69-Year-Old Woman With Dyspnea and Cough Productive of White Sputum

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A 69-year-old woman was admitted to our institution with progressive dyspnea and cough productive of white sputum. Three months earlier, the patient was hospitalized elsewhere for evaluation of fever, headache, and fatigue. Results of a right temporal artery biopsy were consistent with giant cell arteritis (GCA). She was treated with prednisone (50 mg/d) and initially improved, but after 6 weeks of therapy, she again experienced feelings of malaise. Her erythrocyte sedimentation rate (ESR) remained elevated at 75 mm/h. The patient's rheumatologist then added methotrexate (MTX) to her treatment regimen. One week after starting MTX, the patient developed a vesicular rash on the left side of her chest that resolved without intervention, and she did not seek medical attention. Three weeks later, she was admitted to her local facility with complaints of chest pain, dyspnea, fever, and cough productive of white sputum. An adenosine stress test yielded negative results. A ventilation-perfusion lung scan revealed low probability for pulmonary embolism. Chest radiography findings were normal. In addition to deep venous thrombosis (DVT) prophylaxis with heparin, she was treated with intravenous levofloxacin, vancomycin hydrochloride, and ceftazidime. No sputum studies were obtained. After 3 days of antimicrobial therapy, the patient was transferred to our facility because of continued fever and dyspnea.

The patient's history included hypertension and gastroesophageal reflux disease. Her current medications were aspirin, amlodipine, prednisone, MTX, and omeprazole. She lived with her husband in Alabama, had never worked outside her home, and had never smoked. She denied chest pain but did complain of worsening dyspnea, cough productive of white sputum, and fatigue.

On examination, the patient was thin and appeared chronically ill. She was afebrile and had a blood pressure of 127/64 mm Hg, heart rate of 92 beats/min, respiratory rate of 24 breaths/min, and oxygen saturation rate of 93% by pulse oximetry while breathing room air. White plaques were evident on her oral mucosa. The patient did not have jugular venous distention. Cardiac examination revealed normal first and second heart sounds without murmurs, gallops, or rubs. On lung examination, bibasilar crackles were noted with good air excursion. Abdominal examination revealed normal bowel sounds and no tenderness, masses, or organomegaly. The patient had no clubbing, cyanosis, peripheral edema, lymphadenopathy, or rash. A complete blood cell count revealed the following (reference ranges provided parenthetically): hemoglobin, 11.2 g/dL (12.0-15.5 g/dL); white blood cell count, 9.8×10^9/L ($3.5\text{-}10.5 \times 10^9$/L); neutrophils, 7.40×10^9/L ($1.7\text{-}7.0 \times 10^9$/L); lymphocytes, 0.48×10^9/L ($0.90\text{-}2.90 \times 10^9$/L); monocytes, 0.08×10^9/L ($0.30\text{-}0.90 \times 10^9$/L); eosinophils, 0.05×10^9/L ($0.05\text{-}0.50 \times 10^9$/L); creatinine, 0.4 mg/dL (0.6-1.1 mg/dL); lactate dehydrogenase, 398 U/L (122-222 U/L); N-terminal pro-brain natriuretic peptide, 443 pg/mL (≤89 pg/mL); troponin T, less than 0.01 ng/mL (<0.01 ng/mL); ESR, 136 mm/h (0-29 mm/h); and C-reactive protein, 160 mg/L (≤8 mg/L). Results of an influenza swab were negative. Electrocardiography showed normal sinus rhythm without T-wave changes. Chest radiography findings were normal.

1. On the basis of the information provided, which <u>one</u> of the following is the <u>most likely</u> cause of the patient's dyspnea?

a. *Pulmonary manifestations of GCA*
b. *Acute pericarditis*
c. *MTX-induced pneumonitis*
d. *Varicella pneumonia*
e. *Pneumocystis pneumonia (PCP)*

Pulmonary manifestations of GCA occur in less than 10% of patients and usually manifest as a chronic nonproductive cough that resolves quickly when treated with corticosteroids.[1] The patient's symptoms began while she was receiving corticosteroids, and her cough is productive, so this is an unlikely diagnosis. Acute pericarditis is a clinical diagnosis characterized by chest pain at rest relieved by leaning forward. Supportive evidence includes pericardial friction rub, diffuse ST-segment elevation and PR-segment depression on electrocardiography, and/or elevated markers of inflammation. Although the patient presented to her local facility with chest pain, she denied chest pain on admission to our institution. Both her ESR and C-reactive protein levels were elevated, but she had no pericardial friction rub, and electrocardiographic findings and troponin T values were normal, making this an unlikely diagnosis. Methotrexate-induced pneumonitis is a hypersensitivity pneumonitis that usually develops a few days to several weeks after initiation of MTX and most commonly

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See end of article for correct answers to questions.

