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EDITORIAL

Clinical approach for pulmonary alveolar proteinosis in children

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Abstract

In this editorial, we discuss the clinical implications of the article by Zhang *et al*. Pulmonary alveolar proteinosis (PAP) is a rare lung disease characterized by excessive surfactant accumulation in the alveoli. It is classified into four categories: Primary, secondary, congenital, and unclassified forms. Primary PAP is caused by the disruption of granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor signaling, which is necessary for the clearance of surfactant by alveolar macrophages. It is further divided into autoimmune PAP, caused by anti-GM-CSF antibodies blocking alveolar macrophage activation, and hereditary PAP, resulting from mutations in genes encoding GM-CSF receptors. Secondary PAP develops due to conditions affecting the number or function of alveolar macrophages, such as infections, immunodeficiency, hematological disorders, or exposure to inhaled toxins. Congenital PAP is linked to mutations in genes involved in surfactant protein production. Notably, the causes of PAP differ between children and adults. Diagnostic features include a characteristic "crazy-paving" pattern on high-resolution computed tomography, accompanied by diffuse ground-glass opacities and interlobular septal thickening. The presence of PAP can be identified by the milky appearance of bronchoalveolar lavage fluid and histological evaluation. However, these methods cannot definitively determine the cause of PAP. Whole lung lavage remains the standard treatment, often combined with specific therapies based on the underlying cause.

Key Words: Alveolar lavage; Children; Immunodeficiency; Pulmonary alveolar proteinosis; X-linked agammaglobulinemia

Core Tip: Both pulmonary alveolar proteinosis and X-linked agammaglobulinemia are rare diseases in children, each presenting unique challenges in diagnosis and treatment. This article aims to shed light on the clinical approach, diagnosis, and treatment processes for managing these conditions effectively.

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INTRODUCTION

Pulmonary alveolar proteinosis (PAP) is a rare primary interstitial lung disease characterized by the accumulation of surfactant-related lipids and proteins in the alveoli. First identified in 1958, PAP was initially described as a lung disease where the alveoli become filled with periodic acid-Schiff (PAS)-positive proteinaceous material, rich in lipids[1]. The main cause of PAP lies in abnormalities in pulmonary surfactant clearance and production by alveolar macrophages and type II alveolar cells[2]. Its prevalence in the childhood population is exceptionally low, with approximately 2 cases per million[3].

PAP can be classified into four main categories based on its cause: Primary (including autoimmune and hereditary PAP), secondary, congenital, and unclassified forms. Autoimmune PAP is the most common form, affecting over 90% of patients[3,4]. However, it is very rare in children[5]. Conversely, genetic causes of PAP, encompassing both congenital and hereditary forms, are more prevalent in children. Additionally, PAP can occur secondary to infections, immunodeficiency, hematological disorders, or exposure to inhaled toxins[6].

While respiratory symptoms and clinical signs of PAP are non-specific, persistent respiratory symptoms consistent with childhood interstitial lung diseases in children with PAP often reveal a "crazy-paving" pattern, characterized by thickened interlobular septa and intralobular lines superimposed on a background of ground-glass opacities[7]. However, the gold standard for diagnosing PAP remains histopathological confirmation, even when these computed tomography (CT) findings are present[8]. Despite its rarity in children, this article will explore the pediatric aspects of PAP and discuss potential therapeutic strategies.

PATHOPHYSIOLOGY OF PAP

Pulmonary surfactants are essential substances that prevent lung collapse during respiration and defend against microbial pathogens[9,10]. These surfactants are primarily composed of proteins and lipids such as phosphatidylcholine and are secreted by type II alveolar epithelial cells[10]. Maintaining surfactant homeostasis is achieved through a balanced interplay between production and recycling in type II alveolar epithelial cells and catabolism and clearance by alveolar macrophages.

