Current Pulmonology Reports (2021) 10:30–39
https://doi.org/10.1007/s13665-021-00267-1

ENVIRONMENTAL AND OCCUPATIONAL HEALTH (S CHERIAN, SECTION EDITOR)

Pulmonary Alveolar Proteinosis Secondary to Occupational Exposure

Anupam Kumar[1] · Kristin J. Cummings[2]

Accepted: 11 January 2021 / Published online: 8 February 2021

Abstract

Purpose of Review Occupational exposures are associated with a wide array of respiratory disorders that include asbestosis, coal workers' pneumoconiosis and silicosis, asthma, COPD, bronchiolitis, hypersensitivity pneumonitis, pulmonary fibrosis, sarcoidosis, and certain infections. Pulmonary alveolar proteinosis (PAP) is characterized by accumulation of lipoproteinaceous material in the alveoli and alveolar macrophages. Autoimmunity is the most common etiology for PAP and involves autoantibodies targeting GM-CSF signaling. However, certain occupational and environmental inhalational exposures have been considered causative for PAP, although this constitutes a relative minority of the patients. The review article sheds light on the current knowledge of occupational/environmental respiratory exposures that can cause PAP.

Recent Findings There is increased recognition of occupational respiratory exposures implicated in PAP. The role of silica exposure in causing PAP is well recognized and constitutes the most common etiology for occupational PAP. However, since its original description, several other agents have been identified that can trigger PAP in those exposed. Most recently, PAP has been described in a cohort of indium workers who produce indium-tin oxide (ITO), used to manufacture transparent conductive coating for flat panel displays such as liquid crystal displays (LCDs), touch screens, and solar cells. Some exposed workers with PAP have been found to have autoantibodies to GM-CSF.

Summary Besides silica, PAP is associated with a wide variety of vapors, gases, dusts, and fumes. In some patients with occupational exposure, it is possible that the offending agent may trigger autoimmunity against GM-CSF that can induce PAP. Patients with occupational PAP may have concomitant emphysema and/or pulmonary fibrosis. Depending on the degree of manifestations, treatment approach ranges from watchful monitoring to invasive modalities like whole lung lavage. Recognition of an occupational etiology for PAP has implication both for the patient and for co-workers, who may also be at risk. Physician reporting to regulatory and public health authorities can ensure that existing exposure limits and medical surveillance requirements, such as are in place for silica, are enforced and that novel or unregulated exposures are characterized.

Keywords Occupation · Pulmonary alveolar proteinosis · Whole lung lavage

Introduction

Occupational respiratory exposures contribute to a significant burden of non-malignant respiratory disorders worldwide. The spectrum of respiratory disorders includes pneumoconioses such as asbestosis, coal workers' pneumoconiosis and silicosis, asthma, COPD, bronchiolitis, hypersensitivity pneumonitis, pulmonary fibrosis, sarcoidosis, and certain infections. Pulmonary alveolar proteinosis (PAP) is a rare lung disorder marked by deposition of lipoproteinaceous material in the alveoli and alveolar macrophages due to abnormal surfactant homeostasis. While the majority of PAP has an autoimmune etiology (triggered by autoantibodies targeting GM-CSF signaling), PAP can also occur due to genetic defects or secondary to other factors, including hematological disorders, infections, and environmental and occupational exposures. This review will focus on occupational and environmental inhalational exposures that have been implicated in PAP.

This article is part of the Topical Collection on *Environmental and Occupational Health*

✉ Anupam Kumar
anupamkumarmd@gmail.com

[1] Division of Pulmonary & Critical Care Medicine, Baylor College of Medicine, 7200 Cambridge Street, Houston, TX 77030, USA

[2] Occupational Health Branch, California Department of Public Health, Richmond, CA, USA

Classification of PAP

The primary pathophysiologic defect in adult PAP is defective surfactant clearance and altered surfactant homeostasis due to impaired alveolar macrophage function. Our knowledge of the pathogenesis of PAP was significantly enhanced by the landmark discovery of the relationship between GM-CSF signaling and alveolar macrophage function [1] . GM-CSF signaling is crucial for the development of alveolar macrophage metabolic and immune functions [2]. When autoantibodies to GM-CSF deplete bioavailable GM-CSF, it results in autoimmune PAP, formerly known as "primary" or "idiopathic" PAP. This autoimmune mechanism consti tutes the most common type of PAP (> 90%) [3]. Secondary PAP occurs when the underlying problem (hematologic disorder, malignancy, environmental/occupational exposure, drugs, etc.) imparts a defect in macrophage function, either qualitatively or quantitatively [4•] . Among the various causes of secondary PAP, hematologic diseases (myeloproliferative disorders, bone marrow transplantation) tend to be the most common [4•]. Other etiologies are listed in Table 1. Rarely, genetic mutations in genes encoding the GM-CSF receptor α and β chains (*CSF2RA*, *CSF2RB*) also lead to impaired macrophage maturation (hereditary PAP) [22].

Occupational Exposure and PAP

PAP has been reported in association with inhalational exposure to a wide variety of vapors, gases, dusts, and fumes [23•] (Table 2). Recently, the American Thoracic Society (ATS) and European Respiratory Society (ERS) jointly published their official statement on the occupational burden of PAP. Their analysis yielded 1539 cases of PAP with a pooled exposure prevalence of 29% (95% CI: 21–37%) [23]. This finding indicates that a substantial fraction of PAP cases are associated with occupational exposure, although not all of these associations are known to be causative.

