Review Article

Autoimmune Pulmonary Alveolar Proteinosis

Spyros A. Papiris[1], Maria Kallieri[2], Maurizio Zompatori[3‡], Sarah H. Forde[4‡], Spyridon Prountzos[5‡], Lykourgos Kolilekas[6], Andriana I. Papaioannou[7], Matthias Griese[8,9], Effrosyni D. Manali[2]

Affiliation addresses are listed at the end of the article.

ABSTRACT

Autoimmune pulmonary alveolar proteinosis (aPAP) is a rare disease characterized by abnormal accumulation of surfactant in alveoli. Pathogenetically, in aPAP, the presence of granulocyte macrophage-colony stimulating factor (GM-CSF) autoantibodies hinders physiological binding of GM-CSF to its receptor, disrupting terminal differentiation of alveolar macrophages and the activation GM-CSF–PU.1–PPARG1–ABCG1 axis, resulting in a primary reduction in cholesterol efflux from alveolar macrophages and a secondary reduction in surfactant clearance through macrophages from the alveolar surface. APAP is the most common, accounting for more than 90 to 95% of all patients included under the PAP term, which encompasses and classifies all forms of PAP according to etiopathogenetic mechanisms, as primary, secondary, congenital, and unclassified. APAP is worldwide distributed with an estimated prevalence fluctuating between 7.0 and 9.7 cases/million and an annual incidence of 1.65, affecting middle-aged men and women. Clinical manifestation may be gradual and insidious, mainly manifesting with progressive dyspnea, but the natural history is variable, since some patients stabilize for a long period, while others progress to respiratory failure and death; in a minority, spontaneous resolution may be observed, while some develop lung and/or systemic infections, and rarely pulmonary fibrosis. Until recently, whole lung lavage (WLL) was universally accepted as the gold-standard therapeutic modality in aPAP. However, after considerable progress in the past 25 years and the publication of several positive studies, replacing the use of inhaled-GM-CSF as the standard of care for aPAP and conceding WLL a rescue option is becoming more and more concrete. In conclusion, aPAP is the classic paradigm of a scientific disease progressing from the "bench-to-bedside," since several discoveries made in the laboratory setting have become necessary to clarify its pathogenetic mechanisms, define diagnostic tools, and implement new therapeutic modalities, which established the disease as treatable and fully reversible, literally, moving patients from "hell to heaven."

Keywords PAP, GMCSF, autoantibodies, WLL, foamy macrophage, cholesterol

received July 26, 2025 | **accepted after revision** November 04, 2025 | **accepted manuscript online** November 06, 2025 | **article published online** 2025

Bibliography Semin Respir Crit Care Med **DOI** 10.1055/a-2737-7719 **Art ID** SRCCM-25-0107-IR

Issue Theme Alveolar Infiltrative and Filling Disorders **Guest Editors** Chad Lampl, Abhishek Singla, and Cormac McCarthy

‡ These authors contributed equally to this article.

Correspondence Spyros A. Papiris, MD, PhD, FCCP, Pulmonology-Critical Care, Athens Medical School, National and Kapodistrian University of Athens, Athens, Greece, Email: papiris@otenet.gr

Introduction

First described in 1958 as pulmonary alveolar proteinosis (PAP), by Rosen, Castleman and Liebow, in their seminal paper in the NEJM, as a "single" new disease characterized by the accumulation of lipoproteinaceous material in pulmonary alveoli,[1] became thereafter idiopathic PAP (acquired PAP of unknown etiology) to differentiate it, the most common of all, from the secondary and others forms of PAP, as new knowledge was unfolding different types of PAP on the basis of the pathogenetic mechanism involved.[2] Two series of discoveries exactly characterized and properly nominated autoimmune (a)PAP. The unveiling of the role of granulocyte macrophage-colony stimulating factor (GM-CSF) signaling on alveolar macrophages maturation and ability to clear surfactant[3,4] and the identification of polyclonal Immunoglobulin-G autoantibodies, against GM-CSF as the cause of the signal disruption on alveolar macrophages affecting their clearance capacity,[5–7] the necessary step in the process of transition of idiopathic-PAP in its autoimmune era, autoimmune pulmonary alveolar proteinosis (aPAP). In aPAP, the uncontrolled lung flooding with surfactant relates to the fact that alveolar macrophages remain poorly differentiated and cholesterol-stuffed, unable to clear surfactant and handle microbials. Actually aPAP "the supporting column" in the classification of PAP, since not only accounts for >90 to 95% of cases but thanks to modern therapeutic modalities, treatable and fully reversible, is categorized as primary and related to the disruption of GM-CSF signaling by neutralizing autoantibodies, where shares the place with the far rare hereditary PAP where disruption of GM-CSF signaling relates to mutations of GM-CSF receptor α or β subunits. Secondary PAP includes a multitude of conditions responsible for reducing the numbers or functional ability of alveolar macrophages.

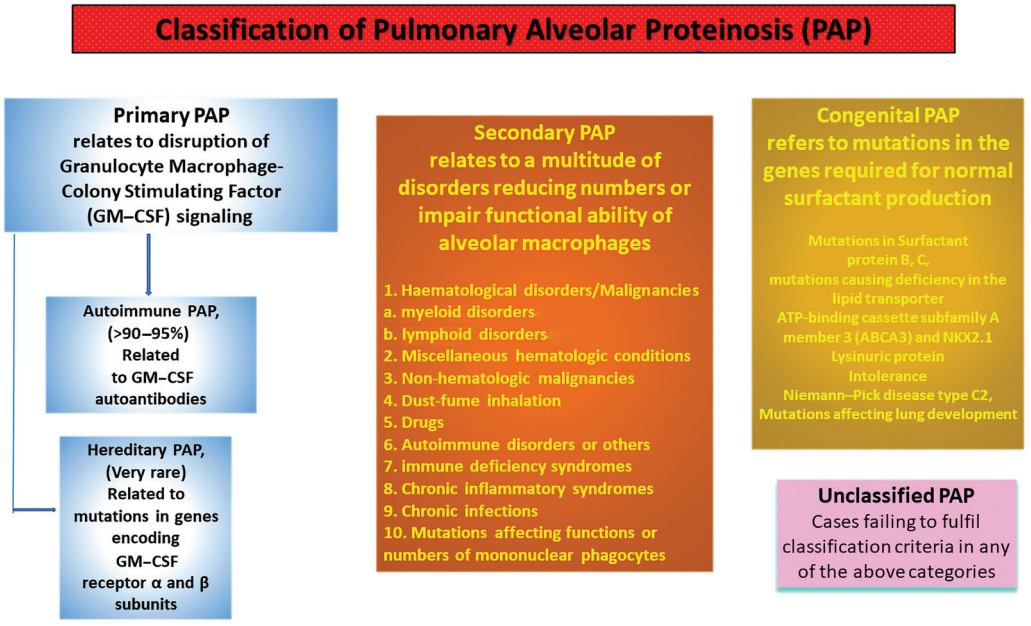

Fig. 1 The classification of pulmonary alveolar proteinosis.

Congenital PAP includes surfactant production disorders and unclassified cases failing to fulfil classification criteria in any of the above categories (**Fig. 1**).[8]

Epidemiology

Besides its first description[1] based on the observation of a series of 27 patients, the natural history, age distribution, demographics, and geographic location unfold gradually. In 1966, Summers from Sacramento reported two new cases, summarized on clinical course and infective complications of the new disease, reviewing the first 93 cases from all over the world.[9] In 1969, Davidson and Macleod reported on three new cases, reviewed the pattern, clinical course, complications, and prognosis of all 139 patients (113 men and 26 women) described and published worldwide since then[10]; in this report, all ages were affected, and infections were confirmed as the main complication of the disease. In 2002, Seymour and Presneill summarized[2] the progress in the first 44 years of PAP describing 410 cases from all over the world registering also the revolution computed over the past 8 years, in the understanding of the pathogenesis of aPAP, which has led to the investigation of innovative treatment approaches such was the subcutaneous administration of GM-CSF, successful in idiopathic-autoimmune PAP, since its first administration.[2,11–13] In 2008, Inoue et al published the largest ever reported single country study, including 248 patients enrolled in a Japanese national registry, and for the first time referring to aPAP (223 patients).[14] In 2018, McCarthy et al published their effort aiming to determine prevalence, healthcare utilization, and costs associated with PAP; prevalence was found slightly higher than in the Japan registry, and most importantly, the study underlines the diagnostic utility of serum GM-CSF autoantibodies (aPAP was found in 91.5% of U.S. PAP patients) permitting to avoid surgery related morbidity and costs.[15] In 2019, Trapnell et al updated data regarding the Japanese national PAP registry refers to a cumulative enrolment between 1999 and 2016 of 952 patients, of whom 877 (92%) had primary PAP, 872 aPAP, 71 (7.5%) secondary PAP, and 4 (<1%) unclassified. On the basis of enrolment over a decade, the annual incidence of aPAP was found to be 1.65 (8). To summarize, an ultimate study from Japan using a national administrative claims database attempted to estimate the national incidence and prevalence of aPAP, secondary (s)PAP, hereditary (h)PAP, and congenital (c)PAP, and further clarify their demographics and survivals by analyzing the years 2014, 2016, 2018, and 2020. Overall, the study revealed an increasing prevalence of aPAP and sPAP over the past decade. Incidence and prevalence were found to be 1.4 and 9.7 per million for aPAP and 0.6 and 3.0 per million for sPAP, respectively. The median (interquartile ranges) ages of the prevalent cases of aPAP, sPAP, cPAP, and hPAP in 2020 were 64 (52–73), 71 (63–78), 1.5 (0.75–5.5), and 4 (3–73) years, respectively; secondary PAP had a significantly poorer prognosis than aPAP (5-year survival rate: aPAP: 82.4%; sPAP: 73.5%).[16] From all the above studies and reports, aPAP emerges as rare, with a worldwide distribution affecting men and women. All ages may be affected, although it is uncommon in children and adolescents. Its clinical manifestation is usually gradual and insidious, manifesting as reported in its first description by "unheralded and creepingly progressive dyspnea," but the natural history throughout the years proved variable, since some patients stabilize for a long period, while others progress to respiratory failure and death; in a minority spontaneous resolution may be observed while some develop lung and/or systemic infections, and rarely pulmonary fibrosis.

