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Pulmonary Alveolar Proteinosis Syndrome

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Synopsis

Pulmonary alveolar proteinosis (PAP) is a rare syndrome characterized by the accumulation of surfactant in alveoli and terminal airways resulting in respiratory failure. PAP comprises part of a spectrum of disorders of surfactant homeostasis (clearance and production). The surfactant clearance disorders are caused by disruption of GM-CSF signaling (primary PAP) or by an underlying disease that impairs alveolar macrophage functions including surfactant catabolism (secondary PAP). Primary PAP is related to alveolar macrophage dysfunction due to the disruption of GM-CSF signaling caused by a high serum level of anti-GM-CSF autoantibody (autoimmune PAP) (~90%) or by the mutations in the GM-CSF receptor genes (hereditary PAP). The surfactant production disorders are caused by mutations in genes required for normal surfactant production. The PAP syndrome can be identified based on history, radiologic and bronchoalveolar lavage and/or histopathological findings. The diagnosis of PAP-causing diseases in secondary PAP requires further studies. Whole lung lavage is the current standard therapy and promising new pharmacologic therapies are currently in development.

Keywords

Pulmonary surfactant; GM-CSF; Alveolar macrophages; GM-CSF autoantibody; CSF2RA; CSF2RB; Whole lung lavage; GM-CSF inhalation therapy

Introduction

Pulmonary alveolar proteinosis (PAP) is a rare syndrome characterized by the accumulation of surfactant in alveolar macrophages and alveoli resulting in hypoxemic respiratory failure. In 1958, Rosen et al. first reported PAP as a disorder consisting of filling of alveoli by a PAS-positive proteinaceous material, rich in lipid¹. The accumulated material is now known

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to be comprised primarily of pulmonary surfactant and smaller amounts of cell debris. PAP is often reported in the medical literature as a disease rather than as a syndrome and by the use of various terms, e.g., as pulmonary alveolar lipoproteinosis, idiopathic PAP, acquired PAP and congenital PAP². However, it should be noted that PAP is not a single disease. These disorders of surfactant homeostasis can be defined in the context of abnormalities of surfactant production or surfactant clearance. Surfactant production disorders are less common, typically occur in neonates and children, and are associated with alveolar wall distortion and varying degrees of accumulation of dysfunctional surfactant. They are caused by genetic mutations in genes that encode surfactant proteins or proteins involved in surfactant lipid metabolism, e.g., mutation in the *SFTPB*, *SFTPC*, *ABCA3* or *Nkx2.1* genes. Disorders of surfactant clearance are caused by disruption of GM-CSF signaling (primary PAP) or by an underlying disease that impairs alveolar macrophage number or functions including surfactant catabolism (secondary PAP) (Table 1). Among these PAP-causing diseases, autoimmune PAP is most common and will be a focus of this review²⁻⁴.

Pathogenesis

Pulmonary surfactant maintains lung function by creating an air-liquid interface on the alveolar surface, reducing surface tension and preventing alveolar collapse. It is comprised of 90% lipid (primary phospholipids) and 10% proteins (SP-A, -B, -C and -D). It is also important for host defense against microbial pathogens⁴. Surfactant is synthesized and secreted by alveolar type II epithelial cells, removed by uptake, recycling and catabolism in these epithelial cells, and by uptake and catabolism in alveolar macrophages. The surfactant pool size is tightly regulated by the balance of secretion and removal by these cells (Figure 1). Studies in *Csf2*^{-/-} (GM-CSF gene deficient) mice study revealed the role of GM-CSF in surfactant homeostasis and suggested the pathogenesis of PAP in 1994^{5,6}. This finding was confirmed by an identical pulmonary phenotype in *Csf2rb*^{-/-} (GM-CSF receptor beta chain gene deficient) mice^{7,8}. These results showed that the catabolism of surfactant in alveolar macrophages requires the presence of GM-CSF in the lungs. Based on these mechanisms, disorders of surfactant clearance are classified as primary PAP, which is caused by disruption of GM-CSF signaling, and secondary PAP, which is associated with an underlying disease that impairs alveolar macrophage functions and/or numbers (Table 1). Although GM-CSF gene deficiency has never been identified in human patients, neutralizing autoantibodies against GM-CSF in BALF from “idiopathic” PAP patients were first reported in 1999⁹. This form of PAP is now classified as autoimmune PAP, which is the most common clinical form of PAP and accounts for 90% of cases. Autoimmune PAP is related to alveolar macrophage dysfunction due to the disruption of GM-CSF signaling, which is in turn caused by a high level of anti GM-CSF autoantibody in the lungs. The pathogenesis of autoimmune PAP was confirmed in a 2009 study where the adoptive transfer of PAP patient-derived autoantibodies into nonhuman primates resulted in PAP¹⁰. The incidence and prevalence of autoimmune PAP is 0.49 and 6.2 per million, respectively, in the general population according to a Japanese cohort study¹¹. Autoimmune PAP is twice as common in males, typically presenting in the third through sixth decades, and is rare in children younger than 10 years of age. Among GM-CSF autoantibody-negative PAP patients, gene mutations of GM-CSF receptor alpha and beta genes (*CSF2RA* and *CSF2RB*, respectively) were