Surfactant proteins (SP-A, SP-B, SP-C, and SP-D) are encoded by the genes SFTPA, SFTPB, SFTPC, and SFTPD. These proteins are synthesized in the endoplasmic reticulum of type II alveolar epithelial cells, where they are assembled and stored in lamellar bodies. SP-A and SP-D are involved in the innate immune response, while SP-B and SP-C are hydrophobic and are stored and secreted alongside surfactant phospholipids, which are crucial for reducing alveolar surface tension[11,12]. NK2 homeobox 1 (NKX2-1) is a vital transcription regulator for surfactant proteins[13], and ATP-binding cassette transporter A3 (ABCA3) is involved in lamellar body formation and phospholipid transport[14]. Mutations in surfactant protein genes can alter the quantity and quality of surfactant produced, making it less effective and causing clearance problems. Also, proteins that are not secreted can build up in type II pneumocytes, damaging the cells. These cellular issues contribute to the development of congenital PAP.

Approximately 70% of used surfactant is recycled by alveolar type II cells, which is crucial for maintaining lung function. The remaining 30% is broken down and eliminated by alveolar macrophages[15]. In healthy lungs, certain proteins from the used surfactant are broken down into cholesterol and fatty acids within the lysosomes of alveolar macrophages. This breakdown leads to the accumulation of cholesterol inside the cells, activating factors such as PU-1, which control gene expression. These factors increase the production of lipid transporters, such as ABCA1 and ABCG1, that help remove excess cholesterol from the cells[15,16]. Laboratory studies have shown that GM-CSF promotes the growth and function of PU-1 in alveolar macrophages. When GM-CSF signaling is disrupted, it reduces the expression of lipid transporters, leading to inadequate removal of cholesterol. Consequently, dysfunctional foamy alveolar macrophages are formed, and surfactant builds up in the lungs[15,16]. The GM-CSF receptor is made up of two subunits, α and β, encoded by the genes CSF2RA and CSF2RB, respectively. Mutations in these genes or the presence of anti-GM-CSF antibodies can interfere with the normal function of GM-CSF[4,17].

Alveolar macrophages play a crucial role in clearing surfactant from the lungs. A reduction in their number or impairment of their ability to metabolize surfactant can lead to its accumulation, resulting in secondary PAP. This condition can arise in individuals with various underlying conditions. These conditions include primary immunodeficiencies, including X-linked agammaglobulinemia (XLA). BTK is a key molecule in the Toll-like receptor (TLR) pathway,

involved in controlling cytokine production, phagocytosis, differentiation, and overall macrophage activity following TLR activation. XLA might directly contribute to the development of PAP. Additionally, children with XLA are susceptible to recurrent lung infections, which can lead to PAP. Therefore, XLA is considered a potential cause of PAP[7]. Other etiologies include chronic infections, hematological malignancies, exposure to toxins or drugs, and autoimmune disorders[17,18]. Secondary PAP has also been reported in some genetic diseases, though the underlying mechanisms are unclear[19]. Finally, there is a small group of individuals with suspected PAP categorized as unclassified PAP due to an unknown cause[17].

ETIOLOGIES IN CHILDHOOD PAP

Although autoimmune PAP is the most common form in adults, it is very rare in children. In contrast, genetic causes predominate in children with PAP, including congenital PAP, hereditary PAP, and secondary PAP resulting from immunodeficiency or genetic diseases.

Congenital PAP

Mutations in surfactant protein genes are the main cause of congenital PAP. Essential genes for surfactant production include SFTPB, SFTPC, ABCA3, and NKX2-1. Although neonatal respiratory distress is common, mutations in SFTPC, ABCA3, and NKX2-1 genes can also occur in children. Notably, the mechanism of mutation differs for SFTPC, as it can result in a gain of toxic function. The NKX2-1 gene encodes thyroid transcription factor 1 (TTF-1), crucial for the thyroid gland and early lung development. Additionally, TTF-1 plays a vital role in the transcription of surfactant proteins, including ABCA3. Interestingly, NKX2-1 is also expressed in the basal ganglia. Mutations in the NKX2-1 gene have been linked to "Brain-Thyroid-Lung" syndrome, characterized by lung disease, neurological findings, and hypothyroidism. Haploinsufficiency due to reduced NKX2–1 expression appears to be the primary mechanism for the disease[11,12].