The Surfactant Homeostasis and the Regulation of Cholesterol Efflux from the Alveolar Macrophages

Since its first recognition, the disease was described histologically by the filling of the alveolar airspaces by a dense, periodic acid-

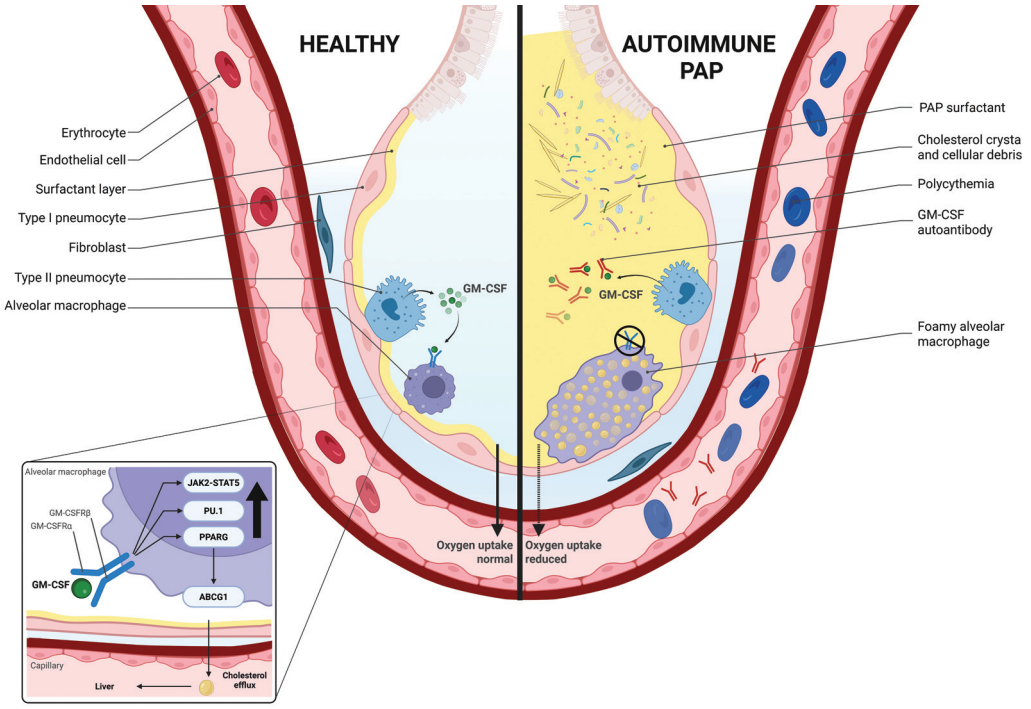

Fig. 2 The pathogenesis of aPAP. Conceptual figure for the pathogenesis of aPAP. In healthy alveoli, pulmonary GM-CSF stimulates the survival, proliferation, differentiation, and functions of alveolar macrophages. All these pleiotropic effects are mediated by heterodimeric cell-surface receptors composed of a low-affinity GM-CSF–binding α chain, an affinity-enhancing β chain (both without known enzymatic activity), and the β chain–associated Janus-activating kinase 2 (JAK2). Ligand binding leads to activation of multiple transcription factors crucial for the terminal differentiation of alveolar macrophages. Recruitment and activation of STAT5 (signal transducer and activator of transcription 5) is crucial in the proliferation, activation, and survival of alveolar macrophages. Activation of transcription factor PU.1 is a cardinal regulator of many alveolar macrophage properties, including cell adhesion, pathogen phagocytosis, and catabolism of surfactant proteins and surfactant lipids. GM-CSF activation of transcription factor PPARG (peroxisome proliferator-activated receptor-γ) leads to increased expression of its target ABCG1, which encodes ATP-binding cassette subfamily G member 1 (ABCG1), a transmembrane lipid transporter protein important in cholesterol efflux from macrophages. In aPAP, the presence of GM-CSF autoantibodies may bind GM-CSF or hinder the physiological binding of GM-CSF to its receptor (neutralizing antibodies), disrupting the GM-CSF–PU.1–PPARG1–ABCG1 axis, resulting in a primary reduction in cholesterol efflux from alveolar macrophages and a secondary reduction in surfactant clearance through macrophages from the alveolar surface. Reduced surfactant uptake by foamy alveolar macrophages engorged with esterified-cholesterol-rich intracytoplasmic lipid droplets is characteristic of the disease. Created in BioRender. Laboratory, B. (2025). https://BioRender.com/4x4uwd6.

Schiff (PAS) stain-positive, granular eosinophilic proteinaceous material rich in lipids, of unknown nature, within normal adjacent alveolar septa, in the absence of inflammation, fibrosis, and necrosis. A few years later, based on similarities of composition, Larson and Gordinier first advanced the "surfactant hypothesis," recognizing the material flooding the airspaces as surfactant and commenting on its altered homeostasis in the pathogenesis of the new disease, named PAP.[17] Although the "surfactant hypothesis" did not receive immediate acceptance from the international community over the next 15 years, several studies applying different methodologies, including physiology, electron microscopy, and immunohistochemistry, confirmed the surfactant nature of the lipoproteinaceous material occupying alveolar airspaces.[10,18–21]

Surfactant is a multilaminar thin-layer fluid film that covers internally the alveolar walls, the air–liquid interface, which, withstanding the Laplace law, acts by reducing surface tension; therefore, avoiding their collapse at the end of expiration. Surfactant's constituents are also an important part of innate immunity. Surfactant structurally consists of 80% polar phospholipids, 10% neutral lipids (mostly free cholesterol), and 10% surfactant proteins (SP B and C active on surface tension, and A and D deputy in host defense). Type II alveolar epithelial cells have the exclusive concern of surfactant production and secretion into the alveolar space while its clearance depends in part from its recycling or catabolism in type II alveolar epithelial cells while another approximately 50% proportion of surfactant is removed by the alveolar macrophages through uptake and catabolism previous the efflux of cholesterol and its transport by blood flow to the liver (**Fig. 2**).[8]

The story regarding the role of GM-CSF in the maturation of alveolar macrophages and surfactant homeostasis begins in 1994 when two independent groups of investigators reported their serendipitous observations on GM-CSF knockout mice.[3,4] In April 1994, Dranoff et al report on their efforts aiming to investigate the in vivo role of murine GM-CSF through the development of a mouse GM-CSF knockout model. The authors registered unimpaired haematopoiesis in homozygous mutant animals but unexpectedly developed the experimental model of the human disease PAP.[3] Two months later, in June 1994, Stanley et al, reporting on their findings in a similar model of mice homozygous for a disrupted GM-CSF gene (Csf−/− mice), made the same observation of the development of PAP in knockout animals,

discovering also in some mice lung infections. This observation implicated a further role of GM-CSF in the completion of innate immunity mechanisms and possibly on alveolar macrophages maturation and their ability to handle local microbials, and in some way describes the full-blown human PAP.[4]

GM-CSF, a haemopoietic 23 kDa glycoprotein cytokine, is mainly produced in the lungs by type II epithelial cells and binds to alveolar macrophages through GM-CSF receptor α and β subunits. GM-CSF binding on alveolar macrophages causes activation of tyrosine-protein kinase JAK2[22–24] and initiation of signaling via multiple pathways, including activation of signal transducer and activator of transcription 5 (STAT5),[25] transcription factor PU.1,[26] peroxisome proliferator-activated receptor-γ (PPARG), implicated in macrophage cholesterol transport and efflux,[27] and others. The above chain of events through further pathways enables alveolar macrophages to perform numerous functions, including cholesterol export, surfactant clearance, and host defense.[8,28,29] GM-CSF activation of transcription factor PPARG and its target ATP-binding cassette subfamily G member 1 (ABCG1), encoding ABCG1, a transmembrane lipid transporter protein important in cholesterol efflux from macrophages, is crucial for the differentiation of alveolar macrophages.[8,30–35] Human studies showed similar results, indicating that in both humans and the murine model of PAP, the GM-CSF–GM-CSFR α and β chains–PU.1–PPARG–ABCG1 axis controls surfactant homeostasis through the regulation of cholesterol efflux from the alveolar macrophages. Therefore, the accumulation of intraalveolar surfactant appears to be a secondary consequence of reduced surfactant uptake by foamy alveolar macrophages engorged with cholesterol. More precisely, in the alveoli, large quantitative changes in lipids related to surfactant, including free cholesterol and cholesteryl ester, are noted, but only moderate changes in lipids derived from cellular debris. Large increases in ceramide and other sphingolipids contribute to a pro-apoptotic alveolar environment in PAP (**Fig. 2**).[8,21]

Anti-GM-CSF Blocking Autoantibodies

In 1999, Tanaka et al from the group of Koh Nakata first reported on the expression of binding factor(s) neutralizing GM-CSF in the lungs of patients with idiopathic-PAP.[5] Soon after, investigators from the same group first discovered autoimmune mechanisms in the pathogenesis of idiopathic-PAP and specifically the identification and presence in high titers of Immunoglobulin G isotype neutralizing autoantibodies against GM-CSF. The above seminal study added to the pathogenetic mechanism of PAP by transitioning idiopathic-PAP in its autoimmune era, autoimmune-PAP.[6] Anti-GM-CSF blocking autoantibodies are composed of a polyclonal population of antibodies of immunoglobulin-G class (mainly 1 and 2 subclasses) targeting several epitopes of the GM-CSF molecule with high specificity and high binding affinity. In this situation, the balance between GM-CSF and anti-GM-CSF antibodies in the alveoli shifts toward the antibodies, leading to the disruption of GM-CSF–GM-CSFR α and β chains–PU.1–PPARG–ABCG1 axis that controls surfactant homeostasis through the regulation of cholesterol efflux from the alveolar macrophages; cholesterol-engorged macrophages are unable to uptake and handle surfactant. The presence of anti-GM-CSF blocking autoantibodies in serum in high titers regards only aPAP and none of the other forms included in PAP, not either other lung disorders or healthy people.[8,36] However, autoantibody serum concentrations appear not to correlate with disease severity in aPAP,[37] although in our experience, patients with very high titers are more difficult to treat with iGM-CSF (slow and delayed response; personal observation, unpublished data). A critical threshold in serum titer is necessary for the development of disease[8,36] as well as for the induction of PAP disease by passive transfer in nonhuman primates.[38] Anti-GM-CSF autoantibody diagnostic testing is provided in PAP expertise centers around the world, the United States, Europe, China, Australia, and Japan, but differences in methodology, costs, and time to attain results require methodological uniformity.

Diagnostic Criteria

Diagnosis of aPAP may be quite challenging.[36] The rarity of the disease, and therefore, the lack of awareness in the general population and expertise in medical caregivers, and the nonspecificity of signs and symptoms, may lead to delays in diagnosis ranging from months to years since the development of first symptoms.[2,7,14,36,39,40] Several patients are initially managed for pneumonia based mainly on the radiologic findings of pulmonary infiltrates before failure of antimicrobials to ameliorate the patient, and persistence/progression of clinical and radiologic manifestations lead to a broader work-up in a setting where PAP may be suspected.[41] In the majority of cases, the presence of ground glass opacities with geographical distribution and superimposed septal thickening (“crazy-paving pattern”) on HRCT prompts consideration of PAP diagnosis in a patient with a compatible clinical history (first criterion; **Fig. 3A–D**). Follows the performance of bronchoscopy, where bronchoalveolar lavage further supports the diagnosis in more than 90% of patients with findings of opaque, milky appearance fluid macroscopically and cellular debris, large foamy macrophages (PAS-positive, oil red O-positive) with intracytoplasmic lipid droplets, and diffuse, extracellular, amorphous PAS-positive staining material on light microscopy (second criterion; **Fig. 4A, B**). The confirmation of autoimmune PAP entails and prerequisites the presence of the third criterion, that of markedly increased titer of anti-GMCSF antibodies in serum.[8,41–44] Titers higher than approximately 7 to 10 μg/mL are only encountered in aPAP, and therefore, are considered mandatory and pathognomonic for the diagnosis of the disease (**Fig. 5**).[41] As a result, the combination of the highly sensitive and specific increased titer of anti-GM-CSF antibodies with any of the two or both radiologic and BAL cytology supporting criteria sets with safety establishes the diagnosis of autoimmune PAP. Lung biopsy was widely performed until 20 years ago.[8,41,42] Nowadays, lung biopsy is still used for the diagnosis of PAP, although it is not necessary in every patient.[45] It might be useful in atypical cases where other entities may also co-exist (e.g., fibrosis, hypersensitivity pneumonitis).[46] The histopathologic characteristics of any form of PAP regard alveoli filled with amorphous granular eosinophilic material, peribronchial lymphocytic infiltrations, and preservation of the parenchymal architecture with no major inflammatory response. Abundant intraalveolar material that stains with periodic acid Schiff, foamy macrophages, and

