

Pulmonary Alveolar Proteinosis

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Summary

Pulmonary alveolar proteinosis is a rare but potentially treatable disease, characterized by impaired surfactant metabolism that leads to accumulation in the alveoli of proteinaceous material rich in surfactant protein and its component. Novel insights from an animal model aided the discovery of granulocyte macrophage colony stimulating factor (GM-CSF) antibodies as a pathogenetic mechanism in human pulmonary alveolar proteinosis. The vast majority of pulmonary alveolar proteinosis occurs as an autoimmune disease; less commonly, it is congenital or secondary to an underlying disorder such as infection, hematological malignancy, or immunodeficiency. The subacute indolent course of this disease often delays the diagnosis by months to years. Crazy-paving appearance in a geographic distribution is a characteristic feature of this disease visible on high-resolution computed tomography (CT). A definitive diagnosis, however, requires lung biopsy, which typically shows partial or complete filling of alveoli with periodic-acid-Schiff-positive granular and eosinophilic material in preserved alveolar architecture. Patients with minimal symptoms are managed conservatively, whereas patients with hypoxemia require a more aggressive approach. Whole-lung lavage is the most widely accepted therapy for symptomatic pulmonary alveolar proteinosis. Correction of GM-CSF deficiency with exogenous GM-CSF is an alternative therapy. The combination of a systemic treatment (GM-CSF) and a local treatment (whole-lung lavage) augmenting the

action of one another is a promising new approach. As the knowledge about this rare disease increases, the role of novel therapies is likely to be better defined and optimized. *Key words:* *pulmonary alveolar proteinosis; surfactant; alveoli; autoimmune disease.* [Respir Care 2011;56(7):1016–1028. © 2011 Daedalus Enterprises]

Introduction

Pulmonary alveolar proteinosis, first described by Rosen et al in 1958,¹ is a rare pulmonary disease with a worldwide distribution. It is a syndrome of altered surfactant homeostasis, characterized by accumulation of periodic-acid-Schiff-positive proteinaceous material in the alveoli. The resultant disturbance leads to clinical manifestation ranging from asymptomatic disease to life-threatening respiratory failure.² New insights gained from knockout mice models,^{3–5} nonhuman primates,^{6,7} and granulocyte macrophage colony stimulating factor (GM-CSF) autoantibodies in human pulmonary alveolar proteinosis suggest a causal role of GM-CSF in the pathogenesis.^{8,9} Although ongoing studies are still evaluating its role, recent data suggest that exogenous GM-CSF therapy (to treat GM-CSF deficiency) has potential in the treatment of autoimmune pulmonary alveolar proteinosis.¹⁰ This review summarizes recent advances in pathogenesis and treatment of this rare but potentially treatable condition.

Methods

For this review we searched the PubMed and Embase databases for reports on the epidemiology, clinical presentation, evaluation, assessment, pathogenesis, and treatment of pulmonary alveolar proteinosis, published in English, up to August 2010. We used free terms, including “pulmonary alveolar proteinosis,” alone and in combination with epidemiology, diagnosis, bronchoalveolar lavage, crazy paving, GM-CSF, autoimmune or idiopathic pulmonary alveolar proteinosis, and whole-lung lavage. We also reviewed the references of primary studies, reviews, case reports, and editorials. All the identified references were reviewed by one of us.

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Epidemiology

Because of the rarity of pulmonary alveolar proteinosis, it is difficult to estimate its true incidence and prevalence. Initial studies reported the prevalence of autoimmune pulmonary alveolar proteinosis at 3.7 cases per million; however, recent reports described a higher prevalence of about 6.2 cases per million.^{9,11,12} That difference in prevalence estimates suggests that the disease has a geographical distribution, but more epidemiological data are required to confirm that suspicion.