identified. Disruption of GM-CSF signaling by recessive mutations in *CSF2RA* or *CSF2RB* causes a hereditary form of PAP that is clinically, physiologically, and histologically indistinguishable from autoimmune PAP¹²⁻¹⁶. These genetic forms of PAP are now classified as hereditary PAP. Hereditary PAP probably account for <1% of cases. Secondary PAP is associated with various underlying diseases such as hematological diseases (myelodysplastic syndrome [MDS], acute myelogenous leukemia, acute lymphoblastic leukemia, chronic myelocytic leukemia, chronic lymphocytic leukemia, aplastic anemia, multiple myeloma, lymphoma, Waldenstrom's macroglobulinemia), nonhematologic malignancies (lung adenocarcinoma, glioblastoma, melanoma), infectious diseases (Cytomegalovirus, Mycobacterium tuberculosis, Nocardia, Pneumocystis jirovecii), immune deficiency/disruption syndromes (acquired immunodeficiency syndrome, amyloidosis, Fanconi's syndrome, agammaglobulinemia, Bechet disease, juvenile dermatomyositis, renal tubular acidosis, severe combined immunodeficiency disease), and toxic inhalation exposures (Table 1). Inorganic dust (aluminum, cement, silica, titanium, indium), organic dust (agricultural, bakery flour, fertilizer, sawdust), and fumes (chlorine, cleaning products, gasoline/petroleum, nitrogen dioxide, paint, synthetic plastic fumes, varnish) have also been reported to be associated with secondary PAP. These underlying diseases or conditions are thought to impair alveolar macrophage number or functions including surfactant catabolism. Hematological disorders (especially MDS) are the major underlying disease in >75% of cases with adult-onset secondary PAP¹⁷. Secondary PAP accounts for 8-9% of all PAP cases, with an incidence and prevalence of approximately 0.05 and 0.5 per million, respectively. Surfactant production disorders are less common and are caused by genetic mutations in genes that encode surfactant proteins or proteins involved in surfactant lipid metabolism, e.g., mutations in the *SFTPB*, *SFTPC*, *ABCA3* or *Nkx2.1* genes. Other genetic defects such as γ -LAT1 (*SLC7A7*) gene mutations which causes lysinuric protein intolerance¹⁸ and Methionyl-tRNA synthetase (*MARS*) gene mutations¹⁹ were reported to be associated with PAP. The precise mechanisms of PAP pathogenesis induced by these gene mutations have not been elucidated.

Clinical Presentation

Common symptoms of PAP include exertional dyspnea, cough, fatigue and weight loss (Table 2). Fever (1% in Japanese cohort, 11% in Italian cohort and 15% in Chinese cohort) and sputum production (4% in Japanese cohort and 1% in Italian cohort) are less common. In 20 patients with hereditary PAP caused by *CSF2RA* mutations and forms of secondary PAP, similar symptoms have been reported^{20,17}. In secondary PAP with MDS, the most common symptoms were fever (45%), dyspnea on exertion (42%), and cough (42%)²¹. In autoimmune PAP, a smoking history is commonly present (57% in Japanese cohort, 79% in German cohort, and 64% in Italian cohort), and dust or fume exposure have been reported (26% in Japanese cohort, 54% in German cohort, and 32% in Italian cohort). In several studies, two-thirds of the patients were men (male: female ratio is 2.2)^{2,11,22-24}. The physical examination is generally unremarkable, but crackles, clubbing and cyanosis have been reported in some patients.

Diagnosis

PAP syndrome can be identified based on a compatible history, typical radiologic findings, bronchoalveolar lavage cytology and/or lung biopsy findings, and compatible biomarkers. However, diagnosis of the specific PAP-causing disease in secondary PAP syndromes requires further studies. If a patient is suspected to have PAP based on history, radiology studies and other findings, early anti GM-CSF autoantibody testing is useful to make the diagnosis of autoimmune PAP, the most common etiology, and can minimize the use of more invasive procedures (see below). A diagnostic algorithm is shown in Figure 2.

