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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

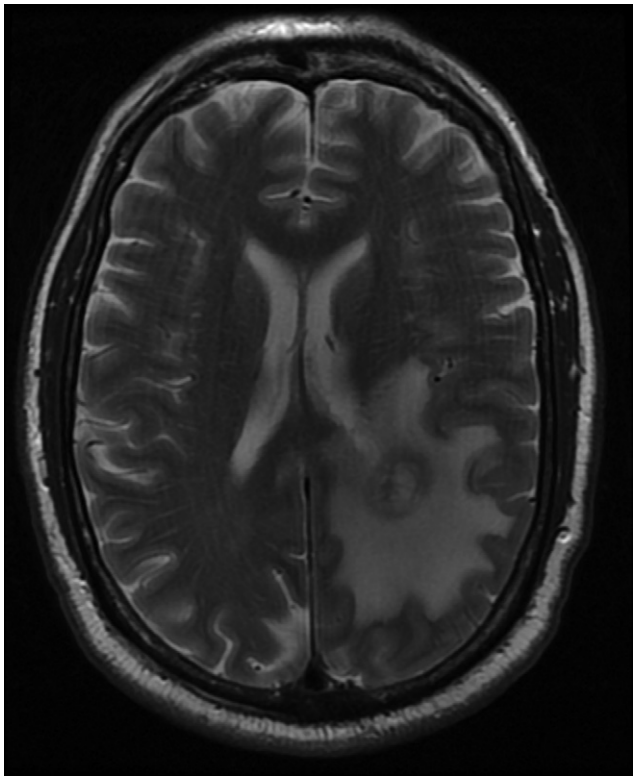

Figure 1 Magnetic resonance imaging of the brain of the index case with *N. farcinica* brain abscess. A heterogeneous rim-enhancing lesion is seen within the left parietal periventricular white matter with surrounding vasogenic edema.

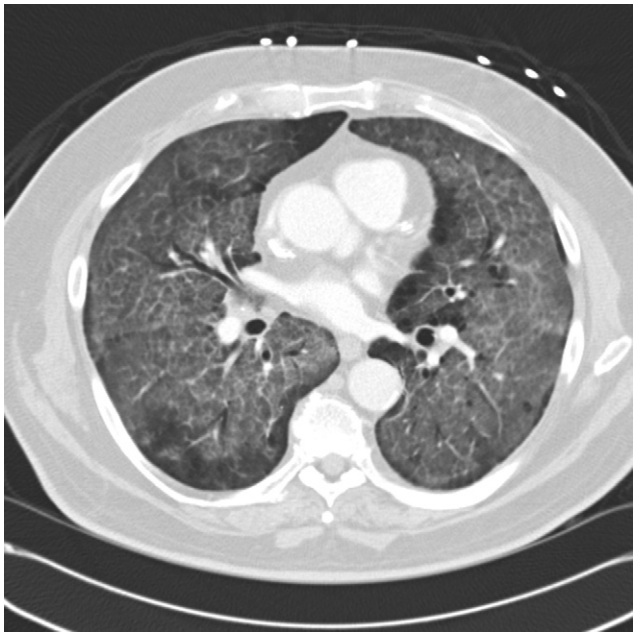

Figure 2 Computed tomography of the chest of the index case with pulmonary alveolar proteinosis. Bilateral diffuse pulmonary infiltrates with relative sparing of the lung periphery.

comprehensive literature review.[6–50] The additional case from our institution was included to arrive at a final cohort of 75 patients.

Demographics (Table 1)

The numbers of patients reported in the literature per decade were as follows: 1940–1949 (1 case), 1950–1959 (7 cases), 1960–1969 (22 cases), 1970–1979 (6 cases), 1980–1989 (2 cases), 1990–1999 (none), and 2000–2010 (3 cases). For 34 patients, the year of diagnosis and management were not explicitly stated. The mean age of our cohort ($n = 75$) was 39 years with a male predominance (65%). Nineteen of 35 patients (54%) were Caucasian. Immune status was stated for 19 patients of whom, 17 were immunosuppressed. The most common cause of immunosuppression was long term steroid use (13 patients) and cancer chemotherapy (10 patients).

