67-Year-Old Man With Dyspnea and Hemoptysis

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A 67-year-old man presented to the emergency department because of worsening shortness of breath. He was in his usual state of health until 2 months before presentation when he experienced generalized fatigue, malaise, nasal congestion, maxillary sinus pressure, and a nonproductive cough. His symptoms gradually progressed and subsequently evolved to include diffuse arthralgias, low-grade fevers, night sweats, productive cough with scant hemoptysis, and worsening dyspnea. Before the onset of these symptoms, he was healthy and had no known chronic medical conditions.

On arrival at the emergency department, he had no symptoms of chest discomfort, volume excess, or lower extremity pain and swelling. He did not have known sick contacts or risk factors for thromboembolism. His vital signs were as follows: temperature, 37.4°C; pulse rate, 95 beats/min; blood pressure, 121/70 mm Hg; respiratory rate, 26 breaths/min; and oxygen saturation, 87% while breathing room air. On physical examination, he was in mild respiratory distress. Cardiac examination revealed a regular heart rhythm, normal S_1 and S_2, no murmurs, and normal jugular venous pressure. Pulmonary examination revealed diffuse rhonchi and inspiratory crackles bilaterally with focal egophony in his left lung base. His lower extremities were symmetric with no swelling or palpable cords. The remainder of his physical examination findings were otherwise unremarkable.

Laboratory studies revealed the following (reference ranges provided parenthetically): hemoglobin, 8.3 g/dL (13.5-17.5 g/dL); leukocytes, 8.6×10^9/L ($3.5\text{-}10.5\times10^9$/L); platelet count, 208×10^9/L ($150\text{-}450\times10^9$/L); and creatinine, 1.4 mg/dL (0.8-1.3 mg/dL). Urinalysis revealed 31 to 49 red blood cells per high-power field (0), more than 25% dysmorphic red blood cells (<25%), no urinary casts, and urinary protein to osmolality ratio of 1.35 (<.27). Chest radiography revealed diffuse lung infiltrates with air bronchograms, most prominently in the left lung and right middle lobe.

The patient was admitted to a hospital ward with a working diagnosis of community-acquired pneumonia, and supplemental oxygen, supportive care, and intravenous antibiotics were administered. Shortly after admission, the patient's condition continued to deteriorate, with increasing dyspnea, hemoptysis, and oxygen requirements. Repeated laboratory studies revealed worsening anemia (hemoglobin, 6.2 g/dL), prompting transfusion with 2 U of packed red blood cells. Repeated chest radiography revealed worsening bilateral pulmonary infiltrates. The patient soon had development of severe respiratory distress with an oxygen requirement of 100% oxygen by nonrebreather mask, prompting transfer to the medical intensive care unit.

1. Which *one* of the following is the *most likely* cause of this patient's acute hypoxemia?

a. Community-acquired pneumonia
b. Transfusion-related acute lung injury
c. Decompensated heart failure
d. Pulmonary embolism
e. Diffuse alveolar hemorrhage (DAH)

Pneumonia is a common and important cause of hypoxia. Hemoptysis may also occur in patients with severe pneumonia. However, the degree of acute blood loss noted in our patient would not be expected in pneumonia. In addition, the patient was afebrile and had no leukocytosis in the setting of a presumed immunocompetent status. Pneumonia would also not explain the patient's 2-month history of malaise, sinus congestion, arthralgias, acute kidney injury, and microhematuria. Finally, the patient's condition worsened despite initial appropriate antibiotic therapy for pneumonia. These factors combined suggest an alternative diagnosis. Transfusion-related acute lung injury is a transfusion-related complication that commonly

See end of article for correct answers to questions.

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manifests as acute hypoxemic respiratory failure with diffuse pulmonary infiltrates. However, because this patient was hypoxemic before his blood transfusions, this diagnosis is unlikely. Decompensated heart failure is unlikely because this patient has no risk factors, symptoms, or physical examination findings that would support the diagnosis. Although progressive hypoxemic respiratory failure in a critically ill patient should prompt consideration of an unrecognized acute pulmonary embolism, the findings of diffuse, worsening pulmonary infiltrates argues against its presence. Our patient's hypoxemia is most likely secondary to DAH because affected patients classically present with hemoptysis, worsening anemia, diffuse pulmonary infiltrates on chest imaging, and hypoxemic respiratory failure.

After arrival in the medical intensive care unit, the patient underwent urgent bedside bronchoscopy, which revealed the presence of gross blood throughout the upper and lower airways. Bronchoalveolar lavage from the lingula revealed progressively bloodier aliquot return, confirming the presence of DAH.