Radiographic Findings

A Chest radiograph may be a useful screening test for THE diagnosis of PAP. The distribution of infiltrates in autoimmune PAP and hereditary PAP is typically bilateral symmetrical opacities in the mid- and lower- lung fields (Figure 3A). High-resolution computed tomography (HRCT) shows ground-glass opacities (GGO) in autoimmune, hereditary and secondary PAP (Figure 3B). GGO presents as a patchy geographic pattern that is distributed in the lower lung fields in autoimmune PAP, whereas GGO typically presents as a diffuse pattern in secondary PAP. A crazing paving appearance (GGO superimposed on septal thickening) and subpleural sparing are frequently seen in autoimmune PAP, but are less frequently apparent in secondary PAP comprising 12% of 27 cases¹⁷ in one study.

Laboratory Findings

Most of routine laboratory tests are normal in PAP. The serum level of LDH is typically elevated, although this finding is nonspecific. LDH and PaO₂ are moderately correlated and LDH and A-aDO₂ are more significantly correlated². Levels of other biomarkers including SP-A, SP-B, SP-C, KL-6, MCP-1, CEA, cytokeratin 19, Cyfra 21-1 and NSE are increased and some of them correlate with disease severity (see below), although none of these findings are specific or diagnostic for PAP.

Pulmonary Function Testing

Pulmonary function testing is of limited usefulness in diagnosing the severity of PAP lung disease. Increased alveolar-arterial oxygen gradient (A-aDO₂) correlates better with disease severity. FVC and FEV₁ are generally within normal limits. Some patients show decreased forced vital capacity (FVC), consistent with restrictive physiology²⁵. The diffusion capacity of the lung for carbon monoxide (DLCO) is frequently reduced and correlates with disease severity¹¹.

Bronchoscopy, Bronchoalveolar Lavage, Microbiologic Culture

Bronchoscopic examination of the airways is unremarkable in PAP but bronchoalveolar lavage (BAL) fluid shows a milky, turbid appearance and thick sediment. BAL is emerging as a useful diagnostic tool for PAP (rising from 4% of 410 published cases in 2002 to 83% in German series in 2011)^{2,22}. In a Japanese cohort, the diagnosis of PAP was based on HRCT and BAL analysis in 58.7% of patients; HRCT, BALF and transbronchial lung biopsy (TBLB) in 34.1% of patients; BAL analysis or TBLB and video-assisted thoracoscopic

surgery (VATS) in 7.2% of patients¹¹. Cytology of PAP BAL fluid reveals Periodic acid Schiff (PAS) stain and oil-red-O stain positive large foamy macrophages and dirty appearing sediment. Fungal, mycobacterial and other infectious etiologies should be ruled out by appropriate staining and culture.

Histopathology

The histopathology of PAP reveals well-preserved alveoli filled with eosinophilic, granular and PAS positive material and foamy alveolar macrophages (Figure 4). It is associated with minimal interstitial inflammation or fibrosis. The combined use of BAL analysis and measurement of serum GM-CSF autoantibody obviates the need for histologic confirmation in many cases of suspected PAP.

Biomarkers

In autoimmune PAPA, only disease-specific biomarker that is known to be elevated in serum is the GM-CSF autoantibody (Figure 5). This test is simple, standardized, and can be used to identify the disease in a large number of patients. The reported sensitivity and specificity for autoimmune PAP approaches 100%²⁶. GM-CSF autoantibody levels in serum do not correlate with duration of disease, disease severity, pulmonary function (FVC%, VC%, FEV1%, DLCO%), or serum biomarkers (LDH, SP-A, SP-D, CEA, KL-6)¹¹. The serum GM-CSF autoantibody also does not correlate with age, gender, smoking status, a history of environmental or occupational dust inhalation exposure, or duration of disease in a Japanese series¹¹, but shows a weak correlation with age and the duration of disease²². GM-CSF autoantibody-negative PAP patients with an underlying disease known to cause PAP are diagnosed with secondary PAP. Serum GM-CSF is elevated in hereditary PAP, likely caused by the absence of receptor-mediated clearance. Although this serum GM-CSF test is not disease specific, the combination of serum GM-CSF autoantibody-negativity and elevated GM-CSF without underlying disease should prompt genetic evaluation for hereditary PAP (Figure 2)¹⁵. Whole blood GM-CSF signaling tests such as the GM-CSF induced STAT5 phosphorylation index test (STAT5-PI) may support the diagnosis of primary PAP¹⁵. Although elevated in a wide range of other lung diseases, serum levels of LDH, SP-A, SP-B, SP-D, KL-6, CEA, M-CSF and MCP-1 are elevated in PAP. Serum levels of LDH, KL-6 and CEA are reported to be correlated with some markers of lung function (PaO₂, AaDO₂, or DLCO%)^{22,25}. Cancer biomarkers other than CEA, such as NSE and Cyfra 21-1, are also elevated in PAP²³. The elevation of serum levels of SP-A, SP-D and KL-6 are also reported in secondary PAP¹⁷. While most of these biomarkers are not very helpful in establishing a diagnosis, they may be useful in monitoring disease activity in patients with PAP.

