Pulmonary Alveolar Proteinosis: A Comprehensive Clinical Perspective

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abstract

Pulmonary alveolar proteinosis is a broad group of rare diseases that are defined by the occupation of a lung's gas-exchange area by pulmonary surfactants that are not properly removed. The clinical and radiologic phenotypes among them are very similar. The age of manifestation plays a central role in the differential diagnosis of the almost 100 conditions and provides an efficient path to the correct diagnosis. The diagnostic approach is tailored to identify genetic or autoimmune causes, exposure to environmental agents, and associations with numerous other diseases. Whole-lung lavages are the cornerstone of treatment, and children in particular depend on the expertise to perform such therapeutic lavages. Other treatment options and long-term survival are related to the condition causing the proteinosis.

Under pathological conditions, the alveolar airspaces can be filled with various materials, which frequently replace the air necessary for gas exchange and give rise to alveolar filling syndromes (Table 1). These conditions have similar clinical and radiologic presentations. This makes their differential diagnosis difficult.

Pulmonary alveolar proteinosis (PAP) is defined by the accumulation of pulmonary surfactants in the alveolar space (Fig 1). Mechanistically, these disturbances of surfactant homeostasis may be caused by an altered surfactant production, removal, or both.[1] PAP is a heterogeneous group of disorders that is caused by different conditions[2] (Table 2). The age of manifestation plays an important role in the diagnostic approach and differential diagnosis (Fig 2). Success of treatment and outcome are related to the underlying condition and, in children, to the technical skills needed to perform whole-lung lavages (WLLs). WLL is the cornerstone of PAP treatment.

EPIDEMIOLOGY

PAP is a rare disease complex that affects <5 cases per 100 000 inhabitants.[3] The first description of PAP[4] as well as the vast majority of data on treatment and prognosis are related to autoimmune PAP. Most pediatric cases are nonautoimmune PAP and distribute almost evenly among many different entities. In childhood, there is a bimodal age distribution; some conditions manifest in the neonatal period (Fig 2, upper portion), whereas others manifest during infancy and childhood.

PATHOLOGY

The expansion of the surfactant pool can be recognized in histopathological specimens. The alveoli are filled with eosinophilic, acellular, and finely granular material (Fig 1E). Clefts made of cholesterol can be found (Fig 1F).[4,5] Sometimes, detached type II pneumocytes, foamy macrophages, or neutrophil granulocytes as well as lamellar bodies of normal lungs can be identified (Fig 1 C and D).

Whereas the intra-alveolar filling does not differentiate between different forms of PAP, histopathological examination of the alveolar wall structures may be normal (Fig 1E)

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or abnormal. The interstitial space is mostly normal; however, several forms show widening from cells or fibrosis.[4,6] When the surfactant dysfunction syndromes were first described, the term "congenital alveolar proteinosis" was used in such newborns.[7] Particularly in children, the PAP histopattern presents in combination with additional histopatterns,[8,9] such as increased cellularity from hyperplasia of type II pneumocytes and collagen fibers or alveolar macrophages.[10] In cohort studies in ~50% to 60% of such biopsies, the PAP histopattern was found,[11,12] and the detection rate was higher in biopsies conducted during the early disease phase.[12] In TTF1 deficiency, pulmonary histology may also show the PAP pattern in addition to the nonspecific interstitial pneumonia pattern and defects in lung development.[13]

CLINICAL PRESENTATION

PAP presents in 2 types: Most frequently (70%–90% of PAP cases), patients develop slowly increasing dyspnea (initially on exertion) and dry coughing.[2] In PAP caused by granulocyte-macrophage colony-stimulating factor receptor alpha (GM-CSF-Ra) mutations, 70% had dyspnea at presentation, 15% had tachypnea, 30% had clubbing, 35% had global respiratory failure, and 15% were intubated and ventilated.[14]

Less frequently (30%–50% of PAP cases), fever, weight loss, fatigue, and chest pain are observed (numbers are for autoimmune PAP[2]). Among the children, 45% had infections (mycoplasma, influenza, or respiratory syncytial virus) before PAP because of GM-CSF-Ra mutations, 26% had a cough, 5% had a fever, and 36% had failure to thrive.[14] PAP caused by affected surfactant production typically presents with idiopathic respiratory distress syndrome (RDS) or idiopathic pulmonary hypertension in a mature neonate.

INVESTIGATIONS AND DIFFERENTIAL DIAGNOSIS

Chest Radiography

The presence of diffuse bilateral mostly symmetrical alveolar, sometimes patchy infiltrates with air bronchograms give first clues to interstitial lung disease due to alveolar filling (Fig 1A). Usually, the perimediastinal regions are more affected than the subpleural regions. Persistence of the cloudy infiltrates after antibiotic treatment is a frequent observation. In neonates with acute RDS, all radiologic stages (including a "white lung") may develop progressively.

Lung Function Tests

Adults and children who are old enough to perform spirometry have a restrictive pattern with small lung volumes and reduced diffusing capacity of the lung for carbon monoxide, although initial tests may also be normal.[6] Of interest, carbon dioxide elimination rarely is a problem in the face of significant hypoxemia. At presentation, 55% of the patients with PAP caused by GM-CSF-Ra mutations had hypoxemia,[14] whereas in adults with autoimmune PAP, hypoxemia at rest was present in approximately one-third and during exercise in more than half of the patients.[3] With treatment of the alveolar filling, abnormal lung function tests are expected to be reversible; if they are not, then additional pathology should be suspected.

