

## CLINICAL CASE OF THE MONTH

# A 35-Year-Old Immunocompromised Man With Cough of Three Weeks Duration

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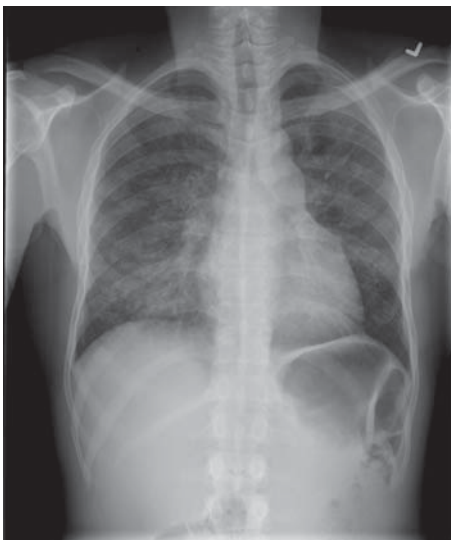
A 35-year-old man with advanced human immunodeficiency virus (HIV) infection presented to the emergency department with a chief complaint of cough for three weeks. His cough was productive of clear sputum, and he also reported progressively worsening shortness of breath. He had subjective fevers and chills, fatigue, and 25-pound weight loss in the few weeks prior to presentation. He denied any hemoptysis, chest pain, and sick contacts. The remainder of the review of systems was negative.

The patient had advanced HIV infection, with a CD4 count of 5 cells/mm<sup>3</sup>, which was diagnosed approximately one year prior. He had not sought care for his HIV infection since that time. He also had a history of ventricular septal defect for which he had undergone surgical repair with VSD patch as a newborn in 1975. The patient worked as a welder and was not taking any prescription medications at the time of presentation. He denied the use of tobacco and illicit drugs. He stated that he formerly abused alcohol, i.e., approximately three pints of liquor daily, but quit three months prior to presentation.

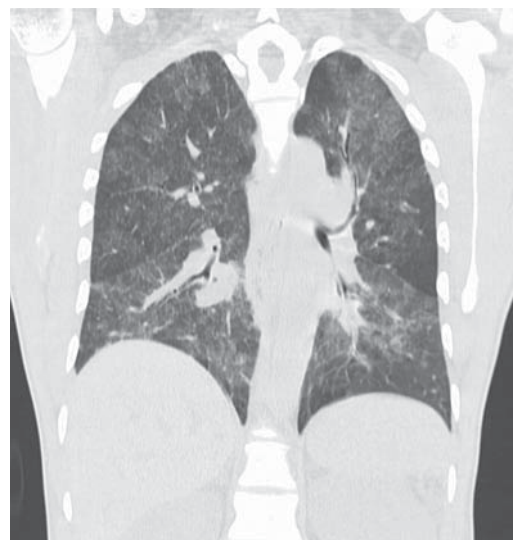
Upon physical examination, the patient's temperature

was 103.5° Fahrenheit, heart rate of 121 beats/minute, blood pressure of 153/87 mm Hg, respiratory rate of 20/min, and oxygen saturation of 94% on ambient air. He weighed 134 pounds and his body mass index was 22. He appeared well nourished, in no apparent distress, and was able to speak in full sentences. Cardiovascular exam revealed tachycardia and a systolic ejection murmur, which was loudest at the left upper sternal border. Auscultation of his lungs revealed diffuse inspiratory and expiratory wheezing bilaterally. A posteroanterior chest radiograph (Figure 1) and a coronal reformatted image from a computed tomogram (CT) of the chest without contrast (Figure 2) showed diffuse, symmetric, ground glass opacities with relative peripheral sparing, typical of *Pneumocystis pneumonia* (PCP).

