REVIEW

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Our new understanding of pulmonary alveolar proteinosis: What an internist needs to know

ABSTRACT

Pulmonary alveolar proteinosis (PAP; the accumulation of surfactant lipids and proteins in the alveoli) has a number of infectious and environmental causes but is usually idiopathic. The clinical presentation of PAP is nonspecific; thus, the diagnosis is frequently missed, leading to inappropriate therapy and unnecessary morbidity. Recent advances suggest that a deficiency in granulocyte-macrophage colony-stimulating factor (GM-CSF) activity may lead to this surfactant accumulation. Anti-GM-CSF antibodies have been found in PAP patients, fueling speculation that PAP may be an autoimmune disease. These findings are being translated into novel forms of therapy.

KEY POINTS

Although the findings on radiographic imaging, physiologic testing, and laboratory analysis of the serum and lavage fluids can suggest PAP, pathologic analysis is usually necessary to confirm the diagnosis.

Whole lung lavage is the standard of care for PAP.

A 32-YEAR-OLD WOMAN SMOKER returns to your office with persistent dyspnea, chest tightness, and a minimally productive cough. This is her third visit to you in the past 6 months with the same complaints. Two courses of oral antibiotics have been tried, with no response. She has no chest pain, hemoptysis, or systemic symptoms.

On physical examination the patient is afebrile with normal vital signs. Her oxygen saturation is 92% by pulse oximetry while breathing room air. Her lungs have bilateral crackles; her cardiac examination is normal. She has no clubbing or edema.

A chest radiograph reveals bilateral perihilar infiltrates without evidence of effusion, adenopathy, or cardiomegaly (FIGURE 1). Spirometry reveals mild restriction. A complete blood count and chemistry profile are normal, with the exception of a moderately elevated lactate dehydrogenase (LDH) level. A test for human immunodeficiency virus is negative.

Considering the potential need for diagnostic bronchoscopy, you refer your patient to a pulmonologist.

PULMONARY ALVEOLAR PROTEINOSIS: UNDERSTANDING IS GROWING

Pulmonary alveolar proteinosis (PAP) is an uncommon disorder characterized by the filling of alveoli with a periodic acid-Schiff-positive substance composed of phospholipids and proteins. It was first described by Rosen et al in 1958.[1] By 1969, 139 cases had been reported,[2] and today well over 300 cases have been documented.[3]

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The patient's chest radiograph before treatment

