IPOPI
INTERNATIONAL
PATIENT ORGANISATION
FOR PRIMARY IMMUNODEFICIENCIES

PRIMARY **IMMUNODEFICIENCIES**

MANAGEMENT OF **aPAP**

ABBREVIATIONS

aPAP	Autoimmune pulmonary alveolar proteinosis
GM-CSF	Granulocyte–macrophage colony-stimulating factor
IgG	Immunoglobulin G
IPOPI	International Patient Organisation for Primary Immunodeficiencies
PAP	Pulmonary alveolar proteinosis
PID	Primary immunodeficiency

Autoimmune pulmonary alveolar proteinosis (1st edition)

Published by IPOPI: **IPOPI.org**

SUMMARY

Autoimmune pulmonary alveolar proteinosis (aPAP) is a rare autoimmune disorder affecting the lungs and is characterised by progressive accumulation of surfactant in the pulmonary alveoli of the lungs. Males and females are equally affected by aPAP, with an age of onset of the disease usually between 30 to 50 years, although reported ages range from childhood to 90 years old.

Autoimmune PAP is caused by the immune system generating antibodies to granulocyte–macrophage colony stimulating factor (GM-CSF), blocking its biological effects in the lungs which leads to dysfunctional alveolar macrophages that are unable to clear surfactant from the alveolar surface. The surfactant accumulates in the alveoli, blocking them and reducing the normal passage of oxygen into the blood, which eventually leads to increased difficulty in breathing. Some people with aPAP may not show symptoms, while others have progressive difficulty breathing and shortness of breath upon exertion. Other symptoms include a dry cough, sometimes with blood (haemoptysis) or phlegm, fever, fatigue, weight loss, cyanosis (bluish skin and fingernails), chest pain and lung infections. aPAP is associated with an increased risk of serious infections, which is consistent with an impaired immune function. The essential criterion for a diagnosis of aPAP is elevated serum antibody levels against GM-CSF.

At present there isn't a cure for aPAP and treatment depends on the severity of symptoms. Whole lung lavage, which is used to remove the excess surfactant from the lungs, is an effective treatment option, with others including off-label use of GM-CSF augmentation therapy, plasmapheresis, bronchodilators, and supplementary oxygen. While the clinical course of aPAP varies considerably from person to person, prognosis has improved with the introduction of whole lung lavage and the 5-year survival is 95%.

INTRODUCTION

This booklet explains what aPAP is, the manifestations of aPAP, how it is diagnosed, treated, and managed.

Autoimmune pulmonary alveolar proteinosis (aPAP) is a rare autoimmune disorder affecting the lungs. Autoimmune PAP is the most common form of pulmonary alveolar proteinosis (PAP), accounting for 90% of cases,[1] and is characterised by progressive accumulation of surfactant in the air sacs of the lungs (pulmonary alveoli) and resulting difficulty breathing (hypoxaemia), disruption of granulocyte/macrophage colony–stimulating factor (GM-CSF) signalling, alveolar macrophage and neutrophil dysfunction, innate immunodeficiency and, in some individuals, serious secondary infections, pulmonary fibrosis, respiratory failure and death.

The other types of PAP are secondary PAP, which develops when an underlying condition reduces either the number and/or the function of alveolar macrophages, and congenital PAP, which is a genetic disorder that results in either insufficient or dysfunctional surfactant.

Autoimmune PAP has an estimated prevalence of 7 to 26 cases per million in the general population,[1,2] and occurs in men, women, and children of all ethnic backgrounds and geographic locations, independent of socioeconomic status.[3] In people with aPAP, males and females are equally affected,[4] with a median age at time-of-diagnosis of 39 to 51 years, although reported ages range from childhood to 90 years old.[1,2] Autoimmune PAP rarely occurs in patients younger than 10 years of age and was reported only in few children who presented in late childhood or adolescence.[5]

WHAT CAUSES aPAP?