Upon admission, arterial blood gas (ABG) on 28% fraction of inspired oxygen (FiO<sub>2</sub>) revealed a pH of 7.48, pCO<sub>2</sub> of 38 mm Hg, pO<sub>2</sub> of 69 mm Hg, and bicarbonate of 28 mmol/L. His alveolar-arterial gradient (A-a gradient) was 60 torr. He was treated with trimethoprim-sulfamethoxazole and prednisone for suspected PCP. A bronchoalveolar lavage (BAL) was performed. Silver stain of the BAL specimen



**Figure 1:** Admission posteroanterior chest radiograph, showing diffuse, symmetric ground glass opacities.



**Figure 2:** Reformatted image from a CT of the chest without contrast shows diffuse ground glass opacities with relative peripheral sparing, typical of PCP.

was positive for PCP (Figure 3) and three acid-fast bacillus (AFB) smears were negative. The patient was eventually discharged with plans to receive a total course of 21 days of trimethoprim-sulfamethoxazole and prednisone taper.

## EPIDEMIOLOGY

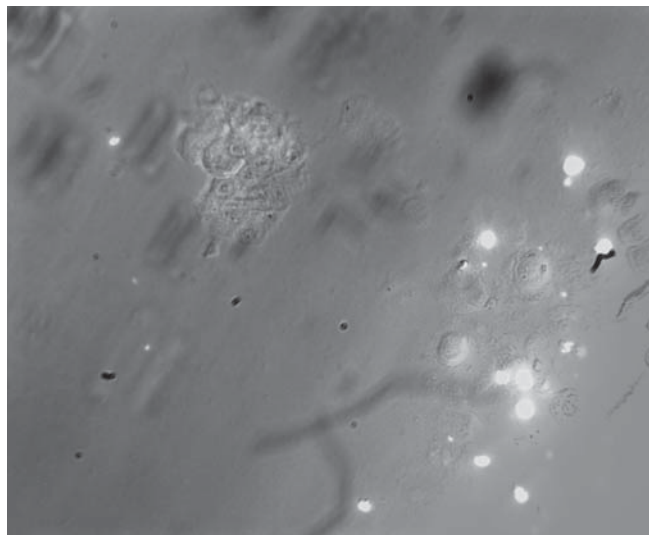
*Pneumocystis pneumonia* (PCP), which is caused by *Pneumocystis jirovecii*, is an opportunistic infection found in immunosuppressed patients, especially among those infected with HIV. PCP continues to be the leading cause of AIDS-defining illness, particularly in those patients with CD4+ counts less than 200 cells/mm<sup>3</sup>. *Pneumocystis jirovecii*, originally classified as a genus of protozoan organisms, is now recognized as a fungus.<sup>1</sup> The organism was first noted to cause pneumonia among malnourished infants in orphanages during World War II. The disease grew in importance in the 1980s with the advent of the HIV epidemic.<sup>2</sup> Although PCP remains the most frequent opportunistic pathogen among the HIV population, the incidence is declining with the use of antiretroviral therapy and PCP prophylaxis.<sup>3</sup>

The transmission of PCP is not fully understood, but studies support person-to-person transmission and environmental acquisition of the organism. Evidence from polymerase chain reaction (PCR) for *Pneumocystis* DNA supports asymptomatic colonization with PCP. The colonization may lead to transmission of the disease or activation of latent disease.<sup>4,5</sup> Studies do not support the spread of PCP from immunocompetent individuals to immunodeficient patients. Although most evidence supports an airborne route of transmission, respiratory isolation is not routinely recommended for those who are infected.<sup>6</sup>

The mainstay of therapy for PCP continues to be trimethoprim-sulfamethoxazole (TMP-SMX). Recently, there has been evidence of drug resistant organisms and failure to respond to TMP-SMX. Studies have shown an association between sulfa drugs and the ability of the organism to form mutations in the dihydropteroate synthase (DHPS) gene of *Pneumocystis jirovecii* in the development of resistance. More research is needed regarding the possible mechanisms of drug resistance and future of therapy for PCP.<sup>5</sup>

## RISK FACTORS

*Pneumocystis pneumonia* remains a leading cause of morbidity and mortality among the HIV-infected patient population. Individuals at highest risk for PCP infection are those with a CD4+ count less than 200 cells per cubic millimeter. Other risk factors include the use of immunosuppressive agents, especially corticosteroids. Malignancies, particularly hematologic malignancies such as lymphoma and leukemia, and hematopoietic stem cell transplantation are risk factors for acquiring PCP. Inflammatory conditions, especially rheumatologic diseases such as polymyositis and systemic lupus erythematosus, and defects in cell-mediated immunity, such as severe combined immunodeficiency, are