Hereditary PAP

The GM-CSF receptor consists of two subunits: The α chain, encoded by the CSF2RA gene on chromosome X, and the β chain, encoded by the CSF2RB gene on chromosome 22. When GM-CSF binds to this receptor, it activates JAK2, initiating signaling pathways involving transcription factors such as PU.1, PPARα, and PPARγ. These transcription factors then regulate the expression of ABCA1 and ABCG1 transporters, which are essential for removing cholesterol and clearing surfactants from alveolar macrophages[15]. Deficient GM-CSF signaling, caused by mutations in the CSF2RA or CSF2RB genes, reduces the expression of ABCA1 and ABCG1. This reduction prevents cholesterol from leaving alveolar macrophages, leading to cholesterol buildup and, ultimately, PAP. Hereditary PAP is usually inherited in an autosomal recessive manner, but some mutations may show incomplete or variable penetrance[20]. Hereditary PAP mostly affects girls, with symptoms usually appearing within the first few years of life, around the age of 3 years on average. However, some patients may be asymptomatic and are found through screening of siblings with the condition[19].

Secondary PAP due to immunodeficiency

Mutations in genes associated with immunodeficiency, including GATA2 deficiency, adenosine deaminase deficiency (ADA), and OAS1 mutations, can also be linked to PAP. GATA2, a transcription factor essential for the differentiation of endothelial and immature hematopoietic cells, also plays a role in the function of alveolar macrophages, particularly in phagocytosis. However, the exact mechanisms by which GATA2 regulates phagocytosis remain unclear. Approximately 11% of patients with GATA2 deficiency develop PAP. These patients often experience severe or chronic mycobacterial infections and extensive bone marrow dysfunction[21]. Inherited defects in the function of ADA lead to severe combined immunodeficiency (SCID), making these patients susceptible to various infections, including Mycobacterium, cytomegalovirus, and adenovirus. Interestingly, the identification of PAP often coincides with these infections in ADA-deficient patients, suggesting a possible link[22]. However, the exact role microbes play in the development of PAP in this context remains unclear. The frequency of PAP among patients with ADA-deficient SCID is around 43%[22]. Gain-of-function mutations in the OAS1 gene lead to dysfunction and apoptosis of monocytes, macrophages, and B cells. While OAS1 mutations have been linked to hypogammaglobulinemia, the specific mechanisms and how they contribute to this condition are not fully understood[23,24]. Notably, PAP has also been reported in other immunodeficiency disorders, including agammaglobulinemia[25], DiGeorge syndrome[26], and hyper-IgM syndrome[27]. This suggests a potential link between impaired immunity and the development of PAP.

Secondary PAP due to genetic diseases

PAP has been linked with various genetic disorders, although the underlying mechanisms remain unclear. For example, lysinuric protein intolerance (LPI) is a condition where PAP is observed in all patients with respiratory involvement. The median age of onset for lung problems in LPI is around 3 years. These patients often face a poor prognosis, with a reported 60% mortality rate due to respiratory failure[28]. Mutations in other genes, such as the methionyl transfer RNA synthetase (MARS) gene, can also cause PAP. This mutation leads to a multisystemic disease commonly known as interstitial lung and liver disease syndrome[19,29].

Autoimmune PAP

Autoimmune PAP has been reported in a small number of adolescents, typically presenting with progressive dyspnea

upon exertion. Diagnosis is confirmed through imaging tests, detection of elevated anti-GM-CSF antibody levels in the blood, and the characteristic milky appearance of bronchoalveolar lavage fluid (BALF)[5].

CLINICAL PRESENTATION

In the newborn period, PAP should be considered in full-term infants with respiratory distress and chest X-ray findings consistent with ground-glass opacities. This consideration is especially important if these symptoms persist after 7-10 days of treatment for other potential causes, as in the case report by Zhang *et al*[7]. In older children, symptoms are often non-specific, including cough and difficulty breathing. Less common symptoms may include chest pain, weight loss, fatigue, and fever. Hemoptysis, if present, is usually mild and could indicate a lung infection. Physical examination findings are typically normal, but cyanosis, clubbing of fingers, and chest crackles may sometimes be observed. The accumulation of cholesterol in alveolar macrophages can impair immune function, making patients more susceptible to infections. Therefore, investigating any evidence of infection in these patients is crucial.