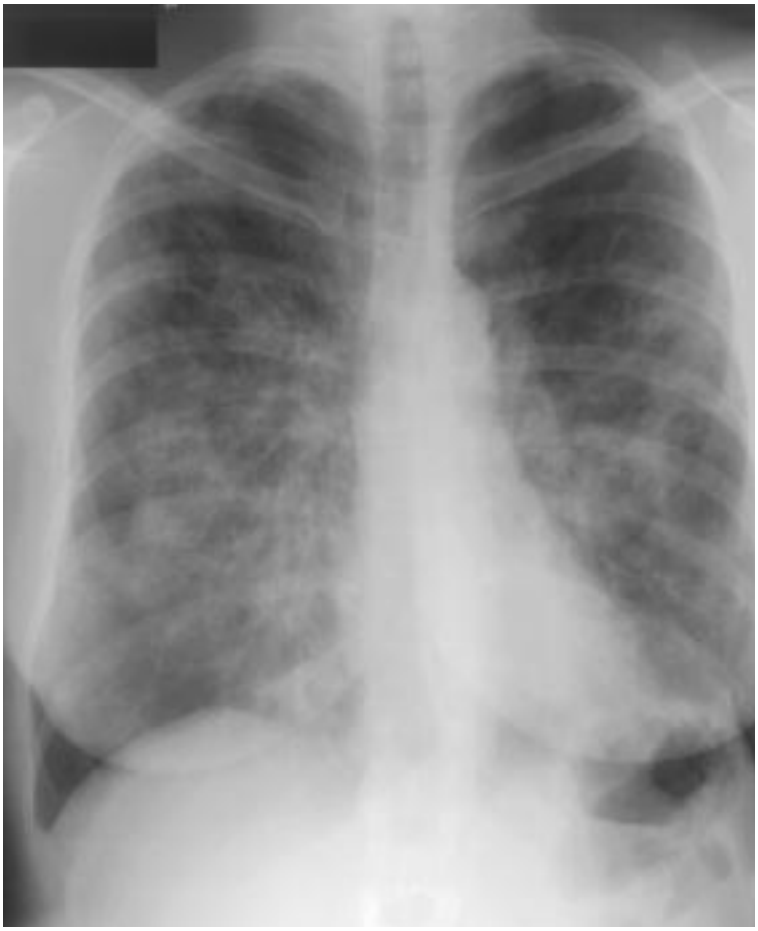

FIGURE 1. Posteroanterior (PA) chest radiograph of the patient revealing bilateral perihilar infiltrates without evidence of cardiomegaly, adenopathy, or effusion.

Given its nonspecific presentation, PAP, although uncommon, may be more common than thought. Mild cases may not come to medical attention. Some believe that a significant portion of patients with PAP have spontaneous resolution of their symptoms and disease.

With experience and observation, the epidemiologic and clinical features have been elucidated. Our understanding of the pathogenesis has advanced only recently with two seminal research findings:

- "Knockout" mice lacking the gene for granulocyte-macrophage colony-stimulating factor (GM-CSF) develop lung disease similar to PAP
- Humans with PAP harbor a neutralizing antibody to GM-CSF.

PAP has two forms, congenital and acquired (adult). The acquired form can be primary (idiopathic) or secondary (associated with a known disorder or exposure).

This review describes acquired PAP, its clinical and laboratory features, pathogenesis, treatment, and implications of the evolving understanding of this disease.

MANY POTENTIAL INFECTIOUS AND ENVIRONMENTAL CAUSES

The average age of patients with idiopathic PAP is approximately 43 years (range 6–73), and most are between age 20 and 50.[1–7] Men outnumber women by about 3:1, and smokers outnumber nonsmokers by 3:1. Familial patterns have been reported in congenital PAP,[8] but have yet to be shown in primary (idiopathic) PAP.

Although the incidence and prevalence remain unknown, PAP is rare. A report from Israel[9] suggested a prevalence of 3.7 per million, and another from Pittsburgh[10] estimated an incidence of 0.2 per million per year.

Secondary PAP can arise in association with many conditions, including hematologic malignancies (predominantly myelogenous leukemias) and exposure to substances such as silica, aluminum, titanium, and nitrous oxide (NO_2). *Pneumocystis carinii* pneumonia (with or without acquired immune deficiency disorder) and infections with agents such as *Mycobacteria*, *Nocardia*, cytomegalovirus (CMV), and anaerobes may precede the development of PAP, but often are seen complicating the disease. The incidence of infections has declined with earlier recognition and treatment of PAP. Other reported associations include amyloidosis and lung transplantation.

CLINICAL PRESENTATION: VARIABLE, NONSPECIFIC

The clinical presentation is variable and nonspecific, often leading to months or years of misdiagnosis. Symptoms are frequently milder than expected from the radiographic findings, with up to 30% of patients having no symptoms.[5] Others, however, present with acute

TABLE 1

Symptoms and signs of pulmonary alveolar proteinosis

SYMPTOMS AND SIGNS	% OF PATIENTS*
Dyspnea	64
Cough	41
Crackles	28
Hemoptysis	21
Weight loss	18
Fever	16
Clubbing	15
Chest pain	14
Cyanosis	14

*Data derived by combining findings from several case series,[1,3–6] representing a total of 167 patients with PAP

symptoms suggestive of pneumonia or subacute to chronic symptoms with nonresolving radiographic infiltrates.

