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Case Report

Pathology Section

Pulmonary Alveolar Proteinosis in a Three-month-old Infant: An Unusual Case Report

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ABSTRACT

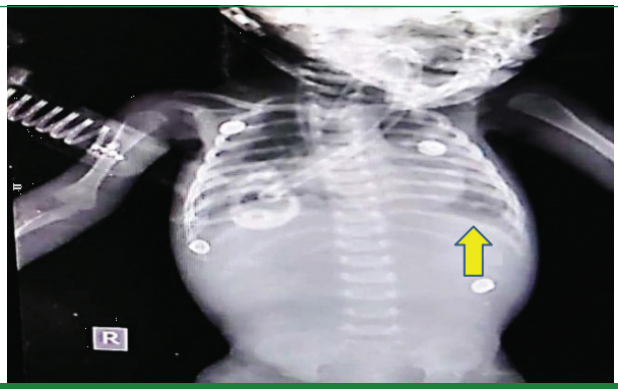
Pulmonary Alveolar Proteinosis (PAP) is an unusual diffuse lung disease characterised by the alveolar accumulation of phospholipoprotein material, with a peak incidence in the 3rd to 4th decades of life and a male predominance. However, it has also been described in children. The recorded prevalence is 0.1 per 100,000 individuals. The major clinicopathogenetic subtypes include the autoimmune (idiopathic) form, which is associated with Granulocyte-macrophage Colony-stimulating Factor (GM-CSF) autoantibodies, the secondary form and the congenital form (associated with surfactant gene mutations). Common presenting features include dyspnoea, cough, low-grade fever, inspiratory crackles and digital clubbing. Pulmonary function tests typically show restrictive ventilatory defects. Herein, the authors present a case of a three-month-old male infant who presented with cough, dyspnoea and failure to thrive over the past 10 days. X-rays revealed a bilateral reticular pattern with non homogeneous opacities. Computed Tomography (CT) of the chest showed features consistent with interstitial lung disease. High-resolution Computed Tomography (HRCT) demonstrated a crazy-paving appearance, suggestive of interstitial lung disease or a surfactant-related genetic disorder. Bronchial Alveolar Lavage (BAL) yielded milky fluid. Characteristic microscopic findings on lung biopsy included the filling of terminal bronchioles and alveolar spaces with deep pink granular Periodic Acid Schiff (PAS)-positive eosinophilic material, while the alveolar architecture remained preserved. Patients with minimal symptoms are managed conservatively, whereas those with hypoxaemia require a more aggressive approach. Whole Lung Lavage (WLL) is the safest and most effective form of treatment. To date, there have been 240 case reports and 410 case series documented in the literature. This is the first case of PAP reported in the study institution. The authors present this case report here due to its rarity and diagnostic significance.

Keywords: Alveolar proteinosis, Respiratory failure, Therapeutic lavage

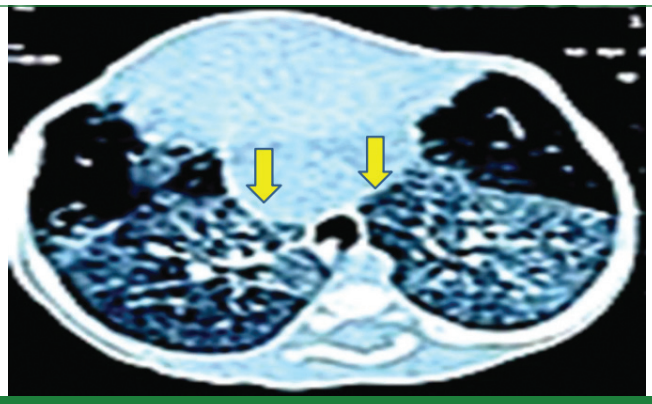
CASE REPORT

A full-term male child, born via caesarean section, presented at the age of three months with cough, rapid breathing, mild fever and failure to thrive over the past 10 days. He is the firstborn male baby, delivered at 37 weeks gestation, with a birth weight of 2.5 kg. On examination, tachycardia and tachypnoea were noted, along with bilateral inspiratory stridor over the suprasternal, superior and inferior clavicular regions. These symptoms persisted despite treatment with antibiotics and he required oxygen, with an SpO_2 of 89% in room air.

