

## *Pneumocystis jiroveci* Pneumonia

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### Introduction

*Pneumocystis jiroveci*, formerly known as *Pneumocystis carinii*, is now believed to be a fungus. *P. jiroveci* pneumonia is a fungal infection, the primary symptoms of which include progressive dyspnea, nonproductive cough, and low-grade fever. These patients are often profoundly hypoxemic, and chest radiographs typically show bilateral, diffuse interstitial infiltrates. While *P. jiroveci* pneumonia is more commonly diagnosed in individuals who have human immunodeficiency virus (HIV) and a depressed cluster-of-differentiation 4 (CD4+) count, it can occur in individuals with other forms of immunosuppression. The presentation can depend on the host; non-HIV patients often have a more fulminant presentation.

We describe the case of a 52-year-old woman who had no obvious risk factors for HIV or other forms of immunosuppression, and who presented with substantial arterial hypoxemia and bilateral lung infiltrates and was subsequently found to have both HIV infection and *P. jiroveci* pneumonia. Her case illustrates the importance of considering *P. jiroveci* pneumonia in any profoundly hypoxemic patient, even if risk factors for HIV or other forms of immunosuppression are not present on initial assessment.

### Case Report

Our patient, a 52-year-old white woman, was on her way to a regularly scheduled clinic appointment with her primary care provider when (for unclear reasons) her car ran off the road into a ditch. She subsequently made it to her clinic appointment, where she was found during the

intake process to have oxygen saturation in the mid-80% range. She was transferred to the local community hospital, where she was found to be hypotensive, with a systolic blood pressure of 85 mm Hg and an oxygen saturation of 96% on 2 L/min oxygen via nasal cannula. A portable chest radiograph performed at the time showed bibasilar consolidation and a question of a widened mediastinum. The latter finding raised concern about an aortic dissection, and she was transferred to our hospital for further trauma work-up and evaluation of this issue. By the time she arrived at our facility, she was requiring 100% oxygen via nonrebreather mask to maintain her oxygen saturation in the upper 90% range.

The patient stated that earlier in the week she had walked 3 miles without distress. On review of systems, however, she also noted an unintentional 50-pound weight loss over a 2-month period, occasional pleuritic chest pain, low-grade fevers, and a 2–3 week history of cough productive of green sputum. Her medical history was notable for hypertension, bipolar disorder, and frequent urinary tract infections. Her surgical history was notable for bilateral ureteral stents, placed at the age of 10, and a hysterectomy. Her medications included paroxetine, hydroxyzine, and felodipine. She was a lifelong nonsmoker and denied any history of alcohol or intravenous drug use. She was divorced and living with her parents in the Pacific Northwest, and stated that she had not been sexually active in several years. Her travel and environmental and occupational exposure histories were unremarkable. She did not own any pets. Her vital signs showed a temperature of 35.4°C, blood pressure of 90/59 mm Hg, heart rate of 70 beats/min, respiratory rate of 22 breaths/min, and oxygen saturation of 100% while on a 100% nonrebreather mask. On examination she appeared chronically ill. She was mildly tachypneic, but was not using accessory muscles of respiration. Her lung examination demonstrated crackles halfway up both lungs. She had a normal cardiac examination, and there was no jugular venous distention, peripheral edema, or clubbing. Basic laboratory studies revealed a white-blood-cell count of  $4.4 \times 10^9$  cells/L, with a differential of 3.65 polymorphonuclear cells and 0.48 lymphocytes. Her chemistry panel showed: sodium 146 mg/dL, potassium 4.5 mg/dL, chloride 115 mg/dL,

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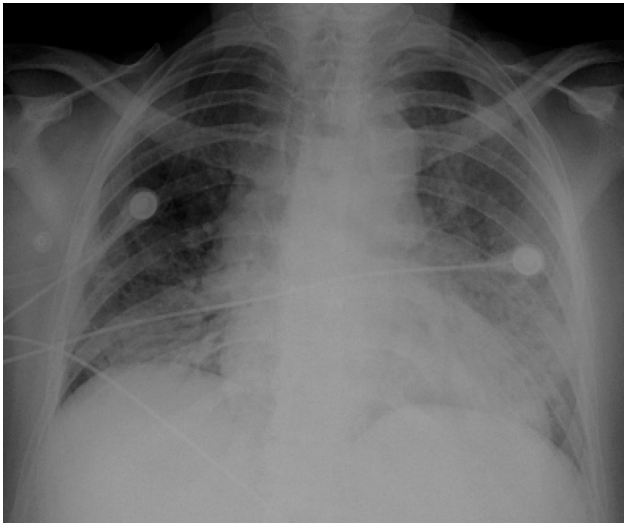