Dyspnea and cough are the most common presenting symptoms. Chest pain, hemoptysis, fever, and weight loss are variably reported.[1,3–6] Crackles, clubbing, and cyanosis all may be detected (TABLE 1).[1,3–6] Uncommon but reported features include pneumothorax and cor pulmonale.[11]

RADIOGRAPHIC FEATURES

Chest radiography

Many patterns of abnormalities on chest radiography can be seen. The classical description is a bilateral, symmetric alveolar filling pattern with perihilar infiltrates extending to the periphery (lower more than upper), sparing the costophrenic angles and yielding a "butterfly" distribution (FIGURE 1).[1] The differential diagnosis for this pattern includes pulmonary edema and *Pneumocystis carinii* pneumonia. The absence of pleural effusions, adenopathy, and cardiomegaly may suggest PAP, but the appearance is generally nonspecific. Interstitial, mixed alveolar and interstitial, nodular, asymmetric, and focal patterns have all been described.[3–6]

The patient's CT scan

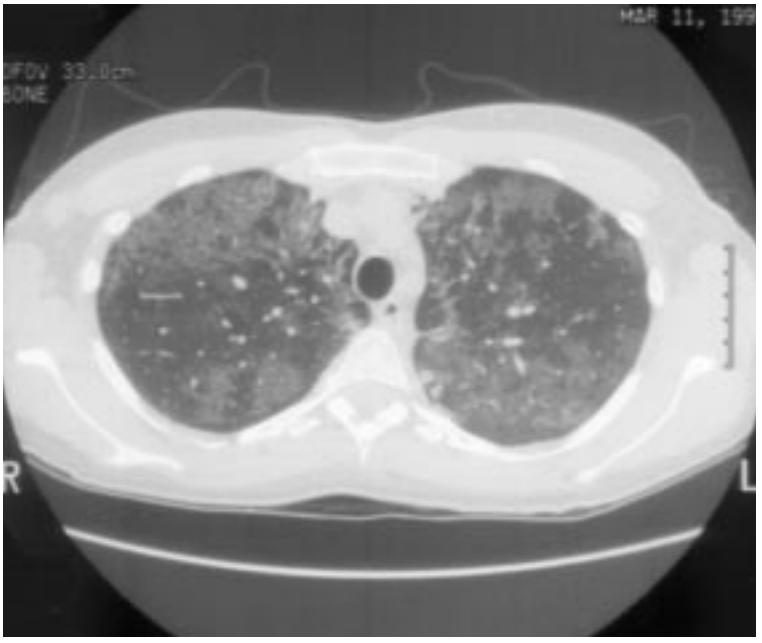

FIGURE 2. Chest computed tomography reveals bilateral, well-delineated alveolar infiltrates typical of PAP.

Computed tomography

Computed tomography (CT), particularly with thin sections, more clearly defines the extent, distribution, and nature of the infiltrates.[12] Again the infiltrates can be patchy or diffuse, and central or peripheral. Reticular, reticulonodular, and ground-glass patterns can be seen, often in the same patient. The infiltrates can be clearly delineated with sharp margins surrounded by normal lung areas. These areas are called "geographical" in appearance. A branching pattern of white linear areas forming geometric shapes of approximately 10 mm in diameter is seen overlying consolidated areas. This pattern is described as "crazy paving" (FIGURE 2) and is thought to be characteristic of PAP,[12] although not everyone agrees.[13] As with chest radiography, pleural effusions and adenopathy are absent.

The chest radiograph shows a 'butterfly' pattern of alveolar filling

Although radiographic appearances correlate with the presence of a restrictive ventilatory defect, reduced diffusing capacity, and hypoxemia,[14] serial chest radiographs and CT scans are not recommended as tools for follow-up.

TABLE 2

Physiologic measures in pulmonary alveolar proteinosis

MEASURE	MEAN VALUE*
Forced vital capacity (FVC)	78% of predicted
Total lung capacity (TLC)	77% of predicted
Forced expiratory volume in 1 second divided by forced vital capacity (FEV_1/FVC)	0.85
Diffusing capacity for carbon monoxide (DLCO)	57% of predicted
Pao_2	67 mm Hg
$Paco_2$	34 mm Hg

*Data derived by combining findings from several case series[3–6]; the values listed represent the mean of each measure in 140 reported PAP patients

PHYSIOLOGIC TESTING

The most common disorders of pulmonary function are mild restriction with a disproportionate reduction in diffusing capacity. Patients are often mildly hypoxemic with an elevated alveolar-arterial oxygen gradient and compensated respiratory alkalosis (TABLE 2).[3–6] The shunt fraction is elevated compared with patients with other diffuse lung diseases.[15]

Knockout mice without GM-CSF develop PAP

HISTOPATHOLOGY

Analysis of bronchoalveolar lavage fluid reveals increased concentrations of cholesterol and surfactant-associated lipids and proteins. Surfactant protein is often elevated out of proportion to the total protein and phospholipid levels. This accumulated PAP material has been shown to have normal surface activity after the laboratory processes the accumulated material to assess its function.

