

***Pneumocystis carinii* Pneumonia with Pleural Effusion in a Non-HIV Host**

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ABSTRACT

Pneumocystis carinii pneumonia (PCP) is a life-threatening opportunistic infection that occurs in immunocompromised hosts, especially patients with the acquired immunodeficiency syndrome (AIDS). However, this infection is increasing in frequency in other immunosuppressed patients, including organ transplant recipients and those with malignancy who are treated with chemotherapeutic regimens. It carries a relatively high mortality in the non-human immunodeficiency virus (HIV) population. Pleural involvement is rare with PCP; all reported cases in the literature are associated with HIV disease and characterized as small effusions. We report a case of a renal transplant recipient with PCP and moderate-sized pleural effusion with pneumocystis cysts.

INTRODUCTION

Pneumocystis carinii pneumonia (PCP) is a life-threatening opportunistic infection that occurs in immunocompromised hosts, especially patients with the acquired immunodeficiency syndrome (AIDS). However, this infection is increasingly diagnosed in other immunosuppressed patients, including those treated with chemotherapy for malignancy and in organ transplant recipients. Pleural effusions are rare with PCP, and when present, are usually small. Previously reported cases of pleural involvement with *Pneumocystis* have been in human immunodeficiency virus (HIV) patients. We report a case of a renal transplant recipient with PCP and moderate-sized pleural effusion with *Pneumocystis* cysts.

CASE REPORT

A 40-year-old female presented to the hospital with

a 2-week history of rhinorrhea, dry cough, and more recent onset of nausea and vomiting. She was treated in the community with moxifloxacin for 3 days, followed by clarithromycin for 4 days for suspected bronchitis. Despite this initial treatment, she continued to have fever, chills, and non-pleuritic chest pain. She complained of progressive dyspnea on exertion for 48 hours prior to admission. She had end-stage lupus nephritis that led to cadaveric renal transplantation 1 year prior to this presentation. Transplant medications included tacrolimus at 3 mg 3 times a day and prednisone at 7.5mg orally once daily. Her other medications were atenolol, atorvastatin, furosemide, vitamin D, and calcium carbonate. She was not on any PCP prophylaxis.

On presentation, the patient appeared comfortable, though mildly cushingoid. She had a temperature of 98.2° F, pulse rate of 78/min, blood pressure of 126/85 mmHg, respiratory rate of 18/min and pulse oximetry of 100% on 2 litres of O₂. There was no rash or palpable lymphadenopathy. Examination findings were significant for right basal crackles with no evidence of wheezing. Laboratory tests revealed a white blood cell count of 6700 cells/cumm (neutrophils 78%, lymphocytes 16%, monocytes 4%, eosinophils 2%), normochromic normocytic anemia (Hgb 7.6 gm/L, Hct 25), renal failure with blood urea nitrogen 67 mg/dl and creatinine 3.2 mg/dl, non-anion gap acidosis with bicarbonate of 17 mg/dl and lactate dehydrogenase (LDH) of 456 U/L. The initial chest radiograph revealed diffuse alveolar-interstitial infiltrates with basilar predominance (Figure 1). As symptoms progressed, the patient developed a right pleural effusion. Computed tomography (CT) scan of the chest revealed bilateral diffuse ground glass infiltrates, right lower lobe atelectasis, and right pleural effusion of moderate size layering out 4 cm in the supine position (Figure 2). Induced sputum for *Pneumocystis* direct fluorescence antibody (DFA), cytomegalovirus antigenemia, and urine legionella antigen were negative. Diagnostic thoracentesis revealed exudative pleural fluid (LDH – fluid 301 U/L, serum 456 U/L; Protein – 3.5 g/dl; white cell count 656 cells/cumm [neutrophils

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40, lymphocytes 4, macrophages 38, and monocytes 12]. Bronchoscopy did not reveal endobronchial or mucosal abnormalities. Bronchoalveolar lavage (BAL) was negative for bacteria, fungi, and acid-fast bacilli. However, BAL was positive for *Pneumocystis carinii* by DFA. Transbronchial biopsies revealed numerous pneumocystis cysts (Figure 3). Multiple *Pneumocystis* cysts were also seen on silver stain of the pleural fluid (Figure 4). Treatment with high dose sulfamethoxazole-trimethoprim resulted in clinical improvement of symptoms over 48 hours and radiographic improvement, including resolution of pleural effusion within 96 hours.