Pathogens (Table 2)

The most commonly reported opportunistic infection in patients with PAP was due to *Nocardia* spp. ($n = 32$, 43%), the majority of which was caused by *N*ocardia *asteroides* ($n = 19$). Mycobacteria accounted for a total of 28 cases (37%), of which 21 were due to *M. tuberculosis*. Fungal infections were diagnosed in 15 (20%), with *Aspergillus* spp. and *Cryptococcus* spp. being the most common (Table 2).

Presenting symptoms

The most common presenting symptoms were cough ($n = 30$, 64%), dyspnea ($n = 29$, 62%), fever ($n = 24$, 51%), and weight loss ($n = 11$, 23%).

Table 1 Demographics.

Characteristics	*n* (%)
Mean Age ($n = 60$)	39 Years (3–68 years)
Gender ($n = 60$)	
Male	39 (65%)
Female	21 (35%)
Race ($n = 35$)	
Caucasian	19 (54%)
Black	7 (20%)
Other[a]	9 (26%)
Immunocompromised ($n = 75$)	
Yes	17 (23%)
No	2 (3%)
Unknown	56 (75%)
Comorbidities[b]	
Corticosteroid therapy[c]	13
Cancer	10
Diabetes Mellitus	2
Hypertension	2
Peptic Ulcer Disease	2

[a] Brazilian 1, Columbian 1, Italian 2, Japanese 2, Mixed race 1, Venezuelan 1, Indian 1.
[b] Underlying comorbidities were not stated for the majority of the patients in this study.
[c] Seven patients had an underlying malignancy and were also treated with corticosteroids.

Table 2 Pathogens.

Pathogen	*n* (%)
Nocardia ($n = 32$)	
N. asteroides	19 (59%)
N. brasiliensis	1 (3%)
N. farcinica	1 (3%)
Nocardia spp.	11 (34%)
Mycobacteria ($n = 28$)	
M. tuberculosis	21 (75%)
M. kansasi	4 (14%)
M. avium intracellulare	3 (11%)
Fungi ($n = 15$)	
Aspergillus spp.	4 (27%)
Cryptococcus spp.	5 (33%)
Histoplasma capsulatum	4 (27%)
Aspergillus spp. and *Cryptococcus* spp.	1 (7%)
Zygomyces	1 (7%)
TOTAL	75

Site of infection (Table 3)

The lungs were the most common site of infection with *Nocardia* spp. ($n = 24$, 75%), mycobacteria ($n = 24$, 86%), and fungi ($n = 12$, 80%). Brain involvement was noted in 6 patients (19%) with *Nocardia* spp. infection. Fungal infection was more likely to be disseminated.

Initial disease

Among 58 patients for whom the time of onset of PAP and infection was stated, PAP was the initial presentation in 19 (33%), infection preceded PAP diagnosis in 23 (40%), and the two were diagnosed concurrently in 16 patients (27%). PAP diagnosis preceded infection by a mean of 16 months (range 2—51 months), whereas, infection preceded PAP diagnosis by a mean of 17 months (range 1.2—36 months).

Table 3 Site of infection.

Site of infection	*n*
Nocardia spp.[a]	
Lung	24
Brain	6
Other[b]	5
Mycobacterium spp.[a]	
Lung	24
Liver	2
Lymph nodes	2
Other[c]	4
Fungi[a]	
Disseminated	7
Lung Only	6
Skin	1

[a] Site of infection was unknown for 1 patient with nocardial infection, 1 patient with mycobacterial infection, and 1 patient with fungal infection.
[b] Other = Abscess 2, Skin 1, Joint 1, Disseminated 1.
[c] Other = Brain 1, Eyes 1, Abscess 1, Bone Marrow 1.

Diagnostic methods

Diagnosis of opportunistic infections was established most often with microbial smears and cultures of sputum, BAL samples, or tissue biopsy specimens ($n = 43$, 72% of cases). Diagnosis was made at autopsy in 17 cases (28%). Over half ($n = 7$, 54%) of fungal infections were diagnosed at autopsy in comparison to 8 (26%) and 2 (13%) of *Nocardia* spp and mycobacterial infections, respectively.