In most reported series there has been a male preponderance, with a male-to-female ratio range of 2.1:1 to 2.7:1.¹² The usual duration of symptoms prior to diagnosis is around 7–10 months.^{9,12,13} In a retrospective review of 410 cases, Seymour et al found a median age at diagnosis of 39 years, with the disease manifesting at a later age in the males. They also reported a bimodal pattern, with a peak age frequency in females of 25–40 years.¹² Similar age distribution and male preponderance was also reported from China in 281 patients.¹³ However, in 2 recent reports of 223 and 38 cases from Japan and Korea, respectively, the mean age at diagnosis was 51 and 52 years, with no sex difference.^{9,14} There was a significantly lower proportion of smokers (57%) in the recent Asian report, than the previously reported prevalence of 72%, which suggests that smoking is only casually associated and that other factors may be involved in the etiology.^{9,12}

Normal Surfactant Physiology

Surfactant phospholipids are synthesized and stored as lamellar bodies in alveolar type II pneumocytes. Upon exocytosis into the alveolar lumen they interact with surfactant proteins and organize into tubular myelin that forms a mono-layer or multi-layer at the air-liquid interface, which reduces the surface tension and prevents alveolar collapse.¹⁵ Approximately 70–80% of the inactivated surfactant is taken up by alveolar type II cells for recycling or catabolism. The remaining surfactant is phagocytosed and degraded by alveolar macrophages or enters the lymphatic stream.² Thus, a balanced production and catabolism tightly regulates the surfactant homeostasis. GM-CSF, which is present in serum and most tissues, binds to its receptors on monocytes, macrophages, and alveolar type II cells to initiate the biological effect.^{3,16,17} In the lungs, GM-CSF stimulates the terminal differentiation of alveolar macrophages

mediated by transcription factor PU.1 to enhance their capacity for uptake and catabolism of surfactant proteins and surfactant phospholipids.¹⁸⁻²⁰ In the presence of high-affinity neutralizing immunoglobulin G (IgG) antibodies against GM-CSF, alveolar macrophages lose their ability for adhesion, chemotaxis, microbicidal activity, phagocytosis, and phagolysosome fusion, leading to disruption of surfactant homeostasis and accumulation within the alveoli.²¹⁻²⁴

Pathogenesis of Autoimmune Pulmonary Alveolar Proteinosis

New insights from ultrastructural,²⁵ biochemical,^{26,27} and functional investigations of bronchoalveolar lavage fluid (BALF) indicate that abnormal clearance, rather than the excessive production, of surfactant is the key mechanism in the pathogenesis of pulmonary alveolar proteinosis.^{2,28} The seminal discovery that knockout mice deficient in GM-CSF or its receptor developed lung lesions similar to pulmonary alveolar proteinosis, and the reversal of those abnormalities with GM-CSF therapy, suggested a potential role for exogenous GM-CSF.^{4,5,29} However, the presence of a normal GM-CSF gene and functionally intact GM-CSF receptor with downward signaling strongly argues against the role of absolute deficiency of GM-CSF as the pathogenetic mechanism in human pulmonary alveolar proteinosis.^{30,31} Subsequently, the discovery of systemic (serum) and local (BALF) neutralizing antibodies against GM-CSF in idiopathic pulmonary alveolar proteinosis but not in healthy controls, resulting in a virtual deficiency of functional GM-CSF, suggested that the pathophysiological abnormality may originate from the generation of autoantibody against GM-CSF.⁸ The strong association of GM-CSF antibodies in human autoimmune pulmonary alveolar proteinosis is further supported by the recent observation of pathology findings similar to human pulmonary alveolar proteinosis in nonhuman primates (*Macaca fascicularis*) after passively transferring highly purified GM-CSF autoantibodies from a patient with pulmonary alveolar proteinosis.^{6,7} Thus, the final common pathway appears to be the deficiency of functionally active GM-CSF. Additionally, the discovery of GM-CSF antibody in an indium tin oxide worker with pulmonary alveolar proteinosis raises the possible role of inhaled agents in the triggering and development of autoimmune pulmonary alveolar proteinosis, though this is speculative and needs confirmation.³²

Pathology

The characteristic findings of pulmonary alveolar proteinosis on light microscopy in lung specimens include partial or complete filling of alveoli with diastase-resistant, periodic-acid-Schiff-positive, granular and eosino-