Natural History

In a Japanese cohort study, one-third of patients with autoimmune PAP were asymptomatic¹¹. In contrast, 5% of patients were asymptomatic in an Italian study²³. The onset of disease is poorly studied because patients become symptomatic present for evaluation only after substantial alveolar filling with surfactant has occurred. The natural history of autoimmune PAP generally follows one of three patterns: spontaneous improvement (ranging from 5 to 7%), persistent, unremitting symptoms, or progressive

deterioration with respiratory failure. Secondary infection occurs in primary and secondary PAP. The 5-year survival among 231 patients with PAP was 85% without therapy and 94% with whole lung lavage therapy². In this study, 72% of deaths were due to respiratory failure and 18% were due to uncontrolled infections. In the Japanese cohort study, the 5-year survival was 100% and significant infection was found in 4% of patients¹¹. The clinical course of secondary PAP is strongly influenced by that of the underlying disease causing PAP and the prognosis is poorer than that of autoimmune PAP. Development of secondary PAP during the course of MDS is an important adverse prognostic risk factor in these patients²¹.

Therapy

Current Therapy

Whole lung lavage (WLL) has been the standard first line therapy since the 1960s²⁷. The WLL procedure is performed under general anesthesia using a double lumen endotracheal tube to ventilate one lung while repeatedly filling and emptying the other with up to 50L of saline to physically remove surfactant from the lung. Although many PAP patients have been treated with WLL (28% in the Chinese cohort, 90% in the German cohort and 54% in the Italian cohort), the procedures are still not standardized and are highly operator-dependent^{2,22-24}. Lobar and segmental lavage performed using a fiberoptic bronchoscope has also been reported. Although segmental BAL may be less effective compared to WLL because of the small lavage volume, one study reported that the two methods appear to be used at similar frequencies in the treatment of patients²⁴. For secondary PAP, approach to treatment is often dictated by the underlying disease. For instance, it has been reported that secondary PAP improves after hematopoietic stem cell transplantation in patients with hematologic diseases²⁸. Therapy for the surfactant production disorders (congenital PAP) is supportive, although successful lung transplantation has been reported²⁹. There is no evidence that corticosteroids are effective for autoimmune PAP³⁰.

Experimental Approaches

The first treatments with exogenous GM-CSF in PAP patients were administered subcutaneously³¹. The use of subcutaneous GM-CSF in escalating doses for 6 to 12 months produced an overall response rate of 48%³². In this study, 85% of patients receiving subcutaneous GM-CSF had local reactions at the site of injection and other minor adverse events. Aerosolized GM-CSF inhalation therapy has also been tested in PAP³³. In 35 patients with autoimmune PAP, 62% of patients receiving inhaled GM-CSF therapy had improvement in the A-aDO₂ gradient, while serum GM-CSF autoantibody levels were unchanged³⁴. Importantly, no serious adverse events occurred in this study³⁴. Among these 35 patients, 66% had a durable response to the inhalation therapy and required no further treatments during the 30 month observation period. A low baseline vital capacity appeared to be a prognostic marker for disease recurrence³⁵. As another potential therapeutic strategy to reduce the level of GM-CSF autoantibodies, anti-B cell therapy with Rituximab for autoimmune PAP has been reported³⁶⁻³⁸. Plasmapheresis for autoimmune PAP is also a potential approach which can remove GM-CSF autoantibodies³⁹. Although some of these experimental approaches are promising, further efficacy and safety studies are necessary

before conclusions can be drawn about their potential utility in the treatment of PAP patients.