Management of opportunistic infections

No specific therapy was stated for 14 patients. Twenty patients (53%) with *Nocardia* spp infection were treated with antibacterial agents alone, while 6 patients (21%) required additional surgical intervention. All 26 patients with mycobacterial infection received antimicrobial therapy alone (which included some combination of isoniazid, rifampin, streptomycin, and ethambutol). Among patients with fungal infection, 2 (29%) received antifungal therapy and 1 (14%) required additional surgical intervention. Overall, 11 of 75 patients (15%) died before receiving any therapy for their underlying infection.

Management of PAP

Sixteen patients from the total cohort underwent bronchoscopy and whole lung lavage for the treatment of PAP. Seven patients who underwent whole lung lavage had an initial diagnosis of PAP (median 15 months prior to infection), 5 had an initial opportunistic infection (median 12 months prior to PAP) and 4 presented with concurrent PAP and an opportunistic infection. All 16 patients survived through the follow-up period. None of the 31 patients who died during follow-up had undergone whole lung lavage. Only one patient (our case) in the entire cohort received GM-CSF therapy in addition to lung lavage for PAP.

Survival and follow-up

Survival data was explicitly stated in 70 of the 75 cases. The median length of follow-up was 19.5 months (range 1—72 months). The overall survival was 56% (39 of 70). Survival was greatest in patients with mycobacterial infection (70%), whereas only 21% of patients with fungal infection survived. Nine out of 10 patients with aspergillosis, histoplasmosis, or mucormycosis died during follow-up. Three of 6 patients with cryptococcal infection died. Twelve of 29 patients (41%) with *Nocardia* spp infection died.

Overall, 31 patients died during the follow-up period. Among them, 5 patients each had an opportunistic infection or PAP as their initial diagnosis, 8 were diagnosed with both concurrently, while specific information was not available for the remainder. Seventeen of these patients were diagnosed with PAP at autopsy, while nine required a diagnostic surgical biopsy. None of these 31 patients underwent whole lung lavage for PAP.

Discussion

PAP was first described by Rosen et al. in 1958 as a rare disorder characterized by the abnormal accumulation of lipoproteinaceous material within the alveoli.[1] The estimated prevalence of PAP is 0.37 cases per 100,000 population.[2] Three forms of PAP are recognized: congenital, secondary, and acquired. Congenital PAP is generally of neonatal onset and rapidly fatal. Secondary PAP has been described in adults following hematologic malignancies, bone marrow transplantation, and following high-level toxic dust exposure. Acquired (autoimmune) PAP accounts for over 90% of the cases, and is a result of anti-GM-CSF antibodies. The median age at diagnosis is 39—51 years, with a male to female ratio of 2:1.[2,3]

Insidious onset of dyspnea is the most common presenting symptom of PAP, although, one-third of patients can be completely asymptomatic. On chest radiography, most patients display bilateral symmetric alveolar infiltrates with peripheral sparing in a "bat wing" or "butterfly" distribution.[1] This appearance resembles a "butterfly" pattern or "bat-wings." BAL reveals a milky lavage fluid, engorged alveolar macrophages, and PAS-positive lipoproteinaceous material.

Research involving genetically altered mice has demonstrated that PAP results from alterations in the GM-CSF pathway.[4] GM-CSF is necessary for the terminal differentiation of alveolar macrophages in order to effectively carry out surfactant homeostasis, antigen presentation, and phagocytosis. Lack of alveolar macrophage differentiation with accumulation of lipoproteinaceous material and concomitant neutrophil dysfunction leads to an enhanced susceptibility to infection.[5] Pulmonary macrophages have also demonstrated ineffective chemotaxis, phagocytosis, and phagolysosomal fusion. Interestingly, normal macrophages incubated in lavaged fluid from patients with PAP become defective, supporting the hypothesis that such defects in pulmonary macrophages are acquired.[51] Auto antibodies against GM-CSF are present in the majority of patients with acquired PAP, and can be measured in the serum or BAL fluid.[52]

In our initial review of the literature, we realized that opportunistic infections due to *Nocardia* spp, mycobacteria, and fungal pathogens were most commonly reported, and hence limited our analysis to infections caused by these organisms. The prevalence of opportunistic infections in patients with PAP is unclear; in a 6-year analysis of a Japanese national registry, 248 patients with PAP (223 with autoimmune PAP) were enrolled. A total of 4 cases of *Aspergillus* spp. and 5 cases of mycobacterial infection were encountered (additional details were not specified). There was no indication of increased risk of other infections in this study.[3]

The majority of patients with PAP in our cohort lacked other traditional risk factors (such as systemic corticosteroid use, HIV infection, cancer chemotherapy, or organ transplantation) for opportunistic infections, thereby reaffirming the unique role played by PAP toward predisposing patients to such infections. Therefore, PAP should be considered and excluded in an apparently immunocompetent patient with an underlying opportunistic infection in the presence of diffuse bilateral alveolar infiltrates on chest imaging. In 17 patients (23%), either systemic corticosteroids or cancer chemotherapy could have contributed to a higher risk of opportunistic infections in addition to PAP.