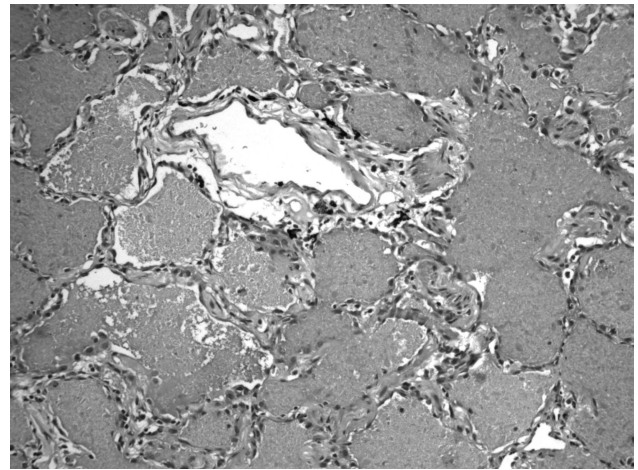


Fig. 1. Eosinophilic granular material filling alveolar spaces, with little reaction in alveolar walls (hematoxylin and eosin stain, magnification $\times 100$).

philic lipoproteinaceous material, and relatively preserved alveolar architecture (Fig. 1).¹ Abnormally enlarged alveolar macrophages and intracellular accumulation of surfactant-like material are also present. Lymphocytic infiltration, fibroblasts, and fibrosis occur occasionally. With anti-surfactant protein A immunostain, substantial accumulation of surfactant protein can be seen in the alveoli.²⁶ Electron microscopic ultrastructural examination of BALF sediment shows amorphous debris and concentrically laminated phospholipid lamellar bodies (Fig. 2).^{25,33-35}

Classification

Pulmonary alveolar proteinosis is classified into 2 main types: congenital and acquired. The acquired form is subdivided into the autoimmune form and the secondary form (ie, due to an underlying disorder). Congenital pulmonary alveolar proteinosis occurs due to mutation in the SFTPB gene entailing a surfactant-protein-B deficiency, gene encoding for ABC transporter A3 and CSF2RB gene encoding GM-CSF receptor β chain.³⁶⁻³⁸ The majority of congenital pulmonary alveolar proteinoses are transmitted in an autosomal recessive manner.^{36,39} They characteristically present with an acute onset of rapidly progressive respiratory distress immediately after birth.

The acquired form is the most common in previously healthy adults. Because of the presence of anti-GM-CSF antibodies, the term "autoimmune pulmonary alveolar proteinosis" has been proposed for the idiopathic variety, which constitutes more than 90% of all reported cases of pulmonary alveolar proteinosis.^{8,9,12,21} Secondary pulmonary alveolar proteinosis is caused by underlying conditions that reduce the number of or functionally impair alveolar macrophages (Table 1).^{35,40-86}

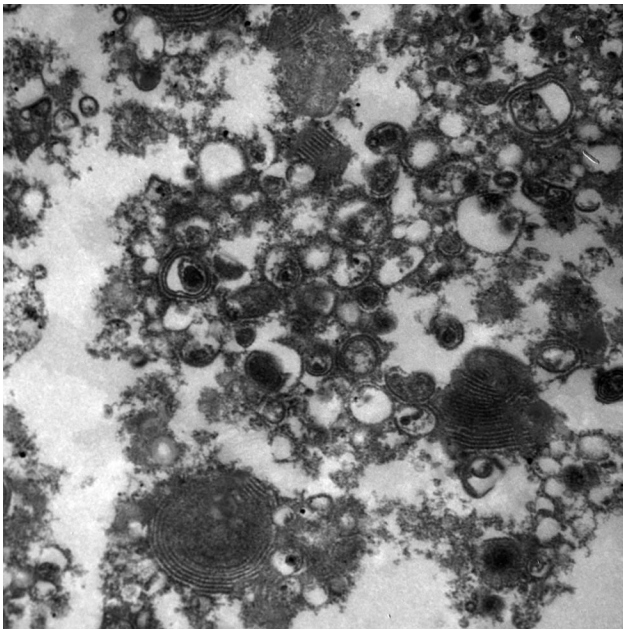


Fig. 2. Ultrastructural examination shows whorled lamellated surfactant bodies in the alveolar spaces (eosin-5-maleimide stain, magnification $\times 6450$).