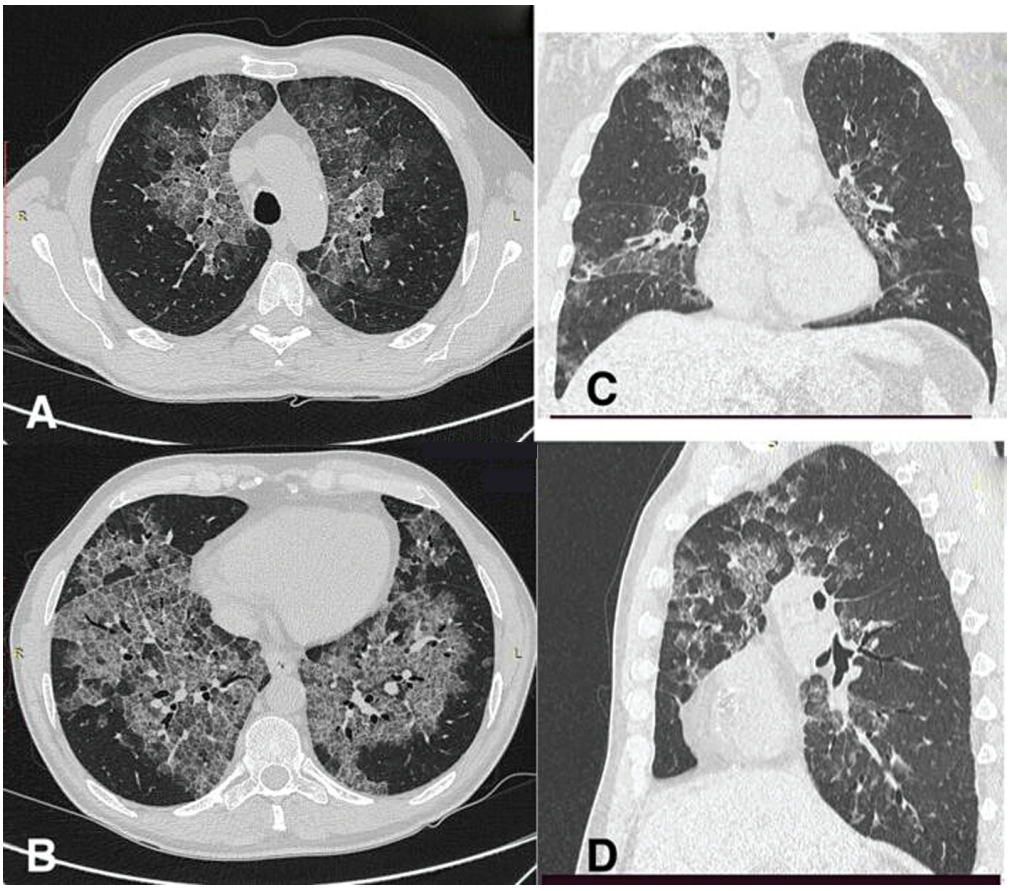

Fig. 3 (**A–D**) Typical crazy paving appearance in both lungs in all views.

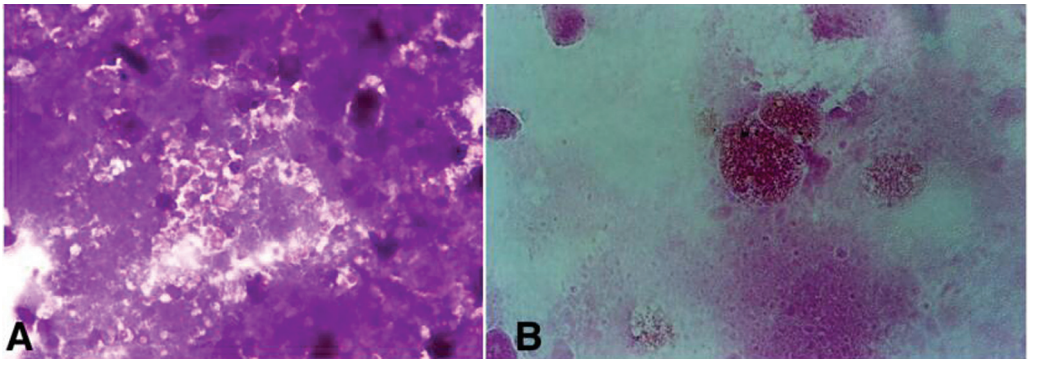

Fig. 4 Cytospins from a patient with aPAP. (**A, B**) Showing cellular debris, large foamy macrophages (PAS-positive, oil red O-positive) with intracytoplasmic lipid droplets and diffuse, extracellular, amorphous PAS-positive staining material on light microscopy.

cholesterol crystals are also present.[19,47–49] Due to the patchy distribution of the disease, lung biopsy (surgical, transbronchial, transbronchial cryobiopsy) may fail to disclose diagnostic PAP findings in around one third of patients and may be associated with morbidity and mortality.[8,50] In any case, it does not identify the autoimmune nature of aPAP, and therefore, should not be considered anymore among the cardinal principles of diagnosis. Recently published ERS guidelines for the diagnosis and management of PAP provide evidence for a strong recommendation for the use of BAL and anti-GMCSF antibodies for the diagnosis of aPAP and a conditional recommendation against the use of lung biopsy for any form of PAP based on the known risk of side-effects and the perceived low benefit of a clear diagnosis from such an invasive procedure.[45] Of note, aPAP may develop in the context of conditions that are traditionally associated with sPAP such significant occupational and environmental exposures and/or hematologic malignancies and immunodeficiency syndromes; as a result, the detection of high titers of anti-GM-CSF antibodies should never stand alone and is advised to be accompanied and supported by a thorough medical examination and work-up as well as a detailed investigation regarding potential toxic exposures.[51–53] Finally, due to the high risk of common and opportunistic

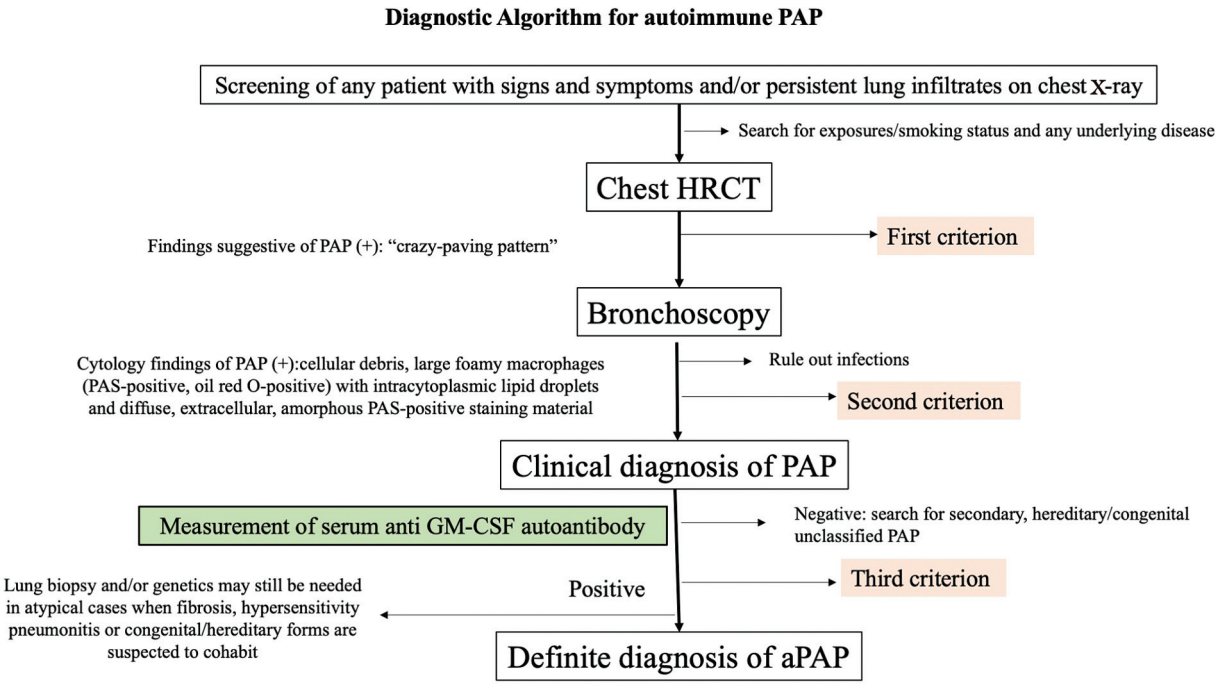

Fig. 5 Diagnostic algorithm of aPAP. The combination of the highly sensitive and specific increased titer of anti-GM-CSF antibodies with any of the two or both radiologic and BAL cytology supporting criteria sets with safety establishes the diagnosis of autoimmune PAP. Lung biopsy is still used for the diagnosis of PAP, although it is not necessary in every patient. It might be useful in atypical cases where other entities may also co-exist (e.g., fibrosis, hypersensitivity pneumonitis).

infections even at the onset of the disease, any diagnostic specimen (BAL, tissue, blood) has to be thoroughly examined to exclude the presence of common and opportunistic pathogens.[54,55] Genetic determinants of aPAP risk do exist, and are mostly related to variants in the major histocompatibility complex region, such as the rs138024423 at 6p21 in patients of Japanese ancestry. These markers are as yet studied only in the context of research, and therefore, are not routinely applied in everyday clinical practice for diagnosis.[56] Genetic testing to investigate the potential of hereditary (CSF2RA, CSF2RB) PAP in the presence of autoimmune PAP is not relevant; however, in cases of very young adults or adolescents with aPAP, it may be justified, especially until the documentation of the autoimmune nature of the disease is secured, due to the fact that aPAP is ultra-rare in this age frame.[57,58] For the rest of adult patients, genetic testing may be performed in case the documentation of aPAP, which is the most frequent form of the disease, fails.[59,60]

Infections

Since the first description of PAP and thereafter in aPAP, pulmonary and systemic infections, especially from uncommon pathogens, constitute a common, sometimes difficult to recognize, complication of the disease, which can be the presenting manifestation at onset and account for a substantial proportion, 18 to 20%, of the attributable mortality.[1,2,7,61,62] The mechanisms underlying this predisposition in patients with primary aPAP relate primarily to the presence of GM-CSF autoantibodies and their disrupting signaling toward the terminal differentiation of alveolar macrophages and their acquisition of normal innate immune functions and ability to handle microbials. The nonactivation of transcription factor PU.1 impairs not only their surfactant clearance ability but also immune functions such as adhesion, pathogen recognition, chemokine secretion and microbial phagocytosis, and others.[8,36] In a similar manner, antimicrobial neutrophil functions are also altered by the autoantibodies related disruption of GM-CSF signaling and present decreased phagocytic and bactericidal capacities. Indeed, the basal functional capacity of circulating neutrophils, including phagocytosis, cellular adhesion, reactive oxygen species production, and bactericidal activity, is impaired.[63] Several microbial pathogens have been involved in lung and systemic infections in aPAP patients, such as bacteria (Nocardia spp., Streptococcus pneumoniae, Legionella pneumophila),[14,64–71] mycobacteria (Mycobacterium tuberculosis, Mycobacterium avium complex, Mycobacterium kansasii),[14,64,65,72–76] fungi (Aspergillus spp., Cryptococcus spp., Histoplasma capsulatum),[14,64,65,77–80] Pneumocystis Jirovecii spp.,[14,64,65,81,82] and viruses (Epstein–Barr virus, cytomegalovirus, human parainfluenza virus).[14,64,65,83–85]

The Role of Imaging

Chest X-ray is often inconclusive, showing diffuse ill-defined opacities or consolidations due to alveolar filling, with a generally symmetrical, perihilar or basal distribution (batwing or butterfly pattern), similar to pulmonary edema but without cardiac enlargement, vascular congestion or pleural effusion (**Fig. 6A**).[86] The lung apices are usually spared, but the distribution is variable and can also be asymmetrical, unilateral, or lobar. More rarely, chest X-ray demonstrates reticulations or reticolonodular opacities with