Analysis of cells from bronchoalveolar lavage fluid reveals a decreased number of macrophages with an increase in both the CD4 and the CD8 lymphocyte populations. The ratio of CD4 to CD8 cells tends to be high, but is variable.

Macroscopically, biopsy or necropsy specimens reveal multiple yellow-gray nodular areas of consolidation measuring 2 to 3 cm. These areas are firm and exude a fatty substance at biopsy.[1,4] Microscopically, the alveoli are filled with a granular and floccular acidophilic material that is periodic acid/Schiff-positive (FIGURE 3). The alveolar and interstitial architecture are typically preserved and the vasculature appears normal.[1,4] Electron microscopy reveals characteristic multi-lamellated structures within the alveolar material, as well as inclusions in the cytoplasm of macrophages.[4]

PROGRESS IN ELUCIDATING THE PATHOGENESIS

Elucidating the pathogenesis of PAP has been difficult and slow, with major leaps in understanding only in recent years.

Early work used a growing knowledge of the composition, synthesis, storage, secretion, and catabolism of surfactant in the nondiseased state[16] to stimulate research into the accumulation of surfactant in PAP.

The alveolar macrophage became a focus of attention. Investigations of alveolar macrophages in PAP suggested that their uptake of surfactant is normal but that they have defects in phagocytosis, migration, phagolysosome fusion, and subsequent killing. Consequently, breakdown of surfactant proteins is decreased, leading to accumulation of surfactant, which subsequently inhibits macrophage function and results in a further decrease in surfactant clearance.[17–22] These defects do not appear to be caused by an intrinsic cellular defect.[23]

In recent years, an understanding of the basis of this decreased clearance of surfactant has come from lessons learned from both murine and human studies.

Lessons from murine studies

Mice that lack the gene for GM-CSF still have normal steady-state hematopoiesis, but the animals develop pulmonary disease consistent with PAP.[24,25] This finding led to speculation that GM-CSF may be important in surfactant homeostasis.

These mice have too much surfactant in their lungs. Further work confirmed that the surfactant had normal bioactivity, but it was

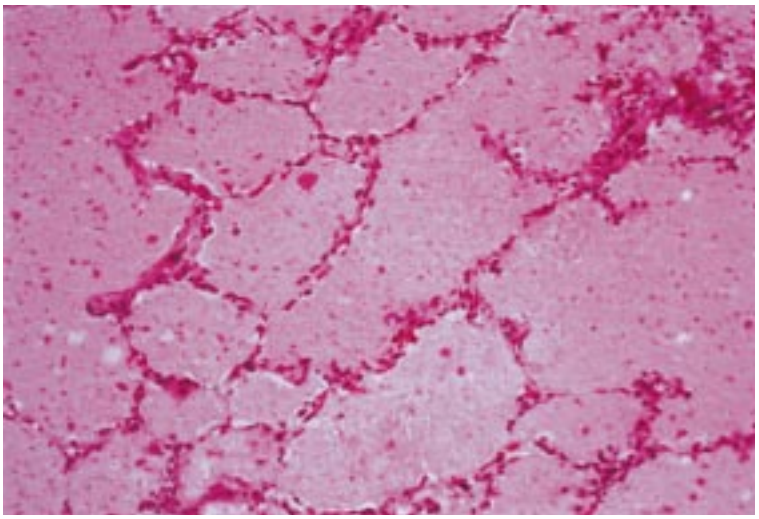

FIGURE 3. Pathology specimen showing eosinophilic material within the alveolar spaces (hematoxylin and eosin stain, × 40).

