Isolated cerebral aspergillus abscess as a complication of pulmonary alveolar proteinosis in a child

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Abstract: Background: Pulmonary alveolar proteinosis (PAP) poses a risk of opportunistic infections with a variety of organisms with Nocardia being the most common pathogen followed by mycobacteria and fungi.

Case presentation: A 7-year-old female child, presented with headache and multiple episodes of vomiting. There was no fever or altered sensorium. On examination, there were no focal deficits or cranial nerve palsies. An MRI brain showed a small T2 hyperintense lesion in the left superior parietal lobe suggestive of an abscess. She was diagnosed as PAP based on CT chest and bronchioloalveolar lavage 7 months earlier and treated with corticosteroids. A left parieto-occipital craniotomy was done with drainage of abscess and abscess wall excision. Histopathology revealed a suppurative lesion with slender septate acute angle branching hyphae which were positive on fungal stains. Culture done on the pus was positive for Aspergillus fumigatus. The patient was treated with voriconazole and stable at 1 year follow-up.

Conclusion: Opportunistic infections are common in patients diagnosed with PAP. High index of clinical suspicion and early diagnosis are important for favorable outcome.

Keywords: Pulmonary alveolar proteinosis, Opportunistic infection, Aspergillus fumigatus, Cerebral abscess

Background
Pulmonary alveolar proteinosis (PAP) is a rare disease characterized by accumulation of lipo-proteinaceous surfactant material in the alveolar and bronchiolar spaces because of defective clearance by alveolar macrophages [1–3]. It is known to occur in three distinct clinical forms: primary/congenital, secondary, and autoimmune. Autoimmune PAP is the most common form of this disease (90%) and is the result of the formation of anti-granulocyte-macrophage colony stimulating factor (GM-CSF) antibodies [2–5]. Primary/congenital PAP is associated with genetic mutations in surfactant proteins or GM-CSF mutations and usually occurs in children. Secondary PAP is associated with functional impairment of alveolar macrophages that is seen in relation to hematological malignancies, exposure to infections and toxins, allogenic stem cell transplantation, and others [2, 3, 6].

About 5% of patients having PAP present with opportunistic infections most commonly with, Nocardia, Mycobacteria followed by fungal infections [2, 5, 7, 8]. A significant number of disseminated infections involve the central nervous system (CNS) with infective organism being fungus [9]. The fungal infections in association with PAP are most commonly due to Cryptococcus, followed by Aspergillus, Histoplasma, and others [2, 9]. Fungal infections associated with PAP have high mortality and usually diagnosed at autopsy [2, 9]. We report a child with autoimmune PAP and isolated cerebral Aspergillus abscess with a favorable outcome due to its extreme rarity.

Case presentation
A 7-year-old female child presented with headache, multiple episodes of vomiting, and speech disturbances. She had no fever, altered sensorium, or focal neurological deficits. She was conscious and coherent with normal motor and sensory functions. She was diagnosed to have PAP on CT chest and bronchiolo alveolar lavage (BAL) in another hospital 7 months earlier and was on treatment with...
corticosteroids (Fig. 1a). There was neutrophil leukocytosis
(6900/cu mm). Rest of the hematological and biochemical
investigations were within normal limits. MRI brain showed
a T2 hyperintense lesion in the left superior parietal lobe
(Fig. 1b). A diagnosis of tuberculoma was made and she was
treated with anti-tuberculous treatment. However, she did
not respond even after three weeks and was symptomatic.
Left parieto-occipital craniotomy was done and per-
operative smears showed necrotic material with neutrophils
and septate hyphae. Abscess drainage and abscess wall exci-
sion were done. Histopathology revealed a suppurative le-
sion with neutrophils and mononuclear cells (Fig. 1c).
Amidst the necrotic material were seen delicate septate hy-
phae with acute angle branching (Fig. 1d–f). The hyphae
were highlighted by Gomori methenamine silver (GMS) and
periodic acid Schiff (PAS) stains (Fig. 1g).

**Discussion**

Complications of PAP include opportunistic infections, interstitial fibrosis, and rare instances of emphysematous
bullae and pneumothorax [10]. Infections associated
with PAP may precede, follow or may also present in
concurrency. PAP was reported as the initial presenta-
tion in 33% patients as seen in our patient [9]. Majority
of the infections were reported in adults with a mean
age of 39 years and male predominance [9]. Our patient
was a 7-year-old female child.

First extensive review of infections in patients with
PAP was done by Seymour et al. who reported that ma-
jority were by *Nocardia* followed by *Mycobacteria*, *Crypt-
tococcus*, *Histoplasma*, *Aspergillus*, and others [2].
Punatar et al. in 2012, reviewed a total of 75 cases from
1950 to July 2010 and identified *Nocardia* (43%) as the
most common pathogen followed by mycobacteria (37%)
and fungi (20%) [9]. Of the 15 cases of fungal infections
in their study, 5 were due to *Cryptococcus* and 4 each
due to *Aspergillus* and *Histoplasma*. The most common
site of infection was lung followed by the brain [9]. CNS
involvement was seen usually in disseminated cases [9].
Our patient had cerebral *Aspergillus* abscess as the sole
manifestation 7 months after the diagnosis of PAP.