Laboratory Blood Tests

Autoantibodies Against GM-CSF

In all cases of suspected PAP, these should be searched. In adults, >90% of the case results are positive.[15–19] Serology has excellent sensitivity and specificity.[20] Autoimmune PAP occurs in children, and it needs to be differentiated from GM-CSF antibodies in healthy individuals at low levels and patients with autoinflammatory diseases such as colitis, Crohn disease, malignancies,[21] or PAP caused by dust exposure.[22–24] Because there is a close correlation between antibody level and PAP development,[25,26] a close link to pulmonary manifestation is mandatory when searching for these autoantibodies.

Lactate Dehydrogenase

Lactate dehydrogenase is increased in 82% of patients with autoimmune PAP.[6] Of interest, this marker readily responds to changes in disease severity and improves after therapeutic lavages.[6,27–29]

Similarly, in serum carcinoembryonic antigen, levels of the surfactant proteins A, D,[30] and KL-6 are markers of disease activity, which can be used to monitor its course. Serum KL-6 accurately predicts disease progression in autoimmune PAP.[29]

In children and adults, autoantibodies including antinuclear antibody, antineutrophil cytoplasmic antibody (eg, cANCA/PR3 and pANCA/MPO), anti–double-stranded DNA, anticentromere, cyclic citrullinated peptide, extractable nuclear antigen (eg, anti–SS-A [Ro], anti–SS-B [La], anti-RNP, anti–Jo-1, anti-Sm, and Scl-70), and rheumatoid factor should be assessed.

Global and specific immunologic function tests need to be done to diagnose underlying immune deficiencies (Table 2).

Genetic Testing

In neonates with the characteristic clinical and radiologic presentation (and after the exclusion of other, more frequent causes), testing for mutations in SFTPB, SFTPC, ABCA3, and TTF1 is recommended (www.childeu.net). In infants and older patients, analysis for mutations in

TABLE 1 Intra-Alveolar Filling With Different Materials Leads to Various Disease Entities

Material Filling the Alveolar Space	Disease
Surfactant	PAP
Erythrocytes, siderophages	Alveolar hemorrhage
Macrophages	Desquamative interstitial pneumonia
Hyaline membranes	Diffuse alveolar damage, RDS
Eosinophils	Eosinophilic pneumonia
Cholesterol crystals, foreign material	Exogenous lipid pneumonia, aspiration pneumonia
Exsudative neutrophilic alveolitis, progressively replaced by macrophages, giant cells, fibroblasts	Meconium aspiration syndrome
Lipoproteins, *Pneumocystis*	*P jiroveci* pneumonia
Calcified microliths	Pulmonary alveolar microlithiasis
Plasma, serum	Pulmonary edema

SFTPC, ABCA3, CSF2RB, CSF2RA, GATA2, SLC7A7, methionyl–transfer RNA synthetase (MARS), NPC2, and possibly NPB (see Table 2) should be done when appropriate.

Bronchoalveolar Lavage

With standardized diagnostics, lavage return typically gets milkier on visual inspection. May-Grünwald Giemsa staining shows cellular debris, acellular globules, and foamy macrophages (Fig 1 C and D). In adults with PAP, experienced centers can make the diagnosis by bronchoalveolar lavage (BAL) in 70% to 74% of the patients with acquired PAP.[3,16] BAL fluid should be investigated for infections (Table 2).

High-Resolution Computed Tomography

Crazy paving pattern, which combines ground-glass opacity (a hazy increase in lung opacity that does not obscure the underlying vessels or bronchial structures) and a superimposed reticular pattern (Fig 1B), is characteristic for PAP but not specific to it. Its differential diagnosis includes edema, hemorrhage, acute RDS, acute interstitial pneumonia, eosinophilic pneumonia, diffuse alveolar damage, pneumonias caused by *Pneumocystis jirovecii*, cytomegalovirus, adenovirus, mycoplasma, bacteria, tuberculosis, nonspecific interstitial pneumonitis, organizing pneumonia, eosinophilic granulomatosis with polyangiitis, radiation pneumonitis, drug-related pneumonitis, sarcoidosis, lipoid pneumonia, and Niemann-Pick disease, among others.[31]

It must be kept in mind that computed tomography (CT) imaging in neonates and infants with high breathing rates is very demanding and needs a lot of technical detail to obtain high-quality scans. Therefore, CT scanning should be reserved for the specialized center performing diagnostic imaging in temporal relation to the lung biopsy.

Lung Biopsy

In infants, biopsies are done as open biopsies or sometimes thoracoscopically. In adults and older children, transbronchial biopsies can be done during a bronchoscopy. Lung biopsies were performed in ~80% of the children to make the diagnosis of PAP.[14] In children, reference reading of the biopsy specimens by a specialized pathologist is highly recommended and can be organized via different networks, such as the European Management Platform for Children's Interstitial Lung Diseases (www.childeu.net).

DIAGNOSIS OF PAP

As with all rare lung diseases, a high degree of suspicion is necessary when taking the diagnosis of PAP into consideration. Red flags in neonates and young infants are nonimproving or slowly improving respiratory distress in the mature neonate (ie, if persistent after 1 or more weeks and excluding cardiac, infectious, central, or metabolic causes). In older infants and children, red flags include slowly developing dyspnea or dyspnea persisting after resolution of an acute respiratory tract infection, together with diffuse alveolar infiltrates on the chest radiograph.

Blood tests are done first, followed by a bronchoscopy with standardized lavage and transbronchial biopsy in most patients (Table 2). When the results obtained are not definitively diagnostic, a lung biopsy is needed to firmly establish the diagnosis.

ETIOLOGY

Categorization of PAP forms according to suspected etiology is helpful for therapy, although frequently the underlying etiology cannot be identified precisely (Table 2).