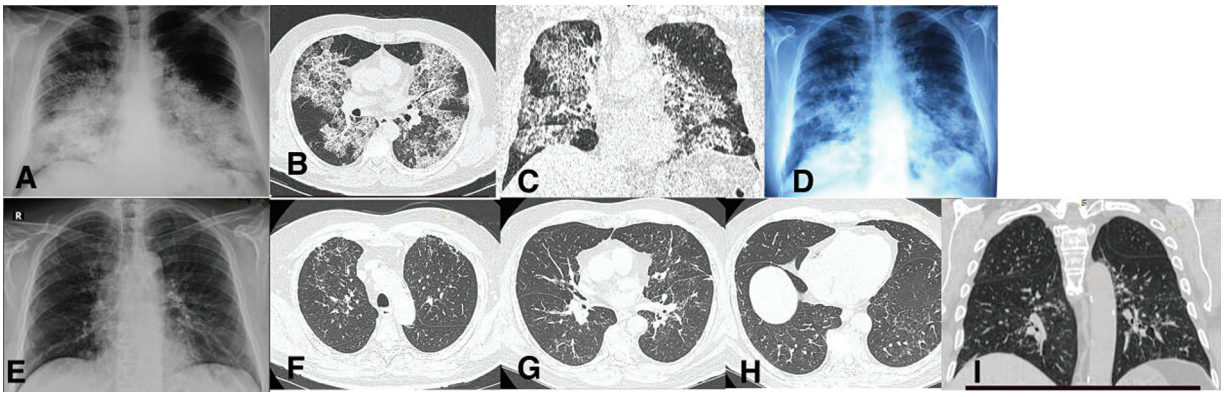

Fig. 6 It regards a 65-year-old male heavy smoker with aPAP. (**A**) Chest X-ray after a rather unsuccessful WLL showing air space consolidations, bilateral, symmetrical, basal and perihilar, with relative sparing of the upper lobes. (**B, C**) Typical crazy paving pattern in sagittal and coronal views. (**D**) Chest X-ray the first few years after the initiation of inhaled GM-CSF 250 μg 4 days on 4 days off, showing a mild reduction of the pulmonary opacities, with similar distribution, slight improvement, but very slow. A daily administration treatment schedule was adopted to attain complete remission and a new regimen. (**E**) Chest X-ray 12 years after the initiation of inhaled GM-CSF at the de-escalation time point 2 days on 4 days off, showing almost complete resolution of the opacities with reticular opacities visible at the basis, especially on the left side. To better clarify interstitial abnormalities, an HRCT scan was performed, showing in (**F–H**) sagittal views and I coronal view, reticular opacities, prevalent in the middle lung zone, without peripheral or central predominance. Findings of fibrosis are minimal, and particularly, honeycombing is absent.

ill-defined nodules. A pneumothorax can be seen due to rupture of subpleural bullae or cysts. Enlarged lymph nodes cannot be seen on a chest X-ray. Localized consolidations, masses, or cavitations can be related to superimposed infections, especially due to Nocardia species, Mycobacterium tuberculosis, atypical mycobacteria, or fungi.

HRCT evaluation is more important and useful than the simple chest X-ray, as it is usually happens in diffuse lung pathology. The main findings[87] are: ground glass opacities with geographic distribution and subpleural sparing in aPAP (**Fig. 3A–D**), more diffuse in sPAP, the so-called crazy paving pattern (75% of the autoimmune cases, 25% of secondary PAP). Crazy paving consists of geographic ground glass with superimposed interlobular and intralobular septa thickening, without fibrotic distortion (**Figs. 3A–D** and **6B, C**). The remaining parenchyma appears normal.[88] More rarely, CT demonstrates consolidations with air bronchograms. Mediastinal lymph node enlargement is generally limited to a few lymph nodes, slightly enlarged.

The clinical course is indolent, subacute, or chronic, and the diagnosis is often delayed even for years, with persistent findings or progressive evolution, with or without superinfections, and in rare cases, spontaneous remission (**Fig. 7A, B**). PAP is one of the few conditions producing extensive alveolar opacities without significant symptoms. In secondary PAP, HRCT can show the crazy paving appearance, but the findings can be less typical, for example, with basal or diffuse ground glass or peripheral distribution.[89] The extent of the opacities broadly correlates with functional impairment.[36] Radiological scores of severity based on HRCT, using deep learning tools, have recently been proposed in the literature, showing a good correlation with clinical symptoms and outcomes.[90,91]

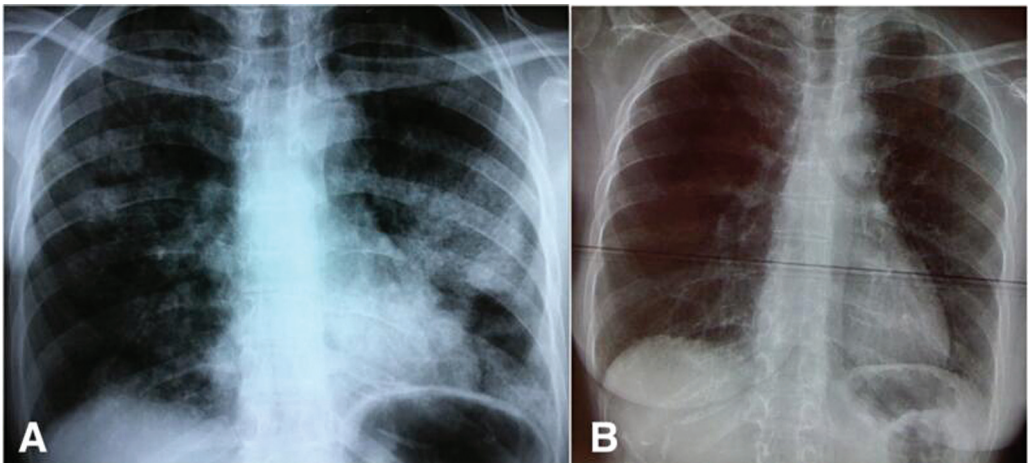

Fig. 7 Large areas of inhomogeneous consolidation are visible in the left lower lobe and lingula, with smaller ill-defined nodules scattered in the right lung. An open lung biopsy performed in another hospital diagnosed PAP. Auto-antibodies against GM-CSF were compatible with aPAP. Nineteen years later, chest X-ray shows almost complete resolution of bilateral pulmonary opacities with persistence only of limited reticulations in the right lower lobe. No treatment of any option was ever adopted.

After whole lung lavage (WLL) and/or medical therapy, HRCT is routinely used in the follow-up, and generally shows remission or improvement of the parenchymal opacities (in more than 80% of the cases), although septal thickening may persist (**Fig. 6E–I**). In untreated cases, evolution toward fibrosis rarely occurs, with reticulations, traction bronchiectasis (20% of the cases), cystic spaces (20%, which can also be smoking related), and honeycombing (5%), in areas of previous crazy paving.[92,93] Fibrotic evolution is more common in neonatal disease than in adults. In silico-proteinosis, the classic crazy paving pattern is not found, while HRCT shows dependent and posterior areas of consolidation, centrilobular nodules, punctate calcifications, and calcified lymph nodes.

In summary, the take-home message for radiologists is that PAP must be carefully considered in patients with subacute or chronic respiratory symptoms associated with a geographic ground glass-crazy paving pattern, but the differential diagnosis is broad.[45] In fact, every time a radiologist comes across a crazy paving pattern, the problem of differential diagnosis arises, because this pattern, once considered pathognomonic of PAP, has also been described in other entities such cardiogenic edema, acute respiratory distress syndrome, diffuse alveolar hemorrhage, infections (Mycoplasma pneumonia, Pneumocystis Jirovecii pneumonia, tuberculosis, COVID 19, cryptococcosis, adenocarcinoma, exogenous lipoid pneumonia, chronic eosinophilic pneumonia or, more rarely, sarcoidosis, nonspecific interstitial pneumonia, organizing pneumonia, drug induced toxicity, radiation pneumonitis, pulmonary veno-occlusive disease).[94] In this regard, the clinical information is paramount, and in particular, it is important to know if the clinical presentation is acute or subacute-chronic.

Physiology

Pulmonary function tests are typically normal in many asymptomatic patients with aPAP, limiting their value for diagnosis and prognosis.[36] In patients with mild disease, lung volume may remain normal, but as the disease advances, a restrictive pattern with reduced lung volumes can develop, according to disease severity.[36,95] The diffusing capacity for carbon monoxide (DLCO) is significantly reduced, out of proportion to the relatively mild decrease in vital capacity, and this reduction in DLCO correlates closely with the disease severity.[2,14,36] Although peripheral oxygen saturation is often normal at rest, a 6-minute walk test (6MWT) can detect exercise-induced desaturation, but the accuracy of this test is limited by differences in patient effort and performance, and it may not show desaturation in patients with mild disease.[36] Arterial blood gas analysis reveals decreased partial pressure of oxygen, increased alveolar-arterial oxygen gradient, and elevated shunt fraction, while partial pressure of CO_2 generally remains normal apart from severe respiratory failure.[36,96] The extent and severity of spirometric impairment and pulmonary gas exchange correlate with the typical patchy or geographic areas of ground glass opacity that are accompanied by interlobular septal thickening (crazy paving) that is observed on HRCT.[2,36] Effective therapies, like iGM-CSF, WLL, or spontaneous remissions, can lead to partial or even complete reversal of these abnormalities.[97–102]

Clinical Presentation

Most patients with aPAP experience progressive dyspnea of gradual onset, initially on exertion, that progresses to dyspnea at rest over a period of months to years.[36,103] In some cases, dyspnea is accompanied by a cough that is usually nonproductive, but in some cases, scanty, milky, or whitish sputum is described.[36,103–105] These symptoms are often mild and can be easily overlooked, leading some patients to seek medical advice after developing a secondary infection that can cause more pronounced symptoms and high fever. Other symptoms that are reported are low-grade fever, weight loss, chest congestion, and chest pain.[36,40,103] In general, physical examination is unremarkable or reveals minor and nonspecific findings such as inspiratory crackles on auscultation, while digital clubbing has been reported, although uncommon.[2,36,105] In severe cases, peripheral cyanosis can be observed.[36,105]

Biomarkers

So far, as already discussed, anti-GMCSF antibodies are the sole disease-specific biomarker in aPAP.[42,106] Unfortunately, anti-GMCSF antibody levels have not been found to correlate with the disease severity or prognosis of aPAP.[37] Furthermore, GM-CSF serum levels by themselves are increased in patients with ultra-rare hereditary PAP due to decreased receptor-mediated clearance, and in combination with the negative anti-GMCSF antibodies, both have diagnostic utility as biomarkers.[107] In everyday clinical practice, one of the most widely used biomarkers both for evaluation of disease severity and response to treatment is serum lactate dehydrogenase, which is found increased in the vast majority of PAP patients, owing most probably to alveolar macrophage cellular turnover. It is thought to reflect the burden of surfactant accumulation and nicely correlates with parameters of functional impairment and response to treatment, such as the A-a-O_2 Gradient.[37] Ongoing research continues to provide evidence for a variety of predictive biomarkers related to proliferated, stimulated, or damaged epithelium (mostly alveolar epithelial type II cells), such as cytokeratin 19 fragment 21.1 (CYFRA21–1), carcinoembryonic antigen, Krebs von Lungen, surfactant protein A, and surfactant protein B, chitinase-3-like protein 1 (YKL-40) and monocyte chemotactic proteins.[108–117]

Whole Lung Lavage, the Gold Standard of Treatment

Far before major achievements in the pathogenesis of PAP, rudimentary efforts to wash out of the lungs the inappropriately flooding lipoproteinaceous material were attempted. Ramirez-Rivera et al at the Veterans' Administration Hospital in Baltimore in 1963 reported the first early-segmental-lung-washing sessions with saline and heparin, previous the placement of a plastic catheter in the left bronchus through an anesthetized site below the cricoid cartilage; after several sessions on the left lung, the right one was washed in sequence. Although bothersome, the new technique proved effective.[118] In 1965, Ramirez-Rivera et al presented an improved lung washing technique performed under local anesthesia and tracheal intubation with a double-lumen

Carlens bronchospirometry tube to sequentially wash one entire lung at a time. Lung washing was performed with the awake patient actively inhaling and exhaling fluid from one lung while breathing 100% oxygen with the other lung.[119] In December 1966, Ramirez-Rivera reported about "new techniques and observations" regarding bronchoalveolar lavage,[120,121] where the filling and emptying of the lung no longer requires the assistance of the patient. The new modified technique included general anesthesia, permitting longer sessions, larger volumes of washing saline, and greater tolerance from the patient in safety.[120]

Since then, the therapeutic WLL, technically further improved, has become widely used and universally accepted as the effective (gold-standard) therapeutic modality in PAP. Further improvements paralleled developments of the new era in (1) bronchoscopy,[122] (2) improvements in the field of anesthesia, (3) in the development and availability of the advanced option of extracorporeal membrane oxygenation, as well as (4) in the involvement of a multidisciplinary team of experts, all critical to the success of the procedure.[123] However, despite progress, no standardized protocol for WLL exists[40,124]; instead, a multitude of technical descriptions, refinements, and modifications have been described and are applied worldwide, reflecting the experience of any single center, all aiming to improve efficacy and safety.[125–130] Although WLL is a major achievement in PAP treatment and has been successfully applied in several centres of excellence worldwide, the modern era in its treatment begins with the first attempts of GM-CSF administration.