Though the true contribution to PAP of inhalational exposure is unknown, there is strong evidence of causation for several exposures. One of the first recognized and most commonly

Table 1 Classification of PAP based on etiology (adapted with permission from reference 2)

Type of PAP	Etiology
Autoimmune PAP (most common in adults, 90–95%)	Anti-GM-CSF antibody–mediated disruption of the GM-CSF signaling pathway
Secondary PAP (5–10% of adult PAP)	Hematopoietic disorders:
	Myelodysplasia (GATA 2 deficiency), plasma cell disorders, myeloid leukemia, lymphoma
	Immune dysregulation:
	Severe combined immunodeficiency (SCID), hypogammaglobulinemia, Fanconi anemia, Behcet's syndrome, bone marrow transplantation, lung transplantation
	Inhalation:
	See Table 2
	Drug induced or iatrogenic:
	Busulfan, chemotherapy/antineoplastic, cyclosporine, dasatinib, fentanyl, hydrofluoric acid (inhaled), imatinib, leflunomide, mycophenolate mofetil, sirolimus, silicon breast implant, status post-hematopoietic stem cell (HSCT), or bone marrow transplantation (BMT)
Congenital/hereditary PAP	Recessive mutations with disruption of GM-CSF signaling:
	CSF2RA mutations, CSF2RB mutations
	Surfactant production disorders:
	SFTPB mutations
	SFTPC mutations
	ABCA3 mutations
Unclassified PAP	Idiopathic/acquired cases and negative anti-GM-CSF antibodies, without background etiology of secondary PAP and congenital/hereditary PAP

Table 2 Examples of occupational exposures reported in association with pulmonary alveolar proteinosis

Exposure class	Exposure or occupation	References
Vapors or gases	Cleaning fluids	[5]
	Gasoline	[6]
	Hair spray	[7–9]
	Paint	[5–10]
	Pesticides	[6–12]
Inorganic dusts	Asbestos	[13]
	Cement	[6–8, 11, 13–15]
	Chalk	[10, 16]
	Coal	[10, 13]
	Silica	[5–9, 11, 14, 15, 17–19]
Organic dusts	Cotton	[20]
	Flour	[5, 6]
	Wood	[5, 9, 13]
	Wool	[10]
Metal dusts or fumes	Aluminum	[6, 14]
	Copper	[10]
	Indium	[21]
	Iron	[12, 17]
	Zirconium	[9]

implicated exposures associated with PAP is silica [24]. In contrast to chronic silicosis (characterized by silicotic nodules and, in advanced cases, progressive massive fibrosis), which evolves after exposure to relatively low concentrations of silica occurs over a longer period of time (> 10 years), silica-related PAP occurs over weeks to months of relatively high silica exposure [24, 25]. Silica-related PAP, or "acute silicoproteinosis," has a dismal prognosis, typically of 2 years [24]. However, lower levels of silica exposure over a longer period of time have also been described in association with PAP [25] .

Features of PAP were described prior to 1930 in workers exposed to silica during abrasive soap manufacture in the USA and UK, although the term PAP was not yet used [26]. Subsequently, in the early 1930s, in what was arguably the largest industrial disaster in US history, hundreds of workers died from acute silicosis during the construction of a tunnel through a high-silica rock near Gauley Bridge, WV [26]. In 1969, a report of acute silicosis in four sandblasters noted the characteristic histological findings of PAP on autopsy, making the explicit connection to silica exposure and introducing the term "acute silicoproteinosis" [27] . Other case reports followed, including recent descriptions of PAP in denim sandblasters in Turkey and artificial stone fabricators in the USA and Australia [28–30]. The recent ATS/ERS statement found that among 786 PAP cases with information on silica exposure, the pooled prevalence of exposure was 5% (95% CI: 2–8%) [23•]. Demonstration of PAP in animals exposed to silica has confirmed a causal role for this exposure [31].

More recently, indium has been implicated in the development of PAP [21, 32]. Indium is used to make indium-tin oxide (ITO), which is applied as a thin film to create a transparent conductive coating for flat panel displays such as liquid crystal displays (LCDs), touch screens, and solar cells. A case series of ten indium oxide– and ITO-exposed workers who developed lung disease included three cases of PAP [32]. The authors observed that patients with relatively short latency period were diagnosed with PAP and those with longer latency were diagnosed with interstitial lung disease (pulmonary fibrosis). Patients initially diagnosed with pulmonary fibrosis, however, also had evidence of PAP on histopathology. There was histopathologic evidence of cystic changes and emphysema in several patients as well. It is possible to infer that PAP precedes inflammatory and fibrotic responses [33, 34]. As with silica, animal models confirm that indium compound exposure causes PAP [35, 36].

Pathogenesis

It has been thought that the mechanism by which workplace inhalational exposures cause PAP involves impaired alveolar macrophage function independent of antibody production against GM-CSF (in contrast with autoimmune PAP). This inference is based on results of studies that have shown absence of antibodies to GM-CSF in patients with other forms of secondary PAP (such as hematological disorders) and animal models that have found macrophage dysfunction with exposure to silica and indium compounds [37–41]. More generally, inhalational injury might reduce the number of alveolar macrophages and/or inflict a qualitative injury to existing alveolar macrophages. There is also evidence that exposure to silica, in particular, stimulates increased surfactant production by type II cells, a protective mechanism that can become pathological over time [42]. The increased production combined with the inability of the functionally impaired alveolar macrophages to remove undegraded surfactant may lead to PAP.

Interestingly though, a subset of individuals with occupational PAP have been found to have anti-GM-CSF antibodies [32, 43, 44]. These findings blur the classification between autoimmune and occupational PAP (typically classified under secondary PAP). It also raises the possibility that occupational exposure, at least in some patients, could be a trigger for the development of autoimmune PAP, perhaps through exposure to or modification of endogenous proteins as a result of apoptosis, setting in motion an environment of self-reactivity [45]. Among patients classified as autoimmune PAP, 26% of patients in the Japanese cohort and 54% of patients in the German cohort reported occupational exposure, lending plausibility to this concept [3, 6]. Whether these patients had preexisting autoantibodies to GM-CSF or whether autoimmunity was induced by occupational exposure remains unknown. A

retrospective series also suggested poorer prognosis for those patients with occupational PAP and negative antibody to GM-CSF [14].

Clinical Features

For inhalation causing PAP, the development of PAP likely depends on the amount and duration of exposure. However, based on epidemiologic data, it most commonly presents in the 3rd to 6th decade [4•]. For all types of PAP, there is a higher than expected proportion of smokers (50–70%) and dust exposure (20–50%), although this does not establish causality [3, 4, 46]. Gender predilection is unclear. Several studies have reported higher dust exposure in males than females, which may reflect increased opportunities for exposure in men than women, rather than a difference in gender susceptibility [3, 6]. In patients with suspected occupational PAP, workup should include identifying the potential culprit agent, both to establish etiology for the patient and assess risk to co-workers. This may be a challenging process, and in situations where diagnosis is unclear, involvement of an occupational medicine specialist is important. Accurate characterization of the exposure may require obtaining safety data sheets (SDS) and other work exposure information from the patient's worksite.