Fig. 1. Anteroposterior radiograph obtained at the time of hospital admission, showing dense bilateral interstitial and alveolar infiltrates.

bicarbonate 23 mg/dL, blood urea nitrogen 49 mg/dL, and creatinine 2.8 mg/dL. She had an erythrocyte sedimentation rate of 90 mm/h, a serum lactate dehydrogenase of 523 U/L (normal value < 200 U/L), and a B-type natriuretic peptide of < 15 pg/mL. Urinalysis showed 1+ protein, 3–8 red blood cells, and 2+ occult blood. Arterial blood gas values while breathing room air were: pH 7.36,  $P_{aCO_2}$  35 mm Hg,  $P_{aO_2}$  50 mm Hg, and bicarbonate 20 mg/dL. The electrocardiogram showed sinus tachycardia and no evidence of ischemic changes. Her chest radiograph showed diffuse bilateral interstitial infiltrates (Fig. 1). A noncontrast chest computed tomogram showed no evidence of aortic injury, but did show extensive bilateral ground-glass opacities (Fig. 2).

The patient was started on empirical antibiotic coverage (ceftriaxone and azithromycin) for community-acquired pneumonia. However, because of the rapidity of her decline and concern about possible pulmonary-renal syndrome, given her renal insufficiency and hematuria, bronchoscopy was performed on the day of admission to facilitate diagnosis. Because of her tenuous oxygenation, she was intubated for the procedure. The complete airway inspection was normal and there was no evidence of diffuse alveolar hemorrhage in the bronchoalveolar lavage fluid (BALF). Following the bronchoscopy, she was started on empirical trimethoprim/sulfamethoxazole and oral prednisone for *P. jiroveci* pneumonia. She was extubated the following morning, at which time the direct fluorescent antibody stain for pneumocystis organisms came back positive. The remainder of the bacterial, viral, and acid-fast bacilli studies were negative. The BALF fluid contained 5.3 million nucleated cells/mL, of which 88% were neutrophils. Blood cultures drawn on admission remained neg-



Fig. 2. Single slice from the noncontrast computed tomogram of the chest, obtained at admission, showing bilateral ground-glass opacities.

ative. Several days later, her HIV enzyme-linked immunosorbent assay was reported as positive. This was subsequently confirmed with western blot analysis. Her absolute CD4+ count was 5 cells/mL and her HIV ribonucleic acid was > 1,000,000 copies/mL. The patient subsequently had an uneventful recovery. Her abnormal renal function, which was eventually determined to be secondary to volume depletion, normalized with fluid administration over the initial days of her hospitalization. She was discharged from the hospital 12 days after admission, with plans to complete a 21-day course of trimethoprim/sulfamethoxazole and a prednisone taper. Initiation of antiretroviral therapy was delayed until her out-patient follow-up visit.

## Discussion

*P. jiroveci* pneumonia is an opportunistic infection commonly seen in patients with HIV infection and other forms of immunosuppression. Among HIV-infected patients, the leading risk factor is a CD4+ cell count < 200/mL<sup>3</sup>.<sup>1</sup> Whether the patient is on prophylaxis against *P. jiroveci* is also important, because patients with CD4+ count below 200 /mL<sup>3</sup> who are not receiving prophylaxis are 9 times more likely to develop the infection than are patients with low CD4+ counts who are on adequate prophylaxis.<sup>2</sup>

Non-HIV-infected patients at risk for *P. jiroveci* pneumonia include patients with hematologic malignancies, solid tumors, or inflammatory disorders, and patients who have undergone bone marrow or solid-organ transplantation.<sup>3</sup> The leading risk factor for infection among such patients is prior immunosuppression, particularly prior steroid use. Yale and Limper,<sup>3</sup> for example, reported that

91% of non-HIV patients with pneumocystis pneumonia had received systemic corticosteroids within 1 month of their diagnosis, at a median dose of 30 mg of prednisone, and for a median duration of 12 weeks prior to the development of pneumonia. Patients with *P. jiroveci* pneumonia typically present with fever, nonproductive cough, and shortness of breath.<sup>4,5</sup> High fever, purulent sputum, and pleuritic chest pain argue against this diagnosis, and are instead more suggestive of a bacterial pneumonia. Although the presenting symptoms are often similar between HIV-infected patients and those with other forms of immunosuppression, the time course of the illness differs between these 2 groups. HIV-infected patients often have a more subacute presentation, with a median duration of symptoms of 3–4 weeks, whereas non-HIV-infected patients present after a median duration of symptoms of only 5 days.<sup>4,5</sup> The rapid worsening of symptoms and oxygenation in our patient was atypical for HIV-infected patients with *P. jiroveci* pneumonia. On physical examination, patients are typically tachypneic and may have inspiratory crackles. Despite what can be a very severe process, 54–70% of patients in 2 large case series had normal findings on auscultation.<sup>4,5</sup>