The Investigation of Innovative Treatment Approaches

The Subcutaneous Administration of GM-CSF

The discovery of the role of GM-CSF on alveolar macrophages soon led to the investigation of innovative treatment approaches, such as the subcutaneous administration of GM-CSF, successful in idiopathic-autoimmune PAP since its first administration.[2,11–13] In 2006, Venkateshiah et al from the group of Kavuru, in some way concluding the early era of subcutaneous administration of GM-CSF, reported on a prospective open-label clinical trial of daily subcutaneous GM-CSF therapy in a group of 25 adult patients with idiopathic PAP, the largest reported since those days, attaining improvement in nearly 50% of them.[131]

Inhaled GM-CSF

It was again in the animal model of the GM-CSF knockout mice that Reed et al first showed in 1999 that aerosolized GM-CSF improved PAP and that surfactant homeostasis can be influenced by local administration of GM-CSF to the respiratory tract. The above experimental evidence was the first to support and suggest the use of inhaled GM-CSF as a potential therapeutic agent for PAP in humans; the authors also delineate that the prerequisite for effectiveness is the integrity of the GM-CSF receptor as well as the entire signal transduction pathway.[132] After the report of the first case in humans of successful inhalation of GM-CSF by Wylam et al published in the form of an abstract in 2000,[133] and the three patients successfully treated by inhaled GM-CSF reported by Tazawa et al, in a study aiming to investigate its mechanism of action in the restoration of the normal function of alveolar macrophages,[134] Wylam et al, in 2006, paved the way for the future use of inhaled GM-CSF in aPAP, proving its high effectiveness in absolute safety.[135] Since then, several studies, including patients of variable severity, with different protocols of treatment, dosages and schedules of administration as well duration of the treatment period, confirmed effectiveness and safety, though with different percentages of response.[97–99,135–138]

Since the first evidence of the successful use of recombinant (rh)GM-CSF inhalation in a-PAP and till 2010,[99,133–135,139–143] the larger studies on inhaled rhGM-CSF were reporting results on a relatively short-term period of treatment, showing effectiveness in a variable proportion of patients; therefore, dividing them into responders and nonresponders. All these studies summarized so far and most of the following used off-label rhGM-CSF (sagramostim) for inhalation. Initiated in 2008 and published in 2014, a small study from Greece retrospectively examined whether long-term administration of inhaled rhGM-CSF (sagramostim) of 250 µg once a day, administered by a jet nebulizer, for 4 days on and 4 days off, for as long as necessary (the "as far as it takes" protocol) was effective in attaining remission in all patients with aPAP.[137] The authors defined remission by three criteria such as the absence of symptoms (no more breathlessness on exertion estimated by the Borg scale), oxygen desaturation less than 4% at the 6MWT, and significant radiographic improvement, or at least two of the above. Upon (partial) remission as above, the authors opted for a very slow and gradual reduction of the inhaled rhGM-CSF dose, for example, 4 days on and 5 days off, a de-escalation process permitting reduce slight the cumulative monthly dose and reevaluated the patient at 3 to 6 months. Despite dose reduction, further improvement was observed. Therefore, a further reduction of the dose administered, for example, 3 days on and 5 days off, was applied, and a reevaluation at 3 to 6 months was scheduled. Following this therapeutic strategy further dose adjustments were possible, in case of improvement, for example, 3 days on and 6 days off followed by 2 days on and 6 days off, and so on; it was a process of searching the lowest-effective dose on a patient by patient basis to attain and consolidate full remission; in case of deterioration the patient was repositioned on the last effective dose. Following this dose-adjustment protocol, years after the start of treatment, some patients attained and remained in full remission for a long period of time at the lowest effective dose. With such doses as once a week (1 day on 6 days off), twice a month (1 day on 14 days off), or even once a month, the time had come to inform shared decision-making with the patient, to withdraw inhaled rhGM-CSF treatment. This is the de-escalation treatment that is actually applied in Greece in everyday clinical practice since 2008. De-escalation of the doses after attaining remission proves not only effective to minimize disease burden but also to reduce treatment costs in a safe manner. This study showed that long-term treatment with inhaled rhGM-CSF permitted disease remission in all patients, avoiding nonresponders. However, the severity of some patients and the new knowledge of the last studies by Tazawa et al[98] (intermittent administration) and Trapnell et al[97] (an arm with daily administration), led to a slight protocol modification to start with daily administration of inhaled rhGM-CSF, proved to be the most effective, and again de-escalating upon improvements as reported, for example, 6 days

on and 1 day off, 5 days on and 2 days off, 4 days on and 3 days off and so on. This is a way of personalization of treatment in aPAP in the ideal context of precision medicine. To summarize, the "as far as it takes" approach consists of the following steps: (1) start inhaled rhGM-CSF daily, (2) de-escalate after partial remission, (3) find the lowest effective dose to sustain remission, and (4) suspend treatment after a consolidated disease free-period. In patients who have remained off-treatment and who experience deterioration, re-administer inhaled rhGM-CSF as initially; use WLL only as rescue therapy.[137] Recently, Campo et al presented the results of an Italian clinical trial, sponsored by the Italian drugs approval agency AIFA and designed in 2009 by Professor Maurizio Luisetti. This trial assessed the efficacy of iGM-CSF in aPAP patients after receiving one WLL at baseline, followed by iGM-CSF. This sequential treatment approach enabled a significant reduction in rescue WLLs due to the improvement of lung function by the administration of iGM-CSF over the study period. This, the last one, prospective, randomized, single-center phase II study, adds to the effectiveness of iGM-CSF to avoid more WLLs.[138] Overall several positive studies, "too many pole positions" but not yet enough to replace WLL as the standard of treatment in aPAP "not yet the final winner" as Bonella, Manali and Papiris state in a recent editorial linked to the Campo et al' study in the ERJ in 2024.[144] However, based on all the cumulated evidence and in particular the Japanese PAGE randomized controlled study published in 2019 by Tazawa et al, in 2024, the Japanese competent authorities approved rhGM-CSF (sagramostim) as a treatment for aPAP in Japan, ahead of the countries in the rest of the world[145]; inaugurating the new era in the treatment of aPAP. Molgramostim, another rhGM-CSF designed for inhaled treatment, was systematically assessed in the IMPALA international clinical trial with positive results published in 2020. However, the FDA required a second study, the IMPALLA II trial, which was very recently published, demonstrating that once-daily inhaled molgramostim led to a greater increase in pulmonary gas transfer than placebo in patients with aPAP, further confirming the beneficial effects of molgramostim in patients with aPAP.[146,147] Now, more than ever, the possibility of using inhaled GM-CSF as the standard of care for the treatment of autoimmune PAP and leaving WLL as a rescue option is becoming more and more concrete.[42,144] A study on inhaled Molgramostim for children with aPAP is currently set up to also bring this urgently needed treatment to children (clinicaltrials.eu).

Alternative to Inhaled rhGM-CSF Treatment

There are various other treatments that have been used for aPAP. Seven case reports, a retrospective case series that included 13 patients, and a single-arm interventional study of ten patients have described the use of the anti-CD20 antibody rituximab in individuals with aPAP.[45,58,148–156] The evidence is limited by the small number of participants and the absence of any control groups. They reported clinical improvement, such as better oxygenation, increased exercise capacity, reduced need for WLL, and/or improvement in lung function. Overall, the certainty of evidence is very low for all reported outcomes, while serious methodological concerns exist due to the small, single-arm, uncontrolled nature of these studies. Plasmapheresis has been used in patients with severe disease that was refractory to other treatments. The concept behind the use of plasmapheresis is the reduction of GM-CSF-neutralizing autoantibodies. Only a small number of case reports have been published with mixed results.[45,157–160] In one case report, the combination of iGM-CSF and plasmapheresis resulted in complete and sustained remission in a patient with severe high-flow oxygen-dependent aPAP.[160] Statins have also been used in a small number of patients with aPAP. In a prospective observational study, 40 patients with aPAP without hypercholesterolemia were treated with statins.[161] After 12 months, 26 (65%) patients showed improvement in clinical symptoms, imaging, and lung function. Given the limited data, this approach cannot be recommended at present. In a recently published case report, daratumumab, an anti-CD38 antibody, was used in a patient with refractory aPAP. One year after completing treatment with this monoclonal antibody, the patient remained in remission, showing clinical and radiological improvement, while the levels of anti-GM-CSF antibodies were reduced.[162] In end-stage and treatment-refractory aPAP, with or without pulmonary fibrosis, lung transplantation can be considered. There are some case reports that have been described; most patients showed clinical improvement after lung transplantation, including better oxygenation and improved quality of life, while recurrence of alveolar proteinosis in the transplant has been reported. The ISHLT registry showed no graft failures due to PAP relapse among 101 transplanted patients.[45,163–167] In a case series reported by Westhölter et al, PAP reoccurred in three out of four patients who received double lung transplantation for long-standing PAP (4–19 years), either progressive or complicated by pulmonary fibrosis, besides optimal treatment. Two were autoimmune, while two were considered secondary. In the literature so far, recurrence was reported in three patients with either unspecified, hereditary, or congenital disease.[168]

Challenges for the Future

The 3-year collaborative work of the Task Force of the European Respiratory Society that preceded the ERS Guidelines document for the diagnosis and management of PAP has provided the opportunity for an exhaustive, comprehensive, and systematic review of all the evidence regarding the diagnosis and management of this rare disease.[45] As a result, it became evident that although amazing progress has been made in the understanding of the pathogenesis of the disease and great achievements in its management, many challenges are still waiting to be addressed. As stated very clearly in the document, these include a variety of research needs such the establishment of criteria regarding the severity of the disease, definitions of minimum clinically important differences in current and new outcomes, definition and diagnostic criteria of fibrotic PAP, the role of opportunistic infections as an indicator of disease severity, the homogenization of WLL protocols, the personalization of treatment with GM-CSF, the role of GM-CSF in aPAP in children, the role and safety of alternative treatments, the role and outcome of lung transplantation, the development of a registry for PAP patients; last but not least the standardization and widespread availability of the anti-GM-CSF antibody measurement test that is still under development and validation.[45,169,170]

In conclusion, aPAP is the classic paradigm of a scientific disease progressing from the "bench-to-bedside," since several discoveries made in the laboratory setting have become necessary to clear its pathogenetic mechanisms, define diagnostic tools, and implement new therapeutic modalities, which established the disease as treatable and fully reversible, literally, moving patients from "hell to heaven."

Author Affiliations

1 Athens Medical School, National and Kapodistrian University of Athens, Athens, Greece

2 2nd Pulmonary Medicine Department, General University Hospital "Attikon," Medical School, National and Kapodistrian University of Athens, Athens, Greece

3 Radiologia, Villa Erbosa, Gruppo San Donato, Bologna, Italy

4 School of Medicine, University College Dublin, Dublin, Ireland

5 2nd Department of Radiology, General University Hospital "Attikon," Medical School, National and Kapodistrian University of Athens, Athens, Greece

6 7th Pulmonary Department, Athens Chest Hospital "Sotiria," Athens, Greece

7 1st Respiratory Medicine Department, National and Kapodistrian University of Athens, Medical School, Sotiria Chest Diseases Hospital, Athens, Greece

8 Department of Pediatrics, Dr. von Hauner Children's Hospital, University Hospital, Ludwig-Maximilians-Universität Munich, Munich, Germany

9 German Center for Lung Research (DZL), Comprehensive Pneumology Center Munich, Munich, Germany

Statements and Additional Information

Conflict of Interest S.A.P. and E.D.M. reports honoraria for lectures by Boehringer Ingelheim, DEMO Hellas, and Elpen Hellas, and support for traveling to participate in meetings and congresses by Boehringer Ingelheim and Elpen Hellas. They report being a member of the ERS Task Force 2024–17 "Childhood interstitial lung diseases (CHILD): definition, characterization, and long-term disease behavior into adulthood." S.P. reports an ESOR fellowship grant. M.G. declares preparation of a clinical trial in children with aPAP to the institution with SAVARA Inc.