In regard to symptoms, patients with PAP may present with a spectrum of clinical manifestations. Acute silicoproteinosis is rapidly progressive and often fatal, while other low-grade exposures may have a longer latency period to manifest as PAP. Up to one-third of patients with PAP can be asymptomatic [(3], [47)]. Often, the diagnosis in these patients may be incidental based on an abnormal radiograph. Studies suggest that 50–90% of patients may develop progressive dyspnea [48]. Cough may be productive. Other symptoms are non-specific and include fatigue, chest discomfort, and joint aches. Fever maybe a manifestation of PAP but should prompt further investigation due to increased risk for opportunistic infections in PAP. Unfortunately, physical exam findings are non-specific, but may include presence of digital clubbing and lung crackles [4•].

Diagnosis

Pulmonary function tests may be normal or reveal restrictive impairment depending on the degree of pulmonary parenchymal involvement [32]. PAP may be associated with reduction of diffusing capacity for carbon monoxide (DLCO), reflecting impairment of gas exchange [3, 4, 6, 32]. There are no specific biomarkers for PAP. Previously, serum levels of lactate dehydrogenase (LDH) generated interest as a diagnostic test. LDH can be elevated in up to 80% of the patients with PAP; however, it also lacks specificity [4•]. Other biomarkers such as KL-6, CYFRA 21-1, CEA, and YKL-40 have been studied; however, most are not routinely used in the USA [49–52] . In Japan, KL-6 has been used as a component of medical surveillance of indium-exposed workers.

In autoimmune PAP, antibodies to GM-CSF can be identified both in the serum and bronchoalveolar lavage (BAL) fluid [3, 53, 54]. In contrast, serum autoantibodies to GM-CSF are not elevated in patients with other forms of PAP [55, 56]. However, as mentioned before, some cases of PAP secondary to exposure with elevated antibodies to GM-CSF blur our ability to categorize these entities into two different disorders [32]. Notwithstanding these discrepancies, the nearly 100% sensitivity and specificity of serum anti-GM-CSF antibody level make it a confirmatory diagnostic test for autoimmune-mediated PAP [57]. Thus, there is a case for checking for autoantibody to GM-CSF even for those with occupational PAP, as GM-CSF is also a therapeutic target. Elevated GM-CSF cytokine levels in the blood indicate impaired clearance and usually indicate hereditary PAP due to receptor mutations, a mechanism different from exposure-related PAP [22]. In occupation-related PAP, this test is of limited value.

Radiology

Chest radiographs are non-specific in PAP. With extensive pulmonary involvement, a "bat wing" appearance with central hilar prominence may be seen. High-resolution chest CT (HRCT) scans are significantly superior in characterizing pulmonary parenchymal involvement. Diffuse ground glass opacification is almost universal [58, 59]. Interlobular septal thickening is present in up to 85% of patients [59] (Fig. 1). The pattern of septal thickening frequently identified with PAP is termed "crazy paving," which refers to the polygonal appearance of the secondary pulmonary lobules with interspersed ground glass attenuation [60]. Crazy paving occurs

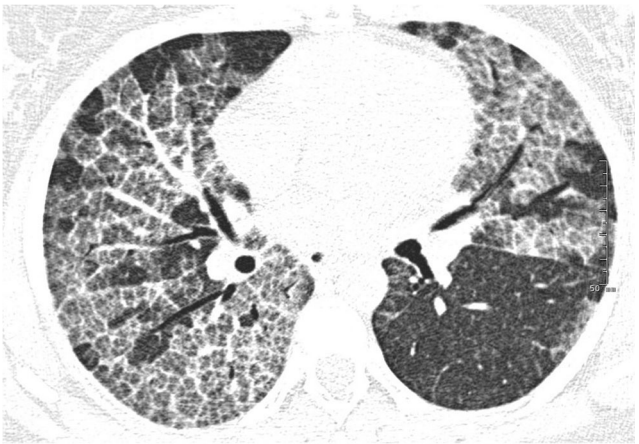

Fig. 1 High-resolution CT (HRCT) scan images of patient with PAP showing diffuse ground glass opacification and "crazy paving" pattern (Figure adapted with permission from reference number 2.)

in more than 80% of patients with PAP [58, 61]. Despite the nearly ubiquitous nature of this radiology finding, it is important to recognize that "crazy paving" is not specific for PAP, as it can be seen in other conditions, including pulmonary edema, organizing pneumonia, alveolar hemorrhage, and pneumocystis pneumonia.

HRCT scans can also differentiate some forms of secondary PAP from autoimmune PAP, as the distribution of ground glass opacities was found to be typically diffuse in PAP secondary to hematologic disorders rather than geographic as seen in autoimmune PAP [58]. One study that examined autoimmunity and occupational exposures found that all 13 patients with autoimmune PAP and an occupational exposure history had geographic distribution and 11 (85%) had crazy paving [14]. However, of 4 patients without autoantibodies to GM-CSF and an occupational exposure history, just 1 had geographic distribution and 1 had crazy paving, suggesting these findings are associated with autoimmune PAP, regardless of occupational history. About 20% of patients with PAP of any kind may develop pulmonary fibrosis, which indicates poor prognosis [62].

Confirmation of Diagnosis

The confirmation of PAP ideally requires tissue diagnosis. Particularly in occupation-related PAP without antibody to GM-CSF, tissue diagnosis could be critical. BAL may demonstrate characteristic opaque or milky-appearing fluid (Fig. 2). Under light microscopy, characteristic acellular oval bodies that are basophilic on May-Grünwald-Giemsa staining may be observed. Transbronchial biopsy increases the diagnostic yield and is a valuable tool in scenarios where diagnosis is in question [3, 6]. Less than 10–20% of patients require surgical biopsy for confirmation [3, 6, 19]. Histopathology demonstrates diffuse dense acellular eosinophilic material in the airways with minimal interstitial inflammation (Fig. 3a, b). The accumulated material is characteristically periodic acid-Schiff (PAS) positive and Oil Red O positive [4, 63]. The use of brightfield and polarized light microscopy to assess the presence, abundance, and types of dust particles can be valuable as well [64]. In lung disease related to indium, other histopathologic changes include cholesterol clefts, brown particles composed of indium, emphysema, and fibrosis [32]. Figure 4 shows a proposed algorithm for the diagnosis of suspected PAP.