DISCUSSION

Pneumocystis carinii (*Pneumocystis jiroveci*) is increasing in frequency in other immunosuppressed patients, including those with malignancy who are treated with chemotherapeutic regimens and recipients requiring long-term immunosuppressive therapy. The incidence of this infection has been described to reach 10% during the first 6 months after transplantation.¹

Although Chagas and then Carinii first identified the organism in the lungs of guinea pigs in the early 1900s, the first cases of active pneumonitis in humans were recognized in premature and malnourished children in Europe during World War II. Prior to the highly active antiretroviral treatment (HAART) era, it was observed that the incidence of PCP in HIV hosts increased as the clusters of differentiation 4 (CD4) count decreased. Generally, PCP did not occur until the CD4 count dropped below 200 cells/mm³. Mansharamani et al studied 22 non-HIV patients with PCP and noted that CD4+ count was <300 cells/μl in 91% of their patients, indicating that low CD4+ counts may predispose to PCP even in patients without HIV infection.²

Pneumocystis has a unique tropism for the lung, where it exists primarily as an alveolar pathogen without invading the host. Patients with HIV disease and pneumocystis pneumonia have a significantly increased number of pneumocystis organisms in their lungs with fewer neutrophils than do patients with pneumocystis pneumonia in the absence of HIV infection.³ In the absence of brisk lung inflammation, pneumocystis has little direct effect on pulmonary function. Exuberant inflammation, however, promotes pulmonary injury during infection. Severe *Pneumocystis* pneumonia is characterized by neutrophilic lung inflammation that may result in diffuse alveolar damage, impaired gas exchange, and respiratory failure. Indeed, respiratory impairment and death are more closely correlated with the degree of lung inflammation than with the organism burden in

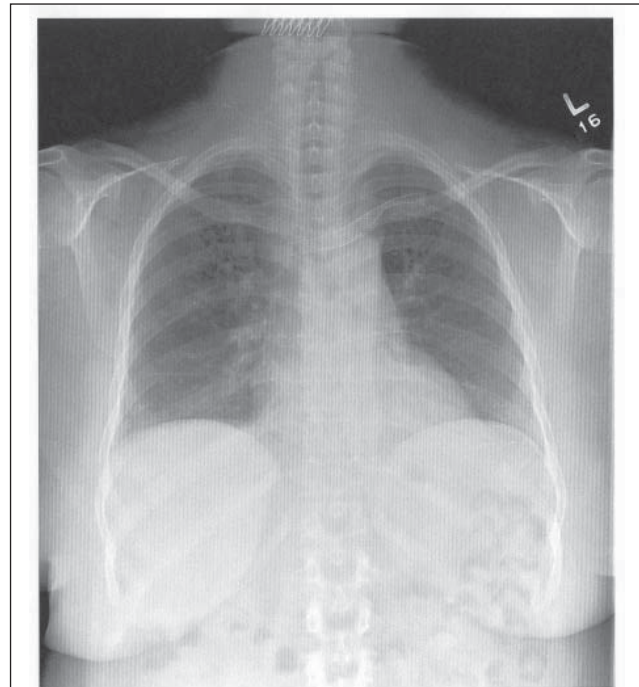


Figure 1. Chest radiograph on admission shows fine bilateral interstitial shadows with no pleural effusion.