The chest X-ray, repeated on multiple occasions, showed hyperinflated lung fields with a bilateral reticular pattern [Table/Fig-1]. The CT chest showed segmental hyperinflation with interstitial thickening, suggestive of childhood interstitial lung disease. The HRCT thorax demonstrated a crazy pavement appearance, suggestive of interstitial lung disease or a surfactant-related genetic disorder [Table/Fig-2]. BAL yielded large amounts of milky white fluid, raising suspicion for PAP [Table/Fig-3]. A biopsy of the lower lobe of the left lung was performed.



[Table/Fig-1]: X-ray chest- Hyperinflated lung with bilateral reticular pattern (arrow).

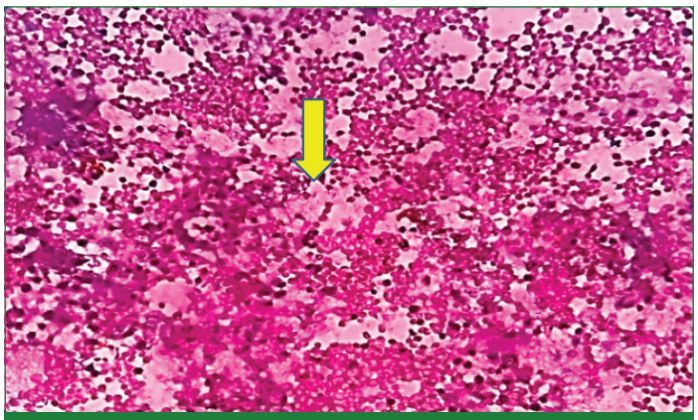


[Table/Fig-2]: HRCT Thorax- Crazy pavement appearance suggestive of interstitial lung disease or surfactant related genetic disorder (arrow).

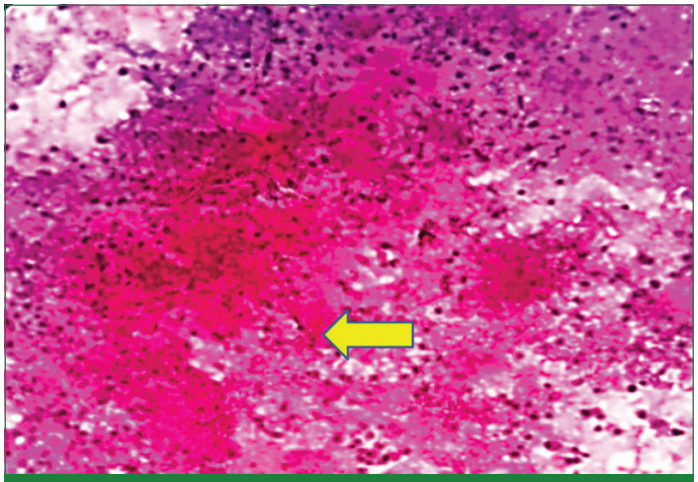
[Table/Fig-3]: Milky white fluid aspirated during bronchoalveolar lavage (arrow).

Microscopic Features

Cytology-BAL: The moderately cellular smear shows predominantly alveolar macrophages (75%), neutrophils (15%) and lymphocytes (10%) in a background of red blood cells and thick proteinaceous material [Table/Fig-4]. The special stain PAS highlights the blotchy pink proteinaceous material [Table/Fig-5].

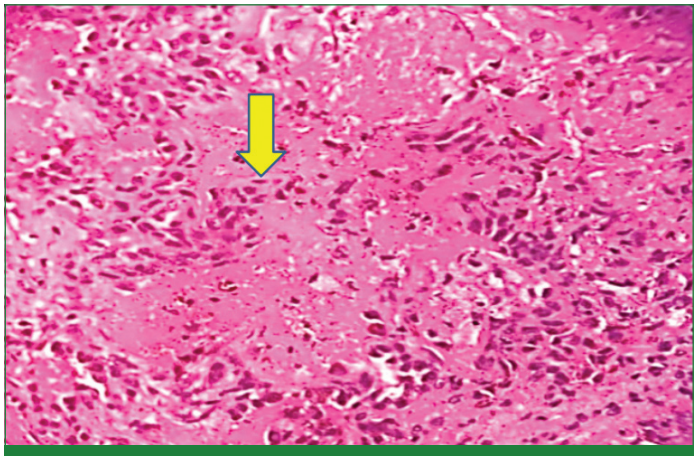


[Table/Fig-4]: BAL cytology- shows predominantly alveolar macrophages (75%), neutrophils (15%) and lymphocytes (10%) in a background of RBC's and thick proteinaceous material (arrow) {Haematoxylin and Eosin (H&E), 40X}.