Treatment

Currently, there are no standardized guidelines for the treatment of PAP. Therapeutic decisions are based on disease severity (symptoms, physiologic impairment) and type of PAP (autoimmune vs non-autoimmune). Patients with a milder degree of severity can be safely monitored for disease progression (worsening of symptoms, serial pulmonary function testing, oxygenation, and chest radiography). Patients with moderate-to-severe disease require closer monitoring and interventions.

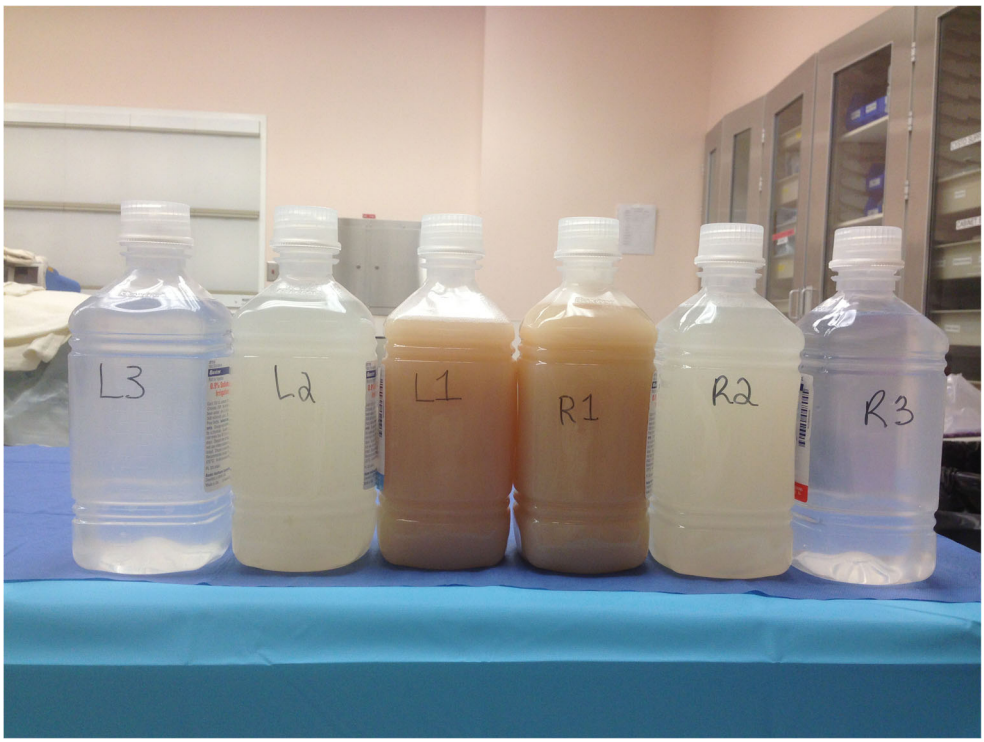

Fig. 2 Characteristic milky or opalescent appearance of fluid return from whole lung lavage in a patient with PAP (Figure adapted with permission from reference number 2.)

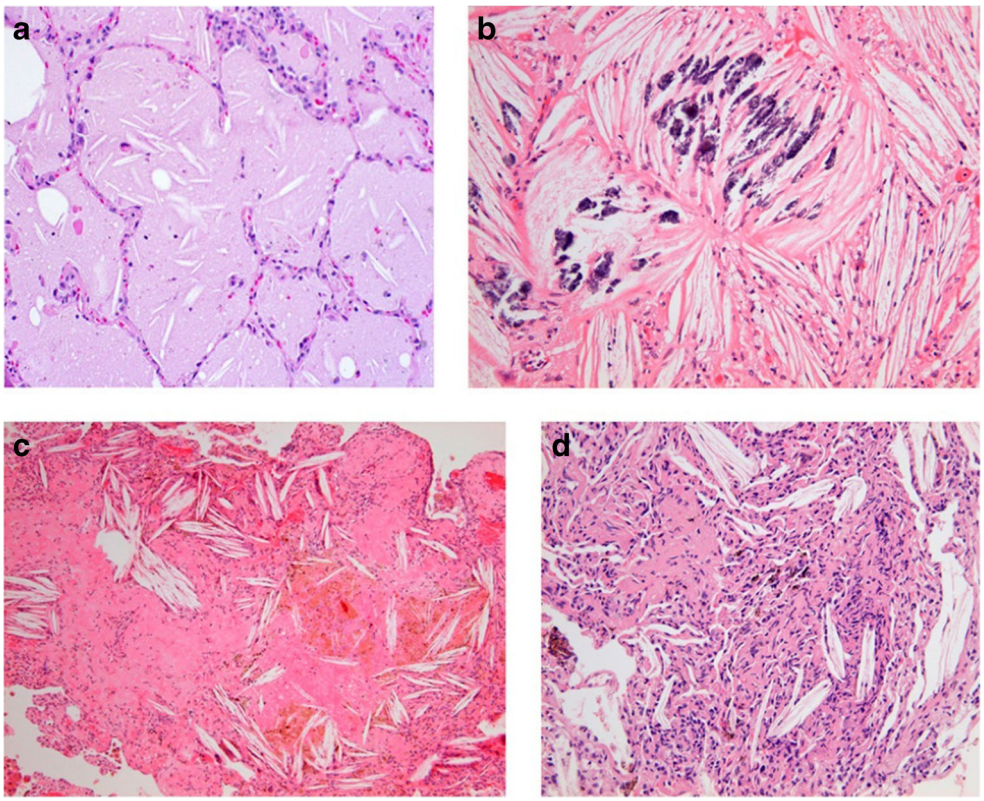

Fig. 3 Histopathology showing spectrum of histopathologic features of indium lung disease (hematoxylin and eosin stains). **a** intraalveolar exudate characteristic of alveolar proteinosis, with occasional cholesterol clefts (magnification 3200). **b** innumerable cholesterol clefts (magnification 3200). **c** intraalveolar exudate characteristic of alveolar proteinosis, cholesterol clefts, and fibrosis (magnification 3100). **d** cholesterol clefts, associated multinucleated giant cells, interstitial fibrosis, and brown particles composed predominantly of indium (magnification 3200) (Figure adapted from Cummings KJ, Nakano M, Omae K, Takeuchi K, Chonan T, Xiao YL, et al. Indium lung disease. *Chest*. 2012 Jun;141(6):1512-21.)

