

# A 63-Year-Old Man with Fever, Chills, Dry Cough, and Dyspnea on Exertion

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## CASE PRESENTATION

### Initial Presentation and History

A 63-year-old Pakistani man with a history of anaplastic astrocytoma of the brain presented to the emergency department with a temperature of 103°F, chills, dry cough, and dyspnea on exertion on climbing 1 flight of stairs. The astrocytoma was resected 2 months prior to presentation and treated with 2 months of radiotherapy and chemotherapy. He denied any hemoptysis, wheezing, weight loss, or loss of appetite. There was no history of recent travel, significant occupational organic or inorganic dust exposure, or contact with tuberculosis, and he did not have any pets or birds. He emigrated to the United States 40 years ago and had last visited Pakistan 6 years ago. The patient did not have a bacille Calmette-Guérin scar, and purified protein derivative tuberculin status was unknown. He was a lifelong nonsmoker and did not consume alcohol. He had retired from a desk job 3 years ago. Other than the recent cerebral tumor, he had no other past medical history. Medications included a tapering course of dexamethasone, which he had been taking for nearly 12 weeks, and esomeprazole. He had no significant family history and had no allergies.

### Physical Examination

Physical examination revealed a temperature of 102°F, blood pressure of 118/72 mm Hg, heart rate of 100 bpm, respiratory rate of 20 to 30 breaths/min, and oxygen saturation as measured by pulse oximetry (Sp<sub>o</sub><sub>2</sub>) of 89% on 40% Fi<sub>o</sub><sub>2</sub>. He was alert and oriented to time, place, and person and was dyspneic at rest. HEENT (head, eyes, ears, nose, and throat) examination revealed no pallor or icterus, moist mucous membranes, and normal oropharynx and nasopharynx. No lymphadenopathy or clubbing, subungual infarcts, or Osler nodes were noted. No jugular venous distension was noted, and no bruits were heard. Systemic examination revealed normal heart sounds, minimal coarse crackles at the base of the left lung, a soft nontender abdomen with no hepatosplenomegaly, and normal bowel sounds. Neurologic examination revealed no cranial nerve deficits, normal tone in all 4 limbs,

4/5 power in left upper and lower extremities, 2+ reflexes in the left upper and lower extremities, and normal power and reflexes on the right side. Plantar reflexes were downward on the right side and withdrawing on the left side. Coordination was intact, and sensory examination was not performed.

### Laboratory and Imaging Studies

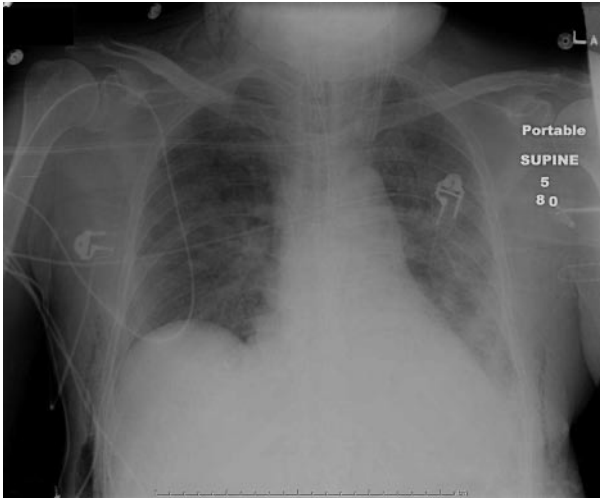
Laboratory studies revealed a normal blood count, normal kidney and liver function, an erythrocyte sedimentation rate of 68 mm/hr (normal, 0–20 mm/hr), L-lactate dehydrogenase level of 464 U/L (normal, 100–200 U/L), and brain natriuretic peptide (BNP) level of 238 pg/mL (normal, < 167 pg/mL). Sputum was negative for acid-fast bacilli, Gram stain was negative for pathologic organisms, and serologic testing for HIV was negative. Arterial blood gas testing on Fi<sub>o</sub><sub>2</sub> of 40% revealed a pH of 7.42, Pao<sub>2</sub> of 66 mm Hg, Paco<sub>2</sub> of 30 mm Hg, and a bicarbonate level of 24 mEq/L. An electrocardiogram was within normal limits. A chest radiograph obtained on admission showed bilateral predominantly perihilar interstitial infiltrate. On hospital day 1, the patient was electively intubated for severe hypoxia and respiratory distress. Despite ventilating with low tidal volumes, the patient developed severe subcutaneous emphysema and pneumomediastinum with no evident pneumothorax. A second chest radiograph (Figure 1) and a computed tomography scan of the chest (Figure 2) were performed 24 hours after admission.

