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REVIEW ARTICLE

Pulmonary Alveolar Proteinosis—Where Do We Stand?

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ABSTRACT

Aim: This review intends to recapitulate the knowledge about pulmonary alveolar proteinosis (PAP) and insight into the advances in the pathogenesis and treatment of this condition.

Background: A PAP is a seldom occurring disease with numerous possible etiologies.

Review results: The disease has an insidious onset and the opinion is mostly delayed due to the fact that patients present late when there is abundant surfactant assimilation in alveoli to diminish gas exchange and cause dyspnea. An appropriate history, typical chest radiographic and high resolution computed tomography (HRCT) findings together with characteristic bronchoalveolar lavage (BAL) fluid help to elucidate the diagnosis in most cases. However, transbronchial lung biopsy (TBLB) or open lung biopsy may be rarely needed for difficult to diagnose cases. Treatment is needed for patients with symptomatic disease and whole lung lavage is the treatment of choice.

Conclusion: A PAP is a rare disease entity with variable natural history. The clinical course varies from respiratory failure to spontaneous resolution.

Clinical significance: This review will help to furnish an outline of the various aspects of this disease in light of fresh scientific advancements in the pathogenesis and treatment of this condition. Knowledge about the disease will serve to better define the role of alternative and new therapies for the same.

Keywords: Pulmonary alveolar proteinosis (PAP) review, Surfactant, Whole lung lavage.

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INTRODUCTION

Pulmonary alveolar proteinosis (PAP) is a distinctive disorderthat is represented by the progressive accumulation oflipo proteinaceous material inside the alveoli, that stains positive with periodic acid–Schiff (PAS).[1]

Rosen et al. first depicted this condition in the year 1958.[1]

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The disease has a variable clinical course that may resolve spontaneously or lead to progressive respiratory insufficiency and death.[1-3]

Epidemiology

Accurate data about the incidence and prevalence of PAP is not known. Initially, the prevalence of autoimmune pulmonary alveolar proteinosis was reported to be at 3.7 cases per million, which has increased to 6.2 cases per million as per recent reports.[2,4]

A study by Hadda et al. indicated that PAP is a seldom occurring disorder that has an incidence of about 5/1100 hospital admissions in a respiratory unit at a tertiary care centre.[5]

The disease dominates in men and the male to female ratio is in range of 2.1:1 to 2.7:1.[2]

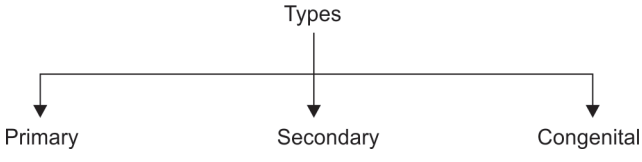
Seymour et al. in their study observed that the disease was diagnosed at a median age of 39 years, while in males, this condition becomes evident at a later age.[2]

Seymour et al. in their meta-analysis observed that 72 % of PAP patients were smokers with the majority being men. However, it was seen that among smokers and non-smokers, there were no differences regarding symptoms or other parameters like the serum levels of LDH, paO2 or the diffusion gradient for oxygen.[2]

A study conducted by Hwang et al., found that active cigarette smoking at the commencement of PAP is related to the severity of PAP.[6]

Classification

The various types that can be seen are primary (idiopathic/autoimmune), secondary and congenital.[2-4]



More than 90% of cases of pulmonary alveolar proteinosis originate as a primary acquired disorder of unknown cause and without any familial predisposition.[1,7-9]

The idiopathic/primary variety is denominated as "autoimmune PAP" because of the presence of anti-granulocyte macrophage colony-stimulating factor (GM-CSF) antibodies. This variety makes up more than 90% of all reported cases of this disorder.[4,2,10]

Secondary pulmonary alveolar proteinosis occurs in league with conditions that involve functional impairment or decreased numbers of alveolar macrophages like lysinuric protein intolerance,[11] acute silicoproteinosis[12] severe combined immunodeficiency disorders, or underlying malignancies almost exclusively of hematopoietic origin.[13,14]

Congenital pulmonary alveolar proteinosis appears due to a mutation in the surfactant protein B (SFTPB) gene resulting in the inadequacy of surfactant-protein-B, the gene encoding for ATP-binding cassette (ABC) transporter A3 and *colony stimulating factor 2 receptor beta (CSF2RB)* gene encoding GM-CSF receptor beta chain.[15,16]

The majority of these are transmitted in an autosomal recessive manner.[15,17]

The adult forms of the disease are mostly autoimmune with the presence of anti-GM-CSF antibodies and/or secondary to toxic inhalation or haematological disorders, without anti-GM-CSF antibodies.