The experience with managing work restrictions for occupational PAP is necessarily limited, but lessons from more common occupational lung diseases, such as work-related asthma, may be informative, with some caveats. Removal from exposure is associated with the best outcomes in work-related asthma and would be expected to be more favorable for occupational PAP as well, although because of the rarity of the disease, data are lacking [65]. It is also important to note that for insoluble dusts like silica and ITO, exposure cessation does not address the material that is already in the lung and interfering with surfactant homeostasis, so it may not have much impact on disease progression.

Nonetheless, for patients still well enough to work, exposure cessation is ideally accomplished through substitution of the hazard or relocating the patient to an area without exposure. If substitution or job reassignment is not possible, removal from work ensures exposure avoidance. However, physicians must consider the adverse economic impact of job change or loss, as well as patient preferences to continue in the same occupation. Transfer to lower levels of exposure and use of respiratory protection with close monitoring for disease progression would also be an option for early disease. Notably, the poor prognosis for silica-associated PAP even with complete exposure removal argues against any continued work with silica regardless of disease stage [24]. Furthermore, the diagnosis of PAP related to silica or another exposure for which occupational exposure limits exist should prompt physician reporting to the Occupational Safety and Health Administration (OSHA) and, in many states, the health department. A workplace inspection can determine compliance with regulations on exposure limits and ensure the patient's co-workers are receiving mandated medical surveillance. For PAP related to a novel exposure or other occupational exposures for which regulations do not exist, the National Institute for Occupational Safety and Health, a research agency within the Centers for Disease Control and Prevention, can provide guidance to physicians and potentially carry out a health hazard evaluation to better understand disease risk [66].

Among treatment options, whole lung lavage (WLL) has been the most commonly used modality for the past several decades. This review will not address the technical details of performing WLL. Despite differences in the technique of performing WLL, the contemporary version of WLL involves performing single or sequential bilateral lavage by isolating each lung using a double-lumen endotracheal tube. In the cases of severe hypoxia, extracorporeal membrane oxygenation (ECMO) to facilitate completion of WLL should be considered [67]. WLL is generally well tolerated though. Most commonly reported complications include fever (18%) and hypoxemia (14%) [68]. In terms of efficacy, there is no robust data. However, cumulative results indicate an improvement in oxygenation parameters [4•]. The median duration before

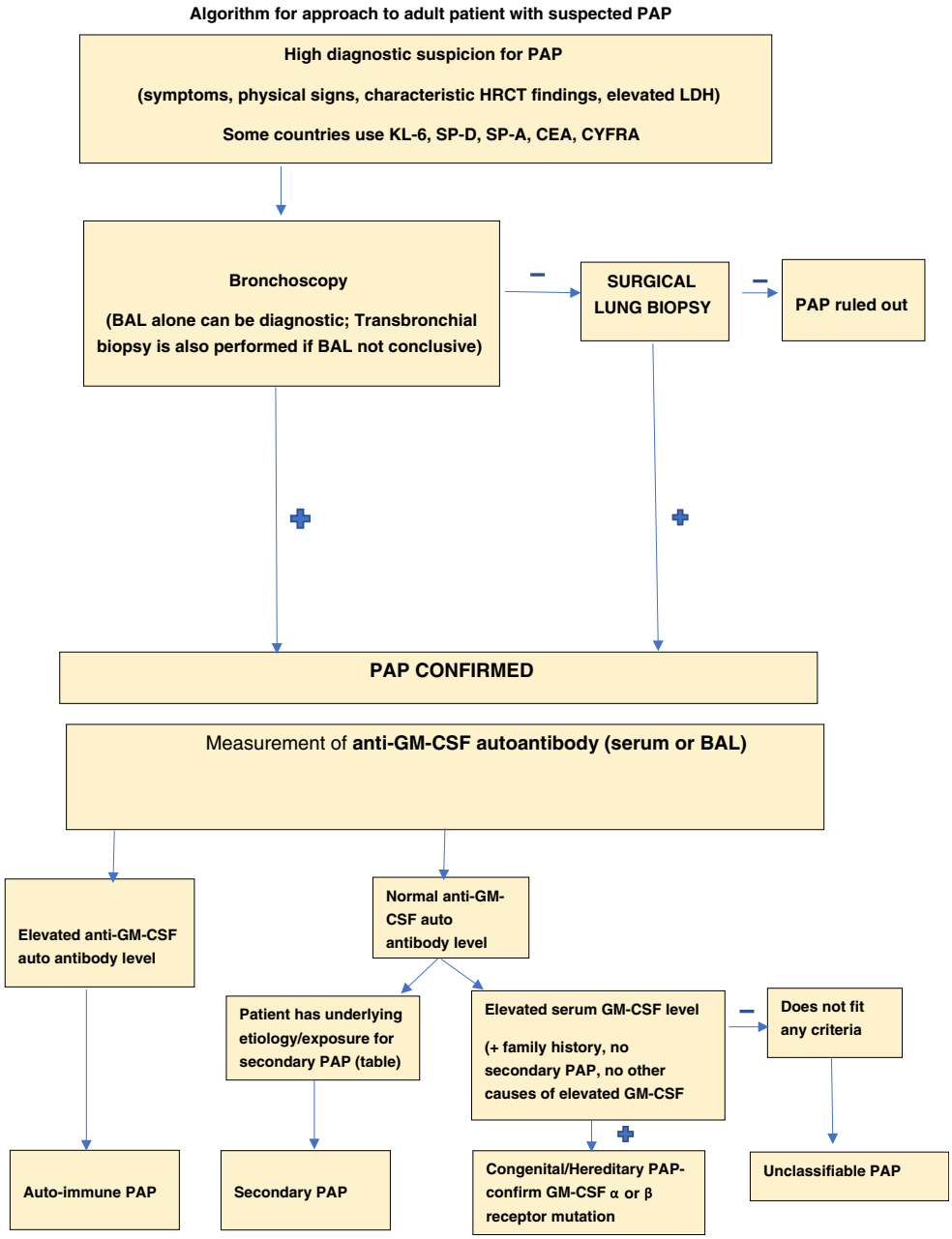

Fig. 4 Suggested diagnostic algorithm for PAP (Note that in some patients with occupational PAP, antibody to GM-CSF may be elevated-prevalence is not known) (Figure adapted with permission from reference number 2.)

recurrence requiring another WLL procedure is about 15 months. It is estimated that up to 50% of patients may experience a relapse [69].

