61-Year-Old Man With Shortness of Breath and Cough

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A 61-year-old man presented with 3 weeks of shortness of breath and cough productive of occasional brown sputum. His medical comorbidities included Crohn colitis, deep vein thrombosis and pulmonary embolism on chronic anticoagulation, obstructive sleep apnea, obesity, impaired fasting glucose, depression, and latent tuberculosis status post 9 months of isoniazid. For the past year, his Crohn disease treatment regimen included methotrexate, and he received his first dose of ustekinumab 6 weeks before presentation. He was also being treated with an albuterol inhaler as needed, citalopram, folic acid, metformin, warfarin, and iron supplementation. He was diagnosed with community-acquired pneumonia 2 weeks prior and subsequently treated with levofloxacin. However, after finishing antibiotics he was still feeling unwell and had home oximeter readings in the low 80s. On physical exam at the time of presentation, he was alert and oriented and responding appropriately to questions. He had dry oral mucosa, regular rate and rhythm without murmurs, and no lower-extremity edema on cardiac exam. He was noted to be tachypneic and had bibasilar and right mid field crackles, but no significant respiratory distress at rest. His abdomen was soft and nontender. There were no motor or sensory abnormalities noted. Initial laboratory values showed an elevated lactate of 3.2 mmol/L (0.5-2.2 mmol/L), leukocytosis of 13.9×10⁹/L (3.4-9.6×10⁹/L), eosinophilia of 1.21×10⁹/L (0.03-0.48×10⁹/L), elevated C-reactive protein of 205 mg/L (≤ 8 mg/L) and erythrocyte sedimentation rate of 40 mm/1 h (0-22 mm/1 h). Chest radiograph revealed consolidation throughout the left mid and lower lung with new consolidation in the right upper lung and right lower lung.

1. What would be the next best step in managing this patient?
   a. Prescribe an additional 7-day course of levofloxacin
   b. Prescribe 5-day course of prednisone
   c. Obtain QuantiFERON Gold testing
   d. Conservative treatment with close outpatient follow-up
   e. Obtain chest computed tomography (CT) scan

   The patient did not previously respond to a full course of levofloxacin for treatment of community-acquired pneumonia; thus, repeating this course of treatment would not be the next best step. Without ruling out infectious etiology for his pulmonary symptoms, a course of prednisone would not be appropriate. Although he does have 3 weeks of productive cough and fever, and he is immunocompromised, testing for tuberculosis with QuantiFERON Gold testing would be an insufficient next step given the broad differential for his presentation. Additionally, the patient has a history of latent tuberculosis that was properly treated, but QuantiFERON Gold testing often remains positive even after treatment. Conservative monitoring with close outpatient follow-up is inappropriate in the setting of new hypoxemia in an immunocompromised host. To further evaluate the pulmonary consolidations in this immunocompromised patient, the next step would be to obtain a chest CT. A CT scan can help define the extent of disease and often reveals abnormalities that were not seen on radiograph. Further, in an immunocompromised individual, a negative radiograph is not sufficient to exclude...
pulmonary involvement if respiratory symptoms are present, as immune response is not as robust in these patients.1

On hospital day 1, chest CT showed extensive multifocal nodular consolidations throughout both lungs. After obtaining blood cultures, cefepime, metronidazole, azithromycin, and vancomycin were initiated. The patient’s hypoxic respiratory failure progressed and by hospital day 6 he was requiring 100% fraction of inspired oxygen via Optiflow and ultimately required transfer to the intensive care unit and intubation.

2. What is the single next best step in workup to evaluate the pulmonary infiltrates in this immunocompromised host?
   a. Bronchoscopy with bronchoalveolar lavage (BAL)
   b. Antineutrophil cytoplasmic antibody (ANCA) vasculitis panel
   c. Galactomannan
   d. Enzyme-linked immunosorbent assay for Coccidioides
   e. Lung biopsy