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presents as progressive dyspnea, fever, and nonproductive cough.[2] Chest radiography usually shows an infiltrate throughout all lung fields.[2] Our patient had a productive cough and normal chest radiographic findings. Also, she did not have eosinophilia, which can occur in 50% of patients with MTX-induced pneumonitis.[2] Varicella pneumonia typically develops 1 to 6 days after the onset of the rash and usually presents with dyspnea, nonproductive cough, and diffuse bilateral infiltrates on chest cardiography.[3] Our patient had a history of a vesicular rash suspicious for herpes zoster 3 weeks before admission, but she presented with a productive cough and normal chest radiographic findings, so varicella pneumonia is unlikely. *Pneumocystis* pneumonia, an opportunistic infection, is the most likely diagnosis. There should be high clinical suspicion for opportunistic infection because of impaired cell-mediated immunity due to treatment with prednisone. Although the patient may be at risk of varicella pneumonia or other opportunistic infections, the clinical picture is particularly worrisome for PCP for several reasons. First, it is not uncommon for patients with PCP to present with normal findings on chest radiography.[4] Second, patients with PCP can have an elevated lactate dehydrogenase level, which is thought to reflect underlying lung injury in PCP.[5] Third, and perhaps most importantly, our patient did not receive PCP chemoprophylaxis.

2. Which one of the following prednisone regimens is often used as an indication for initiating PCP prophylaxis in patients with immunosuppressive disorders, other than human immunodeficiency virus (HIV)?

a. *There is no need for prophylaxis unless the patient is receiving a second immunosuppressant*
b. *Three months, any dosage >30 mg/d*
c. *Three months, any dosage >10 mg/d*
d. *Four weeks, 20 mg/d*
e. *Two weeks, any dosage >30 mg/d*

Among non-HIV patients who are diagnosed with PCP, the most common identifiable risk factor is corticosteroid use.[6] Dosages of prednisone between 16 and 20 mg/d for at least 4 to 6 weeks are great enough to increase the risk of PCP in these patients,[7,8] with 20 mg of prednisone for more than 4 weeks often used as the cutoff dose and duration for initiation of prophylaxis.[9] The other options represent dosages or durations that are not supported by current evidence.

Induced sputum was sent for bacterial Gram stain, and culture, acid-fast smear, fungal smear and culture, respiratory viral cultures, and rapid polymerase chain reaction studies for *Coccidioides*, *Legionella*, *Mycobacterium*, and *Pneumocystis. Legionella* urine antigen, *Streptococcus pneumoniae* antigen, and HIV-1 and HIV-2 antibody evaluations were requested. In addition to DVT prophylaxis, the patient was started on trimethoprim-sulfamethoxazole (TMP-SMX), 15 mg/kg per day based on the TMP component.

The following day, the patient became febrile (temperature, 38.3º C). Her respiratory rate was 32 breaths/min, blood pressure was 110/60 mm Hg, and oxygen saturation was 85% by pulse oximetry while breathing room air. Cardiac auscultation revealed a regular tachycardia rate and no elevation of jugular venous pressure. Lung auscultation revealed increased crackles bilaterally. There was no peripheral edema. Subsequent arterial blood gas determination showed a pH of 7.48, P_{CO_2} of 37 mm Hg, P_{O_2} of 126 mm Hg, and HCO_3 of 28 mmol/L while breathing 4 L of oxygen by nasal cannula. The alveolar-arterial gradient was elevated at 65 torr. Electrocardiography showed a sinus tachycardia rate of 115 beats/min and no ischemic changes. The troponin T level was less than 0.01 ng/mL (<0.01 ng/mL). Chest radiography showed patchy bilateral pulmonary opacities. Induced sputum evaluation was unavailable because the quantity of the specimen was insufficient for testing.