The use of recombinant GM-CSF is based on the premise that repletion of bioavailable GM-CSF can restore alveolar macrophage function and homeostasis. Recombinant GM-CSF may be delivered through inhalation or subcutaneous injections. However, GM-CSF–based therapies are of use only in patients with elevated autoantibody to GM-CSF, i.e., autoimmune PAP. It likely has limited role in PAP strictly due to exposure with no evidence of autoimmunity. Studies that have assessed the impact of recombinant GM-CSF (subcutaneous or nebulized) have not yielded decisive answers though. Cumulative results suggest salutary benefits with 40–60% patients demonstrating a clinical response with improvement in alveolar-arterial oxygen gradient [1, 70–72]. Further studies are required to determine the dosing regimens and selection of appropriate candidates. Corticosteroids are not recommended due to likely harm, while data regarding the use of rituximab or modalities like plasmapheresis for exposure-related PAP is limited [73–75]. For patients with advanced progressive PAP, lung transplantation may be considered. The caveat to lung transplantation for PAP is the potential for recurrence of PAP in the allograft.

Summary

While most of PAP is considered to be autoimmune in nature, due to production of antibodies against GM-CSF, exposure to various inhalational agents has also been implicated in causing PAP. Occupational PAP has been described most commonly secondary to exposure to silica, but a wide variety of vapors, gases, dusts, and fumes have been implicated. In some patients with occupational exposure, it is possible that the offending agent may trigger autoimmunity against GM-CSF that can induce PAP. Patients with occupational PAP may have concomitant emphysema and/or pulmonary fibrosis. Depending on the degree of manifestations, treatment approach ranges from watchful monitoring to invasive procedures like WLL. Physician reporting to regulatory and public health authorities can ensure that existing exposure limits and medical surveillance requirements, such as are in place for silica, are enforced.

Compliance with Ethical Standards

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Tazawa R, Ueda T, Abe M, Tatsumi K, Eda R, Kondoh S, et al. Inhaled GM-CSF for pulmonary alveolar proteinosis. N Engl J Med. 2019;381(10):923–32.
2. Kumar A, Abdelmalak B, Inoue Y, Culver DA. Pulmonary alveolar proteinosis in adults: pathophysiology and clinical approach. Lancet Respir Med. 2018;6(7):554–65.
3. Inoue Y, Trapnell BC, Tazawa R, Arai T, Takada T, Hizawa N, et al. Characteristics of a large cohort of patients with autoimmune pulmonary alveolar proteinosis in Japan. Am J Respir Crit Care Med. 2008;177(7):752–62.
4.• Seymour JF, Presneill JJ. Pulmonary alveolar proteinosis: progress in the first 44 years. Am J Respir Crit Care Med. 2002;166(2):215–35 **Landmark review paper is the largest historic analysis of PAP since its original description**.
5. Davidson JM, Macleod WM. Pulmonary alveolar proteinosis. Br J Dis Chest. 1969;63(1):13–28.
6. 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):1908–16.
7. McEuen DD, Abraham JL. Particulate concentrations in pulmonary alveolar proteinosis. Environ Res. 1978;17(3):334–9.
8. Abraham JL, McEuen DD. Inorganic particulates associated with pulmonary alveolar proteinosis: SEM and X-ray microanalysis results. Appl Pathol. 1986;4(3):138–46.
9. Briens E, Delaval P, Mairesse MP, Valeyre D, Wallaert B, Lazor R, et al. Pulmonary alveolar proteinosis. Rev Mal Respir. 2002;19(2 Pt1):166–82.
10. Guo WL, Zhou ZQ, Chen L, Su ZQ, Zhong CH, Chen Y, et al. Serum KL-6 in pulmonary alveolar proteinosis: China compared historically with Germany and Japan. J Thorac Dis. 2017;9(2):287–95.
11. Campo I, Mariani F, Rodi G, Paracchini E, Tsana E, Piloni D, et al. Assessment and management of pulmonary alveolar proteinosis in a reference center. Orphanet J Rare Dis. 2013;8:40–1172.
12. Asamoto H, Kitaichi M, Nishimura K, Itoh H, Izumi T. Primary pulmonary alveolar proteinosis–clinical observation of 68 patients in Japan. Nihon Kyobu Shikkan Gakkai Zasshi. 1995;33(8):835–45.
13. Fijołek J, Wiatr E, Radzikowska E, Bestry I, Langfort R, Polubiec-Kownacka M, et al. Pulmonary alveolar proteinosis during a 30-year observation. Diagnosis and treatment. Pneumonol Alergol Pol. 2014;82(3):206–17.
14. Xiao YL, Xu KF, Li Y, Li Y, Li H, Shi B, et al. Occupational inhalational exposure and serum GM-CSF autoantibody in pulmonary alveolar proteinosis. Occup Environ Med. 2015;72(7):504–12.
15. Fang CS, Wang YC, Zhang TH, Wu J, Wang W, Wang C, et al. Clinical significance of serum lipids in idiopathic pulmonary alveolar proteinosis. Lipids Health Dis. 2012;11:12–511X.
16. Huang Z, Yi X, Luo B, Zhu J, Wu Y, Jiang W, et al. Induced sputum deposition improves diagnostic yields of pulmonary alveolar proteinosis: a clinicopathological and methodological study of 17 cases. Ultrastruct Pathol. 2016;40(1):7–13.
17. Deleanu OC, Zaharie AM, Şerbescu A, NiȚu FM, MihălȚan FD, Arghir OC. Analysis of bronchoalveolar lavage fluid in a first Romanian pulmonary alveolar proteinosis cohort. Romanian J Morphol Embryol. 2016;57(2 Suppl):737–43.
18. Prakash UB, Barham SS, Carpenter HA, Dines DE, Marsh HM. Pulmonary alveolar phospholipoproteinosis: experience with 34 cases and a review. Mayo Clin Proc. 1987;62(6):499–518.
19. Goldstein LS, Kavuru MS, Curtis-McCarthy P, Christie HA, Farver C, Stoller JK. Pulmonary alveolar proteinosis: clinical features and outcomes. Chest. 1998;114(5):1357–62.
20. Hadda V, Tiwari P, Madan K, Mohan A, Gupta N, Bharti SJ, et al. Pulmonary alveolar proteinosis: experience from a tertiary care center and systematic review of Indian literature. Lung India. 2016;33(6):626–34.
21.• 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(5):458–64 **First observational study that reported indium as a causative agent for occupational PAP**.
22. Suzuki T, Sakagami T, Young LR, Carey BC, Wood RE, Luisetti M, et al. Hereditary pulmonary alveolar proteinosis: pathogenesis, presentation, diagnosis, and therapy. Am J Respir Crit Care Med. 2010;182(10):1292–304.
23.• Blanc PD, Annesi-Maesano I, Balmes JR, Cummings KJ, Fishwick D, Miedinger D, et al. The occupational burden of nonmalignant respiratory diseases. An official American Thoracic Society and European Respiratory Society statement. Am J Respir Crit Care Med. 2019;199(11):1312–34 **American Thoracic Society and European Respiratory Society statement about occupational burden of pulmonary alveolar proteinosis**.
24. Xipell JM, Ham KN, Price CG, Thomas DP. Acute silicoproteinosis. Thorax. 1977;32(1):104–11.
25. Sauni R, Jarvenpaa R, Iivonen E, Nevalainen S, Uitti J. Pulmonary alveolar proteinosis induced by silica dust? Occup Med (Lond). 2007;57(3):221–4.
26. Blanc PD. "Acute" silicosis at the 1930 Johannesburg Conference on silicosis and in its aftermath: controversies over a distinct entity