not being broken down.[26] In the spirit of Koch (who laid down the postulates for proving causation of disease), confirmation that deletion of the GM-CSF gene was the pathologic cause came from studying bitransgenic mice that were engineered to be systemically GM-CSF-deficient but to produce GM-CSF locally in their pulmonary epithelial cells. This local expression of GM-CSF restored surfactant homeostasis.[27] Further confirmation came from the effective use of aerosolized GM-CSF as therapy in these mice.[28]

Patients with PAP have anti-GM-CSF antibodies

Other evidence of the role of GM-CSF in surfactant homeostasis came from studies in mice in which the common beta chain of the receptor complex shared by GM-CSF, interleukin-3, and interleukin-5 had been deleted. Limited hematopoietic changes were noted, but the mice developed pulmonary disease similar to that seen in PAP.[29] Bone marrow transplantation in these mice was shown to halt and reverse the protein accumulation,[30] but did not completely restore pulmonary function.[31]

Lessons from human studies

Human studies have lent support to the role of GM-CSF in the pathogenesis of PAP. Adult patients with PAP display an impaired hematologic response to GM-CSF supplementation.[32,33] These patients have normal or increased numbers and density of receptors and respond normally to granulocyte colony-stimulating factor (a molecule different from GM-CSF). Although the response to GM-CSF was impaired, it was not absent, as high doses could produce a response.[32] The GM-CSF gene is normal, with normal levels of GM-CSF mRNA, but release of the protein from alveolar macrophages is impaired. In vitro, the alveolar macrophages are able to synthesize and respond to GM-CSF.[33]

Interleukin-10 (IL-10) levels are increased.[33,34] Neutralization of IL-10 resulted in enhanced GM-CSF production and release in vitro.[34] By contrast, in pediatric cases a defect in the expression of the common beta chain of the GM-CSF receptor has been seen,[32,35] and the mutation has been identified. This has not been seen in adults.[36] Therefore, in adults, there does not seem to be a lack of GM-CSF or its receptor, but instead an inhibition of its function.

In recent work that lends support for this concept, bronchoalveolar lavage fluid from patients with idiopathic PAP was found to contain a factor that specifically interferes with GM-CSF function. A neutralizing antibody of immunoglobulin G isotype against GM-CSF was then shown to be present in bronchoalveolar lavage fluid and sera of patients with PAP. The antibody was present in all 21 patients with PAP reported in two studies,[23,37] but not in 2 patients with secondary PAP, 53 healthy control patients, or 14 patients with other lung diseases.[37] It is postulated that this neutralizing antibody may lead to alveolar macrophage dysfunction and reduced surfactant clearance.[37]

To summarize, in idiopathic PAP, surfactant is thought to accumulate in the alveolar spaces because of altered clearance mechanisms. The clearance may be reduced owing to dysfunctional alveolar macrophages. This dysfunction may be related to a relative decrease in GM-CSF activity and propagated by the ingestion of the lipoprotein material by macrophages. Activity of GM-CSF may be inhibited through immune mechanisms, particularly the production of a GM-CSF neutralizing antibody (FIGURE 4).

The possible pathogenesis of pulmonary alveolar proteinosis

Pulmonary alveolar proteinosis, a debilitating disease of young people, involves a buildup of surfactant in the lungs. Recent research is elucidating its pathogenesis.