Clinical Features

The onset of clinical disease is insidious, with a sub-acute indolent course that often delays the diagnosis by months to years. This delay is secondary to the time required for sufficient surfactant accumulation in the alveoli to impair gas exchange. Dyspnea, isolated or in combination with cough, occurs in a majority of the patients. Occasional patients may also have white and gummy sputum production, weight loss, hemoptysis, or fever.^{87,88} Physical examination is usually unremarkable, although there may be inspiratory crackles, clubbing, and cyanosis.⁸⁹ Approximately 10–30% of patients are asymptomatic at presentation,^{9,14,90} whereas others present acutely with rapid progression to respiratory failure.^{91–95} Acute and rapid progression can occur because of infection.¹² Pneumothorax and cor pulmonale occur rarely.^{96,97}

Diagnosis

Radiology

Chest radiograph typically shows bilaterally symmetrical ill-defined nodular or confluent alveolar filling pattern, with a perihilar or basal distribution,⁹⁸ but the radiographic pattern can also be asymmetric,⁹⁹ unilateral,^{1,100} peripheral, or lobar.¹ Absence of cardiomegaly, of pleural effusion, and extent of abnormality disproportionate to the

Table 1. Etiologies of Secondary Pulmonary Alveolar Proteinosis

Hematopoietic Disorders

- Fanconi's anemia^{40,41}
- Myelodysplastic syndrome^{42,43}
- Acute myeloid leukemia^{44,45}
- Chronic lymphatic leukemia⁴⁶
- Chronic myelogenous leukemia^{47,48}

Genetic Disorders

- Lysinuric protein intolerance^{49,50}
- Niemann-Pick disease type C^{51,52}

Immunodeficiency Disorders

- Thymic aplasia⁵³
- Immunoglobulin A deficiency⁵⁴
- Immunosuppression for organ transplant^{55,56}
- Severe combined immunodeficiency disorder⁵⁷

Autoimmune Disorders

- Psoriasis⁵⁸
- Amyloidosis⁵⁹
- Immunoglobulin G monoclonal gammopathy⁶⁰

Dust Inhalation

- Silica^{61,62}
- Cotton⁶³
- Cement⁶⁴
- Titanium⁶⁵
- Aluminum⁶⁶
- Indium tin oxide^{67,68}
- Cellulose⁷⁰
- Nitrogen dioxide⁷¹

Infections

- Nocardia*^{72–74}
- Human immunodeficiency virus^{75,76}
- Cytomegalovirus*⁷⁷
- Pneumocystis jirovecii*³⁵
- Histoplasma capsulatum*⁷⁸
- Cryptococcus neoformans*^{79,80}
- Mycobacterium tuberculosis*^{81–84}
- Mycobacterium avium-intracellulare*^{85,86}

symptoms help exclude pulmonary edema, which is the most common cause of perihilar infiltrates.

High-Resolution Computed Tomography

High-resolution CT shows smooth inter-lobular and intra-lobular septal thickening superimposed on a background of ground-glass opacities, which produces the crazy-paving appearance that is characteristic of pulmonary alveolar proteinosis (Fig. 3).^{101,102} Accumulation of proteinaceous material in the air space adjacent to inter-lobular septa, and an interstitial fibrotic process, alone or in combination, have been proposed as a mechanism of crazy paving.^{103,104} The crazy-paving pattern is not pathognomonic of pulmonary alveolar proteinosis, and occurs in other infectious or non-infectious conditions.^{104–114} The subacute or chronic clinical course, absence of architectural distortion, smooth

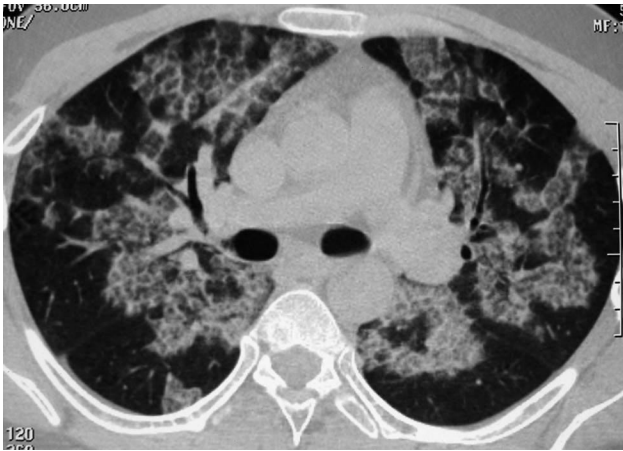


Fig. 3. High-resolution computed tomogram from a patient with pulmonary alveolar proteinosis demonstrates the characteristic crazy-paving appearance.