In the lungs, pulmonary surfactant is a complex mixture of phospholipids and proteins (~90% phospholipids and 10% proteins) that is synthesised by type II epithelial cells. The surfactant forms a monolayer lining the alveoli, lowering the surface tension, and making the lungs easier to expand. Alveolar macrophages clear surfactant and debris from the alveolar surface and are regulated by GM-CSF. In aPAP, immunoglobin G (IgG) antibodies bind to GM-CSF (i.e. anti-GM-CSF antibodies) and block its ability to bind to alveolar macrophages, thereby preventing its biological effects. This leads to dysfunctional alveolar macrophages that are unable to clear surfactant from the alveolar surface.[1] The surfactant accumulates in the alveoli and this build-up makes it more difficult to breathe, and reduces the normal passage of oxygen into the blood leading to low blood oxygen levels. In addition, the macrophages that normally clear away the surfactant now accumulate large lysosomes filled with surfactant and are unable to perform immune functions normally such as phagocytosis, chemotaxis, superoxide production, pathogen-recognition receptor expression, cytokine release and cellular adhesion.[2] Furthermore, lymphocytes and neutrophils are less functional which leads to an increase in opportunistic infections.[1]

It is important to note that the alveolar architecture is usually well preserved in people with aPAP, except when pulmonary fibrosis is also present, which may occur late in the clinical course of the disease.

There has been speculation that cigarette smoke and infectious diseases stimulate the development of anti-GM-SCF antibodies because of the high prevalence of smoking (53–85%) and infections in patients with PAP,[2] but no causal link has been found between cigarette smoke and aPAP.[2]

SIGNS AND SYMPTOMS – CLINICAL PRESENTATION OF aPAP

Clinical presentation of aPAP varies from indolent to emergent and symptoms are often non-specific with one-third of patients being asymptomatic at the time of presentation.[6] Shortness of breath (dyspnoea) is the most common symptom of aPAP usually presenting between the ages of 30 to 50 years. Most patients describe having difficulty breathing while exercising (exertional dyspnoea) that progresses to resting dyspnoea over months to years. Other symptoms include a dry cough, sometimes with blood (haemoptysis) or phlegm, fever, fatigue, weight loss, cyanosis (bluish skin and fingernails), chest pain, and lung infections. Fever and haemoptysis are uncommon unless a secondary infection is also present.

Autoimmune PAP is associated with an increased risk of serious and opportunistic pulmonary and extrapulmonary infections (typically Nocardia, mycobacteria, and fungal infections) at rates exceeding expected complications of their lung disease, which is consistent with an impaired immune function. Causative organisms include community-acquired and opportunistic microbial pathogens. Commonly identified opportunistic pathogens include *Nocardia* spp., *Cryptococcus gattii* (specific for the presence of anti-GM-CSF antibodies in immunocompetent people), Mycobacteria, and *Aspergillus*, and resulting infections are associated with a poor prognosis and increased mortality.[7] Secondary infections are relatively common, they account for 18–20% of deaths attributable to aPAP, can occur at presentation or at any time during the clinical course of the disease and can occur at either intra- or extrapulmonary sites.[3]

Pulmonary fibrosis can occur in aPAP but is among the least well-defined manifestations of the disease.[3] The pathogenic mechanism driving fibrosis in aPAP is not known but has been speculated to result from whole lung lavage or long-term exposure to higher-than-normal oxygen concentrations from supplemental oxygen therapy.