Lungs were the most frequent site involved by any pathogen in these patients, given the localized dysfunction of pulmonary macrophages and presence of GM-CSF autoantibodies.[5] Diagnosis of an opportunistic infection preceded PAP diagnosis by a mean of 17 months in 40% of patients. The initial diagnosis of PAP may have been missed because of the rarity of PAP and a lack of knowledge among health care professionals. Fungal infections were more often diagnosed at autopsy, while patients with mycobacterial infection had the lowest mortality (29%).

Since its first description as a successful therapeutic intervention in 1967, the mainstay of PAP management has been whole lung lavage for patients with moderate to severe symptoms.[53] Therapeutic whole lung lavage has been shown to enhance migration and phagocytic capabilities of alveolar macrophages.[54] Interestingly, all 16 patients who underwent whole lung lavage in our cohort survived. None of the 31 patients who died had undergone whole lung lavage (17 of whom were, in fact, diagnosed with PAP at autopsy).

Experimental GM-CSF therapy has been utilized in small case series of patients with autoimmune PAP with a response rate of 43—48%.[55,56] In our cohort, only one patient received GM-CSF, as most cases predated our understanding of the central role played by GM-CSF in the pathophysiology of PAP. Additional studies are warranted.

Our study has several limitations. Since we performed a retrospective analysis of published cases, details pertaining to individual cases were limited to published information. However, while assessing an uncommon complication (opportunistic infection) of a rare disease (PAP), it is almost impossible to perform a prospective study. Most published reports did not provide sufficient information to assign patients into secondary or acquired (autoimmune) PAP categories. Case reports and short case series are also subject to publication bias. Given the heterogeneity, small numbers of patients in each category of opportunistic infection, lack of contemporary diagnostic and treatment options for several cases, and missing data, a more rigorous statistical analysis could not be performed, and risk factors for mortality could not be ascertained. For the 17 patients who were considered immunocompromised, the relative contributions of PAP and immunosuppressive therapy toward their opportunistic infection remain unclear.

In conclusion, opportunistic infections with *Nocardia* spp., mycobacteria, or fungal pathogens can complicate the clinical course of patients with PAP. Opportunistic infections can precede the diagnosis of PAP by several months. Therefore, a diagnosis of PAP should be considered in any patient with diffuse alveolar infiltrates in the setting of one of the above infections. Bronchoscopy with demonstration of PAS-positive lipoproteinaceous material in lavage fluid is diagnostic of PAP. Likewise, in those patients with underlying PAP, an opportunistic infection should be aggressively sought and treated in a timely fashion to avoid adverse outcomes. Diagnosis of a concurrent opportunistic infection with PAP may be a challenge given the abnormal baseline chest imaging in these patients.