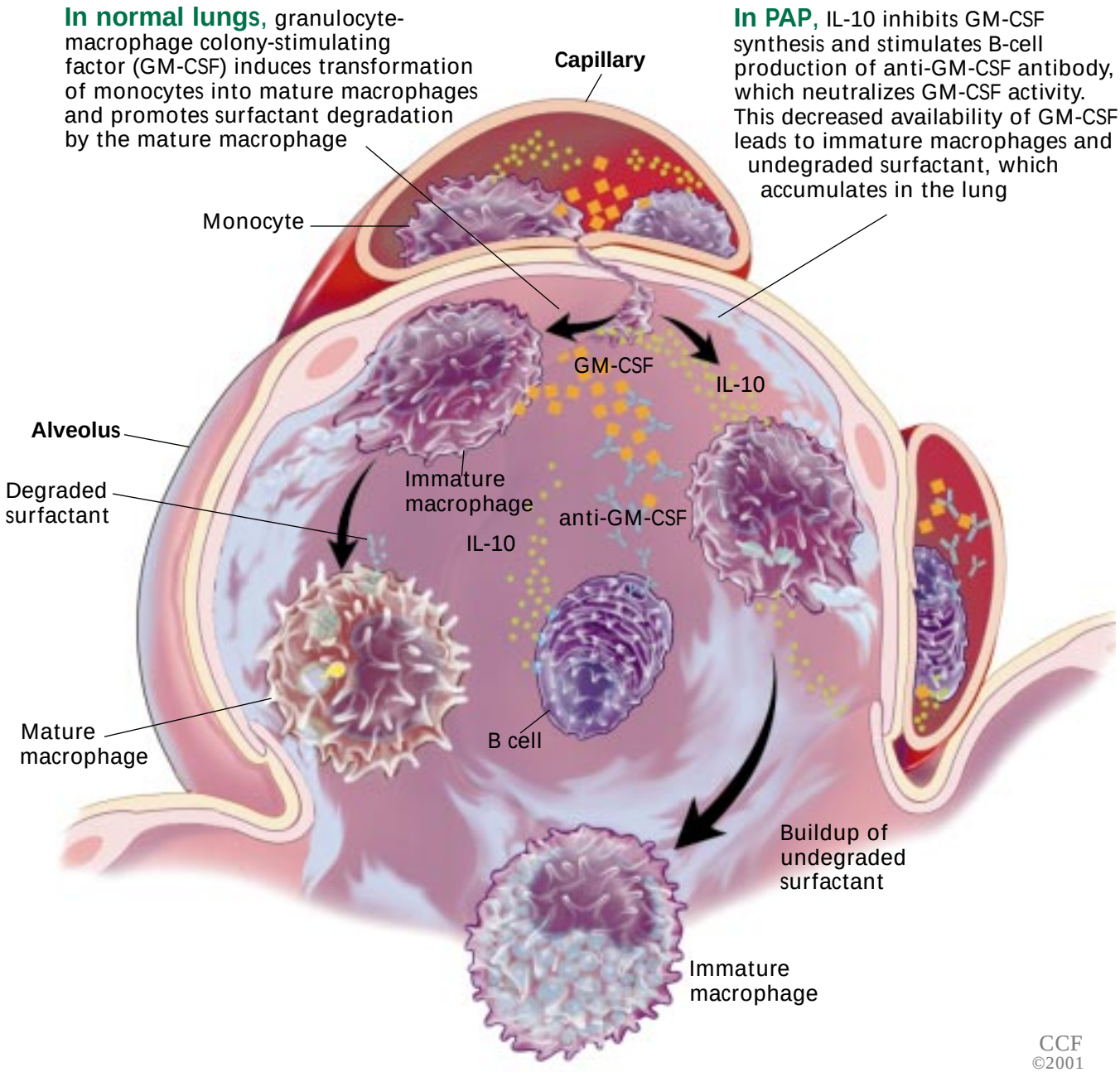

FIGURE 4

Gaps in our understanding

There are still many features of the pathogenesis of PAP that need to be clarified.

- Is the GM-CSF autoantibody an epiphenomenon or is it causally related to PAP?
- What triggers the antibody production in the first place?
- If PAP is, at least in part, an autoimmune disease with the neutralizing antibody producing a relative deficiency of GM-CSF (and hence a dysfunction of alveolar macrophages), do the antibody titers correlate with the disease course, either spontaneously or with therapy?
- How do type II epithelial cells, which are of critical importance in the normal homeostasis of surfactant, contribute to this disease?
- How is PAP acquired?
- Why can PAP have an episodic course with spontaneous remissions?

DIAGNOSIS: BIOPSY IS THE GOLD STANDARD

The findings on the history, physical examination, radiographic studies, and physiologic testing described in the previous sections suggest a diagnosis of PAP. Blood tests and analysis of sputum and bronchoalveolar lavage fluid further support the diagnosis. Further evaluation by transbronchial or open lung biopsy remains the standard diagnostic approach.

