Pulmonary Alveolar Proteinosis

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KEYWORDS

• Pulmonary alveolar proteinosis • Whole lung lavage
• Granulocyte macrophage colony stimulating factor • Pulmonary surfactant

KEY POINTS

- Pulmonary alveolar proteinosis (PAP) is a rare lung disorder characterized by the accumulation of surfactant lipids in the alveoli.
- PAP can be classified by primary, secondary, hereditary, or congenital causes.
- PAP is caused 90% of the time by auto-immune antibodies against granulocyte-macrophage colony stimulating factor.
- Although rare, it is important to distinguish patients with clinical and radiograpic criteria from other diffuse lung diseases.

INTRODUCTION

Pulmonary alveolar proteinosis (PAP) is a rare pulmonary disorder characterized by the abnormal accumulation of surfactant proteins and lipids within the alveoli, leading to impaired gas exchange and respiratory dysfunction. PAP was first described in 1958 by Rosen and colleagues[1] In their initial publication, they described 27 patients that had developed alveolar filling by PAS-positive proteinaceous material. It was not until decades later that this excess proteinaceous material was pulmonary surfactant.[2] Surfactant plays a vital role in healthy lung functioning. It decreases work of breathing by reducing surface tension and preventing atelectasis via creation of a lipid rich film in the alveoli. Additionally, it is pivotal in the defense against pulmonary pathogens.[3] In PAP, excess surfactant builds up in the alveoli due to increased production, decreased clearance by alveolar macrophages or a combination of both of these processes. This progressive deposition and filling of the alveoli, along with impaired macrophage activity leaves patients at risk of dyspnea, hypoxemia, and pulmonary infections, supporting the old adage that "too much of a good thing, is a bad thing".[1,2,4] It is generally a progressive disease; however, its prognosis and clinical course remains unpredictable and varies significantly amongst patients.

PATHOPHYSIOLOGY

To understand how PAP is categorized and classified, it is important to understand the lifecycle of pulmonary surfactant. The alveoli, the terminal entities of the respiratory tract, are made of 3 distinct cellular constituents: type I pneumocytes, type II pneumocytes, and alveolar macrophages. The main functions of the alveoli are to facilitate gas exchange and movement of water and ions out of the lung, decrease work of breathing, and serve as a protective barrier against inhaled particles and pathogens.[3,5,6] Relevant to the understanding PAP, type II pneumocytes are involved with the creation of pulmonary surfactant while alveolar macrophages help catabolize and recycle surfactant. The production and catabolism of surfactant is tightly regulated. The presence of granulocyte-macrophage colony-stimulating factor (GM-CSF)

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Abbreviations	
CLT	conventional lavage technique
CT	computed tomography
DLCO	diffusion capacity of the lungs for carbon monoxide
ETT	endotracheal tube
GM-CSF	granulocyte macrophage colony stimulating factor
HRCT	high-resolution computed tomography
IMPALA	Inhaled Molgramostim in Autoimmune Pulmonary Alveolar Proteinosis
MLT	modified lavage technique
OD	optical density
PAGE	Pulmonary Alveolar Proteinosis Granulocyte Macrophage Colony Stimulating Factor Inhalation Efficacy
PAP	pulmonary alveolar proteinosis
PPARγ	Peroxisome proliferator-activated receptor gamma
WLL	whole lung lavage

is vital in regulating this process.[7] Disruption or inhibition of GM-CSF signaling hinders surfactant clearance by alveolar macrophages, leading to a buildup of surfactant within the alveoli.[7,8]