On laboratory evaluation, these patients often do not have an elevated total white-blood-cell count. Kovacs et al<sup>4</sup> for example, reported an average white-blood-cell count of  $4.9 \times 10^9$  cells/L in HIV-infected individuals and  $4.6 \times 10^9$  cells/L in patients with other forms of immunosuppression, although the range was quite broad in the latter group. The mean serum lactate dehydrogenase is elevated in patients with *P. jiroveci* pneumonia, compared to patients with other forms of lung disease.<sup>6</sup> However, there is a considerable amount of overlap in lactate-dehydrogenase values between the 2 groups, so this test cannot distinguish between different causes of pneumonia. Blood gas analysis may show marked hypoxemia, but the reported range of room air  $P_{O_2}$  values is very broad. Kovacs et al,<sup>4</sup> for example, reported a mean  $P_{O_2}$  of 69 mm Hg (range 35–116 mm Hg) in HIV-infected individuals and a mean  $P_{O_2}$  of 52 mm Hg (range 29–91 mm Hg) in patients with other forms of immunosuppression. Kales et al<sup>5</sup> reported a mean  $P_{O_2}$  of 66 mm Hg. Six of the 109 patients in that series had  $P_{O_2} < 40$  mm Hg, while 21 patients had  $P_{O_2}$  between 80 mm Hg and 110 mm Hg at presentation.

The most common plain-radiograph presentation of *P. jiroveci* pneumonia is bilateral interstitial infiltrates that are granular or reticular in appearance, although other patterns are often seen, including focal infiltrates, cystic or honeycomb patterns, hilar enlargement, and spontaneous pneumothorax.<sup>7</sup> These findings are typically similar between HIV-infected and non-HIV-infected individuals, but cystic disease and pneumothoraces are unusual in non-HIV-infected individuals.<sup>7</sup> The occurrence of a spontaneous pneumothorax in a patient with HIV should prompt strong con-

sideration of *P. jiroveci* pneumonia. Some patients with *P. jiroveci* pneumonia, particularly HIV-positive patients presenting with an indolent course, will have a normal chest radiograph. In such cases, high-resolution chest computed tomogram can assist in diagnosis, with a sensitivity and specificity as high as 100% and 89%, respectively, in one series.<sup>8</sup>

While laboratory and imaging studies may be highly suggestive of *P. jiroveci* pneumonia, diagnosis requires identification of pneumocystis organisms in either sputum, bronchoalveolar lavage fluid, or biopsy specimens. Because *P. jiroveci* is an atypical fungus, it is difficult to culture, and diagnosis is typically made with silver staining or immunofluorescence staining of respiratory-tract specimens. Sputum induction is the initial diagnostic step to obtain adequate specimens. A recent meta-analysis reported a sensitivity of 55% and a specificity of 98% for this procedure, and also noted that immunofluorescence staining has a higher sensitivity than cytochemical staining.<sup>9</sup> Because the burden of pneumocystis organisms is higher in HIV-positive patients than in patients with other forms of immunosuppression,<sup>10</sup> the diagnostic yield of the test is higher in the former population. Successful sputum induction is highly dependent on technique and the patient's ability to tolerate the procedure. In a dyspneic or bronchospastic patient, care must be taken in considering sputum induction because the hypertonic saline may not be well tolerated. If sputum induction fails to yield a diagnosis or cannot be performed, the patient should undergo bronchoscopy and bronchoalveolar lavage. Bronchoscopy following a negative induced sputum has the added advantage of facilitating diagnosis of alternative etiologies and allowing discontinuation of empirical pneumocystis treatment. Given the high yield of this procedure, it is rare for patients to require transbronchial or surgical lung biopsy for diagnosis. Diffusion capacity measurements and exercise arterial blood gas values have been proposed as diagnostic steps for patients with suggestive presentations and normal chest radiographs,<sup>11</sup> but these tests serve only to alter one's suspicion for the diagnosis; they do not obviate confirmatory testing.

When there is reasonable suspicion of *P. jiroveci* pneumonia (or the lack of another more compelling diagnosis), empirical therapy is started, pending the results of diagnostic testing. When a diagnosis has been confirmed, the treatment of choice for mild, moderate, or severe disease is trimethoprim/sulfamethoxazole for 21 days. Mild to moderate disease can be treated with an oral regimen of 2 double-strength tablets (320 mg trimethoprim, 1,600 mg sulfamethoxazole) every 8 hours, while severe disease is managed with intravenous therapy (15–20 mg/kg of the trimethoprim component administered in divided doses every 6–8 h). The doses for both regimens are higher than with other clinical uses of this antibiotic.