The process of diagnosing the etiology of pulmonary infiltrates, especially in immunocompromised hosts, is difficult. Often, invasive testing such as bronchoscopy with BAL is needed to establish a diagnosis when other testing has not been helpful. Bronchoscopy carries significant risks, especially in the setting of decompensated respiratory status and this is generally best performed early in the course of disease while the patient’s respiratory status is stable. It was recommended that our patient undergo bronchoscopy on hospital day 3, before his worsening respiratory status, but this was delayed until hospital day 6 due to a workup for tuberculosis and concerns about the safety of the procedure if he did indeed have tuberculosis. He had been intubated before the procedure and was able to be extubated shortly after. If there is a preference to avoid bronchoscopy, an induced sputum sample can be collected to reliably test for certain studies, especially pneumocystis carinii, mycobacterium, and malignancy, but further evaluation is often needed if a cause is not discovered.2 An ANCA vasculitis panel would help in the workup of a pulmonary vasculitis syndrome that can involve the lungs, such as granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, or microscopic angiitis. Patients with eosinophilia granulomatosis with polyangiitis can present with an elevated peripheral blood eosinophil count and changes on chest CT, including consolidations, both of which our patient presented with. However, patients often have other signs and symptoms that suggest multiorgan involvement of the vasculitis such as glomerulonephritis, sinusitis, alveolar hemorrhage, or skin involvement, which our patient did not present with.2 Galactomannan is an antigen released during the growth phase of invasive aspergillosis. Coccidioides can present similarly to community-acquired pneumonia and is often associated with peripheral eosinophilia.4 Although pulmonary vasculitis, coccidioides, and aspergillus remain in the differential for this patient, an ANCA vasculitis panel, enzyme-linked immunosorbent assay for coccidioides, and galactomannan tests alone would not be comprehensive enough to evaluate his severe presentation at this point. Although a lung biopsy may be needed in the future, the next most appropriate step would be bronchoscopy with BAL.

In our patient, ANCA vasculitis panel, Blastomyces, Histoplasma, and Bordetella polymerase chain reaction tests and acid-fast bacillus smears were negative. Blood cultures were also negative. Bronchoscopy with BAL performed on hospital day 6 showed 62% eosinophils, 19% lymphocytes, and 9% neutrophils.

3. Which one of the following is most likely causing the patient’s symptoms?
   a. Pneumocystis carinii pneumonia (PCP)
   b. Drug-induced lung disease
   c. Idiopathic pulmonary fibrosis
   d. Community-acquired pneumonia
   e. Sarcoidosis

Pneumocystis carinii pneumonia can be tested for with polymerase chain reaction
of the BAL fluid, and this was negative in our patient. Eosinophilia greater than 25% on BAL is indicative of eosinophilic lung disease, such as acute eosinophilic pneumonia, chronic eosinophilic pneumonia, or eosinophilic granulomatosis with polyangiitis.\(^5\) Based on BAL and clinical context, drug-induced lung disease, more specifically, acute eosinophilic pneumonia likely secondary to drugs, in this case ustekinumab, was diagnosed in this patient. Ustekinumab is a monoclonal antibody directed against interleukin 12 and interleukin 23 is most often used in the treatment of Crohn disease and psoriatic arthritis. His peripheral eosinophilia may have been a clue early on that he had an eosinophilic lung disease; however, peripheral blood eosinophils and pulmonary eosinophils do not always correlate, as has been shown in recent chronic obstructive pulmonary disease studies.\(^6\) Increased neutrophils in BAL can be seen with idiopathic pulmonary fibrosis, infection such as pneumonia, and connective tissue disorders, but they are nonspecific.\(^5\) Bronchoalveolar lavage in community-acquired pneumonia has neutrophil predominance, which was not consistent with the patient’s results. Patients with sarcoidosis can have lymphocytosis on BAL with an elevated CD4/CD8 ratio, but this is ultimately a diagnosis of exclusion and requires pathologic evidence of noncaseating granulomas and consistent clinical and radiographic presentation.\(^5\) Other differential diagnoses for peripheral and pulmonary eosinophilia would also include malignancy and parasitic infection.

A variety of medications can cause drug-induced lung disease (DILD); it is usually diagnosed when a patient with lung disease is exposed to a characteristic drug and no other cause for the lung disease is identified.\(^7\) Often, the radiologic and histological findings are nonspecific, but histopathologic patterns that can be seen include interstitial pneumonia, hypersensitivity pneumonia, organizing pneumonia, and granulomatous pneumonitis.\(^7\) Risk factors vary based on the specific drug implicated but include the extremes of age, female sex, exposure to oxidative stress, radiation exposure, and underlying lung disease.\(^7\)

Eosinophilic pneumonia is diagnosed on the basis of peripheral eosinophilia, parenchymal opacities on chest imaging, and eosinophilic infiltration of the lung parenchyma.\(^8\) Causes of eosinophilic pneumonia include DILD and parasitic or fungal infection, and it can be a presenting feature of eosinophilic granulomatosis with polyangiitis.\(^9\) In the time since ustekinumab was approved for use by the US Food and Drug Administration, approximately six cases of eosinophilic pneumonia have been reported in the literature.\(^10\) Most cases are diagnosed based on clinical features and the timing of drug administration and development of symptoms, which is usually 1 to 2 months after exposure.\(^10\) Our patient developed hypoxemic respiratory failure secondary to acute eosinophilic pneumonia after his first exposure to ustekinumab, strongly suggesting this as the etiology. Ustekinumab has also been associated with hypersensitivity pneumonitis and interstitial lung disease with a granulomatous component. In patients taking ustekinumab with respiratory failure and parenchymal opacities on chest radiograph, eosinophilic pneumonia should be considered.