When (and where) a disruption in the lifecycle of pulmonary surfactant exists, determines the classification of PAP: primary (which includes autoimmune and hereditary) PAP describes the process where GM-CSF signaling is disrupted; secondary PAP describes the impairment of pulmonary macrophages clearing surfactant; congenital PAP is marked by genetic mutations affecting the metabolism of pulmonary surfactant; and idiopathic PAP involving any of these pathways in the presence of disease without an underlying identifiable etiology (**Table 1**).[9] Several key studies demonstrate that autoimmune PAP is caused by antibodies against the GM-CSF molecule (anti-GM-CSF autoantibodies). First, patients that have autoimmune PAP, levels of GM-CSF autoantibodies are elevated, which is not seen in other forms of PAP.[9,10] Second, when non-human primates are injected with purified GM-CSF autoantibodies from patients with autoimmune PAP, they develop the key characteristics of PAP.[11] These studies greatly contributed to the understanding of PAP pathophysiology, establishing the abnormal mechanism in auto-immune PAP specifically and laid the groundwork for potential therapeutic options to be discussed as follows in this review. Hereditary PAP develops due to anomalies in the GM-CSF receptor. Defects in the receptor appear to have an autosomal recessive inheritance.[12,13] Mice deficient in the GM-CSF receptor can develop PAP.[14]

Secondary PAP is distinguished by disruptions in macrophage catabolism of surfactant within the alveoli, leading to its accumulation. Hematologic malignancies and related disorders represent the predominant etiologic factors underlying secondary PAP, accounting for up to 75% of cases.[15] Notable examples are multiple myeloma, acute myelogenous leukemia, acute lymphoblastic leukemia, and various lymphomas, among other hematologic pathologies.[16] Other less common causes include infectious diseases (eg, Nocardia, cytomegalovirus, and aspergillosis), toxic inhalation (eg, silica, dust and fumes), and various other systemic disorders (eg, renal tubular acidosis, severe combined immunodeficiency disease, and acquired immunodeficiency syndrome).[17–20] Congenital causes of PAP are associated with defects in surfactant production and receptors that (normally) make them susceptible to metabolism consequently leading to a decrease in catabolism and increase in collection within alveoli.[21] A variety of identifiable mutations and genes are responsible for the development of congenital PAP and have been described previously.[21]

EPIDEMIOLOGY

PAP affects adults and children of all ages, ethnicities, and geographies. Disease prevalence also appears to be independent of socioeconomic standing.[21] The true frequency of PAP remains unknown. The best estimates come from Japan and the United States, where the largest studies of the disease have been conducted and put its prevalence around 6 to 7 cases per million, although this is likely an overall underrepresentation of the disease.[22,23] The rate of congenital PAP is likely much lower with prevalence around 2 cases per million children.[23] In both the Japanese and US cohorts, primary PAP account for most cases, up to 90% or more, while secondary comprised approximately 7.5% and congenital causes accounted for less than 1%.[22,23] Smoking is considered to increase the risk of developing PAP and, although rare, silica dust is the most common occupational exposure associated with the development of PAP.[2,24]

CLINICAL PRESENTATION

The presentation of PAP varies greatly. The age of onset, clinical symptoms, severity, and evolution of disease depends entirely on the underlying cause of PAP. Additionally, even within subsets of PAP (eg, autoimmune or secondary) clinical

Table 1
Classifications and causes of pulmonary alveolar proteinosis

Type	Causes/Risk Factors[a]	Associated Mutations
Autoimmune PAP (Primary)	• Autoantibodies targeting GMCSF • Most common type	• None
Hereditary PAP (Primary)	• Genetic mutations related to GM-CSF signaling	• CSF2RA[b] • CSF2RB[b]
Secondary PAP	• Hematologic disorders (eg, myelodysplastic syndrome, leukemias, lymphomas) • Malignancy (non-hematologic) • Toxic Inhalations (for example, inorganic and organic dusts, fumes • Immunodeficiency conditions (eg, agammaglobulinemia, SCID[c]) • Infectious diseases (*Nocardia, Mycobacterium tuberculosis*)	• SLC7A7[d] • MARS[e]
Congenital PAP	• Genetic mutations causing defects in surfactant metabolism or production	• SFTPB[f] • SFTPC[f] • ABCA3[g] • others

[a] This table is not exhaustive of all causes/risk factors or mutations.
[b] GMCSF receptor alpha; beta.
[c] Severe combined immunodeficiency.
[d] Gene causing lysinurinc protein intolerance.
[e] Methionyl-rRNA synthetase.
[f] Surfactant protein B; C.
[g] ATP-binding cassette A3.