inter-lobular septal thickening, geographical distribution, and discordance between the clinical and radiological features help differentiate pulmonary alveolar proteinosis from other causes of crazy paving. In a study of 42 patients, Ishii et al¹¹⁵ reported differences in the pattern and distribution of ground-glass opacity on high-resolution CT, which help to differentiate secondary from autoimmune pulmonary alveolar proteinosis. They found a higher occurrence of basal distribution of ground-glass opacity and crazy paving in autoimmune pulmonary alveolar proteinosis; however, the ground-glass opacity tended to be patchy or geographic in autoimmune pulmonary alveolar proteinosis, in contrast to diffuse ground-glass opacity in the secondary variety.¹¹⁵ High-resolution CT is also useful to determine the extent of lung involvement and to assess the disease severity before treatment.¹⁰²

Bronchoalveolar Lavage

BAL, with its characteristic appearance and ultrastructure, is helpful in the diagnosis.^{116,117} Grossly the BALF may be milky and opaque, and settles into a thick sediment layer and a translucent supernatant (Fig. 4).¹¹⁸ The BALF contains phospholipids and surfactant proteins A, B, and D, and has relatively lower concentrations of phosphatidylcholine and phosphatidylglycerol.^{27,119,120} The most striking feature on microscopy is enlarged foamy alveolar macrophages engorged with diastase-resistant, periodic-acid-Schiff-positive intracellular inclusions.¹²¹

On electron microscopy, abundant concentrically laminated structures called lamellar bodies are diagnostic of pulmonary alveolar proteinosis (see Fig. 2).^{25,122} On light microscopy, Papanicolaou stained BALF shows fat globules.¹¹⁶ In one study, a cutoff value of > 18 fat globules per slide was highly suggestive of pulmonary alveolar pro-

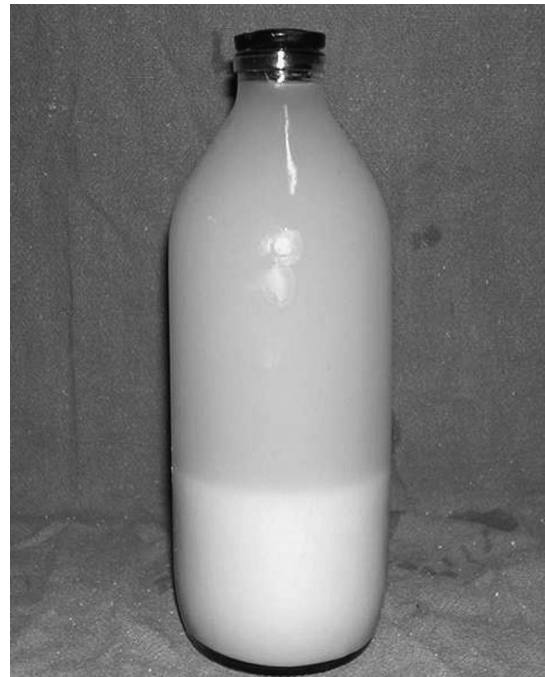


Fig. 4. Lung-lavage fluid from a patient with pulmonary alveolar proteinosis layers into a thick sediment and a translucent supernatant.

teinosis.¹²³ A confident diagnosis of pulmonary alveolar proteinosis can be made with the combination of milky and opaque BALF and characteristic findings on high-resolution CT.¹² Tumor markers, mucin-like glycoprotein, and surfactant proteins also occur in the BALF, but their diagnostic utility is limited, as they are also present in other pulmonary diseases.^{124,125}

Tissue Biopsy

The accepted standard for the diagnosis of pulmonary alveolar proteinosis is lung biopsy, via flexible bronchoscopy or surgery.¹ Bronchoscopic biopsy can reliably establish the diagnosis and may obviate surgical lung biopsy,^{9,87,88,90} but, because of the patchy nature of the disease, a false negative result may be seen with bronchoscopic biopsy, with an additional risk of pneumothorax and hemorrhage.¹²⁶

Granulocyte Macrophage Colony Stimulating Factor Autoantibody

GM-CSF autoantibodies are polyclonal and consist of IgG1, IgG2, and small amounts of IgG3 and IgG4.¹²⁷ Healthy individuals can have low levels of GM-CSF autoantibodies, but the risk of pulmonary alveolar proteinosis is increased if the GM-CSF antibody level is $> 5 \mu\text{g/mL}$.⁷ The latex agglutination test is the most widely used

test for the detection of GM-CSF antibodies. It has diagnostic sensitivity and specificity of 100% and 98%, respectively, so it is the test of choice for autoimmune pulmonary alveolar proteinosis.¹²⁸

Severity Assessment

The clinical course of pulmonary alveolar proteinosis ranges from stable disease with persistent symptoms to progressive deterioration, or, occasionally, spontaneous improvement.^{9,12,100,129} In addition to the subjective assessment of symptoms, pulmonary function tests, exercise capacity, gas exchange, and serum and bronchoalveolar biomarkers are used to assess disease severity and to guide management decisions.