3. Which one of the following is the best diagnostic study at this time?

a. *Bronchoalveolar lavage (BAL)*
b. *Gallium citrate Ga 67 scan*
c. *High-resolution computed tomography (CT) of the chest*
d. *Transthoracic echocardiography*
e. *Pulmonary CT angiography*

The diagnosis of PCP requires microscopic examination of the organism because it cannot be cultured. Induced sputum for *Pneumocystis* polymerase chain reaction testing is the least invasive method for diagnosing PCP. However, in non–HIV-infected patients, the sensitivity of microscopy with induced sputum staining is thought to be less than the sensitivity in HIV-infected patients. This is due to reduced organism load.[10] If sputum studies are nondiagnostic or cannot be performed, BAL should be performed if there is high suspicion for PCP, making this the best diagnostic test at this time. Gallium acts as an iron analogue and, after intravenous injection, is transported in the blood bound to transferrin, then concentrating in areas of malignancy, inflammation, and infection by various mechanisms. Gallium citrate Ga 67 scanning is a highly sensitive test for PCP.[11] However, its role is limited by lack of specificity, high cost, and a 2-day delay in obtaining final results. Although high-resolution CT may help to further characterize parenchymal disease, it is important at this point in the infectious work-up to isolate the organism, making BAL the preferred next diagnostic step. Pulmonary CT angiography is not indicated. Although a pulmonary embolism can cause acute hypoxia and an increased alveolar-arterial oxygen gradient, the patient had a low-probability ventilation-perfusion scan just before admission and had been receiving DVT prophylaxis. Using Wells criteria, she has moderate probability for pulmonary embolism. However, an alternative diagnosis better explains the illness.

Transthoracic echocardiography is helpful in assessing systolic or diastolic ventricular dysfunction. Although the patient had crackles at her lung bases, examination findings were otherwise inconsistent with cardiac dysfunction because she had no jugular venous distention, lower extremity swelling, or S_3 on cardiac auscultation.

Bronchoalveolar lavage was performed, and calcofluor white staining was positive for *Pneumocystis. Legionella* urine antigen, *S pneumoniae* antigen, and HIV-1 and HIV-2 antibody testing yielded negative results.

4. Which one of the following statements about the prognosis of PCP in non-HIV patients compared to patients with HIV is true?

a. *The prognosis is the same in patients both with and without HIV*
b. *In patients with HIV, PCP carries a better prognosis than in non-HIV patients*
c. *In patients with HIV, PCP carries a worse prognosis than in non-HIV patients*
d. *The prognosis of PCP is unknown in both HIV and non-HIV patients*
e. *The prognosis of PCP in non-HIV patients is better because of its subacute onset compared to HIV patients*

The prognosis is not the same for both groups of patients. The survival rate for PCP among patients without HIV is poor relative to that in HIV-infected patients. In most medical centers, the survival rate among HIV patients approaches 90%, whereas the survival rate for non-HIV patients is 40% to 70%.[7,12] Non-HIV patients who develop PCP have significantly fewer organisms in their BAL fluid but a more robust neutrophilic response. The increase in inflammation and resultant poorer oxygenation likely account for the increased mortality.[12] In addition, the presentation is often different between the 2 groups. Patients with HIV have a longer duration of symptoms and higher median arterial oxygen tension while breathing room air,[7] whereas in non-HIV patients, there is typically a more fulminant onset.[12]

5. Which one of the following is the recommended prophylactic agent for PCP prophylaxis in non-HIV immunocompromised individuals?

a. *TMP-SMX*
b *Aerosolized pentamidine*
c. *Dapsone*
d. *Atovaquone*
e. *Caspofungin*