courses can differ making it a difficult disease to diagnose, treat, and triage. In one study, even amongst family members with hereditary PAP, disease severity differed despite identical mutations.[25] The most common form of PAP, autoimmune, often presents in the third to fifth decade of life. The most common symptoms at presentation are dyspnea, cough, and fatigue.[15,21,26] In one Japanese cohort, many patients presented with no symptoms, making it the second most common way to present.[22] In the largest collection of patients with secondary PAP, fever was the most common presenting symptom, along with cough and dyspnea.[27] Because of the range of presentation and non-specific presenting symptoms, the clinician needs to keep a broad differential that includes PAP in the right clinical setting.

DIAGNOSIS

Diagnosis of PAP can be challenging, owing to the wide range of presenting and clinical symptoms along with varying time course of progression of disease. Like any disease, a thorough and detailed history should be obtained. In particular, a focus on predisposing conditions, family history of lung disease or PAP and any potential exposures should be elicited. Physical examination findings are non-specific and can range from a normal pulmonary examination to various adventitious breath sounds.[21] Chest radiography is often the initial imaging modality performed in patients that have PAP and can be a useful screening tool. Although a normal chest x-ray (CXR) does not exclude the diagnosis, patients with autoimmune or secondary PAP often exhibit bilateral symmetric airspace opacities that predominantly involve the mid and lower lung zones (**Fig. 1**A). These opacities typically exhibit a "bat-wing" pattern reflecting the accumulation of proteinaceous material within the alveoli. Additionally, chest radiographs may demonstrate a sparing of the lung apices, creating a "butterfly" appearance. While chest radiography can provide valuable diagnostic information, it lacks sensitivity and specificity, necessitating further imaging evaluation for confirmation and characterization of PAP.[15] High-resolution computed tomography (HRCT) can also be helpful in the diagnosis of PAP (**Fig. 1**B). In patients with PAP, HRCT shows diffuse, bilateral ground glass opacities with subpleural sparing. When ground glass opacities are accompanied by interlobular septal thickening, a "crazy-paving" appearance can be seen which is frequently seen in autoimmune PAP.[15,21] The combination of crazy-paving appearance and subpleural sparing is less commonly seen in secondary PAP.[16] Routine laboratory testing is often normal in patients with

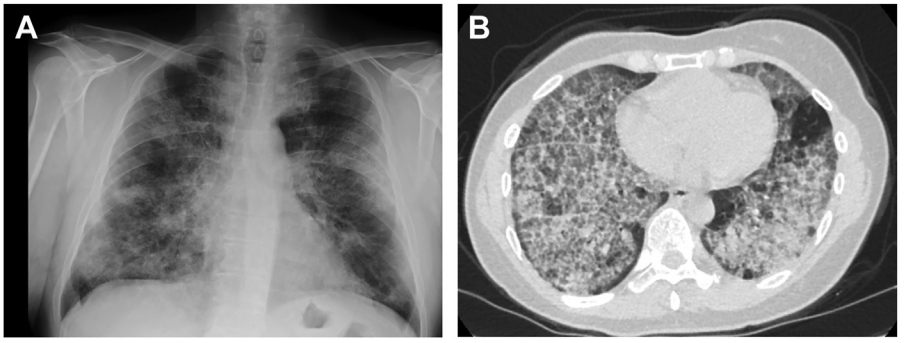

Fig. 1. Characteristic radiographic appearance of PAP (*A*) CXR (*B*) HRCT scan.