References

1 Rosen SH, Castleman B, Liebow AA. Pulmonary alveolar proteinosis. N Engl J Med 1958;258(23):1123–1142

2 Seymour JF, Presneill JJ. Pulmonary alveolar proteinosis: progress in the first 44 years. Am J Respir Crit Care Med 2002;166(02):215–235

3 Dranoff G, Crawford AD, Sadelain M, et al. Involvement of granulocyte-macrophage colony-stimulating factor in pulmonary homeostasis. Science 1994;264 (5159):713–716

4 Stanley E, Lieschke GJ, Grail D, et al. Granulocyte/macrophage colony-stimulating factor-deficient mice show no major perturbation of hematopoiesis but develop a characteristic pulmonary pathology. Proc Natl Acad Sci U S A 1994;91 (12):5592–5596

5 Tanaka N, Watanabe J, Kitamura T, Yamada Y, Kanegasaki S, Nakata K. Lungs of patients with idiopathic pulmonary alveolar proteinosis express a factor which neutralizes granulocyte-macrophage colony stimulating factor. FEBS Lett 1999;442(2–3):246–250

6 Kitamura T, Tanaka N, Watanabe J, et al. Idiopathic pulmonary alveolar proteinosis as an autoimmune disease with neutralizing antibody against granulocyte/macrophage colony-stimulating factor. J Exp Med 1999;190 (06):875–880

7 Trapnell BC, Whitsett JA, Nakata K. Pulmonary alveolar proteinosis. N Engl J Med 2003;349(26):2527–2539

8 Trapnell BC, Nakata K, Bonella F, et al. Pulmonary alveolar proteinosis. Nat Rev Dis Primers 2019;5(01):16

9 Summers JE. Pulmonary alveolar proteinosis. Review of the literature with follow-up studies and report of two new cases. Calif Med 1966;104(06):428–436

10 Davidson JM, Macleod WM. Pulmonary alveolar proteinosis. Br J Dis Chest 1969;63(01):13–28

11 Seymour JF, Dunn AR, Vincent JM, Presneill JJ, Pain MC. Efficacy of granulocyte-macrophage colony-stimulating factor in acquired alveolar proteinosis. N Engl J Med 1996;335(25):1924–1925

12 Kavuru MS, Sullivan EJ, Piccin R, Thomassen MJ, Stoller JK. Exogenous granulocyte-macrophage colony-stimulating factor administration for pulmonary alveolar proteinosis. Am J Respir Crit Care Med 2000;161(4 Pt 1):1143–1148

13 Seymour JF, Presneill JJ, Schoch OD, et al. Therapeutic efficacy of granulocyte-macrophage colony-stimulating factor in patients with idiopathic acquired alveolar proteinosis. Am J Respir Crit Care Med 2001;163(02):524–531

14 Inoue Y, Trapnell BC, Tazawa R, et al; Japanese Center of the Rare Lung Diseases Consortium. Characteristics of a large cohort of patients with autoimmune pulmonary alveolar proteinosis in Japan. Am J Respir Crit Care Med 2008;177 (07):752–762

15 McCarthy C, Avetisyan R, Carey BC, Chalk C, Trapnell BC. Prevalence and healthcare burden of pulmonary alveolar proteinosis. Orphanet J Rare Dis 2018;13(01):129

16 Kimura Y, Jo T, Hashimoto Y, et al. Epidemiology of pulmonary alveolar proteinosis: a descriptive study using a Japanese national administrative claims database. ERJ Open Res 2025;11(01):00666-2024

17 Larson RK, Gordinier R. Pulmonary alveolar proteinosis. report of six cases, review of the literature, and formulation of a new theory. Ann Intern Med 1965;62:292–312

18 McClenahan JB. Pulmonary alveolar proteinosis. Arch Intern Med 1974;133 (02):284–287

19 Costello JF, Moriarty DC, Branthwaite MA, Turner-Warwick M, Corrin B. Diagnosis and management of alveolar proteinosis: the rôle of electron microscopy. Thorax 1975;30(02):121–132

20 Singh G, Katyal SL, Bedrossian CW, Rogers RM. Pulmonary alveolar proteinosis. Staining for surfactant apoprotein in alveolar proteinosis and in conditions simulating it. Chest 1983;83(01):82–86

21 Griese M, Bonella F, Costabel U, de Blic J, Tran NB, Liebisch G. Quantitative Lipidomics in pulmonary alveolar proteinosis. Am J Respir Crit Care Med 2019;200(07):881–887

22 Watanabe S, Itoh T, Arai K. Roles of JAK kinases in human GM-CSF receptor signal transduction. J Allergy Clin Immunol 1996;98(6 Pt 2):S183–S191

23 Matsuguchi T, Zhao Y, Lilly MB, Kraft AS. The cytoplasmic domain of granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor alpha subunit is essential for both GM-CSF-mediated growth and differentiation. J Biol Chem 1997;272(28):17450–17459

24 D'Andrea RJ, Gonda TJ. A model for assembly and activation of the GM-CSF, IL-3 and IL-5 receptors: insights from activated mutants of the common beta subunit. Exp Hematol 2000;28(03):231–243

25 Lehtonen A, Matikainen S, Miettinen M, Julkunen I. Granulocyte-macrophage colony-stimulating factor (GM-CSF)-induced STAT5 activation and target-gene expression during human monocyte/macrophage differentiation. J Leukoc Biol 2002;71(03):511–519

26 Shibata Y, Berclaz PY, Chroneos ZC, Yoshida M, Whitsett JA, Trapnell BC. GM-CSF regulates alveolar macrophage differentiation and innate immunity in the lung through PU.1. Immunity 2001;15(04):557–567

27 Schneider C, Nobs SP, Kurrer M, Rehrauer H, Thiele C, Kopf M. Induction of the nuclear receptor PPAR-γ by the cytokine GM-CSF is critical for the differentiation of fetal monocytes into alveolar macrophages. Nat Immunol 2014;15 (11):1026–1037

28 Ikegami M, Ueda T, Hull W, et al. Surfactant metabolism in transgenic mice after granulocyte macrophage-colony stimulating factor ablation. Am J Physiol 1996;270(4 Pt 1):L650–L658

29 Yoshida M, Ikegami M, Reed JA, Chroneos ZC, Whitsett JA. GM-CSF regulates protein and lipid catabolism by alveolar macrophages. Am J Physiol Lung Cell Mol Physiol 2001;280(03):L379–L386

30 Nakamura K, Kennedy MA, Baldán A, Bojanic DD, Lyons K, Edwards PA. Expression and regulation of multiple murine ATP-binding cassette transporter G1 mRNAs/isoforms that stimulate cellular cholesterol efflux to high density lipoprotein. J Biol Chem 2004;279(44):45980–45989

31 Kennedy MA, Barrera GC, Nakamura K, et al. ABCG1 has a critical role in mediating cholesterol efflux to HDL and preventing cellular lipid accumulation. Cell Metab 2005;1(02):121–131

32 Out R, Hoekstra M, Hildebrand RB, et al. Macrophage ABCG1 deletion disrupts lipid homeostasis in alveolar macrophages and moderately influences

atherosclerotic lesion development in LDL receptor-deficient mice. Arterioscler Thromb Vasc Biol 2006;26(10):2295–2300

33 Baldán A, Tarr P, Vales CS, et al. Deletion of the transmembrane transporter ABCG1 results in progressive pulmonary lipidosis. J Biol Chem 2006;281 (39):29401–29410

34 de Aguiar Vallim TQ, Lee E, Merriott DJ, et al. ABCG1 regulates pulmonary surfactant metabolism in mice and men. J Lipid Res 2017;58(05):941–954

35 Sallese A, Suzuki T, McCarthy C, et al. Targeting cholesterol homeostasis in lung diseases. Sci Rep 2017;7(01):10211

36 McCarthy C, Carey BC, Trapnell BC. Autoimmune pulmonary alveolar proteinosis. Am J Respir Crit Care Med 2022;205(09):1016–1035

37 Seymour JF, Doyle IR, Nakata K, et al. Relationship of anti-GM-CSF antibody concentration, surfactant protein A and B levels, and serum LDH to pulmonary parameters and response to GM-CSF therapy in patients with idiopathic alveolar proteinosis. Thorax 2003;58(03):252–257

38 Sakagami T, Beck D, Uchida K, et al. Patient-derived granulocyte/macrophage colony-stimulating factor autoantibodies reproduce pulmonary alveolar proteinosis in nonhuman primates. Am J Respir Crit Care Med 2010;182(01):49–61

39 Campo I, Mariani F, Rodi G, et al. Assessment and management of pulmonary alveolar proteinosis in a reference center. Orphanet J Rare Dis 2013;8:40

40 Bonella F, Bauer PC, Griese M, Ohshimo S, Guzman J, Costabel U. Pulmonary alveolar proteinosis: new insights from a single-center cohort of 70 patients. Respir Med 2011;105(12):1908–1916

41 McCarthy C, Carey B, Trapnell BC. Blood testing for differential diagnosis of pulmonary alveolar proteinosis syndrome. Chest 2019;155(02):450–452

42 Lettieri S, Bonella F, Marando VA, Franciosi AN, Corsico AG, Campo I. Pathogenesis-driven treatment of primary pulmonary alveolar proteinosis. Eur Respir Rev 2024;33(173):240064

43 Kumar A, Abdelmalak B, Inoue Y, Culver DA. Pulmonary alveolar proteinosis in adults: pathophysiology and clinical approach. Lancet Respir Med 2018;6 (07):554–565

44 Costabel U, Guzman J, Bonella F, Oshimo S. Bronchoalveolar lavage in other interstitial lung diseases. Semin Respir Crit Care Med 2007;28(05):514–524

45 McCarthy C, Bonella F, O'Callaghan M, et al. European respiratory society guidelines for the diagnosis and management of pulmonary alveolar proteinosis. Eur Respir J 2024;64(05):2400725

46 Costa E Silva M, Campainha S, Souto Moura C, Marques I, Neves S. Hypersensitivity pneumonitis in a patient with pulmonary alveolar proteinosis. Pulmonology 2021;27(05):464–466

47 McElvaney OJ, Horan D, Franciosi AN, Gunaratnam C, McElvaney NG. Pulmonary alveolar proteinosis. QJM 2018;111(03):185–186

48 Ussavarungsi K, Kern RM, Roden AC, Ryu JH, Edell ES. Transbronchial cryobiopsy in diffuse parenchymal lung disease: retrospective analysis of 74 cases. Chest 2017;151(02):400–408

49 Kobe H, Hamao N, Niwa T, Ishida T. Cryobiopsy for secondary pulmonary alveolar proteinosis. Cureus 2024;16(05):e60530

50 Alfaro T, McCarthy C, Bonella F, Bendstrup E, O'Callaghan M. Summary for clinicians: ERS guidelines on pulmonary alveolar proteinosis. Breathe (Sheff) 2025;21(02):240224

51 Costabel U, Nakata K. Pulmonary alveolar proteinosis associated with dust inhalation: not secondary but autoimmune? Am J Respir Crit Care Med 2010;181(05):427–428

52 Cummings KJ, Donat WE, Ettensohn DB, Roggli VL, Ingram P, Kreiss K. Pulmonary alveolar proteinosis in workers at an indium processing facility. Am J Respir Crit Care Med 2010;181(05):458–464

53 Imura Y, Yukawa N, Handa T, et al. Two cases of autoimmune and secondary pulmonary alveolar proteinosis during immunosuppressive therapy in dermatomyositis with interstitial lung disease. Mod Rheumatol 2018;28(04):724–729

54 Mabo A, Borie R, Wemeau-Stervinou L, et al; OrphaLung Network. Infections in autoimmune pulmonary alveolar proteinosis: a large retrospective cohort. Thorax 2023;79(01):68–74