**Figure 3:** Immunofluorescence assay detection of *Pneumocystis jirovecii* cysts in a bronchoalveolar lavage specimen overlaid with a phase contrast image to display histology (100x). The eccentric circular structure within the cysts may represent aggressive trophozoites.

also risk factors. It is rare for an immunocompetent host to develop PCP.<sup>7</sup>

## CLINICAL PRESENTATION

Extrapulmonary *Pneumocystis jirovecii* infections may rarely occur, and have been reported in HIV and non-HIV infected individuals. The most common extrapulmonary sites of PCP infection include lesion within the liver, spleen, kidney, and brain. Evidence supports that the use of aerosolized pentamidine for PCP prophylaxis predisposes to extrapulmonary disease.<sup>8</sup> Patients with PCP most commonly complain of low-grade fevers, non-productive cough, and dyspnea. They may also complain of night sweats and weight loss. The progression is usually subacute, with symptoms preceding the presentation by three to four weeks.<sup>3</sup> Much less commonly, the disease may manifest as acute dyspnea in a patient with pleuritic chest pain and development of a pneumothorax. Physical exam usually reveals tachycardia, tachypnea, and clear lungs. The lung exam is only abnormal in about 50% of cases, usually manifesting as bilateral inspiratory crackles. The alveolar-to-arterial oxygen gradient is also commonly widened.<sup>1</sup>

Radiographic findings usually include symmetric perihilar reticular infiltrates, which spread diffusely as the disease progresses. Less commonly, there may be localized infiltrates, lobar distribution of the disease, or hilar adenopathy.<sup>9</sup> Rarely, pneumothorax may be the presenting radiographic feature in a patient with AIDS and PCP. At times, there may also be a normal radiographic appearance of the chest and high-resolution CT may aid in the diagnosis by detecting opacities not seen on plain film radiograph.<sup>1</sup>

## DIAGNOSIS

HIV-infected patients presenting with a combination of low CD4+ count, subacute dyspnea, dry cough, fevers, ground glass infiltrates on chest radiograph, and low oxygen saturation should be evaluated for PCP. Elevated LDH, a marker of underlying lung inflammation, and CD4+ count less than 200 cells/mm<sup>3</sup> are two of the most common laboratory abnormalities encountered among those with PCP. The disease may be difficult to definitively diagnose due to the reliance on microscopic demonstration of the organism since the organism cannot be cultured. Several methods are commonly used to gather microscopic data. Bronchoscopy with bronchoalveolar lavage (BAL) remains the gold standard for the diagnosis of PCP. Several other methods, including expectorated and induced sputum and polymerase chain reaction (PCR), are also commonly used.<sup>1</sup>

Sputum induction is an inexpensive, cost-effective strategy, and the least invasive procedure used to make the diagnosis of PCP. For this reason, it is usually recommended as the first procedure. Overall, sputum induction for diagnosis averages 55% in sensitivity and 98% specificity. The low sensitivity may be attributed to many factors, including collection difficulties and staining techniques. Studies also show variability of organism burden in the lung when PCP occurs in the non-HIV infected patient. The reduced organism burden may attribute to lower sensitivities of sputum induction for the diagnosis of PCP in other immunocompromised states.<sup>10</sup> When sputum induction does not yield a positive specimen for pneumocystis, bronchoscopy with bronchoalveolar lavage (BAL) should generally be performed. BAL, the gold standard for the diagnosis of PCP, has a sensitivity greater than 90%. Research has suggested lower yield for diagnosis of PCP among patients receiving aerosolized pentamidine therapy for PCP prophylaxis. Review of lavage specimens suggests that the use of aerosolized pentamidine may decrease the organism burden in the lung, making it harder to detect the organism.<sup>11</sup>

Many stains have been used to demonstrate the trophic and cystic forms of pneumocystis. Papanicolaou, Wright-Giemsa, and Gram Weigert stains show the trophic forms. Gomori methenamine silver, cresyl echt violet, and calcofluor white stains show the cystic forms of pneumocystis.<sup>1,12</sup> Monoclonal antibodies against pneumocystis are more sensitive and specific, and they are able to show both the trophic and cystic forms.<sup>1</sup>