PAP, and therefore not helpful in advancing the diagnosis. Lactate dehydrogenase may be elevated; however, this finding is non-specific.[2] Routine pulmonary function testing is also not helpful in establishing a diagnosis. Abnormalities can be seen, similar to those in patients that have interstitial lung disease and include restrictive physiology along with a decrease in diffusing capacity. These abnormalities can be normalized following treatment.[28]

Bronchoscopy has become increasingly important in diagnosing PAP in recent decades, reflecting its growing frequency as a diagnostic tool for the condition.[2,29] Although not required as part of the workup, bronchoscopy can solidify the diagnosis when there is uncertainty. Bronchoalveolar lavage and transbronchial biopsies should be obtained in patients undergoing bronchoscopy for the evaluation of PAP. Bronchoalveolar lavage (BAL) often reveals a milky, turbid appearing fluid full of sediment. Specimens should be sent for cytology and microbiologic studies. Cytology shows PAS-positive material along with oil red O-stain positive macrophages (**Fig. 2**). Microbiologic testing is important in helping to identify any underlying, causative infectious etiologies. Additionally, because up to 13% of PAP cases can present with active, concomitant infection, it is important to identify any organisms that may need to be treated.[2,29] Airway inspection is often normal. In a single center cohort of 70 patients, BAL alone was diagnostic in 83%.[29] It was used alone in 49% and in combination with transbronchial biopsy in 31%. A surgical lung biopsy was needed in 20% of cases.

An algorithm for the approach to diagnosis of PAP is seen in **Fig. 3**. For patients in whom PAP is suspected, based on clinical history, imaging characteristics, and/or bronchoscopic specimens, serum GM-CSF autoantibody testing should be done. In patients with auto-immune PAP, the GM-CSF autoantibody approaches 100% sensitivity and specificity and because of these characteristics, is the first test that should be sent when suspicion is high.[30] If the GM-CSF autoantibody is negative and no underlying conditions causing secondary PAP are identified, serum GM-CSF concentration levels should be sent. These levels will be elevated in patients with hereditary PAP.[25] For those in whom GM-CSF autoantibody levels and serum GM-CSF concentration is normal and clinical suspicion remains high, genetic testing for mutations in surfactant protein production should be obtained.[21] Genetic testing for an inherent surfactant metabolism disorder is recommended for infants and young children showing signs of congenital PAP.[31]

MANAGEMENT

The mainstay of treatment for symptomatic PAP is ridding the alveolar space of accumulated proteins and lipids via whole lung lavage (WLL) restoring the function of GM-CSF.

Procedural Approach: Whole Lung Lavage

Ramirez and colleagues first described the process of WLL in the 1960s.[32] It is the treatment of choice for symptomatic PAP patients. Indications include patients with an established diagnosis of PAP and moderate to severe symptoms. Metrics may include low resting Pao_2 (<65 mm Hg), increased resting alveolar-arterial gradient (A-aO_2) (>40 mm Hg), and/or severe dyspnea at rest or with exertion. Lung function tests, as well as radiographic appearances may also play a role. Contraindications include cardiopulmonary instability and uncorrectable clotting disorders.

While modifications will be discussed further later, the basic technique of WLL consists of instillation of aliquots of warmed saline into the affected lung with repeated filling-emptying cycles until the effluent clears.