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References

1. Rosen SH, Castleman B, Liebow AA, Rosen SH, Castleman B, Liebow AA. Pulmonary alveolar proteinosis. *N Engl J Med* 1958;**258**(23):1123—42.
2. Trapnell BC, Whitsett JA, Nakata K, Trapnell BC, Whitsett JA, Nakata K. Pulmonary alveolar proteinosis. *N Engl J Med* 2003; **349**(26):2527—39.
3. Inoue Y, Trapnell BC, Tazawa R, Arai T, Takada T, Hizawa N, et al. Characteristics of a large cohort of patients with autoimmune pulmonary alveolar proteinosis in Japan. *Am journal respiratory Critical Care Medicine* 2008;**177**(7):752—62. Epub 2008/01/19.
4. Seymour JF, Presneill JJ, Seymour JF, Presneill JJ. Pulmonary alveolar proteinosis: progress in the first 44 years. *Am J Respir Crit Care Med* 2002;**166**(2):215—35.
5. Uchida K, Beck DC, Yamamoto T, Berclaz P-Y, Abe S, Staudt MK, et al. GM-CSF autoantibodies and neutrophil dysfunction in pulmonary alveolar proteinosis. *N Engl J Med* 2007;**356**(6): 567—79.
6. Anonymous. Tuberculous adenitis, neutropenia, and lung abnormalities. *S Afr Med J* 1978;**53**(5):193—7.
7. Anonymous. Pulmonary reticulonodular disease with consolidation and abscess formation. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 19-1983. *N Engl J Med* 1983;**308**(19):1147—56.
8. Anonymous. A 30-year-old man with bilateral pulmonary consolidation and cavitation. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 18-1988. *N Engl J Med* 1988;**318**(18):1186—94.
9. Bakhos R, Gattuso P, Arcot C, Reddy VB, Bakhos R, Gattuso P, et al. Pulmonary alveolar proteinosis: an unusual association with Mycobacterium avium-intracellulare infection and lymphocytic interstitial pneumonia. *South Med J* 1996;**89**(8): 801—2.
10. Bedrossian CW, Luna MA, Conklin RH, Miller WC, Bedrossian CW, Luna MA, et al. Alveolar proteinosis as a consequence of immunosuppression. A hypothesis based on clinical and pathologic observations. *Hum Pathol* 1980;**11**(5 Suppl.):527—35.
11. Bergman F, Linell F, Bergman F, Linell F. Cryptococcosis as a cause of pulmonary alveolar proteinosis. *Acta Pathol Microbiol Scand* 1961;**53**:217—24.
12. Burbank B, Morrione TG, Cutler SS, Burbank B, Morrione TG, Cutler SS. Pulmonary alveolar proteinosis and nocardiosis. *Am J Med* 1960;**28**:1002—7.
13. Calderazzo M, Pelaia G, Roccia F, Vero G, Gallelli A. A case of alveolar proteinosis associated with pulmonary nocardiosis [2]. *Eur J Intern Med* 2003;**14**(7):449.
14. Carlsen ET, Hill Jr RB, Rowlands Jr DT, Carlsen ET, Hill Jr RB, Rowlands Jr DT. Nocardiosis and pulmonary alveolar proteinosis. *Ann Intern Med* 1964;**60**:275—81.
15. Carnovale R, Zornoza J, Goldman AM, Luna M, Carnovale R, Zornoza J, et al. Pulmonary alveolar proteinosis: its association with hematologic malignancy and lymphoma. *Radiology* 1977; **122**(2):303—6.
16. Clague HW, Harth M, Hellyer D, Morgan WK, Clague HW, Harth M, et al. Septic arthritis due to Nocardia asteroides in association with pulmonary alveolar proteinosis. *J Rheumatol* 1982;**9**(3):469—72.
17. Claypool WD, Rogers RM, Matuschak GM. Update on the clinical diagnosis, management, and pathogenesis of pulmonary alveolar proteinosis (phospholipidosis). *Chest* 1984;**85**(4): 550—8.
18. Couderc LJ, Epardeau B, Dazza MC, Clauvel JP, Autran B, Grosset J, et al. Disseminated Mycobacterium avium intracellulare infection without predisposing conditions [comment]. *Lancet* 1992;**340**(8821):731.