55 Kerdiles T, Lejeune S, Portais A, et al; GM-Noc Study Group. Nocardia infection in patients with anti-granulocyte-macrophage colony-stimulating factor autoantibodies: a prospective multicenter French study. Open Forum Infect Dis 2024;11 (06):ofae269

56 Sakaue S, Yamaguchi E, Inoue Y, et al. Genetic determinants of risk in autoimmune pulmonary alveolar proteinosis. Nat Commun 2021;12(01):1032

57 Hadchouel A, Drummond D, Abou Taam R, Lebourgeois M, Delacourt C, de Blic J. Alveolar proteinosis of genetic origins. Eur Respir Rev 2020;29(158):190187

58 Griese M, Panagiotou P, Manali ED, et al. Autoimmune pulmonary alveolar proteinosis in children. ERJ Open Res 2022;8(01):00701-2021

59 Papiris SA, Louvrier C, Fabre A, et al. CSF2RB mutation-related hereditary pulmonary alveolar proteinosis: the "long and winding road" into adulthood. ERJ Open Res 2023;9(06):00703-2023

60 Ito M, Nakagome K, Ohta H, et al. Elderly-onset hereditary pulmonary alveolar proteinosis and its cytokine profile. BMC Pulm Med 2017;17(01):40

61 Seymour JF, Presneill JJ. Pulmonary alveolar proteinosis. What is the role of GM-CSF in disease pathogenesis and treatment? Treat Respir Med 2004;3 (04):229–234

62 Gonzalez-Juarrero M, Hattle JM, Izzo A, et al. Disruption of granulocyte macrophage-colony stimulating factor production in the lungs severely affects the ability of mice to control Mycobacterium tuberculosis infection. J Leukoc Biol 2005;77(06):914–922

63 Uchida K, Beck DC, Yamamoto T, et al. GM-CSF autoantibodies and neutrophil dysfunction in pulmonary alveolar proteinosis. N Engl J Med 2007;356 (06):567–579

64 Punatar AD, Kusne S, Blair JE, Seville MT, Vikram HR. Opportunistic infections in patients with pulmonary alveolar proteinosis. J Infect 2012;65(02):173–179

65 Jones CC. Pulmonary alveolar proteinosis with unusual complicating infections; a report of two cases. Am J Med 1960;29:713–722

66 Andriole VT, Ballas M, Wilson GL. The association of nocardiosis and pulmonary alveolar proteinosis. A case study. Ann Intern Med 1964;60:266–275

67 Carlsen ET, Hill RB Jr, Rowlands DT Jr. Nocardiosis and pulmonary alveolar proteinosis. Ann Intern Med 1964;60:275–281

68 Burbank B, Morrione TG, Cutler SS. Pulmonary alveolar proteinosis and nocardiosis. Am J Med 1960;28:1002–1007

69 Clague HW, Harth M, Hellyer D, Morgan WK. Septic arthritis due to Nocardia asteroides in association with pulmonary alveolar proteinosis. J Rheumatol 1982;9(03):469–472

70 Sánchez-Cuéllar S, García-Pérez FJ, Reina MT. [Streptococcus pneumoniae infection: cause or consequence of pulmonary alveolar proteinosis?] Arch Bronconeumol 2008;44(11):645–646

71 Garmilla Ezquerra P, Gómez Roman J, Garcia de la Fuente C, Nan Nan D. [Alveolar proteinosis in an immunocompetent patient with previous Legionella and Nocardia infections]. Rev Clin Esp (Barc) 2014;214(01):e1–e3

72 Witty LA, Tapson VF, Piantadosi CA. Isolation of mycobacteria in patients with pulmonary alveolar proteinosis. Medicine (Baltimore) 1994;73(02):103–109

73 Lathan SR Jr, Williams JD Jr, McLean RL, Ramirez J. Pulmonary alveolar proteinosis. Treatment of a case complicated by tuberculosis. Chest 1971;59(04):452–454

74 Bakhos R, Gattuso P, Arcot C, Reddy VB. Pulmonary alveolar proteinosis: an unusual association with Mycobacterium avium-intracellulare infection and lymphocytic interstitial pneumonia. South Med J 1996;89(08):801–802

75 Couderc LJ, Bernaudin JF, Epardeau B, Caubarrere I. Pulmonary alveolar proteinosis and disseminated Mycobacterium avium infection. Respir Med 1996;90 (10):641–642

76 Reyes JM, Putong PB. Association of pulmonary alveolar lipoproteinosis with mycobacterial infection. Am J Clin Pathol 1980;74(04):478–485

77 Kobayashi T, Ebina M, Oshima M, et al. Case of alveolar proteinosis associated with pulmonary aspergillosis [in Japanese]. Nihon Naika Gakkai Zasshi 1999;88 (01):135–137

78 Björkholm B, Elgefors B. Cerebellar aspergilloma. Scand J Infect Dis 1986;18 (04):375–378

79 Bergman F, Linell F. Cryptococcosis as a cause of pulmonary alveolar proteinosis. Acta Pathol Microbiol Scand 1961;53:217–224

80 Hartung M, Salfelder K. Pulmonary alveolar proteinosis and histoplasmosis: report of three cases. Virchows Arch A Pathol Anat Histol 1975;368(04):281–287

81 Tran Van Nhieu J, Vojtek AM, Bernaudin JF, Escudier E, Fleury-Feith J. Pulmonary alveolar proteinosis associated with Pneumocystis carinii. Ultrastructural identification in bronchoalveolar lavage in AIDS and immunocompromised non-AIDS patients. Chest 1990;98(04):801–805

82 Kotov PV, Shidham VB. Alveolar proteinosis in a patient recovering from Pneumocystis carinii infection: a case report with a review of literature. Cytojournal 2006;3:22

83 Edwards C, Primhak R, Cohen MC. Pulmonary alveolar proteinosis associated with Epstein-Barr virus infection. Eur Respir J 2010;36(05):1214–1216

84 Ranchod M, Bissell M. Pulmonary alveolar proteinosis and cytomegalovirus infection. Arch Pathol Lab Med 1979;103(03):139–142

85 Butnor KJ, Sporn TA. Human parainfluenza virus giant cell pneumonia following cord blood transplant associated with pulmonary alveolar proteinosis. Arch Pathol Lab Med 2003;127(02):235–238

86 Lee KN, Levin DL, Webb WR, Chen D, Storto ML, Golden JA. Pulmonary alveolar proteinosis: high-resolution CT, chest radiographic, and functional correlations. Chest 1997;111(04):989–995

87 Holbert JM, Costello P, Li W, Hoffman RM, Rogers RM. CT features of pulmonary alveolar proteinosis. AJR Am J Roentgenol 2001;176(05):1287–1294

88 Marchiori E, Escuissato DL, Gasparetto TD, Considera DP, Franquet T. "Crazy-paving" patterns on high-resolution CT scans in patients with pulmonary complications after hematopoietic stem cell transplantation. Korean J Radiol 2009;10(01):21–24

89 Ishii H, Trapnell BC, Tazawa R, et al; Japanese Center of the Rare Lung Disease Consortium. Comparative study of high-resolution CT findings between autoimmune and secondary pulmonary alveolar proteinosis. Chest 2009;136 (05):1348–1355

90 Shi S, Zou R, Chen L, et al. Quantitative chest CT assessment of pulmonary alveolar proteinosis with deep learning: a real-world longitudinal study. Quant Imaging Med Surg 2022;12(12):5394–5403

91 Bai JW, Huang JN, Shi SY, et al. Updated severity and prognosis score of pulmonary alveolar proteinosis: a multi-center cohort study in China. Front Med (Lausanne) 2023;10:1058001

92 McCarthy C, Kokosi M, Bonella F. Shaping the future of an ultra-rare disease: unmet needs in the diagnosis and treatment of pulmonary alveolar proteinosis. Curr Opin Pulm Med 2019;25(05):450–458

93 Bonella F, Borie R. Pulmonary alveolar proteinosis. Clin Chest Med 2025;46 (04):633–647

94 Rossi SE, Erasmus JJ, Volpacchio M, Franquet T, Castiglioni T, McAdams HP. "Crazy-paving" pattern at thin-section CT of the lungs: radiologic-pathologic overview. Radiographics 2003;23(06):1509–1519

95 Presneill JJ, Nakata K, Inoue Y, Seymour JF. Pulmonary alveolar proteinosis. Clin Chest Med 2004;25(03):593–613, viii–viii

96 Martin RJ, Rogers RM, Myers NM. Pulmonary alveolar proteinosis: shunt fraction and lactic acid dehydrogenase concentration as aids to diagnosis. Am Rev Respir Dis 1978;117(06):1059–1062

97 Trapnell BC, Inoue Y, Bonella F, et al; IMPALA Trial Investigators. Inhaled molgramostim therapy in autoimmune pulmonary alveolar proteinosis. N Engl J Med 2020;383(17):1635–1644

98 Tazawa R, Ueda T, Abe M, et al. Inhaled GM-CSF for pulmonary alveolar proteinosis. N Engl J Med 2019;381(10):923–932

99 Tazawa R, Trapnell BC, Inoue Y, et al. Inhaled granulocyte/macrophage-colony stimulating factor as therapy for pulmonary alveolar proteinosis. Am J Respir Crit Care Med 2010;181(12):1345–1354

100 Campo I, Kadija Z, Mariani F, et al. Pulmonary alveolar proteinosis: diagnostic and therapeutic challenges. Multidiscip Respir Med 2012;7(01):4

101 Martínez-López MA, Gómez-Cerezo G, Villasante C, et al. Pulmonary alveolar proteinosis: prolonged spontaneous remission in two patients. Eur Respir J 1991;4(03):377–379

102 Papiris SA, Tsirigotis P, Kolilekas L, et al. Pulmonary alveolar proteinosis: time to shift? Expert Rev Respir Med 2015;9(03):337–349

103 Griese M. Pulmonary alveolar proteinosis: a comprehensive clinical perspective. Pediatrics 2017;140(02):e20170610

104 Goldstein LS, Kavuru MS, Curtis-McCarthy P, Christie HA, Farver C, Stoller JK. Pulmonary alveolar proteinosis: clinical features and outcomes. Chest 1998;114 (05):1357–1362

105 Shah PL, Hansell D, Lawson PR, Reid KB, Morgan C. Pulmonary alveolar proteinosis: clinical aspects and current concepts on pathogenesis. Thorax 2000;55(01):67–77

106 Uchida K, Nakata K, Carey B, et al. Standardized serum GM-CSF autoantibody testing for the routine clinical diagnosis of autoimmune pulmonary alveolar proteinosis. J Immunol Methods 2014;402(1–2):57–70

107 Suzuki T, Sakagami T, Young LR, et al. Hereditary pulmonary alveolar proteinosis: pathogenesis, presentation, diagnosis, and therapy. Am J Respir Crit Care Med 2010;182(10):1292–1304

108 Fang SC, Lu KH, Wang CY, Zhang HT, Zhang YM. Elevated tumor markers in patients with pulmonary alveolar proteinosis. Clin Chem Lab Med 2013;51 (07):1493–1498

109 Bai JW, Gu SY, Sun XL, Lu HW, Liang S, Xu JF. CYFRA21-1 is a more sensitive biomarker to assess the severity of pulmonary alveolar proteinosis. BMC Pulm Med 2022;22(01):2

110 Bonella F, Ohshimo S, Miaotian C, Griese M, Guzman J, Costabel U. Serum KL-6 is a predictor of outcome in pulmonary alveolar proteinosis. Orphanet J Rare Dis 2013;8:53

111 Lin FC, Chen YC, Chang SC. Clinical importance of bronchoalveolar lavage fluid and blood cytokines, surfactant protein D, and Kerbs von Lungren 6 antigen in idiopathic pulmonary alveolar proteinosis. Mayo Clin Proc 2008;83(12):1344–1349

112 Bonella F, Long X, Ohshimo S, et al. MUC1 gene polymorphisms are associated with serum KL-6 levels and pulmonary dysfunction in pulmonary alveolar proteinosis. Orphanet J Rare Dis 2016;11:48