Surfactant Dysfunction Syndromes

Mutations in SFTPB, SFTPC, ABCA3, and TTF1 may present with the histologic PAP pattern mostly during the neonatal period,[7,9,32–34] when secretion of surfactant is normally increased more than 10-fold[35,36] and sometimes later as well but to a smaller degree.[37,38] At the same time, the removal of aberrant surfactant may be impaired because of volume- and barotrauma-induced lung injuries,[39] and physiologically increased removal may be disturbed, all of which lead to swamped macrophage-removal systems.[40] If patients survive, the PAP pattern slowly disappears and is replaced by a more fibrotic pattern of lung disease.[10,12] Similarly, such a sequence has been demonstrated for MARS mutations (Table 2).[41] Today, fortunately, conditions are diagnosed genetically, which eliminates the need for a biopsy.

Impaired GM-CSF Signaling

GM-CSF is critical for the regulation of surfactant homeostasis, alveolar

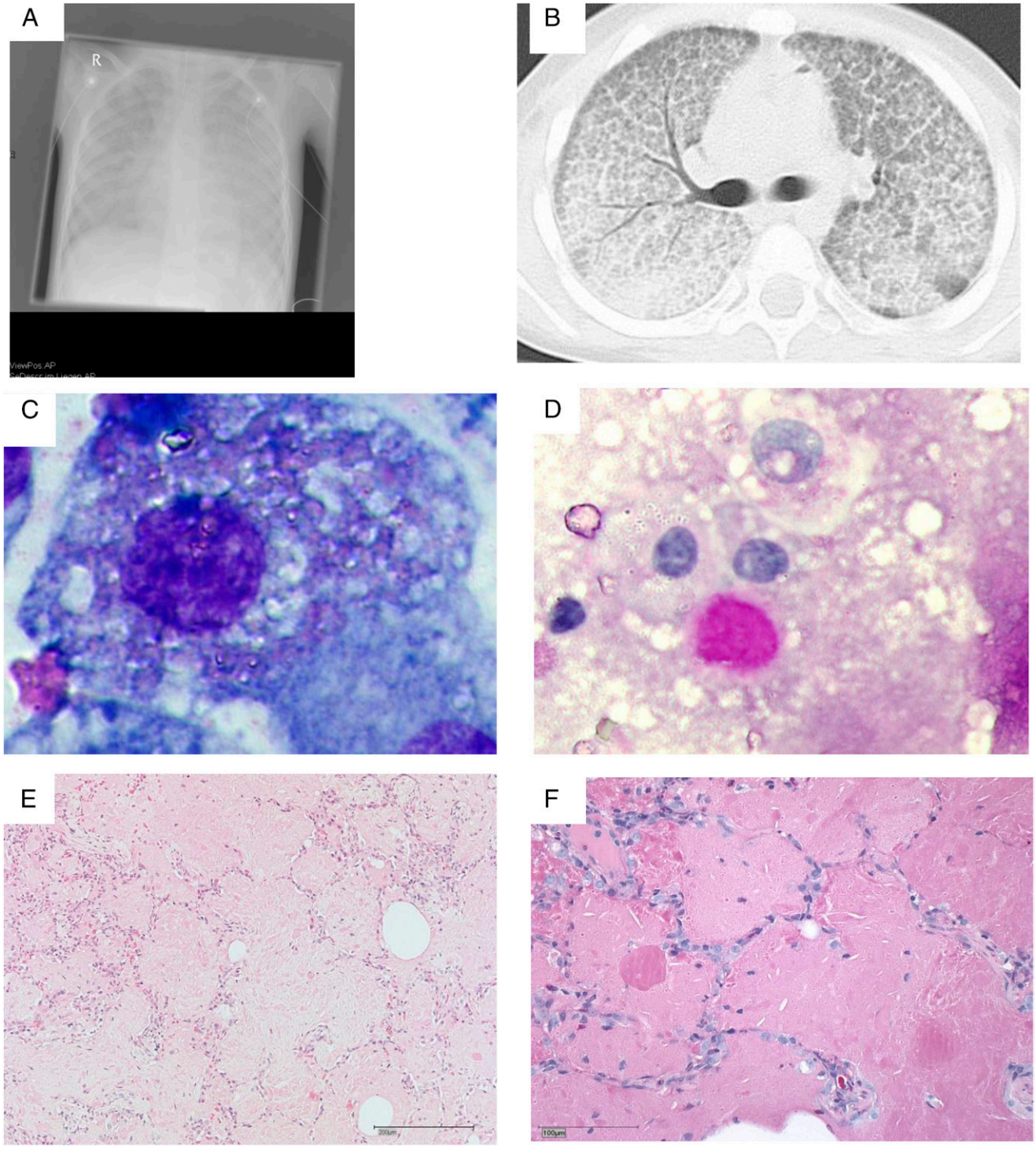

FIGURE 1
Diagnosing alveolar pulmonary proteinosis. A, A chest radiograph shows bilateral, often symmetrical alveolar opacities. If a radiograph appears less dense than what is shown here, a "butterfly" appearance may be recognized. B, A crazy paving pattern from ground-glass opacification and overlaid reticulonodular pattern is shown. C, Foamy macrophage from BAL filled with lipid material (May-Grünwad staining) is seen. D, Periodic acid–Schiff (PAS) staining–positive noncellular globules. A large amount of cell debris is characteristic of PAP lavage. E, Histology from a patient with PAP caused by a homozygous GM-CSF-Ra mutation is shown. Note the alveolar filling and normal alveolar walls (haematoxylin-eosin staining). F, The same biopsy with a PAS stain shows amorphous PAS-positive material with abundant oval bodies.