The serum LDH level is elevated and is higher than in other diffuse lung diseases.[15] It is also increased in bronchoalveolar lavage fluid and correlates with the alveolar-arterial gradient.[38] Surfactant proteins A and D are elevated in the serum and sputum.[39–41]

The presence of the GM-CSF autoantibody in the serum may serve as a highly useful, simple, noninvasive diagnostic test. It remains to be seen if it is sensitive and specific enough to be clinically important. It was present in all patients with PAP tested in two studies.[23,37]

Two recent reports describe spontaneously occurring autoantibodies to GM-CSF.[42,43] The first report noted the presence of low-to-moderate levels in the serum of 41 of 425 patients with a known autoimmune disease (most prevalent in myasthenia gravis).[42] However, the antibodies were neutralizing in only three of the patients. The second report described a very low prevalence of anti-GM-CSF autoantibodies in blood donors (4 of 1,258; 0.3%).[43] These were not tested for neutralizing activity.

Although bronchoalveolar lavage has been used in diagnosis, tissue is usually obtained. Open lung biopsy has been the gold standard. Transbronchial biopsy can be used to accurately make the diagnosis[6]; recent case series reveal a trend towards a greater percentage of cases being diagnosed in this manner.[3,5]

CASE STUDY CONTINUED: DIAGNOSIS

The patient had a CT scan of the chest revealing bilateral alveolar infiltrates (FIGURE 2). She subsequently underwent an open lung biopsy, which demonstrated features consistent with pulmonary alveolar proteinosis.

WHOLE LUNG LAVAGE: STANDARD OF CARE

Many therapies have been used to treat PAP over the years, including antibiotics,[1] corticosteroids, postural drainage, intermittent positive pressure breathing with aerosolized acetylcysteine, heparin, saline, aerosolized ambroxol (a mucolytic agent), and aerosolized trypsin. Nevertheless, whole lung lavage emerged early as the standard of care.

More than half of PAP patients receive at least one lavage

Indications for lavage

No clearly established criteria exist for when to proceed to whole lung lavage. Recommendations include dyspnea affecting a patient's daily activities, a Pa_{O_2} below 60 mm Hg,[5] or a shunt fraction greater than 12%.[7]

Lavage technique

The technique and subsequent application of whole lung lavage in PAP was first described by Ramirez.[11,44,45] The procedure requires general anesthesia and intubation with a double-lumen endotracheal tube so that each lung can be isolated. One lung is lavaged with saline while the other is being ventilated. Serial aliquots of saline are infused and drained until the effluent is almost totally