In the setting of a severe pneumonia and a reported drug allergy to sulfa, desensitization is often proposed, given the marked benefit of trimethoprim/sulfamethoxazole in severe *P. jiroveci* pneumonia. For mild to moderate disease, acceptable alternative regimens include atovaquone, dapsone-trimethoprim, or clindamycin-primaquine for a similar duration, as these agents have equivalent rates of dose-limiting toxicity, therapeutic failure, and survival at 2 months.<sup>12</sup> Patients with severe hypoxemia, marked by a room-air oxygen saturation of < 90%, an elevated alveolar-arterial oxygen difference (> 35 mm Hg), or  $P_{O_2}$  of < 65 mm Hg should also be started on systemic corticosteroids. A dose equivalent to 60 mg of prednisone daily in non-HIV-infected patients and 40 mg twice a day in HIV patients helps to prevent clinical deterioration following initiation of treatment. Such a dose also decreases the duration of mechanical ventilation, intensive care stay, and supplemental oxygen use,<sup>13</sup> without increasing the risk of tuberculosis or other HIV-associated diseases.<sup>14</sup>

Following completion of treatment, patients who will still be exposed to the same degree of immunosuppression that made them susceptible to the disease should be put on pneumocystis prophylaxis. Prophylaxis should also be initiated in HIV-infected patients with CD4+ counts < 200 cells/mL<sup>3</sup>. A specific regimen for non-HIV patients has not been established, but it is generally recommended for patients on long-term high-dose corticosteroid therapy, other immunosuppressants, or with hematologic malignancies. Acceptable regimens include trimethoprim/sulfamethoxazole, dapsone, aerosolized pentamidine, or atovaquone. While aerosolized pentamidine can be used for prophylaxis, only the intravenous form can be used for treatment purposes.

Following initiation of treatment, clinical improvement has been reported to occur in 83% of cases at a mean of  $4.5 \pm 2.5$  days, with radiographic improvement lagging by about 3 days.<sup>15</sup> The reported mortality rates have depended on the period in which the series was completed, whether the patients had HIV or some other form of immunosuppression, and whether they required mechanical ventilation. Reports from the early stages of the HIV epidemic documented mortality of 19–43% in HIV-positive patients,<sup>4,5</sup> while a more recent series from a single center documented a mortality rate of only 6.6%.<sup>16</sup> Higher mortality (34–49%) is reported among patients with non-HIV forms of immunosuppression<sup>3,16</sup> and patients with any form of immunosuppression who require mechanical ventilation (69%).<sup>16</sup> On initial presentation, factors associated with better survival include normal respiratory rate, normal findings on lung examination, higher room-air  $P_{aO_2}$ , and higher serum albumin levels. Repeat hospital admission, elevated serum lactate dehydrogenase, and the presence of concomitant pulmonary infections are associated with worse outcomes.<sup>4,5</sup>

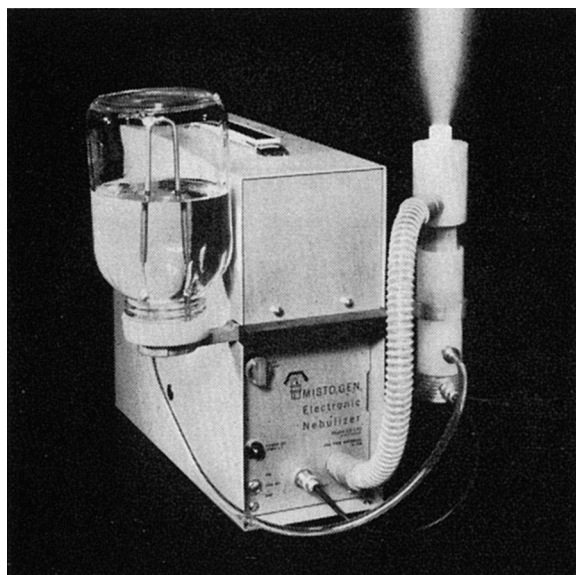
Because of the higher mortality associated with mechanical ventilation in *P. jiroveci* pneumonia, it is important to detect these patients before the disease becomes so severe as to require that high level of respiratory support. Even in the absence of obvious risk factors for HIV infection or other forms of immunosuppression on initial presentation, the presence of marked hypoxemia and diffuse bilateral infiltrates on radiographic imaging without a clear cause should prompt consideration of *P. jiroveci* pneumonia and aggressive measures to rule it out.

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