Cryptococcosis is the most common infection reported
in association with PAP; however, the other fungal infec-
tions include those due to *Aspergillus*, *Histoplasma*,
*Mucor*, *Blastomyces*, *Coccidioides*, and *Pneumocystis*.

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**Fig. 1 a** Plain CT chest showing bilateral diffuse miliary ground glass opacities. **b** MRI brain showing T2 hyperintense ring-enhancing lesion in the left superior parietal lobe suggestive of an abscess. **c** H&E × 40 Abscess wall with dense acute inflammatory exudates. **d** H&E × 400 showing multiple filamentous septate hyphae with acute angle branching. **e** H&E × 400 numerous fungal hyphae embedded in the exudates. **f** Silver methenamine stain × 400 demonstrating grey black colored fungal organisms. **g** PAS stain × 400 showing magenta colored organisms. **h** Sabouraud dextrose agar demonstrating greenish blue colonies with white edges classical for *A. fumigatus*. Lactophenol cotton blue stained smear demonstrating fruiting bodies.
[1, 2, 9, 11, 12]. They are all mycoses controlled by macrophages upon inhalation [12]. Susceptibility to infections is found to be multi-factorial. Possible causes include impaired macrophage function and impaired host defense [12]. When autoantibodies block the GM-CSF pathway, differentiation and function of alveolar macrophages are impaired and the ability to clear surfactants is diminished [2, 11, 12]. As a result, pulmonary alveoli accumulate periodic acid-Schiff (PAS)-positive proteinaceous surfactant components which act as a medium for infection [2, 11, 12]. Since autoantibodies to GM-CSF cause defects in chemotaxis, adhesion, phagocytosis, microbicidal activity, and phagolysosome fusion of alveolar macrophages, patients with PAP are at risk for infections from a variety of respiratory microorganisms including fungal species [2, 11, 12]. In our patient, screening for mutations of surfactant protein or assay for GM-CSF autoantibodies was not done. Corticosteroids were administered after the diagnosis of PAP and possibly it would have augmented the risk for opportunistic infection with Aspergillus.

The first case of CNS aspergillosis in a patient with PAP was described by Björkholm et al. [13]. Kourkoumpetis et al. reported 14 cases of CNS aspergillosis and reviewed 123 reported cases from literature [14]. In their report, CNS aspergillosis was associated with a wide variety of comorbidities including diabetes mellitus, human immunodeficiency virus infection, hematological malignancies, transplant, etc., but none with PAP. Neutropenia was found to be a major contributor to the pathogenesis [14]. However, in the present case, the patient did not have neutropenia. Qualitative rather than quantitative defect in neutrophilic function may be attributed to the opportunistic infections [14]. Diagnosis of CNS aspergillosis is difficult as the clinical symptoms are non-specific [14]. Our patient was initially diagnosed to have CNS tuberculoma on MRI and was treated with ATT before she underwent surgery. Aspergillus fumigatus was found to be the most common pathogen in CNS Aspergillosis as seen in our patient [14, 15]. Mortality rate was high in patients with CNS aspergillosis (28% in who underwent neurosurgery and 67% in who did not undergo neurosurgery) [14]. However, Dotis et al. reported that there is a significant difference in mortality in cases reported before and after 1990 (82% and 39% respectively) which can be attributed to the introduction of amphotericin B and aspergillus sensitive azoles like voriconazole [15]. Our patient underwent surgical excision and received voriconazole and stable at 1 year follow-up.

**Conclusion**

Pulmonary alveolar proteinosis is one of the risk factors for opportunistic infections. High index of clinical suspicion for unusual pathogens like fungus and uncommon sites like CNS should always be considered in patients with PAP. Timely pathological diagnosis and a combination of surgical and antifungal therapy improve the outcome in patients with CNS aspergillosis in association with PAP. This case is reported for its rarity and to emphasize the importance of early diagnosis and treatment for a better clinical outcome.

**Abbreviations**

BAL: Bronchoalveolar lavage; CNS: Central nervous system; GM-CSF: Granulocyte-macrophage colony-stimulating factor; GMS: Gomori methenamine silver; PAP: Pulmonary alveolar proteinosis; PAS: Periodic acid schiff

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**Authors’ contributions**

RK and MKP drafted the manuscript. SSM and RT conceived of the study and participated in its design and coordination and helped to draft the manuscript. CS and VR provided supervision and critically reviewed the manuscript. All authors read and approved the final manuscript.

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**Consent for publication**

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient/parent/guardian/relative of the patient. A copy of the consent form is available for review by the Editor of this journal.

**Competing interests**

The authors declare that they have no competing interests.

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