Given the diagnosis of acute eosinophilic pneumonia likely secondary to ustekinumab, the patient’s ustekinumab was discontinued.

4. In addition to drug discontinuation, which one of the following is the most appropriate initial treatment for this patient’s condition?

a. Plasmapheresis
b. Trimethoprim-sulfamethoxazole
c. Cyclophosphamide
d. Methylprednisolone
e. Rituximab

Plasmapheresis is a therapy often used to remove auto-antibodies or proteins leading to dysregulated immune activation. Plasmapheresis does not have a role in drug-induced pneumonia. As discussed previously, PCP should be considered as an etiology of hypoxia in immunocompromised hosts, for which
trimethoprim-sulfamethoxazole is a first-line treatment, but our patient did not have evidence of PCP. Cyclophosphamide is often used as an adjunctive steroid-sparing therapy for treatment of eosinophilic granulomatosis with polyangiitis but would not be used as a first-line treatment in DILD. In patients with DILD, the offending agent should be discontinued, as was done for our patient. Often, this is effective in improving symptoms, but if refractory symptoms and clinical severity persist, high-dose steroids such as methylprednisolone are often the next step. There is a paucity of data addressing corticosteroid duration; however, the common approach is to slowly taper over 8 to 12 weeks. Rituximab has many clinical uses including treatment for lymphomas and granulomatosis with polyangiitis, but would not be used for acute eosinophilic pneumonia.

As noted above, our patient was treated with ustekinumab discontinuation and also methylprednisolone 500 mg intravenously for 3 days, tapered to 125 mg intravenously for 3 days, followed by a 6-week prednisone taper.

5. Given the patient’s history, which drug should be avoided in the future?
   a. Sumatriptan
   b. Levothyroxine
   c. Cholecalciferol
   d. Nitrofurantoin
   e. Iron-dextran

In a patient with an underlying lung disease and with a history of DILD, it is wise to avoid drugs that may contribute to DILD. Sumatriptan, levothyroxine, and cholecalciferol are not commonly thought of as medications that lead to DILD. Drugs commonly implicated in DILD include bleomycin, amiodarone, nitrofurantoin, and methotrexate as well as amphotericin B, isoniazid, sulfasalazine, rituximab, hydrochlorothiazide, cyclophosphamide, and many others. Iron supplementation can cause anaphylactic reactions, especially when administered intravenously, but is not known to contribute to the development of interstitial lung disease. Pneumotox Online is an international resource available to search up-to-date information on medications that have previously been associated with DILD. After the discontinuation of ustekinumab and treatment with high-dose steroids, the patient’s respiratory status greatly improved. He was on room air by hospital day 16 and he was able to taper off of steroids. Chest CT 1 month after presentation showed significantly improved consolidations.

DISCUSSION
The differential for acute diffuse lung diseases in an immunocompromised host is broad and includes infection, pulmonary edema, aspiration, hypersensitivity pneumonitis, DILD, pulmonary hemorrhage, and acute eosinophilic pneumonia, among others. A few clues that can guide the differential include the tempo of disease, radiological pattern, and the clinical context. Important clinical history includes age, smoking history, history of systemic illness or current systemic illness, immune status, medication reconciliation including over the counter medications and supplements, environmental exposures, and family history.

In a patient with respiratory symptoms, a normal chest x-ray is not sufficient to rule out serious pulmonary disease; a chest CT is required to characterize the disease process. An initial CT scan can also establish a baseline and characterize improvement with subsequent treatment in the future. Previous studies correlate radiographic patterns with causative etiology, but for most infectious causes, this is not specific. More invasive testing, including bronchoscopy with BAL, is required in patients without a clear etiology for their pulmonary disease. When pulmonary disease is diffuse on imaging, the right middle lobe or lingula are preferred areas for BAL as these areas project anteriorly and gravity can assist optimal lavage.

Risk factors for DILD include the extremes of age, female sex, type and dose of drug, concomitant radiation therapy, and previous underlying lung disease. Drug-induced lung
disease should be considered in patients with acute or subacute pulmonary symptoms, especially with an interstitial pattern of involvement. Review of the patient’s entire medication list is paramount. This should include all nonprescribed supplements. High clinical suspicion is necessary as the clinical presentation is typically nonspecific.

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REFERENCES

Correct Answers: 1. e. 2. a. 3. b. 4. d. 5. d.