macrophage maturation and phagocytosis, lung host defense, and innate immunity.[42] Disrupted GM-CSF signaling by neutralizing GM-CSF autoantibodies is the cause of the vast majority of adult cases of PAP.[43] This autoimmune disease, in the beginning called "adult idiopathic PAP" or "primary PAP," is now called

TABLE 2 Categorization of PAP

Disease Causes of PAP	Manifestation Reported in Neonates, Children[a]	Genetically Caused[b]	Exposure Caused	Histologically Intact Lung Interstitial Tissue, Primarily Alveolar Filling
Surfactant-dysfunction syndromes				
SFTPB mutations	Y	Y	N	N
SFTPC mutations	Y	Y	N	N
ABCA3 mutations	Y	Y	N	N
TTF1 mutations	Y	Y	N	N
Impaired GM-CSF signaling				
GM-CSF receptor α chain of mutations	Y	Y	N	Y
Turner syndrome with heterozygous GM-CSF receptor α chain mutations	Y	Y	N	Y
GM-CSF receptor β chain mutations	Y	Y	N	Y
Autoimmune GM-CSF antibodies	Y	N	N	Y
Hematologic disorders and other malignancies				
GATA2 deficiency	Y	Y	N	Y
MDS (most common)	Y	Y	N	Y
Chronic myelomonocytic leukemia	Y	Y	N	n.k.
Acute lymphatic leukemia	Y	Y	N	Y[c]
Congenital dyserythropoietic anemia	Y	Y	N	Y
Fanconi's anemia	Y	Y	N	Y
Hemophagocytic lymphohistiocytosis	Y		N	N
Sideroblastic anemia	Y	N[c]	N	Y[c]
Primary myelofibrosis, chronic lymphocytic leukemia, cutaneous T-cell lymphoma, thymic alymphoplasia, adult T-cell leukemia and/or lymphoma, idiopathic thrombocytopenic purpura, aplastic anemia, chronic myeloid leukemia, overlap myeloproliferative neoplasm, acute myeloid leukemia, hairy-cell leukemia, multiple myeloma and/or plasmocytoma, polycythemia vera, essential thrombocythemia, amyloidosis, Hodgkin disease, non-Hodgkin lymphoma, adenocarcinoma, glioblastoma, melanoma, small-cell lung carcinoma, clear-cell renal cell carcinoma, mesothelioma	N	Y or n.k.	N[c]	Y[c] or n.k.
Systemic diseases				
Lysinuric protein intolerance (SLC7A7 mutation)	Y	Y	N	Y (50%), N (50%)
MARS mutations	Y	Y	N	N
Niemann Pick type C2	Y	Y	N	N
Niemann Pick type B	Y	Y	N	n.d.
Bone marrow, stem cell transplant	Y	N	N	Y[c]
Systemic lupus erythematosus, granulomatosis with polyangiitis, microscopic polyangiitis, membranous nephropathy, dermatomyositis with interstitial lung disease, coincident in many other rheumatologic diseases and interstitial lung diseases, lung transplant	N	N	N	Y[c] or N
Immunologic diseases				
Adenosine deaminase deficiency	Y	Y	N	Y
Agammaglobulinemia	Y	Y[c]	N	n.k.
DiGeorge syndrome type 2	Y	Y	N	n.d.
Monoclonal gammopathy	N	N	N	Y
Selective immunoglobulin A deficiency	N	N	N	Y
Severe combined immunodeficiency	Y	Y	N	Y
X-linked hyper–immunoglobulin M syndrome	Y	Y	N	n.d.
Infections				
Cytomegalovirus	Y	N	Y	N or N[c]
Epstein-Barr virus	Y	N	Y	N or N[c]
HIV	Y	N	Y	N or N[c]
M tuberculosis	Y	N	Y	N or N[c]
Atypical mycobacteria	Y	N	Y	N or N[c]
Nocardia	N	N	Y	N or N[c]
P jiroveci	Y	N	Y	N or N[c]
Drugs				
Chemotherapy, antineoplastic	Y	N	Y	Y

TABLE 2 Continued

Disease Causes of PAP	Manifestation Reported in Neonates, Children[a]	Genetically Caused[b]	Exposure Caused	Histologically Intact Lung Interstitial Tissue, Primarily Alveolar Filling
Busulfan, sirolimus, everolimus, tyrosine kinase inhibitors (including imatinib, nilotinib, and dasatinib), mycophenolate and cyclosporine combination, smoked fentanyl patches, leflunomide, hydrofluoric acid (inhaled)	N	N	Y	Y
Types of dust exposure, inorganic				
Aluminum, cement, marble, indium, iron, silica and silica-leaking breast implants, tin, titanium (and varnish)	N	N	Y	N (except aluminum, silica)
Types of dust exposure, organic				
Bakery flour, chlorine, cleaning products, cotton, fertilizer, agricultural dust, fumes, gasoline, hydrofluoric acid, parrots, pigeons, petroleum, sawdust	N	N	Y	N or N[c]
Miscellaneous conditions				
Osteopetrosis caused by *TCIRG1* gene mutation	Y	Y	N	Y[c]
Total anomalous pulmonary venous return with coarctation of the aorta (single case)	Y	N, Y[c]	N	Y, pulmonary hypoplasia

Y or N indicates highest likelihood and/or firm knowledge from publications; frequently extensive data are lacking and these indications are based on estimation. n.d., not done; n.k., not known.

[a] Manifestation of PAP is proven in this age group (not of disease).

[b] May be germline or clonal in monocytes.

[c] Indicates uncertainty.

"autoimmune PAP"[44] and can also occur in children.