DIAGNOSIS OF aPAP

Non-specific clinical presentation, radiographic appearance, and normal routine laboratory findings often result in the misdiagnosis of aPAP as pneumonia, which delays an accurate diagnosis. The observation of symptoms unexpectedly milder than anticipated based on the presence of extensive radiographic abnormalities is of diagnostic utility and should raise the suspicion of PAP; increased awareness of the disease is also important for an accurate and timely diagnosis. The commercial availability of the serum GM-CSF autoantibody diagnostic test has revolutionised the diagnosis of aPAP and rendered lung biopsies unnecessary in most cases.[8,9] Lung biopsies should be reserved for more complex cases of PAP syndrome.[8,9]

The essential criterion[3,9] for a diagnosis of aPAP is:

- Serum GM-CSF autoantibody levels. In people with aPAP, GM-CSF autoantibody levels are elevated and can be detected through a blood test.2

With supporting criteria[3,9] of any one of the following:

- Pulmonary function testing. Spirometry may be normal in the majority of people with aPAP and may have a mixed obstruction and restrictive pattern in those who smoke.[1] A reduction in diffusion capacity for carbon monoxide is the most common pulmonary function finding in people with aPAP.[1]
- Chest X-rays or computed tomography (CT) scans. Chest radiographs may demonstrate bilateral alveolar opacities in a peri-hilar and basilar distribution without air-bronchograms, which is sometimes referred to as a “batwing distribution.” CT scans may show diffuse ground-glass opacification and superimposed septal thickening, often referred to as “crazy paving.”[1]
- Bronchoscopy. Bronchoalveolar lavage fluid will often appear milky and opaque and cytological examination will reveal large foamy macrophages with amorphous eosinophilic cell fragments/debris and ghost cells.[2]
- Lung biopsy is an invasive procedure that is not recommended by guidelines; however, if performed, histopathology showing alveoli filled with eosinophilic granular sediment, enlarged foamy-appearing alveolar macrophages and/or cholesterol crystals (clefts).[3] Histopathology cannot distinguish aPAP from other forms of PAP syndrome.

Other tests may include:

- Blood tests to check blood oxygen levels with an increase in the alveolar–arterial gradient on arterial blood gas analysis.

TREATMENT FOR AND MANAGEMENT OF aPAP

At this time, there isn't a cure for aPAP. Treatment depends on the severity of the clinical manifestations. Patients with mild dyspnoea or no symptoms can do well with supportive care and monitoring of pulmonary function tests and chest imaging.

WHOLE LUNG LAVAGE

Whole lung lavage to remove lipoproteinaceous material from the lungs should be considered in patients with dyspnoea at rest, resting partial pressure of oxygen (PaO_2) less than 65 mmHg, resting alveolar-arterial gradient greater than 40 mmHg or oxygen desaturations on 6-minute walk test.[1,6] The procedure is performed under general anaesthesia with a double lumen endotracheal tube. One lung is ventilated while the contralateral lung is lavaged with warm (37°C) saline until the returning fluid is clear.[1] Chest percussion is performed during the lavage to loosen and emulsify the accumulated sediment either using a wraparound vest or by manual percussion. The procedure is then repeated on the contralateral lung after 24 hours or more. Approximately half of patients will require a second whole lung lavage; the average duration of benefits following whole lung lavage is 15 months.[2]

GM-CSF AUGMENTATION

Inhaled and systemic GM-CSF has proven to be beneficial and safe treatment in patients with aPAP,[1,2] and can be considered as an alternative to whole lung lavage.[2] Efficacy appears to be greater when GM-CSF is administered by inhalation rather than subcutaneously, and by daily administration rather than daily on alternating weeks. GM-CSF therapy is currently not approved in North America and Europe where it is provided off-label. More data are needed to determine the optimal starting dose, dosing strategy, and treatment duration.

OTHER TREATMENT APPROACHES

Systemic corticosteroids should not be used in patients with aPAP because they are ineffective and increase the risk of pulmonary infection in patients with aPAP.[1]

B-lymphocyte depletion through administration of rituximab, an anti-CD20 monoclonal antibody, has been reported to be effective but the number of patients treated to date is small so should be considered as experimental because it is not approved for the treatment of patients with aPAP. Similarly, plasmapheresis and plasma exchange to decrease circulating levels of anti-GM-CSF antibodies have proved effective but have not been evaluated in large clinical studies.