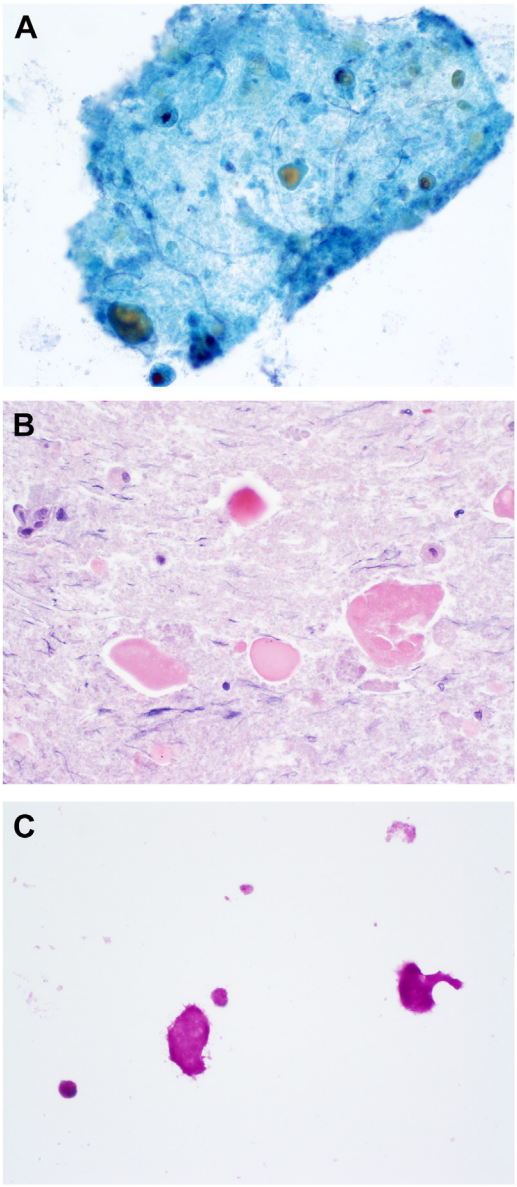

Fig. 2. Pulmonary proteinosis on cytology preparation from a representative bronchioalveolar lavage cytology specimen. (*A*) Thin-prep slide shows thick proteinaceous material with scattered alveolar macrophages (Papanicolaou stain, magnification X400). (*B*) Cell block section shows thick proteinaceous material with scattered alveolar macrophages (Hematoxylin-eosin stain, magnification X400). (*C*) Periodic acid-Schiff (PAS) stain performed on an additional Thin-Prep slide is positive in thick proteinaceous material (PAS stain, Magnification).

The procedure is done under general anesthesia with a double lumen endotracheal tube (ETT). Often, a left sided ETT is used to avoid blocking the right upper lobe (RUL) takeoff and assure an adequate seal.[33] Prior to intubation, the patient should be hyper-oxygenated with 100% oxygen to denitrogenate the alveolar gas. Total intravenous anesthesia is preferred with neuromuscular blockade to prevent coughing. Patient positioning is operator-dependent with supine and full lateral (with ventilated lung down) most often chosen. Both have perceived advantages with supine reducing the risk of ETT displacement and lateral reducing the risk of saline spillage. Trendelenberg adjustments are also sometimes used.

After single lung ventilation is initiated, warmed normal saline is instilled into the non-ventilated lung. Typically, the most affected lung is chosen for initial lavage, although some report lavaging the left first as it is smaller. The saline bags are placed 50 to 100 cm above the mid-axillary line to allow for creation of a hydrostatic pressure gradient needed for instillation.[33] The use of a rapid infuser, while it may shorten procedure time, may increase barotrauma and complications, such as hydropneumothorax and saline leaks.[34,35] Aliquot volume of instillation is operator-dependent but typically ranges from 500 to 1000 mL. Immediately after instillation, the saline is allowed to drain to gravity, although the use of suction is also described.[36] Effluent is typically milky and cloudy initially (**Fig. 4**A). Various methods of chest percussion are employed to agitate the saline within the lung, including manual percussion, oscillating vest, and automatic chest percussion. This process is repeated until the effluent fluid clears (**Fig. 4**B). Total volume instilled is variable with one study reporting a mean of 250 mL/kg.[37] Measurement of optical density (OD) can be used to assist in the assessment of effluent clearing. When an OD of 0.04 or less is used as a metric for procedure termination, the protein level is likely to be less than that in normal healthy subjects.[37] Although some prefer to lavage only a single lung in one sitting, with the contralateral lung lavaged several weeks later, the safety of sequential bilateral lung lavage was recently described.[36,38] Common complications of WLL include fever and hypoxemia, with less frequent observations of fluid leakage and pneumothorax.[38] WLL can have a durable response, with up to 60% to 70% of patients being relapse free long-term.[38–41]

Since its description, there have been several modifications to the WLL technique. Bonilla and colleagues described their modified lavage technique (MLT) in 70 procedures and compared this to 110 conventional lavage techniques (CLT).[42] In the MLT when target OD of less than 0.04 was reached, controlled manual ventilation with 300 mL of room air was applied 5 times during an infusion-recovery cycle after the first 500 mL of