The patient's chest radiograph after treatment

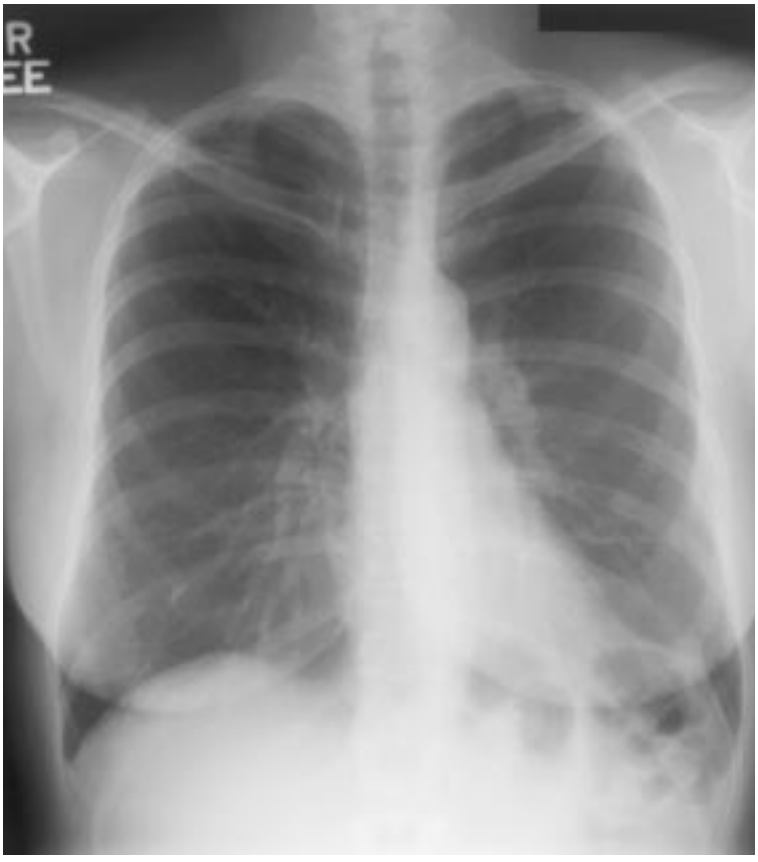

FIGURE 5. Follow-up posteroanterior radiograph after 4 months of GM-CSF therapy reveals clearing of the previously seen infiltrates.

clear. This requires 40 to 50 L of saline. The second lung undergoes the same procedure either the same day or 3 to 7 days later. The procedural details have been described elsewhere.[11,44,46]

Results

Physiologic improvement with whole lung lavage includes increases in forced vital capacity, total lung capacity, Pa_{O_2} at rest and with exercise, and diffusing capacity of the lungs for carbon monoxide, with decreases in the alveolar-arterial gradient and shunt fraction.[7] Others signs of improvement noted have been gradual radiographic clearing,[47] decreased LDH levels,[38] increased ventilation, perfusion, and ventilation/perfusion (V/Q) matching on scintigraphy,[48] and improved alveolar macrophage migration.[22]

Complications of whole lung lavage include hypoxemia (particularly during the drainage phases), spilling of fluid from the lavaged to the ventilated lung, and hydropneumothorax.

The natural history of PAP is variable. From 54% to 75% of patients undergo at least one lavage procedure.[3–5] PAP has been reported to resolve spontaneously, but in our experience this is very uncommon. Over half of those who undergo whole lung lavage have the procedure repeated at a later date because of a worsening or recurrence of symptoms. Death from PAP has become uncommon, but persistence of symptoms is not.

Experimental therapies

Recent advances in our understanding of the pathogenesis of PAP have led to consideration of alternate therapeutic strategies. Treatment directed at the relative GM-CSF deficiency, either through replacement or suppression of the autoantibody, has become a focus of attention.

GM-CSF replacement. Aerosolized GM-CSF has been effective in GM-CSF-deficient mice.[28] In addition, two published studies report success of systemic therapy with GM-CSF in a small number of human subjects.[33,49]

Side effects of this therapy, such as fever, myalgia, malaise, rash, and injection site reaction, are mild and occur in 20% to 30% of patients. Severe events are rare (< 2% of patients) and include bone pain, systemic symptoms, and a first-dose reaction (hypoxemia and hypotension with the first dose). GM-CSF therapy must be given by daily subcutaneous injection, and it is costly. The hematopoietic response to this therapy seen in normal subjects (ie, leukocytosis) is attenuated in PAP patients, and thus elevated blood counts have not been a concern.[33,49]

Anti-IL-10 antibody has shown in vitro efficacy in enhancing GM-CSF production.

Bone marrow transplantation. The hematologic nature of the disease, and a reported recurrence after lung transplantation, have led to speculation that bone marrow transplantation might be of benefit.[50,51] This has met with mixed results in a murine model.[30,31]

Others. If the antibodies to GM-CSF that

are now known to be present are shown to be pathogenic, many other avenues of therapy will become possible.

CASE STUDY CONTINUED: TREATMENT

The patient's condition progressively worsened. Over a 9-year period she underwent 16 whole lung lavage procedures, 10 over the last year and a half. She improved with each but progressively deteriorated afterward. She was sent to The Cleveland Clinic in September of 2000 to be considered for an experimental therapeutic trial of GM-CSF therapy. She has now completed GM-CSF therapy for 6 months. She has not required any further whole lung lavage, and her chest radiograph has dramatically improved (FIGURE 5).

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