later recognized as silicoproteinosis. Am J Ind Med. 2015;58(Suppl 1):S39–47.
27. Buechner HA, Ansari A. Acute silico-proteinosis. A new pathologic variant of acute silicosis in sandblasters, characterized by histologic features resembling alveolar proteinosis. Dis Chest. 1969;55(4):274–8.
28. Akgun M, Gorguner M, Meral M, Turkyilmaz A, Erdogan F, Saglam L, et al. Silicosis caused by sandblasting of jeans in Turkey: a report of two concomitant cases. J Occup Health. 2005;47(4):346–9.
29. Levin K, McLean C, Hoy R. Artificial stone-associated silicosis: clinical-pathological-radiological correlates of disease. Respirol Case Rep. 2019;7(7):e00470.
30. Rose C, Heinzerling A, Patel K, Sack C, Wolff J, Zell-Baran L, et al. Severe silicosis in engineered stone fabrication workers - California, Colorado, Texas, and Washington, 2017-2019. MMWR Morb Mortal Wkly Rep. 2019;68(38):813–8.
31. Eden KG, von Seebach HB. Atypical quartz dust-induced pneumoconiosis in SPF rats. Aspects of the role of the lymphatic system in the pathogenesis of silicosis. Virchows Arch A Pathol Anat Histol. 1976;372(1):1–9.
32. Cummings KJ, Nakano M, Omae K, Takeuchi K, Chonan T, Xiao YL, et al. Indium lung disease. Chest. 2012;141(6):1512–21.
33. Bomhard EM. Particle-induced pulmonary alveolar proteinosis and subsequent inflammation and fibrosis: a toxicologic and pathologic review. Toxicol Pathol. 2017;45(3):389–401.
34. Noguchi S, Eitoku M, Kiyosawa H, Suganuma N. Fibrotic gene expression coexists with alveolar proteinosis in early indium lung. Inhal Toxicol. 2016;28(9):421–8.
35. Badding MA, Fix NR, Orandle MS, Barger MW, Dunnick KM, Cummings KJ, et al. Pulmonary toxicity of indium-tin oxide production facility particles in rats. J Appl Toxicol. 2016;36(4):618–26.
36. Nagano K, Nishizawa T, Eitaki Y, Ohnishi M, Noguchi T, Arito H, et al. Pulmonary toxicity in mice by 2- and 13-week inhalation exposures to indium-tin oxide and indium oxide aerosols. J Occup Health. 2011;53(3):234–9.
37. Lison D, Laloy J, Corazzari I, Muller J, Rabolli V, Panin N, et al. Sintered indium-tin-oxide (ITO) particles: a new pneumotoxic entity. Toxicol Sci. 2009;108(2):472–81.
38. Badding MA, Stefaniak AB, Fix NR, Cummings KJ, Leonard SS. Cytotoxicity and characterization of particles collected from an indium-tin oxide production facility. J Toxicol Environ Health A. 2014;77(20):1193–209.
39. Huaux F, De Gussem V, Lebrun A, Yakoub Y, Palmai-Pallag M, Ibouraadaten S, et al. New interplay between interstitial and alveolar macrophages explains pulmonary alveolar proteinosis (PAP) induced by indium tin oxide particles. Arch Toxicol. 2018;92(4):1349–61.
40. Vallyathan V, Shi XL, Dalal NS, Irr W, Castranova V. Generation of free radicals from freshly fractured silica dust. Potential role in acute silica-induced lung injury. Am Rev Respir Dis. 1988;138(5):1213–9.
41. Iyer R, Hamilton RF, Li L, Holian A. Silica-induced apoptosis mediated via scavenger receptor in human alveolar macrophages. Toxicol Appl Pharmacol. 1996;141(1):84–92.
42. Hamilton RF, Thakur SA, Holian A. Silica binding and toxicity in alveolar macrophages. Free Radic Biol Med. 2008;44(7):1246–58.
43. Chew R, Nigam S, Sivakumaran P. Alveolar proteinosis associated with aluminium dust inhalation. Occup Med (Lond). 2016;66(6):492–4.
44. Shaughnessy GF, Lee AS. Pulmonary alveolar proteinosis, barbecue smoke, and granulocyte-macrophage colony-stimulating factor therapy. Am J Med. 2016;129(1):e7–8.
45. Cooper GS, Miller FW, Germolec DR. Occupational exposures and autoimmune diseases. Int Immunopharmacol. 2002;2(2–3):303–13.
46. Zhao YY, Huang H, Liu YZ, Song XY, Li S, Xu ZJ. Whole lung lavage treatment of Chinese patients with autoimmune pulmonary alveolar proteinosis: a retrospective long-term follow-up study. Chin Med J. 2015;128(20):2714–9.
47. Shah PL, Hansell D, Lawson PR, Reid KB, Morgan C. Pulmonary alveolar proteinosis: clinical aspects and current concepts on pathogenesis. Thorax. 2000;55(1):67–77.
48. Suzuki T, Trapnell BC. Pulmonary alveolar proteinosis syndrome. Clin Chest Med. 2016;37(3):431–40.
49. 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):1344–9.
50. Arai T, Inoue Y, Sugimoto C, Inoue Y, Nakao K, Takeuchi N, et al. CYFRA 21-1 as a disease severity marker for autoimmune pulmonary alveolar proteinosis. Respirology. 2014;19(2):246–52.
51. Bonella F, Long X, He X, Ohshimo S, Griese M, Guzman J, et al. Serum YKL-40 is a reliable biomarker for pulmonary alveolar proteinosis. Respirology. 2017;22:1371–8.
52. 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;8:53–1172.
53. Bonfield TL, Russell D, Burgess S, Malur A, Kavuru MS, Thomassen MJ. Autoantibodies against granulocyte macrophage colony-stimulating factor are diagnostic for pulmonary alveolar proteinosis. Am J Respir Cell Mol Biol. 2002;27(4):481–6.
54. Lin FC, Chang GD, Chern MS, Chen YC, Chang SC. Clinical significance of anti-GM-CSF antibodies in idiopathic pulmonary alveolar proteinosis. Thorax. 2006;61(6):528–34.
55.• Kitamura T, Tanaka N, Watanabe J, Uchida KS, Yamada Y, et al. Idiopathic pulmonary alveolar proteinosis as an autoimmune disease with neutralizing antibody against granulocyte/macrophage colony-stimulating factor. J Exp Med. 1999;190(6):875–80 **First description of role of GM-CSF in pathogenesis of autoimmune PAP**.
56. Kitamura T, Uchida K, Tanaka N, Tsuchiya T, Watanabe J, Yamada Y, et al. Serological diagnosis of idiopathic pulmonary alveolar proteinosis. Am J Respir Crit Care Med. 2000;162(2 Pt 1):658–62.
57. Uchida K, Nakata K, Carey B, Chalk C, Suzuki T, Sakagami T, 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.
58. Ishii H, Trapnell BC, Tazawa R, Inoue Y, Akira M, Kogure Y, et al. Comparative study of high-resolution CT findings between autoimmune and secondary pulmonary alveolar proteinosis. Chest. 2009;136(5):1348–55.
59. Holbert JM, Costello P, Li W, Hoffman RM, Rogers RM. CT features of pulmonary alveolar proteinosis. AJR Am J Roentgenol. 2001;176(5):1287–94.
60. 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(6):1509–19.
61. Mehrian P, Homayounfar N, Karimi MA, Jafarzadeh H. Features of idiopathic pulmonary alveolar proteinosis in high resolution computed tomography. Pol J Radiol. 2014;79:65–9.
62. Akira M, Inoue Y, Arai T, Sugimoto C, Tokura S, Nakata K, et al. Pulmonary fibrosis on high-resolution CT of patients with pulmonary alveolar proteinosis. AJR Am J Roentgenol. 2016;207(3):544–51.