Pulmonary Function Tests

The most common spirometric abnormality in pulmonary alveolar proteinosis is restrictive defect, manifested by decreased vital capacity and lung volume.^{9,12,13} Alveolar filling is reflected by a disproportionately reduced diffusing capacity for carbon monoxide.^{9,13} Following lung lavage these variables improve, which suggests a good correlation with the disease severity.¹²⁹

Gas Exchange

Hypoxemia without abnormal arterial pH or P_{aCO_2} , and increased alveolar-arterial oxygen difference ($P_{(A-a)O_2}$) that widens with exercise are prominent features of pulmonary alveolar proteinosis.^{9,12,129-131} These abnormalities occur due to intrapulmonary shunting of blood through poorly ventilated alveoli filled with proteinaceous material.¹³⁰ Post-lavage improvement in these variables makes them convenient for monitoring the disease.^{129,130}

Granulocyte Macrophage Colony Stimulating Factor Autoantibody Titers

Several initial reports suggested a relationship between serum anti-GM-CSF antibody titers and disease activity.^{132,133} Lin et al found a significant correlation between BALF (but not the serum GM-CSF antibodies) and other severity indicators, and subsequent requirement of therapeutic lung lavage.¹³⁴ This could be related to compartmentalization leading to differences in BALF and serum antibody levels. Similarly, Seymour et al found no relationship between the serum anti-GM-CSF antibody concentration and disease severity or predicting the response to GM-CSF therapy.¹³⁵ The neutralizing capacity of the antibody has been stated to be a more accurate marker of disease severity.¹³⁶

Biomarkers

Abnormalities in the concentrations of proteins synthesized by the respiratory epithelium occur in pulmonary alveolar proteinosis, but their exact role in the severity assessment is uncertain.¹³⁷ High levels of surfactant proteins, KL-6, and lactate dehydrogenase in serum and BALF have been described as evidence of severe disease.^{12,138-142} Several investigators have emphasized the value of these biomarkers in the diagnosis and severity assessment,^{27,142} but, due to their low specificity, they are seldom utilized. Similarly, tumor markers, such as squamous-cell carcinoma antigen, carcinoembryonic antigen, carbohydrate antigen 19-9, and cytokeratin 19 fragments, have been used in assessing pulmonary alveolar proteinosis.^{143,144} However, the clinical value of measuring these tumor markers in serum or BALF for diagnosis or severity assessment remains inconclusive.¹²⁴

Treatment

The treatment of pulmonary alveolar proteinosis depends on the etiology (Fig. 5). Treatment of the congenital form depends on the patient's age at presentation, severity of symptoms, and anticipated disease course. In mild disease, supportive treatment may suffice.¹⁴⁵ In severe disease, therapy may be individualized. Despite the technical difficulty, whole-lung lavage,¹⁴⁶ lung transplantation,^{147,148} and heart and lung transplantation¹⁴⁹ have been reported in congenital pulmonary alveolar proteinosis. The most effective treatment for secondary pulmonary alveolar proteinosis is treatment of the underlying condition.¹⁵⁰

Whole-Lung Lavage

Whole-lung lavage has been the most widely accepted and effective therapy for more than 4 decades. Beginning with "segmental flooding" to physically remove the accumulated material, then extending the procedure to the first successful whole-lung lavage under local anesthesia, Ramirez et al revolutionized the concept of whole-lung lavage in pulmonary alveolar proteinosis.^{151,152} Over the years this original procedure has been refined and modified to achieve good results with less procedural difficulty and fewer complications.^{95,126,153-172} The modifications include routine use of general anesthesia,^{153,154} larger lavage volume,^{154,155} lobar lavage,¹⁶² positional clearance,¹⁶¹ and chest percussion.^{159,161} Additionally, successful completion of bilateral sequential¹²⁶ and simultaneous¹⁶³ whole-lung lavage in the same session has been achieved. Special circumstances such as advanced pulmonary alveolar proteinosis or cor pulmonale may dictate modification of the technique, including hyperbaric oxygen,¹⁵⁸ inhaled nitric oxide,^{167,172} and extracorporeal membrane oxygenation.¹⁷⁰