Knowledge Gaps and Future Research

The critical role of GM-CSF signaling in primary PAP (autoimmune and hereditary PAP) pathogenesis has been revealed by effects of GM-CSF autoantibodies or GM-CSF receptor gene (*CSF2RA* or *CSF2RB*) mutations to disrupt the clearance of pulmonary surfactant by alveolar macrophages. However, the molecular mechanisms of PAP pathogenesis beyond the loss of GM-CSF signaling are largely unexplored. Further, the reasons that GM-CSF autoantibodies are produced in autoimmune PAP is not clear. Although a smoking history and dust or fume exposure are often observed in autoimmune PAP patients, the role of these inhalations in autoantibody production has not been elucidated. Although WLL is a standard therapy for PAP, no clinical practice guidelines have been established. Future studies are needed to define the optimal indications, timing and conduct of WLL procedure (e.g. - volume of saline infused, use of mechanical percussion, positioning of the patient etc.). In experimental approaches, a clinical study with inhaled GM-CSF in autoimmune PAP was shown to be safe and effective. However, the mechanisms underlying the therapeutic effect has not been determined. Further studies investigating the optimal dose, timing, duration of administration and long-term safety are necessary. In hereditary PAP, WLL is also a current standard therapy. Pulmonary macrophage transplantation and gene therapy have shown promising results in a mouse model of hereditary PAP⁴⁰ and represent promising future research directions.

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Key Points

- Pulmonary alveolar proteinosis (PAP) is a syndrome characterized by the accumulation of surfactant in alveoli and terminal airways resulting in hypoxemic respiratory failure.
- Surfactant is synthesized and secreted by alveolar type II epithelial cells, removed by uptake, recycling and catabolism in these epithelial cells and by uptake and catabolism in alveolar macrophages.
- Autoimmune PAP is related to alveolar macrophage dysfunction due to the disruption of GM-CSF signaling caused by high level of anti GM-CSF autoantibody in the lungs.
- Elevated serum GM-CSF autoantibody is diagnostic for autoimmune PAP in patients with typical history, radiologic findings, bronchoalveolar lavage cytology findings with a milky, turbid appearance and/or lung biopsy.
- Whole lung lavage (WLL) is the standard first line therapy and GM-CSF inhalation for autoimmune PAP is promising therapy under clinical study.

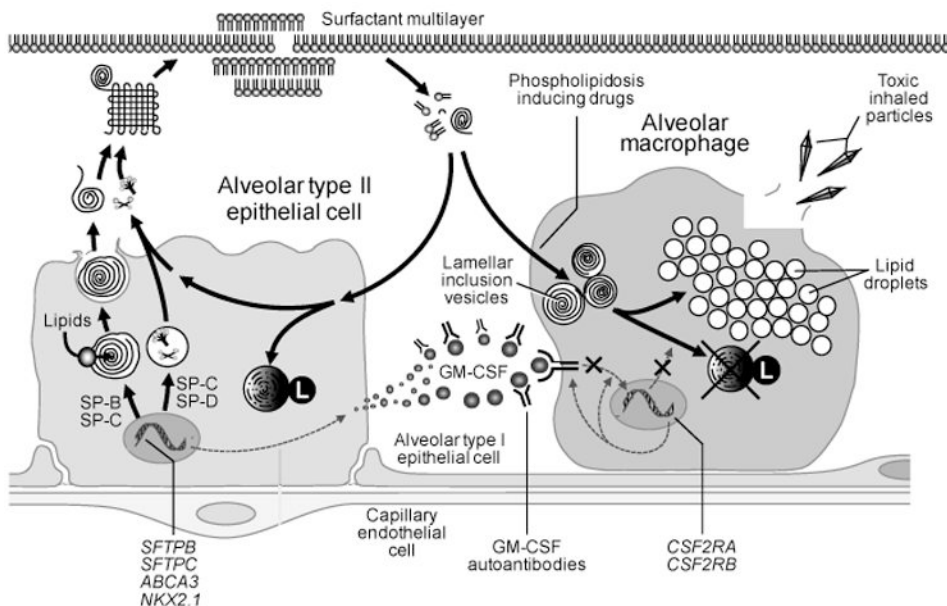


Figure 1. Regulation of surfactant homeostasis. Surfactant lipids and proteins (SP-A, -B, -C and -D) are synthesized in alveolar type II epithelial cell, secreted into the intra-alveolar space, and adsorb to surfactant layer at the air-liquid-tissue interface. The primary function of surfactant is to reduce surface tension within the alveolus to limit collapse of small airspaces. Surfactant lipids and proteins are removed by uptake and recycling in type II epithelial cells or by uptake and catabolism in alveolar macrophages. GM-CSF, a critical regulator of surfactant catabolism in alveolar macrophages, functions by binding to heterooligomeric receptors on alveolar macrophages and stimulating surfactant catabolism. Impaired GM-CSF signaling by GM-CSF autoantibodies or gene mutations in the GM-CSF receptor (*CSF2RA*, *CSF2RB*) cause alveolar macrophage dysfunction, which leads to impaired clearance and accumulation of surfactant in the lung (primary PAP).