113 Bonella F, Long X, He X, et al. Serum YKL-40 is a reliable biomarker for pulmonary alveolar proteinosis. Respirology 2017;22(07):1371–1378

114 Takahashi H, Sano H, Chiba H, Kuroki Y. Pulmonary surfactant proteins A and D: innate immune functions and biomarkers for lung diseases. Curr Pharm Des 2006;12(05):589–598

115 Létuvé S, Kozhich A, Arouche N, et al. YKL-40 is elevated in patients with chronic obstructive pulmonary disease and activates alveolar macrophages. J Immunol 2008;181(07):5167–5173

116 Akasaka K, Amano M, Nakamura T, et al. Cytokine profiles associated with disease severity and prognosis of autoimmune pulmonary alveolar proteinosis. Respir Investig 2024;62(04):610–616

117 Larose C, Leduc C, Chevrier M. Napsin-A immunohistochemistry in the diagnosis of pulmonary alveolar proteinosis. Arch Pathol Lab Med 2025;149(06):568–572

118 Ramirez J, Schultz RB, Dutton RE. Pulmonary alveolar proteinosis: a new technique and rationale for treatment. Arch Intern Med 1963;112:419–431

119 Ramirez J, Campbell GD. Pulmonary alveolar proteinosis. endobronchial treatment. Ann Intern Med 1965;63:429–441

120 Ramirez J. Bronchopulmonary lavage. New techniques and observations. Dis Chest 1966;50(06):581–588

121 Kylstra JA. Simplified technique of lavage of the lung. Results in dogs. Acta Physiol Pharmacol Neerl 1960;9:225–239

122 Panchabhai TS, Mehta AC. Historical perspectives of bronchoscopy. Connecting the dots. Ann Am Thorac Soc 2015;12(05):631–641

123 Sikachi R, Anders M. Whole lung lavage: considerations from the anesthesiology perspective. Curr Opin Pulm Med 2025;31(01):53–58

124 Campo I, Luisetti M, Griese M, et al; WLL International Study Group. Whole lung lavage therapy for pulmonary alveolar proteinosis: a global survey of current practices and procedures. Orphanet J Rare Dis 2016;11(01):115

125 Cheng SL, Chang HT, Lau HP, Lee LN, Yang PC. Pulmonary alveolar proteinosis: treatment by bronchofiberscopic lobar lavage. Chest 2002;122(04):1480–1485

126 Kavuru MS, Popovich M. Therapeutic whole lung lavage: a stop-gap therapy for alveolar proteinosis. Chest 2002;122(04):1123–1124

127 Beccaria M, Luisetti M, Rodi G, et al. Long-term durable benefit after whole lung lavage in pulmonary alveolar proteinosis. Eur Respir J 2004;23(04):526–531

128 Morgan C. The benefits of whole lung lavage in pulmonary alveolar proteinosis. Eur Respir J 2004;23(04):503–505

129 Bonella F, Bauer PC, Griese M, Wessendorf TE, Guzman J, Costabel U. Wash-out kinetics and efficacy of a modified lavage technique for alveolar proteinosis. Eur Respir J 2012;40(06):1468–1474

130 Grutters LA, Smith EC, Casteleijn CW, et al. Increased efficacy of whole lung lavage treatment in alveolar proteinosis using a new modified lavage technique. J Bronchology Interv Pulmonol 2021;28(03):215–220

131 Venkateshiah SB, Yan TD, Bonfield TL, et al. An open-label trial of granulocyte macrophage colony stimulating factor therapy for moderate symptomatic pulmonary alveolar proteinosis. Chest 2006;130(01):227–237

132 Reed JA, Ikegami M, Cianciolo ER, et al. Aerosolized GM-CSF ameliorates pulmonary alveolar proteinosis in GM-CSF-deficient mice. Am J Physiol 1999;276(04):L556–L563

133 Wylam METR, Katzmann JA, Clawson M, Prakash UBS, Anderson PM. Aerosolized GM-CSF improves pulmonary function in idiopathic pulmonary alveolar proteinosis. Am J Respir Crit Care Med 2000;161:A889

134 Tazawa R, Hamano E, Arai T, et al. Granulocyte-macrophage colony-stimulating factor and lung immunity in pulmonary alveolar proteinosis. Am J Respir Crit Care Med 2005;171(10):1142–1149

135 Wylam ME, Ten R, Prakash UB, Nadrous HF, Clawson ML, Anderson PM. Aerosol granulocyte-macrophage colony-stimulating factor for pulmonary alveolar proteinosis. Eur Respir J 2006;27(03):585–593

136 Tazawa R, Inoue Y, Arai T, et al. Duration of benefit in patients with autoimmune pulmonary alveolar proteinosis after inhaled granulocyte-macrophage colony-stimulating factor therapy. Chest 2014;145(04):729–737

137 Papiris SA, Tsirigotis P, Kolilekas L, et al. Long-term inhaled granulocyte macrophage-colony-stimulating factor in autoimmune pulmonary alveolar proteinosis: effectiveness, safety, and lowest effective dose. Clin Drug Investig 2014;34 (08):553–564

138 Campo I, Carey BC, Paracchini E, et al. Inhaled recombinant GM-CSF reduces the need for whole lung lavage and improves gas exchange in autoimmune pulmonary alveolar proteinosis patients. Eur Respir J 2024;63(01):2301233

139 Arai T, Hamano E, Inoue Y, et al. Serum neutralizing capacity of GM-CSF reflects disease severity in a patient with pulmonary alveolar proteinosis successfully treated with inhaled GM-CSF. Respir Med 2004;98(12):1227–1230

140 Price A, Manson D, Cutz E, Dell S. Pulmonary alveolar proteinosis associated with anti-GM-CSF antibodies in a child: successful treatment with inhaled GM-CSF. Pediatr Pulmonol 2006;41(04):367–370

141 Robinson TE, Trapnell BC, Goris ML, Quittell LM, Cornfield DN. Quantitative analysis of longitudinal response to aerosolized granulocyte-macrophage colony-stimulating factor in two adolescents with autoimmune pulmonary alveolar proteinosis. Chest 2009;135(03):842–848

142 Rodríguez Portal JA, Rodríguez Becerra E, Sánchez Garrido A. [Response to inhaled granulocyte-macrophage colony-stimulating factor in a patient with alveolar proteinosis]. Arch Bronconeumol 2009;45(03):150–152

143 Yamamoto H, Yamaguchi E, Agata H, et al. A combination therapy of whole lung lavage and GM-CSF inhalation in pulmonary alveolar proteinosis. Pediatr Pulmonol 2008;43(08):828–830

144 Bonella F, Manali ED, Papiris SA. Will inhalational GM-CSF replace whole lung lavage as a treatment for autoimmune pulmonary alveolar proteinosis? Many pole positions, not yet the final winner. Eur Respir J 2024;63(01):2301982

145 Tazawa R, Nakata K. A new era in the treatment of autoimmune pulmonary alveolar proteinosis. Respirology 2025;30(06):463–465

146 Trapnell BC, Inoue Y, Bonella F, et al; IMPALA-2 Trial Investigators. Phase 3 trial of inhaled molgramostim in autoimmune pulmonary alveolar proteinosis. N Engl J Med 2025;393(08):764–773

147 Seymour JF. GM-CSF in autoimmune pulmonary alveolar proteinosis. N Engl J Med 2025;393(08):812–816

148 Kavuru MS, Malur A, Marshall I, et al. An open-label trial of rituximab therapy in pulmonary alveolar proteinosis. Eur Respir J 2011;38(06):1361–1367

149 Soyez B, Borie R, Menard C, et al. Rituximab for auto-immune alveolar proteinosis, a real life cohort study. Respir Res 2018;19(01):74

150 Amital A, Dux S, Shitrit D, Shpilberg O, Kramer MR. Therapeutic effectiveness of rituximab in a patient with unresponsive autoimmune pulmonary alveolar proteinosis. Thorax 2010;65(11):1025–1026

151 Bird D, Evans J, Pahoff C. Rituximab rescue therapy for autoimmune pulmonary alveolar proteinosis. Respir Med Case Rep 2022;37:101637

152 Garber B, Albores J, Wang T, Neville TH. A plasmapheresis protocol for refractory pulmonary alveolar proteinosis. Lung 2015;193(02):209–211

153 Keske A, Destrampe EM, Barksdale B, Rose WN. Pulmonary alveolar proteinosis refractory to plasmapheresis and rituximab despite GM-CSF antibody reduction. Case Reports Immunol 2022;2022:2104270

154 Meybodi FA, Fard SK, Zarch MB, Babai M. Rituximab therapy in pulmonary alveolar proteinosis: a rare case report. J Clin Diagn Res 2018;12(04):OD07–OD8

155 Hunt S, Miller AL, Schissel S, Ross JJ. A crazy cause of dyspnea. N Engl J Med 2010;363(25):e38

156 Nagasawa J, Kurasawa K, Hanaoka R. Rituximab improved systemic lupus erythematosus-associated pulmonary alveolar proteinosis without decreasing anti-GM-CSF antibody levels. Lupus 2016;25(07):783–784

157 Jézéquel A, Kerjouan M, Lederlin M, et al. [Plasmapheresis failure in the treatment of auto-immune pulmonary alveolar proteinosis]. Rev Mal Respir 2017;34 (03):240–243

158 Kavuru MS, Bonfield TL, Thomassen MJ. Plasmapheresis, GM-CSF, and alveolar proteinosis. Am J Respir Crit Care Med 2003;167(07):1036, author reply 1036–1037

159 Luisetti M, Rodi G, Perotti C, et al. Plasmapheresis for treatment of pulmonary alveolar proteinosis. Eur Respir J 2009;33(05):1220–1222

160 Papiris SA, Kolilekas L, Kallieri M, et al. The therapeutic potential of inhaled-GM-CSF in severe a-PAP. Pneumon (Athens) 2020;33(02):1–2

161 Shi S, Gui X, Ding J, et al. Assessment of statin treatment for pulmonary alveolar proteinosis without hypercholesterolemia: a 12-month prospective, longitudinal, and observational study. BioMed Res Int 2022;2022:1589660

162 Strong A, Sun Y, Pilcher D, Kaplan Z, Stirling RG. The novel use of daratumumab in the treatment of refractory autoimmune pulmonary alveolar proteinosis. Respirol Case Rep 2025;13(06):e70246

163 Liang J, Chen Y, Zheng M, et al. Single lung transplantation for idiopathic pulmonary alveolar proteinosis with intraoperative veno-venous extracorporeal membrane oxygenation support. Transpl Immunol 2022;74:101627

164 Tagawa T, Yamasaki N, Tsuchiya T, et al. Living-donor lobar lung transplantation for pulmonary alveolar proteinosis in an adult: report of a case. Surg Today 2011;41(08):1142–1144

165 Murata H, Hara T, Matsumoto S, Inoue H, Yamashita H, Sumikawa K. Anesthetic management of a patient with a double inferior vena cava and pulmonary alveolar proteinosis who underwent bilateral living-donor lobar lung transplantation. J Anesth 2009;23(04):583–586

166 Parker LA, Novotny DB. Recurrent alveolar proteinosis following double lung transplantation. Chest 1997;111(05):1457–1458

167 Ono M, Saito R, Tominaga J, Okada Y, Ohkouchi S, Takemura T. Pathological features of explant lungs with fibrosis in autoimmune pulmonary alveolar proteinosis. Respirol Case Rep 2017;5(05):e00255

168 Westhölter D, Opitz M, Rawitzer J, et al. Recurrent pulmonary alveolar proteinosis after lung transplantation: a case series. Respir Med 2025;244:108167

169 Nakata K, Sugi T, Kuroda K, et al. Validation of a new serum granulocyte-macrophage colony-stimulating factor autoantibody testing kit. ERJ Open Res 2020;6(01):00259-2019

170 Carey B, Chalk C, Stock J, et al. A dried blood spot test for diagnosis of autoimmune pulmonary alveolar proteinosis. J Immunol Methods 2022;511:113366