Interruption of GM-CSF signaling by hereditary factors, such as mutations in the α (CD116) or β (CD131) chain of the GM-CSF receptor (which is also used by the interleukin-3 and interleukin-5 receptors),[45,46] will all lead to hereditary PAP forms. These cases most likely manifest in childhood but may also be diagnosed in adults.[14,47,48]

Hematologic Disorders and Other Malignancies

Hematologic disorders widely contribute to PAP causes, both in children[49] and adults[50] (Table 2). Prolonged neutropenia and reduction of alveolar macrophages by myeloablative chemotherapy or leukemic infiltration have been implicated in the pathogenesis of pediatric PAP.[51] Autoantibodies against GM-CSF may be elevated in BAL fluid, whereas in sera, they were below sensitivity.[52] Among patients with GATA2 haploinsufficiency, ~20% develop PAP, often in association with familial myelodysplastic syndrome (MDS) (84%); acute myeloid leukemia (14%); chronic myelomonocytic leukemia (8%); severe infections (including mycobacterial and fungal infections); human papillomavirus– or Epstein-Barr virus–associated tumors; venous thrombosis; lymphedema; sensorineural hearing loss; miscarriage; and hypothyroidism.[53]

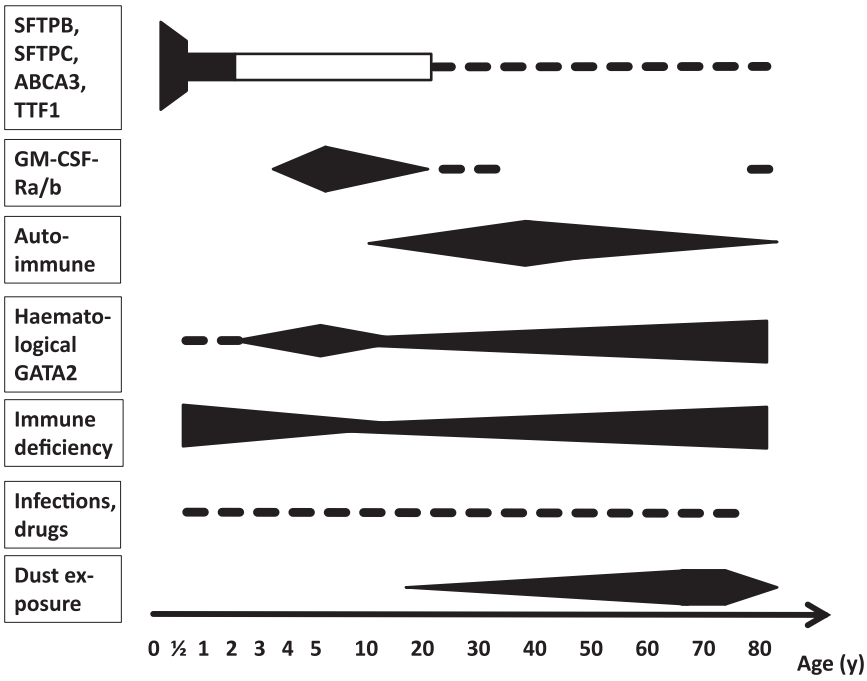

FIGURE 2
Schematic of age dependency of the manifestation of various alveolar pulmonary proteinosis forms and qualitative estimates of age at clinical manifestation in the major groups of PAP. Note the size of the graphs does not represent their absolute frequency. Autoimmune PAP represents ~90% of all cases if age of manifestation is not considered.

Systemic Diseases

Lysinuric protein intolerance is an inherited defect of cationic amino acid (lysine, arginine, and ornithine) transport at the basolateral membrane of epithelial cells and is caused by mutations in SLC7A7.[54] The condition can be considered a disorder of bone marrow–derived monocytes differentiating into dysfunctional alveolar macrophages.[55] Lung involvement was observed in 71% of children, which showed fibrosis on histopathology or CT scan in addition to PAP.[56]

MARS deficiency by missense mutations leads to PAP, which is endemic on Réunion Island in the Indian Ocean.[41] The disease starts in infancy with PAP then frequently progresses to pulmonary fibrosis with cholesterol granulomas.[57]

Niemann-Pick diseases are hereditary neurovisceral lysosomal lipid-storage disorders, which can present with respiratory symptoms at any age. In type C2, PAP may be caused by reduced NPC2 protein expression in alveolar macrophages. The composition and function of surfactants in this form of PAP are abnormal.[58] PAP has been reported in Niemann-Pick type B; however, it was unclear if this was a coincidence with autoimmune PAP.[59]

Immunologic Diseases

Of infants with adenosine deaminase deficiency, ~50% have PAP with typical lung pathology and without additional abnormalities, except for coincident identification of various pathogens.[60] For several other immunologic diseases, cases of PAP have been reported (Table 2).

Infections

In a recent review of the literature, all reported cases of PAP and opportunistic infections between 1950 and 2010 were searched, and 75 cases were reviewed. Forty-three percent of the patients had nocardia infection, 37% had mycobacterial infection (of those, 75% were *Mycobacterium tuberculosis*), and 20% had fungal infections.[61] Opportunistic infections can either precede or follow a diagnosis of PAP. PAP should be considered in apparently immunocompetent patients who present with an opportunistic infection and diffuse alveolar infiltrates. For *Pneumocystis* and the viruses indicated in Table 2, individual cases of PAP were reported.