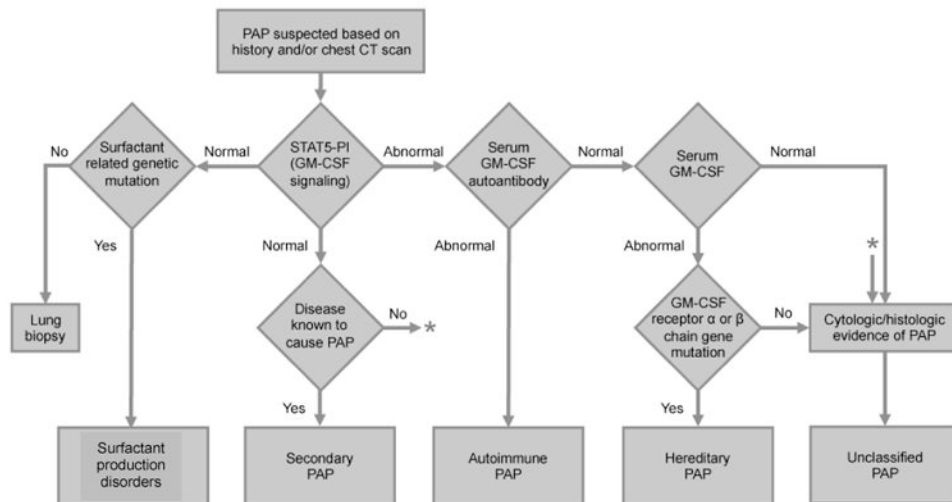


Figure 2.

Algorithm used for the differential diagnosis of PAP syndrome. The diagnosis of PAP is made based on a compatible history, typical radiologic findings, compatible biomarkers, and characteristic lung biopsy or bronchoalveolar lavage cytology findings. Patients with high serum GM-CSF autoantibodies but without underlying diseases known to be associated with PAP are diagnosed with auto immune PAP. Patients with negative serum GM-CSF autoantibodies and with underlying diseases known to cause PAP are diagnosed with secondary PAP. Patients with negative serum GM-CSF autoantibodies and elevated levels of serum GM-CSF without apparent underlying diseases known to be associated with PAP need further evaluation for hereditary PAP by analyzing GM-CSF receptor gene (*CSF2RA* or *CSF2RB*) mutations. Whole blood GM-CSF signaling tests such as the GM-CSF induced STAT5 phosphorylation index test (STAT5-PI) may support the diagnosis of primary PAP. Surfactant production disorders are diseases due to the gene mutations of *SFTPB*, *SFTPC*, *ABCA3* and *NKX2.1*. * Indicates that patients with normal STAT5-PI and no known disease to cause PAP need to be evaluated for cytologic/ histologic evidence of PAP. (From Trapnell BC, Luisetti M. Pulmonary alveolar proteinosis syndrome. In; Broaddus VC, Mason RJ, Ernst JD, et al, eds. Murray and Nadel's textbook of pulmonary medicine, 6th edition. Philadelphia: Elsevier Saunders; 2015; with permission.)