Trimethoprim-sulfamethoxazole is the first-line agent for PCP prophylaxis and has been the most studied. One meta-analysis found that the number needed to treat to prevent 1 PCP infection is 15. Prophylaxis was associated with a 91% reduction in infection occurrence.[6] It is additionally recommended by several organizations, including the Infectious Diseases Society of America and the Centers for Disease Control and Prevention. Accepted regimens include 1 double-strength tablet daily or 3 times weekly, as well as 1 single-strength tablet daily. In another meta-analysis, no difference in the rate of PCP infections was found after daily vs thrice-weekly TMP-SMX prophylaxis.[6] It has the additional benefit of preventing toxoplasmosis. Other agents have not been extensively studied in non-HIV patients. Aerolized pentamidine is associated with cough, wheezing, and the development of pneumocystosis but has the benefit of monthly dosing. In recent years, dapsone or atovaquone has become preferred over pentamidine.[9] Dapsone requires testing for glucose-6-phosphate dehydrogenase deficiency and can cause fever, gastrointestinal upset, and methemoglobinemia. Similar to TMP-SMX, atovaquone can cause rash and gastrointestinal upset. Both dapsone and atovaquone require adding pyrimethamine and leucovorin for toxoplasmosis coverage. Controversy exists as to whether PCP responds to echinocandins such as caspofungin.[9] It is not one of the currently recommended treatment or prophylactic agents because of the lack of randomized controlled clinical data. For non-HIV patients, prophylaxis can often be discontinued after the offending agents are no longer exerting their effect.[9] However, one should be aware that some agents such as cyclophosphamide can exert their immunosuppressive effects for months after treatment discontinuation. Some experts suggest monitoring CD4 cell counts and only stopping prophylaxis when counts greater than 200 cells/μL are maintained for at least 6 months.[13] However, there is not as convincing a correlation between peripheral CD4 counts and developing PCP in the non-HIV population.[9]

The patient continued treatment with TMP-SMX and improved. After 14 days of treatment, the patient was given PCP prophylaxis, to be continued for the duration of her treatment with corticosteroids.

DISCUSSION

Our case highlights the outcome of not providing prophylaxis for a patient at risk of PCP infection. Patients at risk include those with a wide range of conditions ranging from cancer to posttransplant to those with autoimmune and inflammatory conditions who are receiving prolonged immunosuppressive therapy, such as corticosteroids. Non-HIV patients who are receiving immunosuppressive medications or who have an underlying immunodeficiency should receive prophylaxis against PCP.[4,9,14] The current recommendation for dosage and duration of prednisone therapy that places a non-HIV patient at risk of PCP is the equivalent of prednisone 20 mg/d for more than 4 weeks.[7-9]

Even though the number of cases among HIV-infected patients has decreased during the past decade, PCP is a serious problem among other patients who are immunosuppressed.[9] There continues to be an underuse of PCP prophylaxis in appropriate patients despite published reports. In one report, up to one-third of physicians never used PCP prophylaxis and only 17% of patients receiving prednisone at 20 mg or more a day for at least 4 weeks were found to have received appropriate PCP prophylaxis.[15]

Additional patient groups that warrant PCP prophylaxis include patients receiving other immunosuppressive agents,[16] certain cancer patients,[17] patients with Wegener granulomatosis who are taking cyclophosphamide and especially if also receiving corticosteroids,[18] transplant recipients (allogeneic stem cell, autologous peripheral blood stem cell, and solid organ), and those with primary immunodeficiency disorders (severe combined immunodeficiency, idiopathic CD4 T-cell lymphocytopenia, and hyper-IgM syndrome).[19] In a retrospective analysis of non-HIV patients with connective tissue diseases including systemic lupus erythematosus, polyarteritis nodosa, and polymyositis or dermatomyositis who at the time of PCP diagnosis were receiving immunosuppressive agents, mainly corticosteroids, the attack rate was less than 2%, with the greatest attack rate seen in those with Wegener granulomatosis (12%).[20] The risk in allogeneic hematopoietic stem cell transplant recipients and solid organ transplant recipients who are not receiving prophylaxis is 5% to 15%.[7]

Our patient had signs of immunosuppression, including oral candidiasis and herpes zoster, before admission to our institution. Her presentation is somewhat atypical for a non-HIV patient, in that it was more insidious, as opposed to the more fulminant presentation that often marks PCP in non-HIV, immunosuppressed individuals. Initial sputum testing was nondiagnostic, as is often the case in PCP, especially in non-HIV patients who have a reduced organism load that renders a lower diagnostic yield on induced sputum tests. In both HIV and non-HIV patients, initial chest radiographic findings may be negative. Pneumocystic pneumonia prophylaxis in non-HIV patients who are immunosuppressed is especially important, given the increased mortality in such patients.

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Correct answers: 1. *e*, 2. *d*, 3. *a*, 4. *b*, 5. *a*