Pathophysiology

Normal Surfactant Physiology

The surfactant is composed ofa combination of lipids (mainly phosphatidylcholine) and proteins produced by type II alveolar epithelial cells. There are four main surfactant proteins are SP-A, SP-B, SP-C and SP-D that are encoded by the corresponding genes SFTP A, B, C, and D.[18] Surfactant lipids and proteins are synthesized by type 2 pneumocytes and removed from the alveoli by recycling and degradation by type 2 cells and also, to some extent by the alveolar macrophages.[19]

The surfactant consisting of 90% lipids and 10% proteins, not only reduces the alveolar surface tension but also has a significant role in the immunological mechanisms of lung natural defense and possibly other mucous surfaces.[20]

Thus, the surfactant homeostasis is regulated by its balanced production and catabolism. GM-CSF is found in serum and many tissues, and attaches to its receptors present on various cells like monocytes, macrophages, and alveolar type 2 pneumocytes and executes its biological effect.[21]

Transcription factor PU.1 acts on GM-CSF that further governs the terminal differentiation of alveolar macrophages in the lungs, further adding to their competence m for uptake and breakdown of surfactant proteins and surfactant phospholipids.[22]

It has been seen that PAP arises from faulty clearance and accumulation of surfactant in pulmonary alveoli.[19]

Insight into the disease pathogenesis was provided in 1994 when it was detailed that knockout mice that had a deficiency of GM-CSF/its receptor developed lung lesions corresponding to PAP.[22] Thus, lack of GM-CSF, causing flawed processing of surfactant by alveolar macrophages is strongly thought of.[19]

The transcription factor PU.1 is instrumental in controlling the expression of GM-CSF in mouse alveolar macrophages PU.1 knockout mice exhibit PAP, and re-expression of PU.1 averts the development of PAP.[23]

Subsequently, there was detection of a neutralizing immunoglobulin G (IgG) antibody against GM-CSF[11] and this autoantibody was seen to vitiate function of neutrophils, increasing susceptibility to infections in these patients.[24]

Clinical Manifestations

Pulmonary alveolar proteinosis (PAP) occurs more frequently in males than females, with usual beginning in the fifth decade of life.[7]

The common clinical manifestations include dyspnea and cough, with fever, chest pain and hemoptysis being rare manifestations.

There are usually no significant findings on physical-examination, but an occasional patient may present with inspiratory crackles, clubbing, and cyanosis.[25]

Diagnosis

Radiology

Chest radiograph findings include bilaterally symmetrical airspace disease with an ill-defined nodular or confluent alveolar filling pattern, with a perihilar or basal distribution,[26] but the radiographic findings may also have asymmetric,[27] unilateral[1,8] peripheral or lobar1 pattern of distribution (Fig. 1)

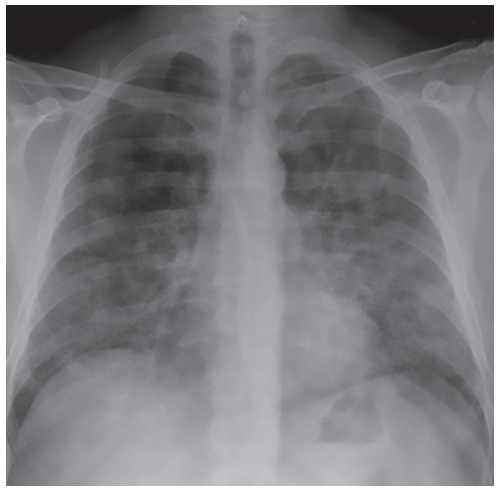


Fig. 1: Chest X-ray in pulmonary alveolar proteinosis

The characteristic findings on HRCT chest (Fig. 2) appear as patchy, ground glass opacifications, superimposed with interlobular septal and intralobular thickening. This configuration is commonly referred to as "crazy paving".[28,29]

High resolution computed tomography (HRCT) can also be used to ascertain the spread of lung involvement and forassessing the severityof disease before beginning treatment.[28]

Pulmonary Function Tests

The pulmonary function tests demonstrate restriction with decreased values of forced vital capacity (FVC) and total lung capacity (TLC) and severe diminution of carbon monoxide diffusing capacity.[2,26]

Bronchoalveolar Lavage

Bronchoalveolar lavage (BAL) fluid adds to the diagnosis by the appearance of fluid that is opaque and milky on gross examination, and it separates into a thick sediment layer and a translucent supernatant on standing.[30]

Microscopic examination of BAL fluid reveals enlarged foamy alveolar macrophages that are filled with PAS-positive intracellular inclusions that are diastase resistant.[31]

Transbronchial Biopsy

Transbronchial biopsy (TBLB) specimens provide a tissue diagnosis,[32] but they may not yield any results due to patchy nature of the disease.