Drugs and Dust Exposure

Although PAP caused by dust exposure has not been reported in children, a detailed occupational and environmental history has to be taken for diagnoses in every new patient regardless of age. In adults, between 23% and 39% of patients with PAP were exposed to compounds shown to induce PAP.[2,3]

Miscellaneous Conditions

Any disease involving the lungs may potentially cause PAP, and thus PAP needs to be included in the differential diagnosis. Alternatively, PAP could be coincident with another lung disease; thus diagnostic workup for different causes is mandatory.[62]

GENERAL TREATMENT APPROACH

Therapeutic WLL

WLL remains the current standard of care for PAP. Over the years, the technique has been improved in dedicated centers.[6,63,64] Bilateral sequential WLL in the same treatment session is aimed at, but is dependent on, the clinical condition of the patient. In adults and older children in whom a double-lumen tube can be safely placed repetitively, one of the lungs is ventilated and the other is filled with aliquots of warmed saline by infusion with gravity or gentle pressure via a 50-mL syringe. After recovery of the fluid, the next washing cycle begins.[15] For smaller children or infants, we have developed and extensively tested a novel technique.[65] In this technique, 1 lung is occluded with a pulmonary artery balloon catheter (which is continuously watched with a small endoscope for its tight fit into the bronchus) and used for lavage of that lung, and the other lung is ventilated.[27,66] Indication for WLL is given when respiratory symptoms impair the quality of life (eg, oxygen treatment is necessary), development of weight is impaired, or lung function deviates from normal.

Extracorporeal Membrane Oxygenation and Lung Transplants

Sometimes, severe hypoxemia precludes immediate WLL, and patients need to be supported by extracorporeal membrane oxygenation to allow for the procedure and recovery or to have it serve as a bridge to the lung transplant.[65] Several patients with PAP (in its various forms) have had a lung transplant. However, the recurrence of PAP disease has been reported in some patients.[67,68]

NATURAL COURSE, SPECIFIC TREATMENT OPTIONS, AND OUTCOME

Each etiologic group of PAP has its own clinical course, treatments and outcome, and due to rarity of cases, has not been described in detail for most.

Autoimmune PAP

In autoimmune PAP, historical comparisons suggest that patients before the advent of therapeutic lung lavages had higher mortality than after therapeutic lung lavages had become an established treatment.[6] In ~5% to 10% of

patients, spontaneous remission may occur,[3,6] and in ~50%, only 1 WLL treatment is necessary for long-term remission.[2] Mortality during follow-up in large centers is <10%.[16] WLL is the standard treatment; however, additional options have been developed.[69] To overcome the endogenous GM-CSF autoantibodies that neutralize GM-CSF, recombinant and exogenous GM-CSF has been tested.[69,70] Administration of aerosolized GM-CSF appeared more attractive and more effective in a controlled prospective trial of 50 patients with a response rate of 62%.[71,72] Of interest are studies with a goal of decreasing the GM-CSF amounts necessary by combining it with WLL.[73] Another approach combined WLL and plasmapheresis to reduce the circulating level of GM-CSF autoantibodies; however, the results for clinical efficacy are controversial.[74,75] Rituximab, a humanized B-lymphocyte–depleting antibody, is able to reduce neutralizing GM-CSF autoantibodies and showed improved lung function in high-resolution CT scans.[2,76–78] There is no rationale for all the latter approaches in nonautoimmune PAP.

GM-CSF Receptor α or β Chain Mutation–Caused PAP

WLL treatment is the mainstay of therapy in patients with receptor mutations and has been used in the majority of cases reported so far (78%).[14] In some patients with the same mutation, treatment every 4 to 8 weeks over several years was necessary,[27] whereas in others, only few or no lavages were sufficient in maintaining a stable clinical course.

The protein amounts recovered from the lungs were similar to those in adults with autoimmune PAP[79] (Fig 3). WLLs within a few days are less efficient than lavages repeated at least 2 or more weeks apart (Fig 3C). The amount of protein recovered over time changes with disease activity and with the lavage volume necessary until the effluent is clear (Fig 3 D and E). The outcome depends mainly on WLL treatment, which was successfully performed in ~90% of all published cases.[14] In these forms of PAP, hematopoietic stem cell transplants may be successful to correct a defect that is localized in alveolar macrophages. A recurrence of PAP in such a child (M. Castelle, MD, personal communication, 2015) or an inadvertent outcome have been reported[45]; however, this scenario needs to be investigated further.

PAP Caused by Affected Surfactant Production

Several infants previously labeled as having congenital PAP have been treated with limited success or without success by WLLs.[6] An infant with PAP likely caused by a surfactant-dysfunction disorder was treated with liquid ventilation.[82] An infant girl with familial congenital PAP who was not responsive to lavages recovered 3 times from respiratory failure after intravenous immunoglobulin G administration; a mutation in SFTPB was excluded.[83] PAP reports from children with molecularly defined surfactant-dysfunction disorders are scarce. In our cohort of patients with SFTPC mutations, we reported 5 patients suffering from PAP who have been treated with WLLs.[12] No clinical success was observed in a child with mutation C121F,[81] whereas reasonable success was observed in a patient with severe course and mutation I73T.[8] The amount of protein recovered in these conditions was much lower than in other PAPs (Fig 3). This clearly indicates that in addition to alveolar filling with surfactants, other disease mechanisms play a major role for respiratory failure.[84] We are not aware of WLLs in patients with mutations in SFTPB, ABCA3, or TTF1. The outcomes of these patients are only initially related to PAP severity; and later, pulmonary fibrosis predominates.

PAP Caused by Hematologic Disorders

These patients present with respiratory insufficiency and fever in 24% of cases, particularly in patients with prolonged neutropenia from chemotherapy,[85] which demands suspicion for this complication. Initial attempts to treat PAP caused by MDS with WLLs were not successful,[52] although later survival improved.[50] WLL may be used as a bridge to bone marrow transplants, as reported for an adult patient[86] and also recently for a small 6-year-old child, for whom we performed 14 WLLs over a period of 1 year until a suitable donor was found. PAP resolved rapidly after the transplant.[49] The amount of protein recovered in this condition was similar to the amount in autoimmune PAP or GM-CSFR mutations (Fig 3).

