Fever and Dyspnea in a 61-Year-Old Woman With Metastatic Breast Cancer

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A 61-year-old woman presented to her oncologist complaining of a 3-day history of fever, chills, fatigue, anorexia, and mild shortness of breath without cough or chest pain. She had recently received a diagnosis of invasive ductal carcinoma of the breast with liver metastases. She had completed her third cycle of palliative chemotherapy 3 weeks prior to presentation. Her chemotherapy regimen consisted of doxorubicin, cyclophosphamide, pegfilgrastim, dexamethasone (10 mg IV), and lorazepam. She also received oral dexamethasone, 4 mg twice daily for 3 days, after every cycle for nausea. Her medical history included hypertension, and she had recently quit smoking (40 pack-year smoking history). She denied contacts with sick persons, pets, travel, or history of malignancy among parents or siblings. She was admitted to the hospital and treated for community-acquired pneumonia without improvement. After 3 days, she required transfer to the ICU for worsening hypoxemia with persistent fever and leukocytosis.

**Physical Examination**

The patient was in moderate respiratory distress, emaciated, and ill-appearing. Her temperature was 38.6°C, pulse was 104 beats/min, BP was 123/89 mm Hg, and respiratory rate was 22 breaths/min. The oxygen saturation was 91% while breathing 90% oxygen by face mask. There was no jugular distension. Chest examination revealed bilateral crackles. A left chest single-lumen port was imaged with chest radiograph and CT scan.
appeared to be normal. The rest of the examination findings were unremarkable.

**Laboratory and Radiographic Findings**

A CBC showed leukocytosis with a WBC count of $16.9 \times 10^3$ cells/µL (86% neutrophils, 8% lymphocytes, and 6% monocytes). Her hemoglobin concentration was 10.7 g/dL, and the platelet count was $360 \times 10^3$ cells/µL. Renal and hepatic function test results were normal. Serology test results for HIV were negative. Nasal wash testing was negative for influenza. Urine analysis, including testing for the Legionella antigen, was negative. ECG findings were normal, and an echocardiogram showed normal systolic function unchanged from 2 months before. A representative chest radiograph (Fig 1A) and a CT scan image of the chest (Fig 1B) are shown. Flexible bronchoscopy was performed with bronchial washing samples and BAL fluid showing the presence of *Candida albicans*. The findings of direct fluorescent antibody testing for *Pneumocystis jirovecii* and acid-fast staining for mycobacteria on the BAL fluid samples were negative. Cytologic examination of the BAL fluid was negative for malignancy.

**Question:** What is the best next step in establishing the diagnosis?

**What is the diagnosis?**
Answer to question: Transbronchial biopsy. The biopsy specimen showed a frothy eosinophilic exudate within the airspaces (Fig 2), containing organisms visible as minute dot-like structures within small “bubbles.” The alveolar septa showed mild chronic inflammation and fibrosis, and were lined by prominent type 2 pneumocytes. A Grocott methenamine-silver stain showed a few scattered round, folded and helmet-shaped cysts (Fig 3) within the frothy intraalveolar exudate, with morphologic features of \textit{P. jirovecii}. Results of Ziehl-Neelsen staining for mycobacteria were negative.

Diagnosis: \textit{P. jirovecii} pneumonia in an HIV-negative immunocompromised patient

Discussion

While the incidence of Pneumocystis pneumonia (PCP) in HIV-positive patients has decreased in the past 2 decades due to antiretroviral therapy and prophylactic regimens, the incidence in HIV-negative immunocompromised patients is increasing. We present an HIV-negative, immunocompromised patient with respiratory distress, whose BAL fluid sample was negative for PCP but whose lung biopsy specimen confirmed the diagnosis. We review here the challenges surrounding the diagnosis of PCP in this particular population.

In HIV-negative patients, immunosuppression is almost mandatory for PCP infection to occur, with steroid exposure being the most common risk factor. Other predisposing conditions, alone or in conjunction with steroid exposure, include the following, with their associated incidence of PCP infection: 22 to 45% in patients with acute leukemia and non-Hodgkin lymphoma; 25% in patients with severe combined immunodeficiency syndrome; 25% in patients with rhabdomyosarcoma; 1.3% in patients with solid tumors who are receiving treatment with steroids; 5 to 10% in all transplant patients (except for patients undergoing allogenic bone marrow transplantation where the risk is very low, and those undergoing heart/lung transplantation where the incidence is >25%); and <2% in patients with connective tissue diseases, except for those with Wegener granulomatosis, among whom the risk is 10 to 20%. Prevalence data are unknown, but colonization inferred from the presence of pneumocystis DNA in BAL fluid is noted to be 20% in the nonimmunocompromised population, and 44% with prednisone exposure of >20 mg daily.