DNA amplification by polymerase chain reaction (PCR) is a newer tool to aid in diagnosis. PCR is the most sensitive method in detecting PCP from sputum induction and BAL compared to the conventional methods of staining. The use of PCR in diagnosis is an area of active research. Its use is limited due to cost and lack of availability. The estimated prevalence of PCP, financial resources, and technical capabilities available will generally guide the diagnostic workup.<sup>12</sup>

## PROPHYLAXIS AND TREATMENT

Primary PCP prophylaxis is recommended in patients who are HIV-infected when the CD4+ count is less than 200 cells/mm<sup>3</sup> and in patients with oropharyngeal candidiasis regardless of CD4+ count. Prophylaxis may be considered when the CD4+ cell percentage is less than 14% or in patients with an AIDS-defining illness. Therapy should be continued lifelong or until the CD4+ count is above 200 cells/mm<sup>3</sup> for at least three months with HAART therapy. Patients who are not infected with AIDS and are immunocompromised for other reasons, such as immunosuppressive medications and acquired immunodeficiencies, should also receive prophylaxis. The preferred medication for PCP prophylaxis is oral trimethoprim-sulfamethoxazole (TMP-SMX), double-strength, daily. Alternatively, trimethoprim-sulfamethoxazole (TMP-SMX), double-strength, administered three times weekly, or TMP-SMX, single-strength, administered daily can also be considered. Oral dapsone, 100 mg daily, is typically used for patients who are intolerant of TMP-SMX. Monthly aerosolized pentamidine and daily oral atovaquone are other alternatives for prophylactic treatment.<sup>1</sup>

The preferred treatment of PCP consists of trimethoprim-sulfamethoxazole. Patient allergies, treatment toxicities, and disease severity directs therapy. Patients presenting with A-a gradients above 45 mm Hg, partial pressure of arterial oxygen below 60 mm Hg, or those at risk for respiratory failure should generally be given intravenous trimethoprim-sulfamethoxazole dosed 15-20 mg/kg/day of trimethoprim every six to eight hours. Oral TMP-SMX is dosed as two double-strength tablets every eight hours. The use of TMP-SMX is limited by hepatotoxicity, neutropenia, and hyperkalemia.<sup>13</sup> Patients presenting with hypoxia, defined as partial pressure of arterial oxygen less than 70 mm Hg breathing room air, or alveolar-arterial gradient greater than 35 benefit from corticosteroid therapy. The recommended dose of prednisone is 40 mg twice daily for five days, then 40 mg daily on days 6 through 11, and 20 mg daily on days 12 – 21. Patients may clinically worsen two to three days after initiation of therapy due to inflammation in the lungs associated with the death of organisms. Corticosteroids are believed to improve this effect when started with PCP therapy.<sup>14</sup>

Alternative therapies for treatment include daily pentamidine, twice daily atovaquone, or a combination of daily primaquine plus clindamycin three times daily. Some of the major side effects for these regimens include nephrotoxicity, hypo- and hyperglycemia, hypokalemia, gastrointestinal distress, hemolytic anemia, and neutropenia. Although TMP-SMX is the preferred treatment for PCP based on efficacy and toxicity, there has been no significant difference in survival rates among studies comparing these other therapies.<sup>15</sup>

The duration of treatment is typically 21 days for PCP related to HIV infection. Once therapy is completed, prophylaxis against PCP must be started. Inpatient therapy is recommended if presentation of disease is severe enough



to warrant therapy with corticosteroids or if IV therapy is needed. If patients do not show clinical improvement within four to eight days, this is considered treatment failure, and it is generally recommended to switch from oral to intravenous therapy. It is also important to search for other co-infections in patients without clinical improvement, such as cytomegalovirus, histoplasmosis, and cryptococcosis. The prognosis of patients with PCP is related to the degree of hypoxemia at the time of presentation. Although the appropriate timing for initiation of HAART has yet to be determined, it is suggested to initiate therapy within two weeks of PCP treatment.<sup>15</sup>

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