Xue et al[87] described a patient with PAP and MDS due to idic(20q–) who was too sick to be lavaged. Consider a timely transfer of patients to centers experienced in WLL technique.

An important report indicates that empirical corticosteroid treatment in PAP secondary to MDS is a risk factor for infection and contributes to poor prognosis.[88] We had a similar experience in a patient with PAP caused by a GM-CSF-Ra mutation,[27] which suggests the need for caution with immunosuppressive therapy in these conditions. In an adult patient with PAP caused by GATA2 deficiency and infection with *Mycobacterium avium intracellulare*, WLL was not helpful.[49]

The outcome of these conditions is strongly determined by the underlying condition and is generally poorer than in autoimmune PAP. Median survival time was only 20 months in a Japanese cohort[50,88]; in another cohort, the death rate in such subjects was ~50%.[16] The causes of death were hematologic disease (33%), respiratory insufficiency

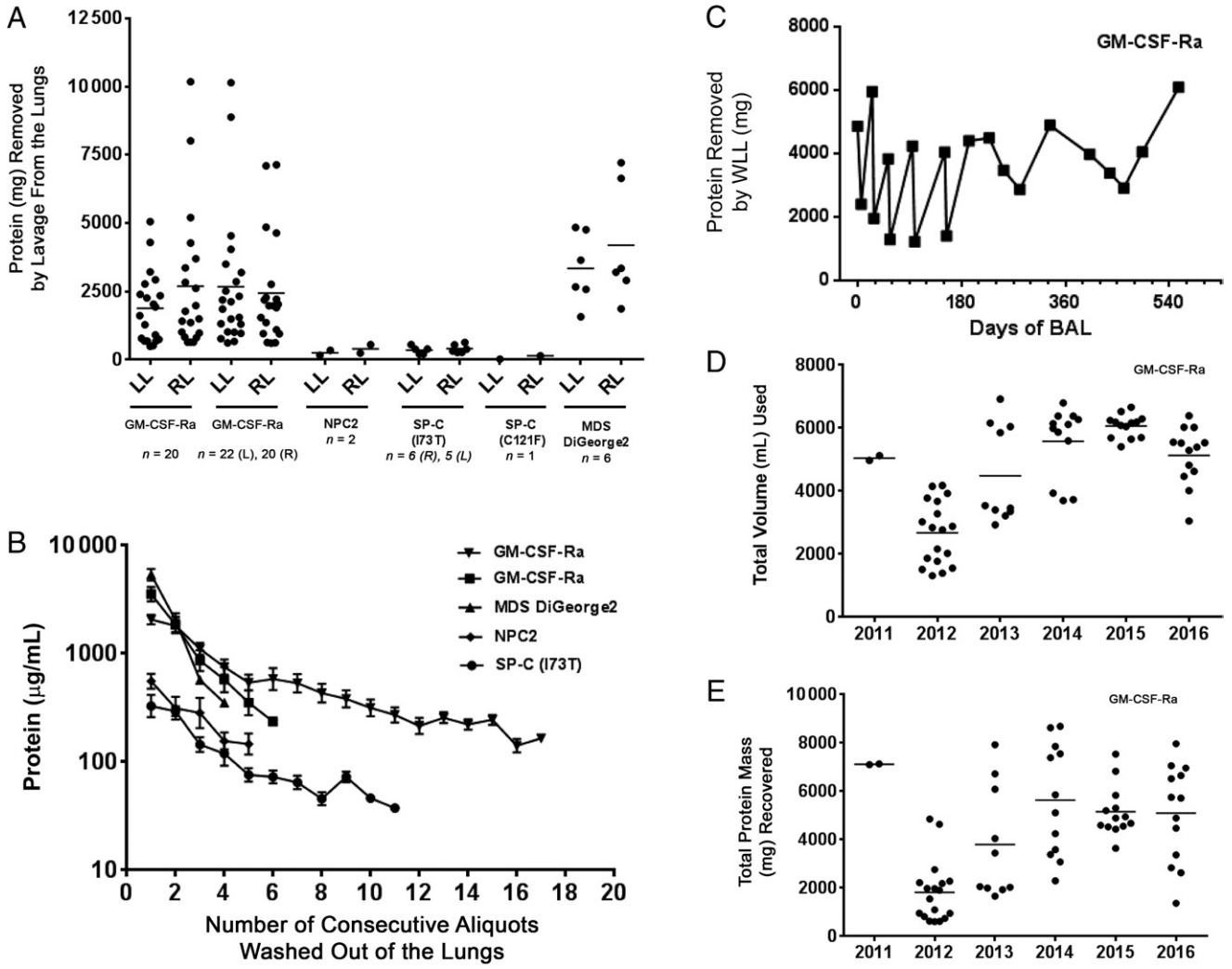

FIGURE 3

Analytical results of WLL effluents in patients with different molecularly defined forms of PAP. A, The total amount of protein removed from the left lung (LL) and right lung (RL) during repetitive WLL. Each dot indicates a single WLL. B, Washout kinetics of protein concentration in lavages from different patients are shown. GM-CSF-Ra #1, *n* = 26; GM-CSF-Ra #2, *n* = 28; MDS DiGeorge, *n* = 9; NPC2, *n* = 4; SP-C, *n* = 11. C, WLL protein removed varies with intervals used until next lavage. From day 0 through 180, lavage intervals were 1 to 4 days, then 4 weeks, then 1 to 4 days, etc. Note the low amount of protein removed after a short interval from the previous lavage. From day 180 through 540, lavage intervals were always at least 2 weeks and usually 3 to 4 weeks. D, Over-time variation of volume necessary until clear effluent is shown. E, Over-time variation of protein washed out is shown. The detailed descriptions of the PAP cases used here can be found for GM-CSF-Ra -1 in Griese et al,[27] for GM-CSF-Ra -2 in Hildebrandt et al[14] (subject I), for NPC2 in Reunert et al[80] (subject 1), for SP-C (I73T) in Brasch et al,[8] for SP-C (C121F) in van Hoorn et al,[81] and for MDS DiGeorge2 in Griese et al[49] (subject 7). Ethics approval is documented in the individual studies.