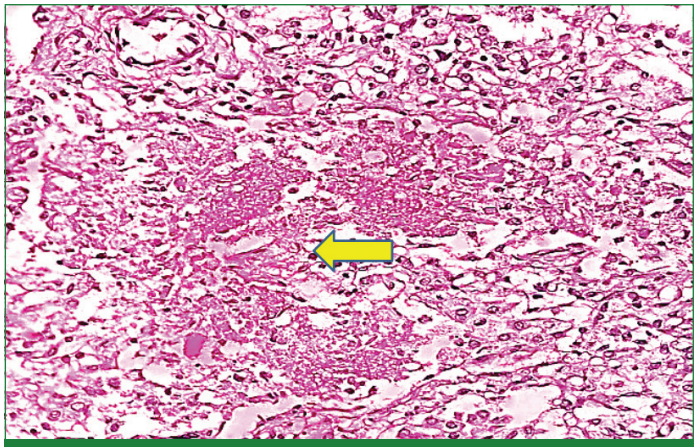


[Table/Fig-5]: BAL- Special stain PAS- Highlights the blotchy pink proteinaceous material (arrow) (PAS, 40X).

Lung biopsy: The section shows lung parenchyma with alveolar spaces of varying sizes filled with amorphous eosinophilic material [Table/Fig-6]. Fibrosis is observed, along with a few haemosiderin-laden macrophages. The special stain PAS positive shows the amorphous eosinophilic material in the intra-alveolar spaces [Table/Fig-7]. A diagnosis of PAP was made. The patient was started on antibiotics (inj. piperacillin+tazobactam). The baby was intubated, but the health condition deteriorated and the patient succumbed to death.



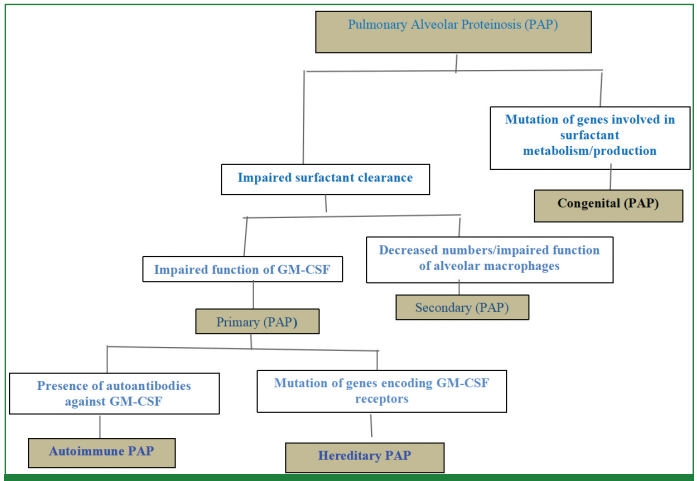
[Table/Fig-6]: Varying sizes of alveolar spaces filled with amorphous eosinophilic material (H&E, 40X) (arrow).



[Table/Fig-7]: Special stain PAS shows amorphous eosinophilic PAS positive material in Intra-alveolar spaces (PAS, 40X) (arrow).

DISCUSSION

The PAP is extremely uncommon in the paediatric age group; only a few cases have been documented in the literature [1,2]. The disease has a polymorphic manifestation and several underlying causes, including autoimmune, acquired, idiopathic and genetic (familial) factors [3]. GM-CSF autoantibodies, changes in genes encoding surfactant proteins, associations with cancers, inhalation of chemicals and infections are the pathophysiological factors of PAP [Table/Fig-8]. In comparison to other literature case series, most children had a history of fever, cough, progressive dyspnoea and tachypnoea [4,5], as well as other manifestations like weight loss, haemoptysis and chest pain [6]. However, due to the non specific symptomatology and variability in disease severity, the diagnosis of PAP can often be delayed or missed by physicians [7].



[Table/Fig-8]: Classification of Pulmonary Alveolar Proteinosis (PAP) [1].