63. Burkhalter A, Silverman JF, Hopkins MB, Geisinger KR. Bronchoalveolar lavage cytology in pulmonary alveolar proteinosis. Am J Clin Pathol. 1996;106(4):504–10.
64. Sanyal S, Crawford JA, Abraham JL. Overlooked role of histopathology in evaluations for occupational/environmental exposures. Am J Respir Crit Care Med. 2020;201(12):1581.
65. Jolly AT, Klees JE, Pacheco KA, Guidotti TL, Kipen HM, Biggs JJ, et al. Work-related asthma. J Occup Environ Med. 2015;57(10): e121–9.
66. Cummings KJ, Suarthana E, Edwards N, Liang X, Stanton ML, Day GA, et al. Serial evaluations at an indium-tin oxide production facility. Am J Ind Med. 2013;56(3):300–7.
67. Chauhan S, Sharma KP, Bisoi AK, Pangeni R, Madan K, Chauhan YS. Management of pulmonary alveolar proteinosis with whole lung lavage using extracorporeal membrane oxygenation support in a postrenal transplant patient with graft failure. Ann Card Anaesth. 2016;19(2):379–82.
68. Campo I, Luisetti M, Griese M, Trapnell BC, Bonella F, Grutters J, et al. Whole lung lavage therapy for pulmonary alveolar proteinosis: a global survey of current practices and procedures. Orphanet J Rare Dis. 2016;11(1):115–016.
69. Gay P, Wallaert B, Nowak S, Yserbyt J, Anevlavis S, Hermant C, et al. Efficacy of whole-lung lavage in pulmonary alveolar proteinosis: a multicenter international study of GELF. Respiration. 2017;93(3):198–206.
70. Tazawa R, Trapnell BC, Inoue Y, Arai T, Takada T, Nasuhara Y, et al. Inhaled granulocyte/macrophage-colony stimulating factor as therapy for pulmonary alveolar proteinosis. Am J Respir Crit Care Med. 2010;181(12):1345–54.
71. 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(3):585–93.
72. Venkateshiah SB, Yan TD, Bonfield TL, Thomassen MJ, Meziane M, Czich C, et al. An open-label trial of granulocyte macrophage colony stimulating factor therapy for moderate symptomatic pulmonary alveolar proteinosis. Chest. 2006;130(1):227–37.
73. Akasaka K, Tanaka T, Kitamura N, Ohkouchi S, Tazawa R, Takada T, et al. Outcome of corticosteroid administration in autoimmune pulmonary alveolar proteinosis: a retrospective cohort study. BMC Pulm Med. 2015;15:88–015.
74. Kavuru MS, Malur A, Marshall I, Barna BP, Meziane M, Huizar I, et al. An open-label trial of rituximab therapy in pulmonary alveolar proteinosis. Eur Respir J. 2011;38(6):1361–7.
75. Jezequel A, Kerjouan M, Lederlin M, Laine-Caroff C, Camus C, Delaval P, et al. Plasmapheresis failure in the treatment of autoimmune pulmonary alveolar proteinosis. Rev Mal Respir. 2017;34(3):240–3.