A few case reports have included patients without any of the above risk factors. Additionally, PCP is the presenting illness in 20% of children who are affected by severe combined immunodeficiency syndrome, and has been described in a 3-year-old asthmatic child after receiving treatment with inhaled triamcinolone, 450 \( \mu \)g/d for 7 months. The median steroid dose of prednisone is 30 to 40 mg/d with a median duration of exposure of 12 to 16 weeks prior to the development of PCP. The lowest reported steroid doses are 16 mg daily with monotherapy and 5 mg daily in conjunction with other immunosuppressive drugs. Cases have been reported in patients with Cushing disease without exogenous steroid exposure. Increased incidence is noted while tapering steroid therapy or during pulse therapy. The intensity of chemotherapy and the duration of neutropenia, are proportional to the incidence of PCP, but no specific duration of neutropenia appears to be a threshold for infection.
Although PCP incidence is inversely related to absolute CD4+ lymphocyte count in HIV-positive patients, there is no clear cutoff threshold for CD4+ count in HIV-negative patients, conferring increased susceptibility. Lymphopenia (ie, lymphocyte count of < 800 cells/μL) is a predisposing factor.

The presentation of PCP in HIV-negative immunocompromised patients is often more acute, rapidly progressing to respiratory failure. Fever, dyspnea, and dry cough are often the presenting symptoms. No radiographic differences have been described between HIV-positive and HIV-negative patients with PCP. Chest radiograph findings may be normal at presentation, even with diffuse parenchymal involvement, but frequently display a diffuse interstitial pattern. The most common high-resolution CT scan finding is ground-glass opacity sparing the lung periphery, as was seen in our patient, displaying a mosaic or nearly homogeneous pattern. Less typical findings, seen in < 10% of cases, include airspace consolidation, patchy linear-creticular opacities, solitary or multiple nodules, parenchymal cavitary lesions, and pneumothorax. Definitive diagnosis usually requires visualization of the organism using immunofluorescence techniques or direct histopathologic identification in samples of sputum, BAL fluid, or tissue obtained by lung biopsy.

Bronchoscopy with multilobe, site-directed BAL is recognized as the procedure of choice for the diagnosis of PCP in HIV-positive patients, with sensitivity and specificity approaching 100%. However, prior studies have suggested that BAL is insufficient in the HIV-negative immunocompromised population. In one case report and an additional case series of three HIV-negative immunocompromised cancer patients with PCP in which BAL and transbronchial biopsy findings were negative, only open lung biopsy was diagnostic. With these reports and the lack of controlled studies comparing the different modalities for PCP diagnosis, BAL of multiple sites with transbronchial biopsy should be the rule in cases of suspected PCP, and open lung biopsy should be considered the “gold standard” in the HIV-negative immunocompromised population if all other investigations are negative and the suspicion for PCP is high.

Historically, the use of induced sputum in the HIV-positive population has been found to be a helpful but not perfect tool for the detection of PCP. Surprisingly, a published retrospective review of induced sputum analysis also suggested that it was clinically useful for the diagnosis of PCP in HIV-negative patients. In contrast to prior reports, the authors found that transbronchial biopsy appeared not to add any diagnostic value. PCP was diagnosed in eight of the nine cases from sputum samples; two of these case were detected with testing of a second sputum sample, when the first test result was negative. BAL findings were positive on only one of the negative sputum samples, and transbronchial biopsy findings were negative in all patients with negative findings for sputum samples. The authors, however, cautioned that with negative sputum sample results they recommend proceeding with more invasive strategies if the diagnosis was strongly suspected, given the low infectious burden in this population.

Once diagnosed, *P. jirovecii* is very susceptible to treatment with trimethoprim/sulfamethoxazole. Systemic steroids should be added to therapy for hypoxic patients. In a retrospective study of 73 patients with PCP, 46 of whom were HIV-positive, the course of disease and outcome were worse in the HIV-negative patients; 75% of patients required intubation compared to 13% of HIV-positive patients, and the mortality rate was higher (48%) compared to HIV-positive patients (17%). HIV-negative patients with PCP have a mortality rate of 60% if mechanical ventilation is required for treatment of respiratory failure; additional poor prognostic factors include high APACHE (acute physiology and chronic health evaluation) III scores, a delay in initiating mechanical ventilation, longer duration of mechanical ventilation, and the development of pneumothorax. The timely establishment of diagnosis and initiation of treatment for PCP in both HIV-positive and HIV-negative populations appears to be the most important factor in improving survival.

**Clinical Course**

In our case, we identified the patient early as being at risk for infection with PCP. We proceeded quickly to invasive means to obtain the diagnosis, including not only BAL but simultaneous transbronchial biopsy. Although our BAL fluid specimen was negative for PCP, we were able to obtain a diagnosis based on transbronchial biopsy findings and initiate treatment (with both trimethoprim/sulfamethoxazole and prednisone) prior to the development of respiratory failure. Our patient required 1 week of therapy with high-flow oxygen without mechanical ventilation and was safely discharged from the hospital to home without the use of supplemental oxygen 16 days after hospital admission.

**Clinical Pearls**

1. PCP should be considered a possible diagnosis in HIV-negative patients.
2. In HIV-negative immunosuppressed patients with pneumonia, PCP should always be in the differential diagnosis.
3. PCP in HIV-negative patients carries a worse prognosis; although the organism load is lower, the
severity of disease is generally greater. Respiratory failure is more common, and mortality increases if mechanical ventilation is required.

4. Given the low burden of organisms in HIV-negative patients, if PCP is suspected, bronchoscopy with multiple-site BAL and transbronchial or open lung biopsy should be performed.

5. Early initiation of treatment for PCP is the most important factor in improving survival.

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SUGGESTED READINGS


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