RADIOLOGICAL FINDINGS

Chest radiography

In PAP, chest X-rays typically show symmetrical opacities in both lungs, concentrated around the lung hilum and bases [7]. These opacities do not have air bronchograms which are typically seen in consolidation cases. Unlike acute pulmonary edema, PAP does not cause enlargement of the heart or pleural effusion. In milder cases, the chest X-ray may only show ground-glass opacities, appearing hazy on the film[31].

Chest CT scan

Chest CT scans play a crucial role in diagnosing PAP. The observed CT scan pattern can strongly indicate the disease, leading to further BALF evaluation. Key CT scan abnormalities in PAP include ground-glass opacities, interlobular septal thickening, and intralobular septal thickening with consolidation. Reticulations often appear on ground-glass opacities, forming a distinctive "crazy-paving" pattern[6,7]. Ground-glass opacities and subpleural sparing are more common in autoimmune PAP compared to diffuse ground-glass opacities and lung cysts in surfactant protein disorders[7,30]. There is usually no specific distribution pattern across lung zones. However, lower lung regions are often more frequently involved. Large focal areas of consolidation are uncommon and should raise suspicion for an opportunistic infection. Also, PAP usually does not lead to mediastinal adenopathy or pulmonary nodules[31].

The correlation between histological findings and radiological findings helps to explain the underlying cause of the abnormalities seen on CT scans. Ground-glass opacities often indicate a buildup of lipoproteinaceous material within the air sacs of the lungs[32]. However, the significance of reticulation patterns is less straightforward. These patterns might suggest inflammation, edema, or the accumulation of lipoproteinaceous material in the lung lobes or along their edges [31]. Nonetheless, it is crucial to note that a crazy-paving pattern on a CT scan, while suggestive of PAP, is not specific to this condition. Furthermore, it can manifest in other lung diseases such as acute respiratory distress syndrome, lipoid pneumonia, organizing pneumonia, pulmonary hemorrhage, or *Pneumocystis jirovecii* pneumonia[33].

BRONCHOALVEOLAR LAVAGE FLUID STAINING

BALF analysis is crucial for diagnosing PAP. Characteristic features observed in samples obtained from affected lung areas typically display a milky appearance due to lipoproteinaceous material[6-8]. Conversely, BALF from healthy lung zones may appear normal or slightly abnormal, depending on the material present[31]. As part of the diagnostic workup, cytological examination, and PAS staining are essential. In PAP, BAL fluid often exhibits increased cellularity, with a higher proportion of lymphocytes compared to healthy controls. Microscopic examination reveals large, foamy macrophages containing eosinophilic granules[17,31]. Another hallmark finding is the presence of extracellular, globular hyaline material with strong positivity on PAS staining. Additionally, ultrastructural analysis, if performed, may reveal numerous lamellar bodies with a structural resemblance to myelin[31].

ADDITIONAL TESTING

Identifying the underlying cause is crucial, especially in children, in addition to diagnosing PAP itself. This helps determine the overall clinical picture and prognosis of the patient, providing valuable insights for treatment planning. Genetic testing should prioritize mutations in surfactant protein genes and the GM-CSF receptor gene for a comprehensive assessment. Depending on the specific presentation of the case, a pediatric specialist in immunology or rheumatology may recommend further genetic testing for other possible underlying conditions[6]. However, next-generation sequencing (NGS) panels offer an efficient alternative, accelerating the diagnostic process. These NGS panels, specifically designed for PAP, encompass all the genes potentially involved in the disease, streamlining the diagnostic process and

facilitating timely interventions[19].

Anti-GM-CSF antibodies serve as a specific marker for autoimmune PAP. Typically rare in children, these antibodies are crucial indicators of the condition. While low concentrations (usually less than 1 μg/mL) can be detected in healthy individuals, people with malignancies, inflammatory conditions, and even some cases of secondary PAP, autoimmune PAP patients typically have high levels of serum GM-CSF autoantibodies (greater than 9 μg/mL). The diagnostic test for autoimmune PAP is highly specific and sensitive, with a standardized procedure demonstrating 100% accuracy. Receiver operating characteristic curve analysis has established a threshold of 5 μg/mL as optimal for diagnosing autoimmune PAP. GM-CSF autoantibody testing is currently available at specialized centers in the United States, Europe, China, and Japan, facilitating accessibility for patients worldwide[17].