(25%), infection (25%), and unspecified bleeding (13%).

Systemic Diseases

Lysinuric Protein Intolerance (SLC7A7 Mutation)

Children present with failure to thrive and gastrointestinal symptoms from pancreatic insufficiency. In 2 children <2 years old, WLLs were performed without efficacy.[56] However, at least 1 case of long-lasting remission after WLL has been described in a PAP associated with lysinuric protein intolerance.[55] This suggests that in selected cases, WLL may be helpful and could be attempted by experienced specialists. GM-CSF therapy may be an additional option.[89,90]

MARS Mutations

Recently, we identified biallelic missense mutations in MARS as the cause of a specific form of pediatric PAP.[41] Patients develop PAP early in their disease course, and several received empirical WLLs.[57] An analysis of the cohort of 34 patients suggested that WLL did not have an influence on survival rates.[57] The protein content, the composition, and the concentration of surfactant proteins A, B, C, and D as well as lipid composition and material removed from the lungs were not different from autoimmune PAP (M.G., unpublished observations). Overall outcome of this

condition is poor, with a median age at death of ~17 years.[57]

Niemann Pick Type C2

Early lung disease in patients with Niemann-Pick disease type C2 may be associated with PAP.[58,80] In Griese et al[58] and Reunert et al,[80] empirical treatment with WLL in those patients was only transiently effective, reducing the need for oxygen and improving imaging. The amount of protein recovered was low, which also differentiated this form of PAP from the others (Fig 3 A and B). Such treatments may be helpful in less severe cases or when bridging to other treatments is the goal. The outcome is frequently determined by other organ complications from the underlying condition.

Immunologic Diseases

PAP caused by immunologic diseases is best treated by correcting the underlying defect if possible[60,91] or by symptomatic treatment (eg, immunoglobulin therapy). A 15-year-old boy with agammaglobulinemia and recurrent PAP was treated with additional WLL without any complications.[92] A 6-year-old child we treated with bridging WLL until a successful stem cell transplant was performed had underlying syndromic immunodeficiency associated with DiGeorge syndrome type 2.[49]

Infection

There is an ongoing "chicken or the egg" debate as to whether specific infections in PAP are causes or symptoms, which may be clarified by therapeutic intervention. The case of a 3-year-old boy with histologically proven PAP, a high load of Epstein-Barr virus, and a response to ganciclovir treatment supports the view that specific infections may induce PAP.[93] Early WLL may reduce complications by infections from nocardiosis or mucormycosis.

Drugs

After 9 months of treatment with sirolimus, PAP was diagnosed in a heart-lung transplant patient. The drug was discontinued, GM-CSF therapy was started, and 3 WLLs were performed to relieve respiratory distress.[94] A patient treated with the disease-modifying anti–rheumatoid arthritis drug leflunomide developed PAP (verified by a biopsy specimen) and was treated with WLL and subsequently discontinued taking the leflunomide.[95]

Dust Exposure

WLL may be symptomatically beneficial, but stopping exposure is pivotal. WLL may be ineffective after long-standing or extensive exposure, as additional pathologies such as cholesterol granuloma and fibrosis may have developed.[96]

CONCLUSIONS

The label PAP is merely an overall description of alveolar filling with surfactant. It is very important to classify all cases definitively according to etiology and on the basis of new knowledge generated by translational research. PAP of all etiologies known may be observed in children. The diagnostic algorithm as well as treatment options strongly depend on age at presentation (Fig 2, Table 2).

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This review is based on my experience as a pediatric pulmonologist caring for children of all ages with PAP, my experience as a researcher interested in PAP running a laboratory for the determination of GM-CSF autoantibodies, and a review of the literature on PAP. Diagnosis and treatment of PAP are the result of a team approach and would not have been possible without the many people involved, including T. Nicolai, K. Reiter, C. Schön, F. Hoffmann, A. Schams, T. Wesselak, E. Kaltenborn, M. Kappler, J. Ripper, J. Hildebrandt, P. Lohse, F. Brasch, M. Hofmann, I. Eckerlein, and the many coworkers on published research projects and the cooperators in internal medicine and pulmonology including M. Luisetti, I. Campo, S.A. Papiris, E.D. Manali, U. Costabel, and F. Bonella. Finally, I thank the families and children for their longstanding confidence. I apologize to other researchers of many excellent articles and reviews of the condition who were not included because of limited space.

ABBREVIATIONS

BAL: bronchoalveolar lavage
CT: computed tomography
GM-CSF: granulocyte-macrophage colony-stimulating factor
MARS: methionyl–transfer RNA synthetase
MDS: myelodysplastic syndrome
PAP: pulmonary alveolar proteinosis
RDS: respiratory distress syndrome
WLL: whole-lung lavage

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Pulmonary Alveolar Proteinosis: A Comprehensive Clinical Perspective

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