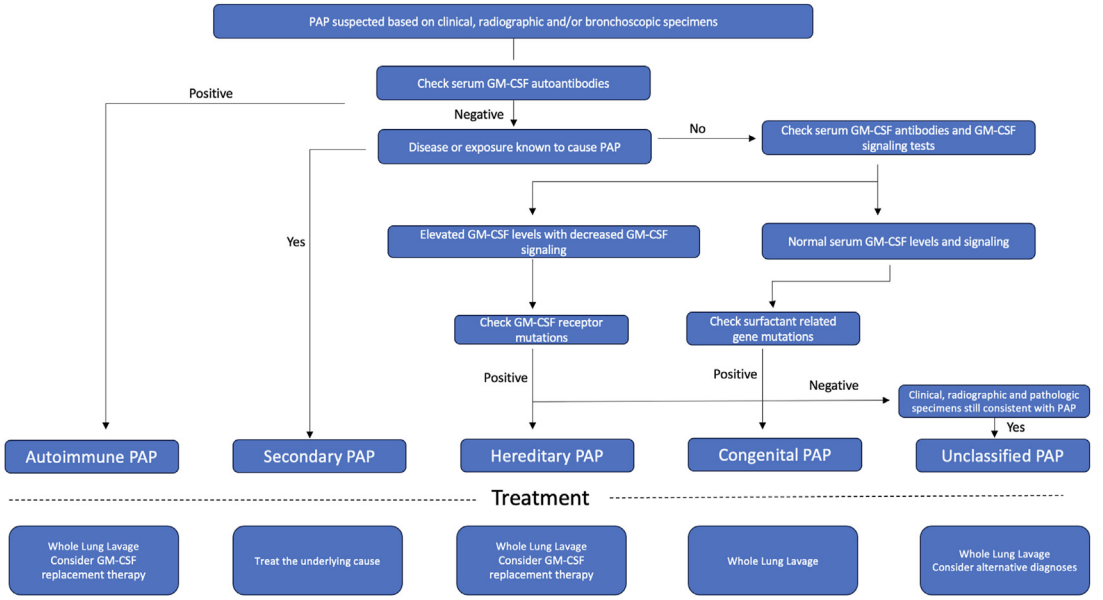

Fig. 3. An algorithm for the approach to diagnosis of pulmonary alveolar proteinosis.

saline was instilled. This was continued until an OD of less than 0.04 was reached for a second time. The MLT resulted in a higher volume of saline instilled, more protein removed, and importantly a significantly prolonged time until relapse. The CLT was further modified by Grutters and colleagues recently who described the use of manual ventilation (up to a maximum ventilation pressure of 40 cm H2O) every 3 cycles of 1000 mL instilled rather than at the conclusion of the case.[43] This modification led to less overall volume instilled and reduced procedure time. Mariani and colleagues also studied lower volume instillation in their "mini-WLL".[44] In their study, comparatively to large volume of instillation (14 – 15L), they found that instillation of 9L led to similar outcomes including A-aO_2 gradient, diffusion capacity of the lungs for carbon monoxide (DLCO) and time to repeat procedure, as well as improved vital capacity, forced vital capacity, and total lung capacity.

Medical/Pharmacologic management

Granulocyte-macrophage colony stimulating factor augmentation therapy Over the past 20 y administration of GM-CSF has emerged as a beneficial therapeutic strategy for the treatment of auto-immune PAP. Anti-GM-CSF antibodies neutralize the biologic activity of GM-CSF, impairing macrophage-mediated surfactant clearance leading to the accumulation in the alveolar space.[45] While WLL described earlier is effective in washing the accumulated proteins from the pleural space, in many patients it will reaccumulate.