Previous literature has shown that there is an average delay of 4.5 months between the onset of symptoms and the diagnosis of PAP in patients. In some cases, like the one discussed in this article, the delay can be even longer. In the present case study, there was a delay of 1.5 months between the first clinical manifestations and the provisional diagnosis. This delay can be attributed to the complex clinical course of the disease, as well as limited access to diagnostic modalities [8]. In resource-limited healthcare settings like India, the diagnosis of PAP may be delayed or overlooked due to the lack of diagnostic and treatment facilities, especially in rural and marginalised areas. This can result in late or undetected cases of PAP [9].

One of the key challenges in diagnosing PAP in such settings is the scarcity of diagnostic techniques, such as Bronchoalveolar Lavage (BAL) fluid examination and genetic work-up. This scarcity can make it difficult for both physicians and pathologists to accurately identify and treat PAP patients. Additionally, the characteristic radiological appearance of PAP, which includes bilateral, symmetric

and perihilar airspace consolidation in a batwing distribution, may not always be evident in resource-limited settings [10]. In some cases, the radiological findings may suggest non homogeneous opacities, which have been noted in previous studies of PAP. Overall, the limited access to diagnostic tools and treatment facilities in resource-limited healthcare settings can pose significant challenges in the timely diagnosis and management of PAP. Efforts to improve access to these resources and raise awareness about the condition are crucial in addressing this issue [11].

While the most common presentation of PAP is a crazy-paving pattern in imaging studies, there have also been reported cases with interstitial and nodular patterns. Routine haematological and biochemical investigations may not always be specific in the diagnosis of PAP, but they provide clues to an underlying cause. One of the characteristic bedside findings in PAP is the presence of opaque, milky BAL fluid. The BAL fluid is often rich in foamy alveolar macrophages and acellular proteinaceous debris [12].

Microscopically, the lung biopsy shows that the hallmark of the process is the accumulation of an amorphous eosinophilic (but sometimes basophilic) PAS-positive material of predominantly phospholipid nature in the alveolar lumina, associated with a minimal infiltrate of lymphocytes, macrophages and desquamated pneumocytes. The airspace exudate is usually affiliated with only mild interstitial abnormalities, including a lymphocytic infiltrate with minimal associated fibrosis [13]. In patients with underlying haematological disorders or those who are otherwise immunocompromised, alveolar proteinosis may be associated with infections such as nocardiosis, pneumocystis, histoplasmosis, cryptococcosis, aspergillosis, tuberculosis, or cytomegalovirus, making the appropriate use of special stains and other microbiologic assays mandatory in this context [14].

Whole Lung Lavage (WLL) has emerged as a convenient and effective method of treating patients with late-onset PAP in the paediatric age group. This procedure has shown promising results in managing this rare disease, providing hope and relief to patients and their families [15].

Correction of GM-CSF deficiency using exogenous GM-CSF is an alternative therapy for patients with PAP. Combining systemic treatment with GM-CSF and local treatment through whole-lung lavage has shown to enhance the effectiveness of both methods. This innovative approach is paving the way for novel therapies in the treatment of PAP, as the medical community continues to expand its understanding of this rare disease through research and literature [16].

Based on imaging, the differential diagnosis includes pulmonary oedema, Pneumocystis jirovecii pneumonia, pulmonary amyloidosis, acute silicosis, alveolar mucinosis and pulmonary haemorrhage [Table/Fig-9] [17]. Published cases are tabulated in [Table/Fig-10] [2,3,7,8-10,12,13,18]. Various differential diagnosis have been documented in the literature based on overlapping clinical and histomorphological features, making it important to rule out these conditions.