Anti GM-CSF Antibodies

Anti GM-CSF Autoantibodies are also raised.[33] These antibodies are specific to autoimmune PAP.

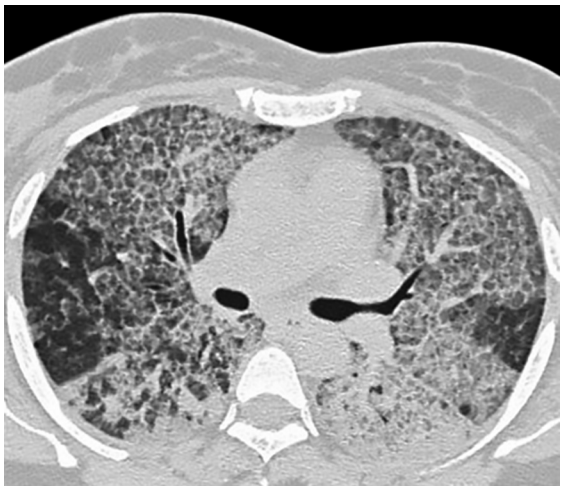


Fig. 2: HRCT chest in pulmonary alveolar proteinosis

Other Markers

Routine blood investigations are mostly unremarkable. The serum levels of lactate dehydrogenase (LDH) are found to be raised in half of the cases and between two and three times the normal range in the rest. Carcinoembryonic antigen and Krebs von den Lungen 6 (KL-6) levels are observed to be in a higher range as compared to the levels seen in other diffuse interstitial pneumonia and these levels could be associated with disease severity.[4] These markers, however, do not contribute in either the diagnosis orin the therapeutic decision making

One may also find increased levels of the surfactant proteins SP-A, SP-B and SP-D and these could be associated with disease severity.[4]

Treatment

Without any therapy, the five-year survival of this disease has been estimated to be around 85%.[2]

Management of of pulmonary alveolar proteinosis depends on the underlying etiology.

Patients inflicted with moderate to severe disease necessitate therapy with whole lung lavage (WLL).

Whole lung lavage (WLL) has been successfully used for the treatment of primary pulmonary alveolar proteinsis ever since the early 1960s, and it remains the standard of care even today.[34]

The major indication for and timing of whole-lung lavage is an asymptomatic disease with dyspnea that limits activity and progressive deterioration of arterial oxygenation.[26]

Clinical,[34] functional,[8,34] and radiological[35] improvements are apparent in about 80% of patients after the first whole-lunglavage. The median persistence of benefit can extend up to as longas 15 months but still, repeat lavage is required in the majority of patients.[2]

Whole lung lavage (WLL) is performed under general anesthesia. It requires the introduction of a double lumen endobronchialtube. The two lungs are isolated. This is followed by ventilating both lungs with 100% oxygen for at least 20 minutes. The lung to be treated is then isolated at the end of expiration. The procedure involves repeatedly accumulating and washing out the isolated lung with warm saline with or without chest percussion to emulsify and physically remove the alveolar surfactant. The temperature, the volume of saline instilled, and fluid balance is regulated. The earliest fluid that comes backis very milky or turbid and the procedure of filling and draining the lungswith saline is repeated until the effluent becomes clear. Total volumes of saline required can range from 20 to 40 liters. At the end of theprocedure the residual saline is drained andaspirated from the lung and ventilation with 100% oxygen is resumed. The double

lumen tube is replaced by an endotracheal tube and patient is observed for one hour in the recovery unit.[36,37]

The lavage needs to be repeated every 6 months in around 15% of patients, andless than 10% are nonresponders.[36]

Corticosteroids are not recommended for treating PAP.[2]

Therapy involving GM-CSF has been attempted in those who do not respond to WLL. Many prospective phase-2 trials of GM-CSF therapy in patients with pulmonary alveolar proteinosis have been conducted, but the role of this therapy is not entirely clear.[38]

Other promising therapy for autoimmune PAP includesplasmapheresis intending to lower levels of anti-GM-CSF antibodies.[39]

Another novel approach involves de-escalating autoantibody levels by depleting B lymphocytes.

Rituximab, a monoclonal antibody directed against the CD20 antigen of B lymphocytes, has been tested.[40]

Complications

There is a susceptibility to develop infections, mainly due to opportunistic pathogens and these account for approximately 18% of reported deaths from pulmonary alveolar proteinosis.[2,3,24]

CONCLUSION

A PAP is a rare disease entity with variable natural history. The clinical presentationvaries from severe pulmonary inadequacy to spontaneous resolution.

Much has been learned about this condition and with the advancement of our knowledge, further insights into this disease entity shall be provided.

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