Oral cholesterol lowering therapies (statin) are associated with clinical, physiological and radiological improvements in aPAP patients, probably because in these patients their alveolar macrophages have a marked increase in cholesterol and pulmonary surfactant has an increase in the ratio of cholesterol to phospholipids.[10]

Specific activation of the GM-CSF intracellular pathway using the proliferator-activated receptor gamma (PPARγ) agonist pioglitazone was found to be effective in a patient with aPAP who was resistant to first-line therapies such as GM-CSF augmentation.[11]

Bronchodilators may be of benefit to improve airway patency and ease breathing, and supplemental oxygen through a face mask or nasal tubes may improve oxygen exchange in the lungs. It is possible that people with severe aPAP and lung damage may eventually require lung transplant surgery. aPAP may, however, recur in the lungs after lung transplant surgery.

PROGNOSIS

The clinical course of aPAP varies with the majority people having unremitting/slowly progressive disease, spontaneous improvement occurring in approximately 5–7% of people, and rapid progression and/or pulmonary fibrosis, respiratory failure, and death in others. As a result of this varied disease course, the prognosis is unpredictable. That said, prognosis has improved with the introduction of whole lung lavage and the 5-year survival is 95%.[1]

LIVING WITH aPAP

The outlook for people with aPAP has improved with the introduction of whole lung lavage but the clinical course remains variable. An important consideration for patients includes avoiding or quitting smoking.

REFERENCES

[1] Borie R, Danel C, Debray MP, et al. Pulmonary alveolar proteinosis. Eur Respir Rev 2011; 20: 98–107.

[2] Trapnell BC, Whitsett JA, Nakata K. Pulmonary alveolar proteinosis. N Engl J Med 2003; 349: 2527–2539.

[3] McCarthy C, Carey BC, Trapnell BC. Autoimmune pulmonary alveolar proteinosis. Am J Respir Crit Care Med 2022; 205: 1016–1035.

[4] Campo I, Mariani F, Rodi G, et al. Assessment and management of pulmonary alveolar proteinosis in a reference center. Orphanet J Rare Dis 2013; 8: 40.

[5] Griese M, Panagiotou P, Manali ED, et al. Autoimmune pulmonary alveolar proteinosis in children. ERJ Open Res 2022; 8: 00701-2021.

[6] Kamboj A, Lause M, Duggirala V. Severe Pulmonary Alveolar Proteinosis in a Young Adult. Am J Med 2018; 131: e199–e200.

[7] Ataya A, Knight V, Carey BC, et al. The Role of GM-CSF Autoantibodies in Infection and Autoimmune Pulmonary Alveolar Proteinosis: A Concise Review. Front Immunol 2021; 12: 752856.

[8] McCarthy C, Carey B, Trapnell BC. Blood Testing for Differential Diagnosis of Pulmonary Alveolar Proteinosis Syndrome. Chest 2019; 155: 450–452.

[9] McCarthy C, Bonella F, O'Callaghan M, et al. European Respiratory Society guidelines for the diagnosis and management of pulmonary alveolar proteinosis. Eur Respir J 2024; 64: 2400725.

[10] McCarthy C, Lee E, Bridges JP, et al. Statin as a novel pharmacotherapy of pulmonary alveolar proteinosis. Nat Commun 2018; 9: 3127.

[11] Dupin C, Hurtado M, Cazes A, et al. Pioglitazone in pulmonary alveolar proteinosis: promising first clinical experience. Respir Med Res 2020; 78: 100756.

FURTHER INFORMATION AND SUPPORT

This booklet has been produced by the International Patient Organisation for Primary Immunodeficiencies (IPOPI). Other booklets are available in this series. For further information and details of PID patient organisations worldwide, please visit **IPOPI.org**.

'Information presented within this leaflet is based on published literature at the time of production. The leaflet is intended to provide a broad overview rather than be a guide on clinical practice – for this, please consult the treatment guidelines in your country.'

SAVARA

Supported by an educational grant from Savara.