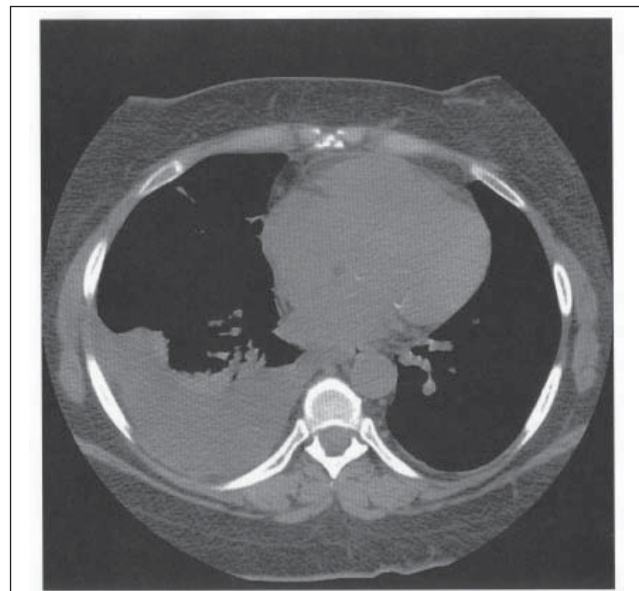


Figure 2. Axial view of a CT scan of the chest shows moderate-sized right pleural effusion with underlying atelectasis. Not shown are the parenchymal windows with bilateral interstitial ground glass infiltrates.

pneumonia. Therefore, non-HIV patients seem to have a more fulminant onset of symptoms than the indolent presentation observed in HIV-infected patients.³ The mortality rate among patients with pneumocystis pneumonia in the absence of HIV infection is 30%-60%.⁴

PCP is a relatively rare infection in kidney transplant

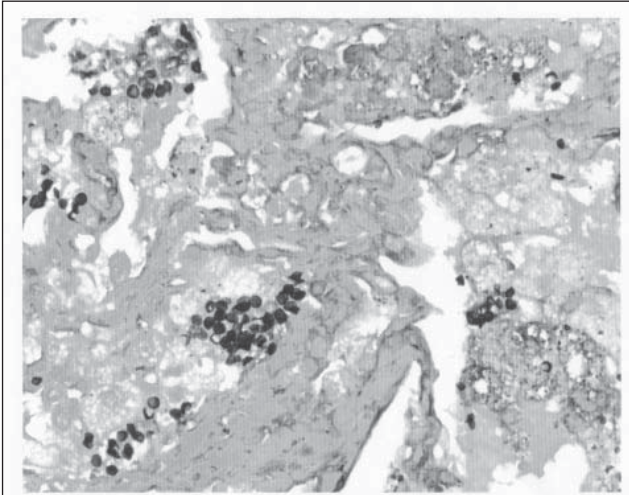


Figure 3. Gomori methanamine silver stain of transbronchial lung biopsy shows intra-alveolar clusters of oval to helmet shaped *Pneumocystis* cysts (Magnification X 400).

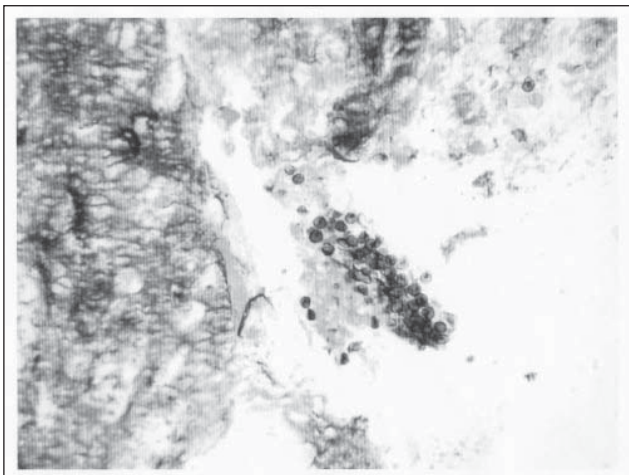


Figure 4. Gomori methanamine silver stain of pleural fluid shows *Pneumocystis* cysts identical to those seen on the biopsy (Magnification X 400).

recipients due to the practice of primary prophylaxis. Gordon et al reported the incidence of PCP to be as low as 0.4%. PCP is associated with a high mortality rate that ranges between 29% and 50% in kidney transplant recipients.⁵