19. Doyle AP, Balcerzak SP, Wells CL, Crittenden JO, Doyle AP, Balcerzak SP, et al. Pulmonary alveolar proteinosis with hematologic disorders. *Arch Intern Med* 1963;**112**:940—6.
20. Garcia Rio F, Alvarez-Sala R, Caballero P, Prados C, Pino JM, Villamor J, et al. Six cases of pulmonary alveolar proteinosis: presentation of unusual associations. *Monaldi Arch Chest Dis* 1995;**50**(1):12—5.
21. Garrido L, Mata-Essayag S, Hartung de Capriles C, Eugenia Landaeta M, Pacheco I, Fuentes Z, et al. Pulmonary histoplasmosis: unusual histopathologic findings. *Pathol Res Pract* 2006; **202**(5):373—8.
22. Goldschmidt N, Nusair S, Gural A, Amir G, Izhar U, Laxer U, et al. Disseminated Mycobacterium kansasii infection with pulmonary alveolar proteinosis in a patient with chronic myelogenous leukemia. *Am J Hematol* 2003;**74**(3):221—3.
23. Harris JO, Castle JR, Swenson EW, Block AJ, Harris JO, Castle JR, et al. Lobar lavage: therapeutic benefit in pulmonary alveolar filling disorders. *Chest* 1974;**65**(6):655—9.
24. Hartung M, Salfelder K, Hartung M, Salfelder K. Pulmonary alveolar proteinosis and histoplasmosis: report of three cases. *Virchows Arch A Pathol Anat Histol* 1975;**368**(4):281—7.
25. Jones CC. Pulmonary alveolar proteinosis with unusual complicating infections; a report of two cases. Jones CCi-pPwuci, Jones, 1960-3679196440/PAP with unusual complicating infections, Jones, 1960.pdf. *Am J Med* 1960;**29**:713—22.
26. Kariman K, Kylstra JA, Spock A, Kariman K, Kylstra JA. Pulmonary alveolar proteinosis: prospective clinical experience in 23 patients for 15 years. Spock Ai-pPipfy, Lung, Kariman, 1984-3948181525/PAP in 23 pts for 15 yrs, Lung, Kariman, 1984.pdf. *Lung*. 1984;**162**(4):223—31.
27. Larson RK, Gordinier R, Larson RK, Gordinier R. Pulmonary alveolar proteinosis. *Tuberculol Thorac Dis* 1965;**22**:55—62.
28. Lathan Jr SR, Williams Jr JD, McLean RL, Ramirez J, Lathan Jr SR, Williams Jr JD, et al. Pulmonary alveolar proteinosis. Treatment of a case complicated by tuberculosis. *Chest* 1971;**59**(4):452—4.
29. Maderazo EG, Quintiliani R, Maderazo EG, Quintiliani R. Treatment of nocardial infection with trimethoprim and sulfamethoxazole. *Am J Med* 1974;**57**(4):671—5.
30. Martinez-Maldonado M, Ramirez de Arellano G, Martinez-Maldonado M, Ramirez de Arellano G. Pulmonary alveolar proteinosis, nocardiosis and chronic granulocytic leukemia. *South Med J* 1966;**59**(8):901—5.
31. Morinari H, Terashi R, Okubo S, Homma S, Tanaka M, Morinari H, et al. Remission of pulmonary alveolar proteinosis during antituberculous chemotherapy. *Eur J Respir Dis* 1987;**71**(1):54—5.
32. Pascual J, Gomez Aguinaga MA, Vidal R, Maudes A, Sureda A, Gomez Mampaso E, et al. Alveolar proteinosis and nocardiosis: a patient treated by bronchopulmonary lavage. *Postgrad Med J* 1989;**65**(767):674—7.
33. Payseur CR, Konwaler BE, Hyde L, Payseur CR, Konwaler BE, Hyde L. Pulmonary alveolar proteinosis; a progressive, diffuse, fatal pulmonary disease. *Am Rev Tuberc* 1958;**78**(6): 906—15.
34. Pereira-Silva JL, Marinho MM, Veloso TV, Coelho JJ, Pereira-Silva JL, Marinho MMMA, et al. Pulmonary alveolar proteinosis and tuberculosis in a diabetic patient: a rare or a seldom diagnosed association? *Braz J Infect Dis* 2002;**6**(4):188—95.