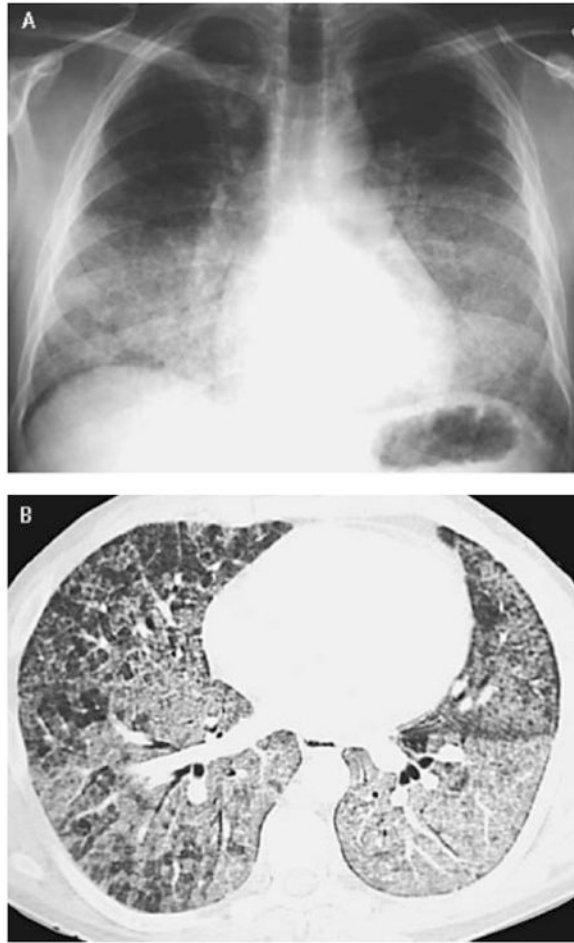


Figure 3. Chest radiograph and chest computed tomography (CT) in autoimmune PAP. (A) Chest radiograph shows diffuse, bilateral infiltrates suggestive of pulmonary edema but without findings suggestive of cardiovascular disease. (B) Chest CT shows a geographic pattern of ground-glass opacification superimposed on thickened interlobular septa commonly referred to as 'crazy paving'. (From Trapnell BC, Whitsett JA, Nakata K. Pulmonary alveolar proteinosis. *N Engl J Med* 2003;349:2528, with permission.)

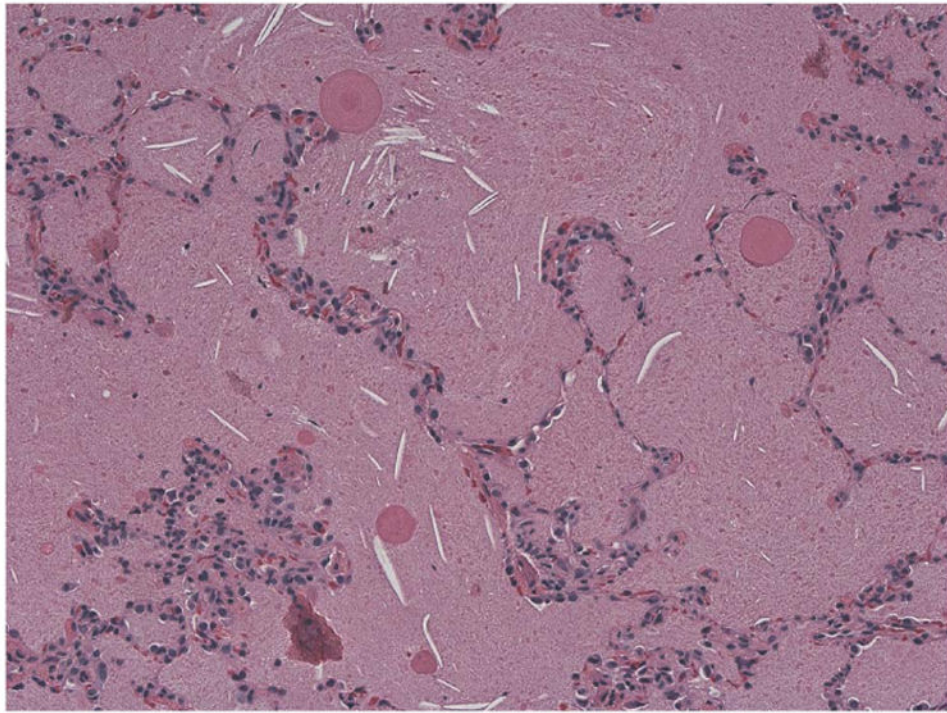


Figure 4. Lung histopathology in auto immune PAP. The alveoli are completely filled with amorphous, acellular eosinophilic material. The alveolar architecture is well preserved, and the alveolar walls are essentially unremarkable. (Periodic acid-Schiff (PAS) stain, original magnification $\times 20$).