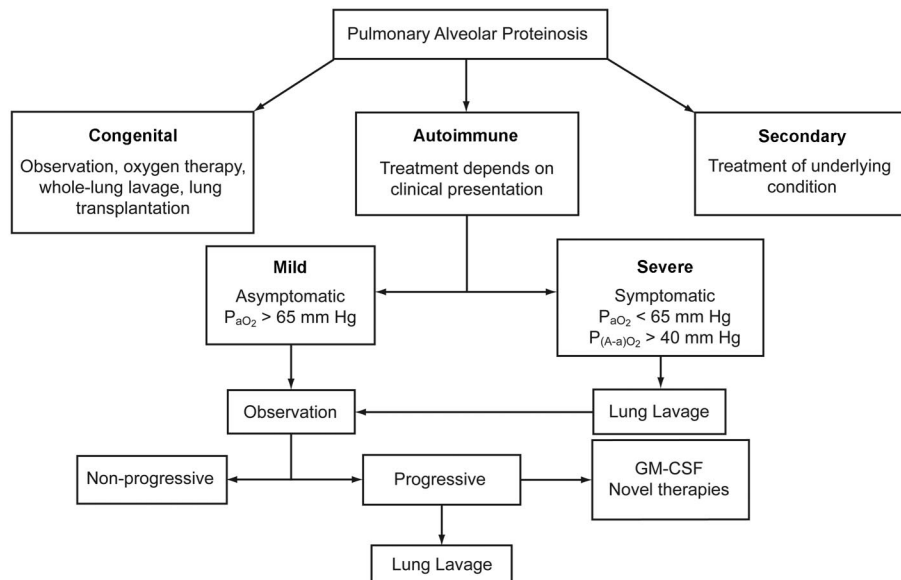


Fig. 5. Treatment algorithm for pulmonary alveolar proteinosis. $P_{(A-a)O_2}$ = alveolar-arterial oxygen difference. GM-CSF = granulocyte macrophage colony stimulating factor.

In milder disease, lung lavage may be performed via flexible bronchoscopy in a conscious patient; however, the effectiveness of that procedure is unclear.^{173,175} Physical therapy (manual percussion, vibration, and chest compression) started during the last two thirds of infusion of saline and continuing till drainage can significantly increase the amount of material removed.^{159,174} Combination of physical therapy and gravity drainage optimizes the effective removal process. The benefits of whole-lung lavage are related to the physical removal of proteinaceous material and the local anti-GM-CSF antibodies, which restores the migration and phagocytic functions of alveolar macrophages.¹⁷⁴⁻¹⁷⁶

The major indication for and timing of whole-lung lavage is symptomatic disease with dyspnea that limits activity and progressive deterioration of arterial oxygenation.⁹⁸ In some centers, $P_{aO_2} < 65$ mm Hg, $P_{(A-a)O_2} > 40$ mm Hg, or a shunt fraction > 10 – 12% are used as threshold values for therapeutic lung lavage.^{129,130} Clinical,^{129,130,177} functional,^{100,129,177} and radiological¹⁷⁸ improvement are seen in approximately 80% of patients after the first whole-lung lavage, and the median duration of benefit can be as long as 15 months, but the majority require repeat lavage.¹² Approximately 15% require lavage every 6 months, and lack of response is reported in less than 10%.^{126,130} Whole lung lavage provides only temporary symptom relief, without correcting the underlying defect, and has the additional disadvantage that it is a complex procedure that may require prolonged general anesthesia and has a risk of pneumonia, sepsis, acute respiratory distress syndrome, and pneumothorax.¹⁷⁹⁻¹⁸¹ Despite these challenges, whole-lung lavage remains the therapy of choice and is associated

with significantly better 5-year survival, compared to those who do not receive lavage.¹²