In a retrospective series of 116 non-HIV patients, 90% had received systemic corticosteroids before developing PCP, with a median dose of 30mg/day of prednisone. However, 25% of the patients developed PCP while receiving <16mg/day of prednisone.⁶ Though our patient was only on 7.5mg of prednisone daily, she was also on tacrolimus. Tacrolimus is known to inhibit T lymphocyte activation. Rats treated with tacrolimus showed dose-dependent increase in incidence

of severe *Pneumocystis carinii* pneumonitis similar to those treated with high dose dexamethasone.^{7,8} In another case series done to analyze risk factors for PCP in kidney transplant recipients, 17 cases of PCP were diagnosed in 240 recipients, of which only 5 patients were on a combination of immunosuppression that included tacrolimus. Although there was a trend toward increased susceptibility with tacrolimus, the results did not achieve statistical significance.⁹

The mechanisms by which steroids predispose to the development of PCP are poorly understood, but long-term corticosteroid therapy results in a relative decrease in CD4 lymphocytes.^{10,11} Several observations in animal models suggest that CD4+ T lymphocytes mediate an effective host response to PCP in the absence of HIV infection, and limited reports suggest that CD4+ counts may be low in cases of non-HIV-related PCP.^{12,13} In the study by Mansharamani et al, 16 of 22 patients were on corticosteroids prior to diagnosis of PCP.² In addition to lymphocytes, alveolar macrophages participate in host defense against *P. carinii* by phagocytosis,^{14,15} and these cells are adversely affected by corticosteroids.

Typical radiographic features of *Pneumocystis* pneumonia are bilateral perihilar interstitial infiltrates that become increasingly homogeneous and diffuse as the disease progresses. A high-resolution computed tomography scan demonstrates multiple nodular opacities with irregular margins surrounded by an area of ground-glass attenuation characteristically referred to as the “Halo” sign. Less common findings include solitary or multiple nodules, upper-lobe infiltrates in patients receiving aerosolized pentamidine, pneumatoceles, and pneumothorax.

Pleural effusions and thoracic lymphadenopathy are rare. In a study of hospitalized HIV patients by Afessa et al, 160 of 1097 hospital admissions (14.6%) had pleural effusion on chest radiograph. Pleural effusions were reported in 47% of admissions with bacterial pneumonia, but only 5 of 85 (6%) hospital admissions with PCP, indicating this as a rare manifestation of PCP.¹⁶ In a prospective study of 58 radiographs of HIV-infected patients with pleural effusions, PCP was the cause in only 6 cases, and these were characterized as small. Furthermore, 2 of the 6 patients also had heart failure that could have been an alternative cause for the effusion.¹⁷ Several case reports and case series have characterized PCP-associated pleural effusions to be small (defined by obliteration of costophrenic angle on chest radiograph).¹⁶⁻²⁰ Pleural effusion in our case was moderate-sized, layering 4 cms on the CT scan, which was also unusual.

Pneumocystis pleural disease appears to be an anatomic extension of smoldering subpleural Pneumocystis pneumonia.²¹ Histologic examination of the pleura and the subpleural lung revealed vasculitis and infarctlike necrosis as well as *P carinii* in the tissue.²² Pleural fluid in our case revealed multiple Pneumocystis cysts consistent with anatomic extension of subpleural disease.

A previous study on *P carinii* pleural effusion noted that all the patients had a pleural fluid to serum LDH ratio of >1.0 and fluid protein of <3.0 gms.²¹ This observation was based on a study of 3 patients. In our patient, pleural fluid characteristics differed in that the pleural fluid to serum LDH ratio exceeded 0.6 and the protein level was above 3.0 gm/dl. One wonders whether this difference in characteristics could be attributed to the nature of the host, as this is the first non-HIV case reported in literature.

CONCLUSION

Pleural effusion with PCP is now a well-described manifestation, although still a relatively rare presentation. All previous cases in the literature have been in association with HIV infection. To the best of our knowledge, this is the first case reported of moderate-sized Pneumocystis pleural effusion in a non-HIV host. Though rare, PCP should be considered as an etiology in the evaluation of pleural effusion in an immunocompromised host.

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