S. No.	Diagnosis	Age/Sex	Clinical history	Microscopy	Special stain
1.	Pulmonary oedema	6-10 years/ M>F	Progressive Dyspnoea, Tachypnoea, crackles	Alveolar walls are thickened due to acute distension of capillaries and interstitial oedema. Alveolar lumen filled with transudate (pale – eosinophilic, fine granular), a liquid which replaces the air	PAS+
2.	Pneumocystis jirovecii pneumonia	HIV/ immune compromised children	Fever, non productive cough, difficulty breathing, chest pain, fatigue and chills	Alveolar spaces filled with pink, foamy/honey combed amorphous material composed of proliferating fungi and cell debris	GMS+, Giemsa+, crystal violet+, Diff quik+. PAS-
3.	Pulmonary amyloidosis	M:F 3:2, adults	Dyspnoea, cough	Alveolar septae thickened amyloid appears as glassy amorphous eosinophilic material.	Congored+, crystalviolet+, thioflavinT+. Trichrome -
4.	Acute silicosis	Adults M>F	Rapid progression of dyspnoea, weight loss, fatigue and diffuse bilateral crackles	Alveoli are filled with granular eosinophilic material with large globules	PAS+
5.	Alveolar mucinosis	Young adults M:F 1:2	Slowly progressive dyspnoea, dry cough, respiratory distress, fatigue and clubbing	Intra-alveolar spaces are filled with mucin	PAS+
6.	Pulmonary haemorrhage	Infants from 2 to 4-day-old, adults M>F	Dyspnoea, cough, haemoptysis	Diffuse alveolar haemorrhage with capillaritis and haemosiderin laden alveolar macrophages in the alveolar spaces	Prussian blue+

[Table/Fig-9]: Differential diagnosis of Pulmonary Alveolar Proteinosis (PAP) [17].
HIV: Human immunodeficiency virus; PAS: Periodic acid- Schiff; GMS: Grocottmethenamine silver

Authors	Year of publication	Age/Sex	Clinical features	Radiological findings	Treatment	Outcome
Garg G et al., [9]	2009	4 months male	Progressive respiratory distress since birth and failure to thrive	Diffuse opacification with air bronchogram in bilateral lung fields except in the right middle lobe	Home oxygen therapy, Surfactants	Death
Verhasselt-Crinquette M et al., [7]	2009	2 months male	Respiratory distress	Bilateral alveolar syndrome	O_2 therapy, Supportive treatment	Death
Tabatabaei SA et al., [3]	2010	28 months male and female	Dry cough, fever,failure to thrive, cyanotic attacks	Diffuse alveolar infiltrates	Antibiotics, O_2 therapy, Whole Lung Lavage (WLL)	100% survival for 2 cases and death for 4 cases
Hammami S et al., [8]	2013	3 months male	Chronic tachypnoea, weight loss, dyspnoea, respiratory distress	Diffuse alveolar Infiltrates	Three lung lavages	Death
Al-Haidary AS et al, [10]	2017	5 years male	Progressive dyspnoea	Widespread bilateral airspace disease	WLL	100%survival
IyengarJN and Reddy BK [2]	2018	6 months male	Mild fever, tachypnoea, cheat retractions and bilateral crepitaions	Hyperinflated lung fields with bilateral non homogeneous opacities	Home oxygen therapy oral prednisone ventilator support	100% survival
Zhang FZ et al., [18]	2020	9 months male	Cough, tachypnoea	Bilateral ground-glass density images in lungs	Imipenem, erythromycin, methylprednisolone, human immunoglobulins	100% survival
Bush A and Pabary R, [12]	2020	Newborn-term male baby	Cough, progressive dyspnoea, respiratory distress	Ground glass shadowing with thickening of the secondary interlobular septa (cobblestoning)	WLL	Lost to follow-up

Goetz DM et al., [13]	2021	Neonates	Cough, dyspnoea, respiratory distress	Ground glass appearance with interlobular and intralobularseptae thickening- crazy paving	WLL	Lost to follow-up
Present case	2024	3 months male	Cough, fever, progressive dyspnoea and failure to thrive	Bilateral non-homogenous opacities with reticular pattern	Antibiotics, O_2 therapy, Ventilator support	Death

[Table/Fig-10]: Comparison of published literature with present case [2,3,7,8-10,12,13,18].

CONCLUSION(S)

It is essential to emphasise the importance of early and accurate diagnosis through clinical evaluation, imaging and histopathological examination. Therapeutic approaches may include WLL, immunomodulatory therapies and, in some cases, lung transplantation. Understanding the underlying genetic or environmental factors is crucial for guiding treatment and improving outcomes for paediatric patients with PAP. It is important for paediatricians and pathologists to be aware of the symptoms and diagnostic challenges associated with PAP. Early recognition and prompt diagnosis are critical for improving outcomes for patients with this condition. By understanding the potential delays in diagnosis and treatment, physicians can work towards better management of PAP and ultimately improve the quality of life for those affected by this rare condition.

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