### WHAT IS YOUR DIAGNOSIS?

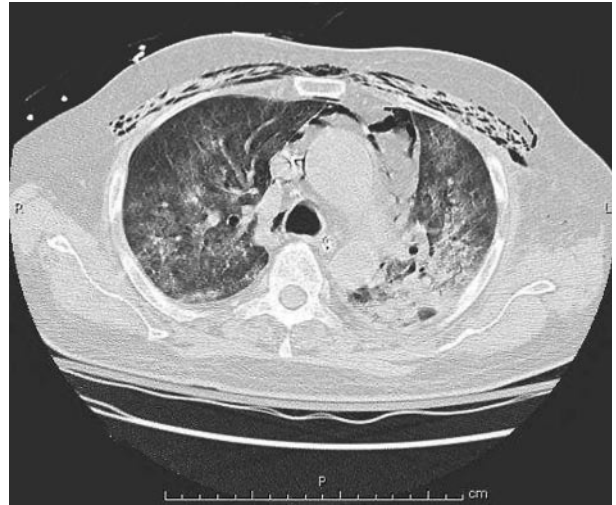
- (A) Acute congestive heart failure
- (B) Acute extrinsic allergic alveolitis
- (C) Acute interstitial pneumonia
- (D) Miliary tuberculosis
- (E) *Pneumocystis jiroveci* pneumonia

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**Figure 1.** Chest radiograph obtained 24 hours after presentation showing diffuse ground-glass changes and interstitial infiltrate. Severe subcutaneous emphysema is visible in the neck and axillae.



**Figure 2.** Computed tomography of the chest confirms bilateral ground-glass attenuation. Pneumomediastinum and subcutaneous emphysema were also noted in the anterior chest wall.

## ANSWER

The correct answer is (E) *Pneumocystis jiroveci* pneumonia (PCP).

## DISCUSSION

All of the above listed conditions can present as acute hypoxic respiratory failure. Although patients with interstitial pneumonia and PCP can present with similar symptoms (eg, fever, dry cough, dyspnea), the development of spontaneous pneumomediastinum and subcutaneous emphysema in interstitial pneumonia would be unusual. Additionally, PCP is more likely in the setting of immunosuppression. Heart failure is less likely given this patient's normal electrocardiogram and moderate elevation in BNP (BNP levels > 400 pg/mL are predictive of heart failure). The patient had not been exposed to organic or inorganic dust to support a diagnosis of allergic alveolitis. Although tuberculosis is a possibility given this patient's ethnicity, miliary tuberculosis appears as mostly uniform, fine nodular infiltrate on chest radiograph, whereas this patient's chest radiograph showed predominantly perihilar interstitial infiltrate.

## CLINICAL COURSE OF CASE PATIENT

The case patient was empirically started on intravenous trimethoprim-sulfamethoxazole (TMP-SMX) for suspected PCP. Bronchoalveolar lavage (BAL) fluid obtained while the patient was intubated was stained with Gomori's methenamine silver, which confirmed the diagnosis of PCP (**Figure 3**). The final diagnosis was

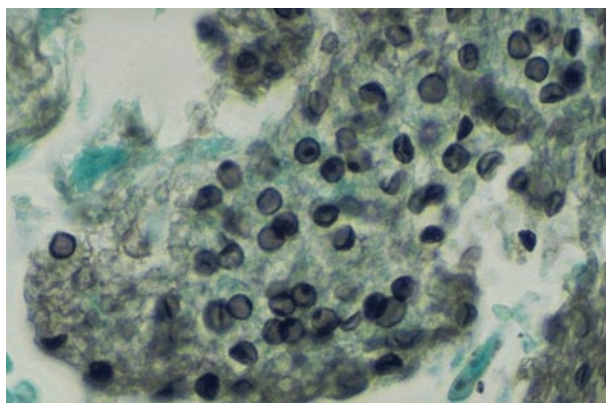
PCP caused by immunosuppression, complicated by pneumomediastinum and subcutaneous emphysema on mechanical ventilation. The patient was eventually extubated on day 14 and discharged on day 21 with persisting interstitial changes on chest radiograph. He was continued on long-term oral TMP-SMX for PCP prophylaxis.

## PNEUMOCYSTIS JIROVECI PNEUMONIA

*P. jiroveci*, formerly known as *P. carinii*, was initially misclassified as a protozoan on the basis of the morphologic features of the trophic and cystic forms. RNA analysis has established that *P. jiroveci* instead is related to ascomycetous fungi.<sup>1</sup> *P. jiroveci* has a unique tropism for the lung, where it exists primarily as an alveolar pathogen without invading the host. In rare cases, *P. jiroveci* disseminates in the setting of severe immunosuppression.