Serum lactic dehydrogenase, carcinoembryonic antigen, and CYF21-1 are valuable serum markers for evaluating disease activity in PAP. These markers can also indicate how a patient responds to different PAP treatments. However, more research is necessary to establish these markers as standard tools for monitoring PAP[34].

TREATMENT

PAP presents a challenge in pediatric care due to the absence of a single standardized treatment. However, treatment options vary depending on factors such as the underlying etiology and disease severity. Among these options, whole lung lavage stands out as the current standard of care for children with PAP[6]. This procedure involves removing accumulated surfactant material from the lungs, with the aim to improve oxygenation and overall respiratory function.

Whole lung lavage is typically performed under general anesthesia in an operating room or intensive care unit. During the procedure, a double-lumen endotracheal tube is inserted to isolate and ventilate one lung at a time. Fiberoptic bronchoscopy is then used to confirm the proper placement of the tube. The patient is positioned either dorsally or in lateral decubitus with the lung to be lavaged facing upwards, while a mechanical ventilator supports breathing in the other lung. A sterile saline solution, warmed to body temperature (37°C), is instilled into the lavaged lung. Gravity aids the drainage of fluid through an outflow tube, and additional techniques such as manual or mechanical chest percussion may be used to improve drainage. The lavage process is continued until the returning fluid becomes progressively clearer. Following this procedure, the time to extubation depends on the patient's condition. If necessary, the other lung can undergo lavage within 24-48 hours. Close monitoring for complications, such as low oxygen saturation, seizures, pneumothorax, pleural effusion, and fever, is crucial, as they may indicate an infection[6,18,31].

The response of whole lung lavage in children with PAP, particularly those with congenital PAP, is often poor. In these cases, other strategies such as lung transplantation might be necessary[35,36]. For hereditary PAP, hematopoietic stem cell transplantation (HSCT) has shown some success[37,38]. Additionally, in cases with MARS gene mutations, methionine supplementation can also be beneficial[29]. Treatment for autoimmune PAP in adults is often applied in children, including whole lung lavage, inhaled GM-CSF to increase levels, plasmapheresis to remove neutralizing antibodies, and rituximab to suppress antibody production. However, the availability of these options may vary depending on the treatment center. Despite this variability, inhaled GM-CSF appears to be a promising non-invasive and well-tolerated therapeutic approach[5].

HSCT offers a good response in PAP caused by mutations in genes associated with immunodeficiency, such as GATA2 deficiency[21]. However, the outcome for ADA and OAS1 mutations is often poor[22-24]. Additionally, PAP can be a complication of primary immunodeficiency disorders such as agammaglobulinemia, SCID, and hyper-IgM syndrome. While HSCT is the primary treatment for these underlying conditions, other therapies such as regular intravenous immunoglobulin (IVIG) or thymosin replacement therapy can sometimes normalize chest imaging and improve respiratory function in cases of secondary PAP arising from immunodeficiency[26,27]. Furthermore, children with primary immunodeficiency are prone to recurrent pulmonary infections, which can increase the risk of developing PAP. Therefore, addressing the underlying immunodeficiency with IVIG therapy may improve the overall prognosis for these patients, as in the case report by Zhang *et al*[7].

CONCLUSION

PAP is a condition characterized by the accumulation of surfactant material in the lungs, often resulting in respiratory impairment. PAP can occur as a complication of primary immunodeficiency disorders, including agammaglobulinemia. Additionally, children with primary immunodeficiency are prone to recurrent pulmonary infections, which can increase the risk of developing PAP. Diagnostic features of PAP include a characteristic "crazy-paving" pattern on high-resolution computed tomography, accompanied by diffuse ground-glass opacities and interlobular septal thickening. The presence of PAP can be confirmed by the milky appearance of BALF. Further diagnostic confirmation can be obtained through microscopic examination, which reveals large, foamy macrophages containing eosinophilic granules and the presence of extracellular, globular hyaline material with strong positivity on PAS staining. In addition to whole lung lavage, treating the underlying immunodeficiency with IVIG therapy may normalize chest imaging, improve respiratory function, and ultimately enhance the overall prognosis for these patients.

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