Recently, 2 large placebo-controlled trials have demonstrated efficacy of inhaled GM-CSF administration.[46,47] The Pulmonary Alveolar Proteinosis GM-CSF Inhalation Efficacy (PAGE) trial was a placebo-controlled study of GM-CSF administered via inhalation daily for 7 d followed by every other week for 24 w. In contrast to this group's prior phase II study, which included severe PAP

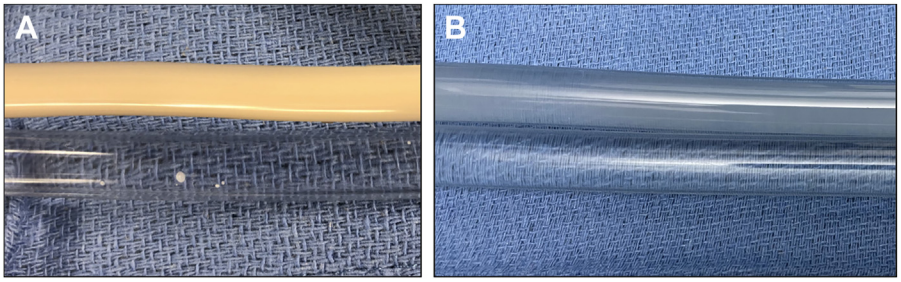

Fig. 4. (*A*) Initial milky appearing effluent (*top*) comparatively to normal saline instillation (*bottom*) (*B*) Final effluent (*top*) appears similar to instilled normal saline (*bottom*).

patients, this was performed in those with mild-moderate disease as defined by resting Pa_{O_2}.[48] There was overall improvement in A-aO_2 gradient and CT scan appearance with minimal adverse events noted. Notably, in this group there was no significant difference in clinical parameters. Additionally, there was less of an effect in smokers, postulated to be due to airway remodeling and mucus affecting the distribution of the drug.

The Inhaled Molgramostim in Autoimmune Pulmonary Alveolar Proteinosis (IMPALA) trial compared 2 routes of daily inhaled GM-CSF (continuous vs every other week) to placebo.[47] Similar to the PAGE study, a significant improvement in A-aO_2 gradient and CT scan appearance was noted particularly in the continuous group (relative to both placebo and intermittent dosing). Clinical symptoms—as measured by the St. George's Respiratory Questionnaire—was also improved. There were no notable differences in 6 min walk test and need for WLL. Notably, this study did include patients with severe symptoms at baseline. The optimal treatment duration with inhaled molgramostim is not yet defined, and an ongoing trial (IMAPALA-2) aims to define the efficacy of continuous long-term use.

It is notable that in addition to inhalational route of administration, subcutaneous injections have also been investigated. A meta-analysis, performed prior to the 2 aforementioned studies included 10 studies and a total of 115 patients receiving GM-CSF by either subcutaneous injection or inhalation.[49] Inhaled GM-CSF was associated with a higher response rate and a more marked improvement in Pa_{O_2} and A-aO_2 gradient. Additionally, there was a lower relapse rate in patients younger than 45 year old. Inhalation likely results in a higher alveolar deposition resulting in greater efficacy.

While prior studies regarding efficacy of GM-CSF compared its efficacy to WLL, a recent study demonstrated how the therapies can be complimentary.[50] In this study, 18 patients with moderate to severe PAP underwent WLL and were then randomized to inhale GM-CSF versus no therapy for 30 mo. The primary endpoint of need for "rescue" WLL was longer in those treated with GM-CSF (30 vs 18 mo), with the no therapy group having a 7-fold increase in relative risk for need for WLL. Additionally, those treated with GM-CSF after initial WLL had a greater improvement in Pa_{O_2}, A-aO_2, and DLCO.

Treatment for refractory disease and future directions The most robust evidence of treatment efficacy is with WLL and GM-CSF augmentation; however, despite these treatments, disease may have a refractory course. In severe refractory disease, lung transplantation has been pursued. This can be complicated by disease recurrence in the transplanted lung.[51] The following reviews secondary treatment options with varying level of efficacy.