## Clinical Presentation and Radiologic Features

In patients who do not have AIDS, PCP typically presents as fever and acute onset respiratory insufficiency, which may correlate with a tapered or increased dose of immunosuppressive medication; dry cough may be present. PCP typically appears on chest radiograph as bilateral interstitial infiltrates that become increasingly homogenous and diffuse as the disease progresses. Less common findings include solitary or multiple nodules, upper lobe infiltrates (in patients receiving aerosolized pentamidine), pneumatoceles, and pneumothoraces.<sup>2</sup> Pleural effusions and lymphadenopathy are rare. When chest radiographic findings are normal, high-resolution



**Figure 3.** Gomori's methenamine silver staining of bronchoalveolar lavage fluid showing cysts of *Pneumocystis jiroveci* in the lung parenchyma; these have the appearance of crushed ping-pong balls.

computed tomography may reveal extensive ground-glass attenuation or cystic lesions.

### Diagnosis

The diagnosis of PCP requires visualization of characteristic morphologic forms on microscopic examination of the sputum, BAL fluid, or lung tissue, as it cannot be cultured. Sputum induced with hypertonic saline has a diagnostic yield of 50% to 90% and should be the initial procedure.<sup>2</sup> If the initial sputum specimen is negative, then bronchoscopy with BAL should be performed. Transbronchoscopic or surgical lung biopsy is rarely needed. Trophic forms of *P. jiroveci* can be detected with modified Papanicolaou's, Wright-Giemsa, or Gram-Weigert stains. Cysts can be stained with methenamine silver stain. Staining with monoclonal antibodies has a higher sensitivity and specificity for detecting *P. jiroveci* in induced sputum compared with Wright-Giemsa stains,<sup>3</sup> and antibodies are able to stain both trophic forms and cysts.

### Treatment

Oral or intravenous TMP-SMX (trimethoprim 15–20 mg/kg, sulfamethoxazole 75–100 mg/kg) is effective for treating severe PCP. Primaquine plus clindamycin, atovaquone, and pentamidine are alternate choices. Corticosteroids are beneficial in HIV-infected patients with PCP who have hypoxemia ( $\text{PaO}_2 < 70$  mm Hg or alveolar-arterial gradient  $> 35$ ).<sup>4</sup> These patients should receive prednisone 40 mg twice daily for 5 days, 40 mg daily on days 6 through 11, and 20 mg daily on days 12 through 21. In non-HIV-infected patients with severe pneumonia, prednisone 60 mg or more daily resulted in a better outcome than lower doses of pred-

nisone.<sup>5</sup> The mortality rate among patients with PCP in the absence of AIDS is 30% to 60%, with a greater risk of death among patients with cancer than among patients undergoing treatment with steroids or in those with a connective tissue disease.<sup>6,7</sup>

### Prophylaxis

Patients who are not infected with HIV but who are receiving immunosuppressive medications or have underlying acquired or inherited immunodeficiency should receive prophylaxis against PCP.<sup>5</sup> In a retrospective series, a corticosteroid dose equivalent to 16 mg of prednisone or more for 8 weeks was associated with a significant risk of PCP in patients who did not have AIDS.<sup>7</sup> Similar observations have been noted in patients with cancer or with a connective tissue disease who were treated with corticosteroids.<sup>4,6</sup> Medications used for prophylaxis include TMP-SMX, dapsone, dapsone with pyrimethamine, pentamidine, and atovaquone. TMP-SMX 160/800 mg once daily is the first choice for prophylaxis.

### CONCLUSION

PCP is a well-recognized entity in HIV-infected patients, but its importance and recognition is rising in the non-HIV-infected population. Physicians should maintain a high index of suspicion for PCP in non-HIV-infected patients who are currently receiving glucocorticoids. Despite being on high-dose steroids, the case patient had not received prophylaxis, which likely contributed to his morbidity. This case highlights the need for prophylaxis for PCP and outlines the potential complications that could be encountered in the clinical course of the disease.

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### REFERENCES

1. Cushion MT. Taxonomy, genetic organization, and life cycle of *Pneumocystis carinii*. *Sem Respir Infect* 1998;13:304–12.
2. Santamauro JT, Stover DE. *Pneumocystis carinii* pneumonia. *Med Clin N Am* 1997;81:299–318.
3. LaRocque RC, Katz JT, Perruzzi P, Baden LR. The utility of sputum induction for diagnosis of *Pneumocystis* pneumonia in immunocompromised patients with human immunodeficiency virus. *Clin Infect Dis* 2003;37:1380–3.
4. Walzer P. *Pneumocystis carinii*—new clinical spectrum [editorial]? *N Engl J Med* 1991;324:263–5.
5. Thomas CF Jr, Limper AH. *Pneumocystis* pneumonia. *N Engl J Med* 2004;350:2487–98.
6. Kovacs JA, Hiemenz JW, Macher AM, et al. *Pneumocystis carinii* pneumonia: a comparison between patients with the acquired immunodeficiency syndrome and patients with other immunodeficiencies. *Ann Intern Med* 1984;100:663–71.
7. Yale SH, Limper AH. *Pneumocystis carinii* pneumonia in patients without acquired immunodeficiency syndrome: associated illnesses and prior corticosteroid therapy. *Mayo Clin Proc* 1996;71:5–13.