35. Preger L. Preger Li-pP, Radiology, Preger, 1969-2991735317/PAP, Radiology, Preger, 1969.pdf. *Radiology* 1969;**92**(6):1291—5. Pulmonary alveolar proteinosis.
36. Raich RA, Casey F, Hall WH, Raich RA, Casey F, Hall WH. Pulmonary and cutaneous nocardiosis. The significance of the laboratory isolation of Nocardia. *Am Rev Respir Dis* 1961;**83**:505—9.
37. Ramirez J, Ramirez J. Pulmonary alveolar proteinosis. Treatment in a case complicated by tuberculosis. *Am Rev Respir Dis* 1967;**95**(3):491—5.
38. Reyes JM, Putong PB, Reyes JM, Putong PB. Association of pulmonary alveolar lipoproteinosis with mycobacterial infection. *Am J Clin Pathol* 1980;**74**(4):478—85.
39. Rubin E, Weisbrod GL, Sanders DE, Rubin E, Weisbrod GL, Sanders DE. Pulmonary alveolar proteinosis: relationship to silicosis and pulmonary infection. *Radiology* 1980;**135**(1):35—41.
40. Saltzman HA, Chick EW, Conant NF, Saltzman HA, Chick EW, Conant NF. Nocardiosis as a complication of other diseases. *Lab Invest* 1962;**11**:1110—7.
41. Smego Jr RA, Moeller MB, Gallis HA, Smego Jr RA, Moeller MB, Gallis HA. Trimethoprim-sulfamethoxazole therapy for Nocardia infections. *Arch Intern Med* 1983;**143**(4):711—8.
42. Steer A, Steer A. Focal pulmonary alveolar proteinosis in pulmonary tuberculosis. *Arch Pathol* 1969;**87**(3):347—52.
43. Summers JE, Summers JE. Pulmonary alveolar proteinosis. Review of the literature with follow-up studies and report of two new cases. *Calif Med* 1966;**104**(6):428—36.
44. Sunderland WA, Campbell RA, Edwards MJ, Sunderland WA, Campbell RA, Edwards MJ. Pulmonary alveolar proteinosis and pulmonary cryptococcosis in an adolescent boy. *J Pediatr* 1972;**80**(3):450—6.
45. Supena R, Karlin D, Strate R, Cramer PG, Supena R, Karlin D, et al. Pulmonary alveolar proteinosis and Nocardia brain abscess. Report of a case. *Arch Neurol* 1974;**30**(3):266—8.
46. Taleghani-Far M, Barber JB, Sampson C, Harden KA, Taleghani-Far M, Barber JB, et al. Cerebral nocardiosis and alveolar proteinosis. *Am Rev Respir Dis* 1964;**89**:561—5.
47. Udani PM, Mukerji S, Udani PM, Mukerji S. Pulmonary alveolar proteinosis. *Indian J Child Health* 1963;**12**:256—8.
48. Walker DA, McMahon SM, Walker DA, McMahon SM. Pulmonary alveolar proteinosis complicated by cerebral abscess: report of a case. *J Am Osteopathic Assoc* 1986;**86**(7):447—50.
49. Watanabe K, Sueishi K, Tanaka K, Nagata N, Hirose N, Shigematsu N, et al. Pulmonary alveolar proteinosis and disseminated atypical mycobacteriosis in a patient with busulfan lung. *Acta Pathol Jpn* 1990;**40**(1):63—6.
50. Witty LA, Tapson VF, Piantadosi CA, Witty LA, Tapson VF, Piantadosi CA. Isolation of mycobacteria in patients with pulmonary alveolar proteinosis. *Medicine* 1994;**73**(2):103—9.
51. Shah PL, Hansell D, Lawson PR, Reid KB, Morgan C. Pulmonary alveolar proteinosis: clinical aspects and current concepts on pathogenesis. *Thorax* 2000;**55**(1):67—77.
52. Greenhill SR, Kotton DN, Greenhill SR, Kotton DN. Pulmonary alveolar proteinosis: a bench-to-bedside story of granulocyte-macrophage colony-stimulating factor dysfunction. *Chest* 2009;**136**(2):571—7.
53. Ramirez J, Ramirez J. Pulmonary alveolar proteinosis. Treatment by massive bronchopulmonary lavage. *Arch Intern Med* 1967;**119**(2):147—56.
54. Hoffman RM, Dauber JH, Rogers RM, Hoffman RM, Dauber JH, Rogers RM. Improvement in alveolar macrophage migration after therapeutic whole lung lavage in pulmonary alveolar proteinosis. *Am Rev Respir Dis* 1989;**139**(4):1030—2.
55. Seymour JF, Presneill JJ, Schoch OD, Downie GH, Moore PE, Doyle IR, et al. Therapeutic efficacy of granulocyte-macrophage colony-stimulating factor in patients with idiopathic acquired alveolar proteinosis. *Am journal respiratory Critical Care Medicine* 2001;**163**(2):524—31. Epub 2001/02/17.
56. Venkateshiah SB, Yan TD, Bonfield TL, Thomassen MJ, Meziane M, Czich C, et al. An open-label trial of granulocyte macrophage colony stimulating factor therapy for moderate symptomatic pulmonary alveolar proteinosis. *Chest* 2006; **130**(1):227—37. Epub 2006/07/15.