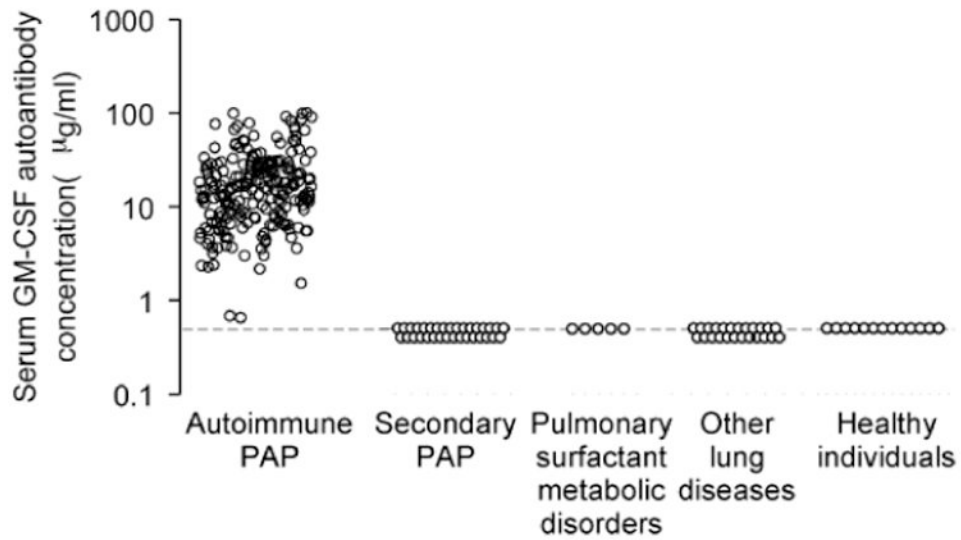


Figure 5. Serum GM-CSF autoantibody testing and diagnosis of autoimmune PAP. A serum level of GM-CSF autoantibody is specifically elevated in autoimmune PAP. The autoantibodies are not elevated in patients with other forms of PAP or other lung diseases or in normal persons. (From Trapnell BC, Luisetti M. Pulmonary alveolar proteinosis syndrome. In; Broaddus VC, Mason RJ, Ernst JD, et al, eds. Murray and Nadel's textbook of pulmonary medicine, 6th edition. Philadelphia: Elsevier Saunders; 2015; with permission.)

Table 1
Classification of Diseases and Risk Factors Reported in Association with PAP Syndrome¹

PAP Classification	Risk factor
Primary PAP ²	GM-CSF Autoantibodies ³ <i>CSF2RA</i> mutations ⁴ <i>CSF2RB</i> mutations ⁴
Secondary PAP ⁵	Hematologic diseases ⁶ Non-hematologic malignancies Immune deficiency/disruption diseases ⁷ Chronic inflammatory/infectious diseases Toxic inhalation exposures ⁸ <i>SLC7A7</i> mutations <i>MARS</i> mutations ⁹
Surfactant Production Disorders ¹⁰	<i>SFTPB</i> mutations <i>SFTPC</i> mutations <i>ABCA3</i> mutations <i>TTF1 (NKX2.1)</i> mutations

¹Abridged list. The strength of association of risk factors with the occurrence PAP varies widely.

²Defined as PAP associated with a primary disruption of GM-CSF signaling.

³Neutralizing GM-CSF autoantibodies mediate disease pathogenesis of what is now called autoimmune PAP (previously idiopathic, acquired, other names), which represents ~85-90% of all patients with PAP syndrome. The presence of serum GM-CSF autoantibodies is 100% sensitive and specific for this disease.

⁴The associated disease is commonly referred to as hereditary or familial PAP.

⁵Defined as PAP associated with an underlying clinical condition secondarily affecting alveolar macrophage

⁶Myelodysplastic syndrome (MDS) is the most common current disease in this category although many hematologic diseases have been reported in association with PAP.

⁷Includes acquired immunodeficiency syndrome, agammaglobulinemia, amyloidosis, Bechet's disease, juvenile dermatomyositis, and Fanconi's syndrome.

⁸Includes inorganic dusts (aluminum, cement, silica, titanium, indium), organic dusts (agricultural, bakery flour, fertilizer, sawdust), and fumes (chlorine, cleaning products, gasoline/petroleum, nitrogen dioxide, paint, synthetic plastic fumes, varnish).

⁹Biallelic MARS mutations cause a lung and liver phenotype and are prevalent in a population on Reunion Island.

¹⁰Defined as PAP associated with genetic mutations resulting in abnormal surfactant protein or lipid production.

Table 2
Clinical Presentation in Patients with PAP Syndrome¹

Study	Inoue	Bonella	Campo
Geographic location of patients	Japan	Germany	Italy
Number of patients	223	70	73
Disease / disease category			
Autoimmune PAP (%)	100	91	100
Secondary PAP (%)	0	9	0
Symptom / Sign	Frequency (% of patients)		
Dyspnea	52	94	67
Cough	23	66	31
Fatigue	0	49	0
Weight loss	0.4	43	0
Fever	1	0	11
Sputum	4	0	1
None	31	0	5
Reference	[11]	[22]	[23]

¹ Only reports with a comprehensive symptom inventory are shown here. Studies with incomplete symptom assessment and symptom frequency in other PAP-causing diseases can be found in the text.

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