Targeting granulocyte macrophage colony stimulating factor autoantibodies Several therapies aimed at removing or neutralizing autoantibodies to GM-CSF have had mixed results and are typically reserved for refractory disease. Plasmapheresis can reduce levels of GM-CSF autoantibodies, but this effect is of unclear clinical significance.[52] Rituximab, a monoclonal antibody against the B-lymphocyte antigen CD20 is used in several autoimmune diseases. Two studies evaluating the use of rituximab in PAP patients have had variable outcomes. One study of 9 patients demonstrated minimal improvement in A-aO_2, as well as lung function and CT scan appearance after 6 mo of treatment.[53] However, another of 13 patients demonstrated no improvement after 6 mo of treatment, calling into question the use of rituximab even as a second-line therapy.[54]

Targeting cholesterol Recent studies have focused on the role of impaired cholesterol clearance by alveolar macrophages in the development of autoimmune PAP (aPAP). Peroxisome proliferator-activated receptor gamma (PPARγ) expression is reduced in alveolar macrophages due to reduced GM-CSF signaling, which in turn impairs cholesterol transport.[55] Based on positive data in GM-CSF deficient mice, a first in human phase I/II trial of pioglitazone (the PioPAP trial), a PPARγ agonist is underway.[56] Statins have also demonstrated efficacy in mouse models in augmenting cholesterol efflux from alveolar macrophages, and in a case series of 2 patients with aPAP improved clinical symptoms, lung function, oxygenation and CT scans.[55] In a recent a study of 49 aPAP patients without concurrent hypercholesterolemia, 65% of those treated with statin therapy for 12 mo had a significant increase in Pa_{O_2} and DLCO with resultant decrease in disease severity score.[57] Statin therapy appears to be a promising and widely available therapeutic option for patients.

Treatment for non-autoimmune pulmonary alveolar proteinosis There is less evidence regarding the optimal treatment of secondary, hereditary, and congenital PAP. The most common cause of secondary PAP is myelodysplastic syndrome and generally improves with treatment of the underlying process as WLL has a variable effect. Hematopoietic stem cell transplantation (HSCT) has been used successfully in several

case reports as treatment but can result in treatment related side effects and has also been described as the cause of secondary PAP.[58] Recent work has demonstrated that hereditary PAP, due to mutations in the GM-CSF receptor, can possibly be treated by pulmonary macrophage transplantation.[59] If successful, this would obviate the need for preconditioning chemotherapy and immunosuppression associated with HSCT.

OUTCOMES

The prognosis and time course of PAP varies greatly. Because many patients present symptomatically, it is not clear how the disease progresses from initial onset. For those with autoimmune and hereditary PAP, the progression of disease typically manifests in 1 of 3 patterns: progressive decline, stable yet persistent disease or (much less commonly) spontaneous resolution. Spontaneous resolution has been seen in up to 5% to 7% of cases.[2,22] Prognosis is highly variable and dependent upon the underlying cause and whether a patient receives treatment or not. In one study, 10 y survival was 68% in all-cause cases of PAP.[2] Those that died did so 90% of the time from respiratory failure or infection secondary to their underlying PAP. Survival was improved in those that underwent WLL. Secondary PAP portends a much poorer overall prognosis with median survival of less than 20 mo and 2-y survival around 40%.[27,60] This difference in survival compared to auto-immune PAP is likely reflective of the underlying disease causing PAP rather than PAP itself. Congenital PAP prognosis depends entirely on the underlying mutation and can range from death in the neonatal period to survival with progressive disease into adulthood.[60]

SUMMARY

PAP is a rare lung disease with variable presentation and clinical course with evolving effective management strategies. Current therapeutic options, such as WLL and, in select cases, GM-CSF augmentation therapy, have shown promising outcomes in symptom management and disease stabilization.

CLINICS CARE POINTS

- PAP clinical syndromes can vary greatly, from asymptomatic patients to those with fulminant respiratory failure.
- Common presentations of PAP include dyspnea, cough, and hypoxemia and characteristic CT images showing a "crazy-paving" pattern.
- WLL remains the mainstay of treatment for autoimmune PAP although there has been burgeoning evidence for alternative or complimentary treatments (eg, GM-CSF replacement therapy, statins).

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DISCLOSURE

C. Morton and E. DeBiasi have no disclosures related to this article.

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