Exogenous Granulocyte Macrophage Colony Stimulating Factor Therapy

Based on the pathophysiology of pulmonary alveolar proteinosis, treatment aimed at relieving functional GM-CSF deficiency by administering exogenous GM-CSF or suppressing the neutralizing antibody has been utilized simultaneously or even as an alternate to whole-lung lavage. Several reports found favorable response with systemic (subcutaneous) or localized (aerosol) GM-CSF.^{10,132,136,142,182-191} Prompt improvement with resumption of GM-CSF in patients who relapsed with GM-CSF therapy suggests that disease resolution was not attributable to spontaneous remission and that GM-CSF does have therapeutic activity.¹⁸³

Response is generally slow after GM-CSF therapy: the majority of patients show $P_{(A-a)O_2}$ improvement of ≥ 10 mm Hg only after 4–6 weeks.¹⁸¹⁻¹⁹⁰ Despite the slower improvement in oxygenation with GM-CSF, the magnitude of therapeutic effect achievable with GM-CSF or whole-lung lavage may be similar.¹⁸⁴ The observed delay in response is due to the time required for immature precursor cells to be recruited to the lung and stimulated by GM-CSF to differentiate into functional alveolar macrophages. The predictors of response with GM-CSF are yet to be determined, but one study found pre-treatment variables such as longer time from diagnosis, higher vital capacity, normal serum lactate dehydrogenase level, and higher plasma surfactant-protein-B level to be significantly

associated with response to GM-CSF. Similarly, peak eosinophil count following GM-CSF was the only treatment-related variable associated with response.¹⁸⁴ GM-CSF is generally well tolerated, but flushing, tachycardia, hypotension, musculoskeletal pain, dyspnea, nausea and vomiting, rigors, involuntary leg spasms, and syncope may occur following the first dose. These symptoms usually last for 10 min and do not recur with subsequent doses.¹⁹² Currently, one open-label and one randomized trial of GM-CSF in pulmonary alveolar proteinosis is underway, the results of which will clarify the future standard of therapy.

Novel Therapies

In patients who fail to respond to GM-CSF or whole-lung lavage (or require repeated lavage), novel therapies have been tried.^{2,193}

Plasmapheresis. Plasmapheresis to reduce the number of anti-GM-CSF antibodies and restore surfactant catabolism in alveolar macrophages is one novel approach. Plasmapheresis promptly improved symptoms, oxygen saturation, and radiographic appearance, with reduction in antibody titer, in one patient who was unresponsive to whole-lung lavage and subcutaneous GM-CSF.¹³² However, Luisetti et al found that lowering the GM-CSF level from 250 $\mu\text{g/mL}$ to 156 $\mu\text{g/mL}$ was not accompanied by clinical improvement after ten 1.5-L plasma exchanges in autoimmune pulmonary alveolar proteinosis with persistent disease, despite supplemental whole-lung lavage. They concluded that the small reduction in GM-CSF autoantibody level with plasmapheresis is not expected to have a therapeutic effect.¹⁹⁴ Whether the combination of a systemic treatment (plasmapheresis) and a local treatment (whole-lung lavage) can act synergistically to lower the production of GM-CSF autoantibodies requires further evaluation.

Biological Therapies. Reducing autoantibody levels by depleting B lymphocyte is another novel approach. Rituximab, a monoclonal antibody directed against the CD20 antigen of B lymphocytes, has been tested.^{195,196} Although decrease in anti-GM-CSF activity was evident within 3 months of rituximab infusion, the clinical response was evident only after 9 months.¹⁹⁵ The delayed response may be related to recruitment of functional macrophages to the alveoli to stimulate surfactant clearance.

Other Potential Therapies. There have also been reports of treatment with trypsin, chymotrypsin, ambroxol, antibiotics, IgG, and enzymatic debridement, but the clinical value of those therapies is unclear.¹⁹⁷⁻²⁰³

Summary

In the appropriate clinical setting, with typical chest radiographic and high-resolution CT findings, a diagnosis of pulmonary alveolar proteinosis can be established with the help of anti-GM-CSF antibodies and/or BALF and transbronchial lung biopsy. In selected patients, however, open or video-assisted lung biopsy may be required. Asymptomatic patients can be observed with periodic assessment. Patients with milder symptoms can be offered GM-CSF therapy or combined bronchoscopic lung lavage and GM-CSF therapy. In severe cases, whole-lung lavage with a double-lumen endotracheal tube under general anesthesia is the therapy of choice. With advancement of our knowledge of this rare disease, the roles of alternative therapies are likely to be better defined and optimized.

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