobes. For some conditions, for example pulmonary fibrosis, the calcification and ossification may be a marker of disease severity and accelerated morbidity. It may also be idiopathic [77, 78]. Two histological types of pulmonary ossification have been described [79]: (1) a nodular circumscribed form and (2) a dendriform type.

The nodular form is characterized by lamellar deposits of calcified osteoid material situated within the alveolar spaces often without marrow elements. The nodular form is typically associated with preexisting cardiac disorders that result in chronic pulmonary venous congestion such as mitral stenosis, chronic left ventricular failure, and idiopathic hypertrophic subaortic stenosis [77, 78, 80, 81]. In contrast, dendriform ossification refers to interstitial branching spicules of bone and marrow elements that may protrude into the alveoli [79] (fig. 5) and is usually idiopathic. Based on this simplified morphologic classification for pulmonary ossification, it is interesting to speculate that some cases of IPO may represent a sequela of previously unidentified lung injuries.

IPO is most often found in men over the age 60 but has also been reported in younger adults and in women. Familial clustering has been reported suggesting a genetic predisposition [82, 83]. Patients can be asymptomatic or have minimal complaints, and usually IPO represents an unexplained radiographic finding. Many cases are diagnosed at autopsy. A restrictive pulmonary physiology with low diffusion capacity is present when disease is extensive [82–84]. In the secondary forms, signs, symptoms, and the physiologic abnormalities are more likely due to

the accompanying disorder. It is uncommon for pulmonary ossification to be seen on the chest radiograph. When present, it involves the lower lobes, appearing as nonspecific reticulonodular densities; CT scan findings are more specific showing irregular lines with bone density prevalent in the lower lobes [85] (fig. 6).

The pathogenesis of pulmonary ossification is unknown. Serum calcium and phosphorus levels are usually normal. Unlike heterotopic ossification that occurs around joints in association with spinal cord injuries [86], the serum alkaline phosphatase levels in pulmonary ossification are generally within normal limits, although this has not been consistently evaluated. In cases associated with pulmonary venous congestion, chronic intra-alveolar hemorrhage has been implicated as a predisposing factor for subsequent fibrosis and ossification [87]. Ossification is the sequela of a series of events beginning with degeneration of the arterial media, followed by inflammation and hyalinization of the perivascular tissue. Growth factors from cells involved in this extracellular matrix formation and resolution of inflammation may also play a role in ossification. Transforming growth factor-β is elaborated by inflammatory macrophages and damaged epithelial cells and represents a critical growth factor for collagen and the extracellular matrix. Transforming growth factor-β, strongly implicated in idiopathic pulmonary fibrosis and other fibrotic pulmonary diseases [88], also stimulates osteoblast and chondrocyte proliferation. Another growth factor that may play an important role in ectopic pulmonary ossification is bone morphogenic protein, a member of the transforming growth factor-β superfamily [89]. Bone morphogenic protein, which is likely important in the development of familial primary pulmonary hypertension [90], induces ectopic bone formation in the rat submandibular gland [91]. Interleukin-1 has also been shown to enhance bone morphogenic protein-induced hereotopic ossification in laboratory animals [92]. The profibrotic cytokine interleukin-4, in conjunction with monocyte-colony-stimulating factor, may also transform human alveolar macrophages to osteoclasts, a cell important in bone remodeling [93]. Although the role of fibrogenic, angiogenic, and osteogenic growth factors and cytokines in idiopathic and secondary pulmonary ossification has not been explored, their influence may potentially induce ossification in fibroproliferative pulmonary disorders such as idiopathic pulmonary fibrosis.

Pulmonary Alveolar Microlithiasis

Pulmonary alveolar microlithiasis (PAM), a rare disorder of unknown etiology, is recognized by the intra-alveolar accumulation of spherical calcified concretions [94, 95]. Most patients are between 30 and 50 years of age when first discovered. Although there is a familial association in at least 50% of the cases, common environmental factors could also account for this observation [96, 97]. This disease is especially prevalent in Turkey, representing 33% of the world literature [98]. There is no evidence that infection plays a role. An isolated inborn error of calcium metabolism in the lungs has been proposed, but circulating calcium and phosphorus levels are consistently normal in PAM. It is speculated that, due to an unknown stimulus, changes in the alveolar lining membrane or secretions result in greater alkalinity, promoting intra-alveolar precipitation of calcium phosphates and carbonates [99].

Asymptomatic cases, even with extensive radiographic involvement, are often discovered incidentally. Cough and dyspnea are the most common presenting symptoms and usually occur late in the course of the disease. Normal or mild restrictive pulmonary physiology may be present in the asymptomatic individual. With progressive disease, severe lung restriction may ensue with impairment of the diffusing capacity and gas exchange abnormalities. The chest radiograph shows bilateral, sand-like, micronodular calcified densities known as microliths or calcispherites, which are usually less than 1 mm in diameter [100]. They appear concentrated in the lower two thirds of the lung, often obliterating the diaphragmatic, mediastinal, and cardiac borders. The greater radiographic density at the lung bases is likely due to the larger lower lobe volumes rather than selective predisposition. The predominant HRCT findings are intra-alveolar calcifications with a subpleural posterior and lower lobe predominance. A perilobular and centrilobular distribution of the calcifications may be seen [100]. HRCT may in addition reveal ground-glass opacities that are interspersed with microcysts and the calcispherites [100]. In addition to the fine nodulation, HRCT may show polygonal-shaped calcified densities caused by the accumulation of microliths in the periphery of the lobules rather than actual thickening or deposition of calcium within alveolar septa [100, 101]. Although ^{99m}Tc bone scintigraphy can also help confirm the calcific nature of the lesions, the standard chest radiograph is often characteristic for PAM. The diagnosis is made on the basis of the characteristic chest radiographic and HRCT findings; this usually obviates lung biopsy.

Identification of microliths in expectorated sputum or BAL is diagnostic. Histologically, the lesion of PAM consists of intra-alveolar calcispherites, which represent laminated calcium phosphate concretions. This appearance is distinct from metastatic and dystrophic calcifications in which the calcification is in the interstitial or vascular compartments. With progression, interstitial inflammation and fibrosis will occur and result in significantly diminished lung volumes, sometimes finger clubbing and eventually right heart failure. There is no known therapy for PAM. Corticosteroids, chelating agents, and BAL have demonstrated no benefit, and the role for the use of bisphosphonates remains to be proven [102]. The few cases with response to corticosteroids are more likely to be related to attenuation of the accompanying interstitial disease [103]. In symptomatic cases, nasal continuous positive airway pressure improves gas exchange by decreasing the physiologic intrapulmonary shunt [104]. Bilateral lung transplantation is a viable option for far advanced cases.

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