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Opportunistic infections in patients with pulmonary alveolar proteinosis☆

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Summary *Objectives:* To describe the demographics, clinical manifestations, treatment, and outcomes of patients with pulmonary alveolar proteinosis (PAP) who developed an opportunistic infection with *Nocardia* spp., mycobacteria or fungal pathogens.
Methods: A case of PAP and *Nocardia* spp. brain abscess is described. A comprehensive review of the English-language literature was conducted to identify all reported cases of PAP and opportunistic infections between 1950 and July, 2010.
Results: Seventy five cases were reviewed. Thirty two patients (43%) had nocardial infection, 28 (37%) mycobacterial infection, and 15 (20%) fungal infection. Thirty nine patients (65%) were male. Seventeen patients (23%) were immunosuppressed. Twenty patients (27%) were active smokers. PAP was the initial diagnosis in 19 patients (33%), while infection presented first in 23 patients (40%); 16 patients (27%) had a concurrent diagnosis of PAP and infection. The average interval between PAP diagnosis and an opportunistic infection was 16 months. Lungs were the most common site of infection; extra-pulmonary infection was present in 27 patients (32%). Thirty nine patients (57%) survived through the follow-up period, while 31 died.
Conclusions: Opportunistic infections can either precede or follow a diagnosis of PAP. PAP should be considered in apparently immunocompetent patients who present with an opportunistic infection and diffuse alveolar infiltrates.

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Introduction

In 1958, Rosen et al. reported 27 cases of a rare disease characterized by the filling of pulmonary alveoli by periodic acid-Schiff (PAS) positive lipoproteinaceous material.[1] It is now recognized that PAP occurs in three clinically distinct forms: congenital, secondary, and acquired. The congenital form is associated with genetic mutations in surfactant proteins or granulocyte macrophage colony-stimulating factor (GM-CSF) receptor. Secondary PAP occurs in association with functional impairment or reduced number of alveolar macrophages following high-level toxic dust exposure, hematologic malignancies, or allogeneic stem cell transplantation. Acquired PAP accounts for 90% of all cases and is the result of anti-GM-CSF antibodies leading to macrophage dysfunction and impaired processing of pulmonary surfactant (autoimmune PAP).[2,3]

Patients with PAP are at an increased risk of opportunistic infections caused by *Nocardia* spp., mycobacteria, and fungal pathogens due to impaired macrophage and neutrophil function.[3–5] Herein, we describe a case of *Nocardia farcinica* brain abscess in a patient with PAP and summarize published cases of PAP and opportunistic infections.

Patients and methods

A case of *N. farcinica* brain abscess with subsequent diagnosis of PAP 4 months later prompted an investigation into the reported cases of opportunistic infections in patients with PAP.

Literature review

We conducted a comprehensive search of the English-language medical literature from 1950 through July, 2010 using Pub Med, the U.S. National Library of Medicine database, to identify articles reporting patients with opportunistic infections (*Nocardia* spp, mycobacteria, and fungal pathogens) and PAP. The search terms "Alveolar Proteinosis", "Pulmonary Alveolar Proteinosis", and "Pulmonary Alveolar Lipoproteinosis" were combined with "Zygomyces", "Mucormycosis", "Aspergillus", "Histoplasmosis", "Coccidiodomycosis", "Blastomycosis", "Cryptococcus", "Nocardia", "Mycobacterium", "Fungus", and "Infection". All search terms were exploded to maximize yield. The search was repeated with the EMBASE database. References cited by all articles were reviewed to identify any additional cases.

Inclusion criteria

Patients had to meet criteria for PAP diagnosis (PAS-positive lipoproteinaceous material filling pulmonary alveoli demonstrated by lung biopsy or bronchoalveloar lavage [BAL]) and confirmed infection due to *Nocardia* spp., mycobacteria, or fungal pathogens (pertinent clinical manifestations, imaging studies, and growth of the pathogen in culture). Patients were required to have a minimum follow-up of one month from the time of presentation. Patients diagnosed at autopsy with either PAP or opportunistic infection but met the above criteria were also included.

Exclusion criteria

Cases were excluded if sufficient data and follow-up was lacking, if PAP diagnostic criteria were not met, or if infection by pathogens of interest was not confirmed.

Definitions

'Follow-up' was defined as the time interval between the initial presentation of either PAP or opportunistic infection until the patient was no longer followed, or died. 'Survival' was defined as the patient being alive for at least 1 month after the diagnosis of either an opportunistic infection or PAP (whichever came last). 'Disseminated infection' referred to the involvement of 2 or more non-contiguous organs. 'Immunocompromised state' was defined as patients with hematologic or solid-organ malignancy, cancer chemotherapy or radiation therapy, organ transplantation, HIV infection, and receipt of immunosuppressive medications such as, but not limited to, corticosteroids.

Software and statistics

Data tabulation was carried out using Microsoft Excel (Microsoft Corp, 2003). Data analysis was performed using the online statistical software program *Interactive Statistical Pages* (http://statpages.org).

Results

Case description

A 65-year-old male with a history of hypertension, hyperlipidemia, and diabetes mellitus presented to our institution following an episode of syncope. Chest computed tomography (CT) demonstrated patchy alveolar consolidation in the bilateral upper lobes. Magnetic resonance imaging of the brain revealed a 2 $\times$ 2 cm left parietal periventricular ring-enhancing lesion (Fig. 1). Culture of the purulent material obtained by stereotactic brain biopsy confirmed *N. farcinica* brain abscess. The patient received combination antimicrobial therapy for 12 months with resolution of the abscess.

However, four months after the diagnosis of brain abscess, he presented with dyspnea, cough, and intermittent fevers. Chest CT demonstrated bilateral diffuse alveolar infiltrates with peripheral sparing (Fig. 2). Bronchoscopy with BAL revealed abundant alveolar PAS-positive material confirming PAP. The patient was successfully treated with 3 bilateral whole lung lavages and subcutaneous injections of 300 mcg of GM-CSF every other day for 16 weeks with complete resolution of PAP. GM-CSF autoantibody testing was not performed prior to GM-CSF administration. There was no evidence of PAP recurrence over the next 2 years.

Total cohort

A total of 74 patients with PAP and concurrent infection with one of the pathogens of interest were identified in our