2. To further evaluate the cause of the patient's DAH, which *one* of the following would be the *most appropriate* next step?

a. No further work-up is necessary
b. Laboratory evaluation for inflammatory markers, antineutrophil cytoplasmic antibodies (ANCAs), anti–glomerular basement membrane (GBM) antibodies, antiphospholipid antibodies, antinuclear antibodies, and anti–double-stranded DNA
c. Surgical lung biopsy
d. Echocardiography
e. Urine drug screen

Diffuse alveolar hemorrhage is a clinical syndrome that presents as a consequence of an underlying pathologic process; therefore, not pursuing further work-up is inappropriate. This syndrome is caused mainly by 3 broad histopathologic disease categories: bland hemorrhage (capillary stress failure), diffuse alveolar damage, and capillaritis.[1] Among these categories, pulmonary capillaritis will frequently manifest as a consequence of systemic vasculitides and connective tissue diseases. Because our patient's DAH is associated with a multitude of other findings suggestive of a systemic and locoregional inflammatory illness, further laboratory evaluation for inflammatory markers and appropriate autoimmune serologic markers is indicated. A surgical lung biopsy would be a reasonable option only if less invasive investigations such as laboratory testing and renal or sinonasal biopsy were unable to establish this patient's diagnosis. Echocardiography could reveal the presence of severe mitral stenosis or markedly elevated left ventricular end-diastolic pressure that could result in bland pulmonary hemorrhage.[1] However, this study would not be indicated given this patient's lack of clinical findings for heart failure or valvular heart disease. Although illicit drug use with crack cocaine is a recognized cause of diffuse alveolar damage that may lead to DAH,[1] this diagnosis is improbable because our patient does not have any known risk factors such as history of drug abuse or physical examination findings that would suggest crack cocaine use; thus, a urine drug screen would not be indicated.

Further laboratory evaluations yielded the following results: erythrocyte sedimentation rate, 78 mm/1 h (0-22 mm/1 h); C-reactive protein, 219 mg/L (≤8.0 mg/L); cytoplasmic ANCA (c-ANCA) titer, 1:64 (negative); perinuclear ANCA (p-ANCA) titer, negative; proteinase 3 (PR3) antibodies, 1.7 U (<0.4 U); myeloperoxidase (MPO) antibodies, <0.2 U (<0.4 U); anti-GBM antibodies, <1.0 U (negative); antinuclear antigen and extractable nuclear antigen panel, negative; and eosinophils, 0.20×10^9/L ($0.05\text{-}0.50\times10^9$/L).

3. Which *one* of the following is the *most likely* diagnosis in this patient?

a. Eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss syndrome)
b. Microscopic polyangiitis (MPA)
c. Granulomatosis with polyangiitis (GPA)
d. Systemic lupus erythematosus (SLE)
e. Anti-GBM antibody disease (Goodpasture disease)

Granulomatosis with polyangiitis, MPA, and EGPA are ANCA-associated vasculitides. Microscopic polyangiitis, GPA, SLE, and anti-GBM antibody disease can potentially present with a pulmonary-renal syndrome due to their potential to cause pulmonary (DAH) and renal (glomerulonephritis) manifestations. These diseases often can be distinguished based on

Mayo Clin Proc. ■ May 2015;90(5):e47-e52 ■ http://dx.doi.org/10.1016/j.mayocp.2014.09.013
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laboratory analysis and clinical presentation. The absence of asthma and lack of peripheral blood eosinophilia in our patient argue against the presence of EGPA. In addition, DAH is rare in EGPA, renal involvement is seen in only 25% of patients with EGPA, and EGPA is most commonly associated with p-ANCA/MPO. Unlike in the present case, MPA would usually involve the combination of a p-ANCA pattern on immunofluorescence and a positive MPO-ANCA test result. The combination of sinusitis and a c-ANCA pattern on immunofluorescence with positive PR3-ANCA findings is strongly suggestive of GPA. Negative results for antinuclear and anti-GBM antibodies strongly argue against SLE and anti-GBM antibody disease, respectively.

Granulomatosis with polyangiitis was diagnosed, and appropriate therapy was initiated.

4. Which *one* of the following is the *most appropriate* induction of remission therapy plan for this patient?

a. High-dose glucocorticoids alone
b. Methotrexate monotherapy
c. High-dose corticosteroids and rituximab
d. Plasma exchange alone
e. Intravenous immunoglobulin alone

Monotherapy with high-dose glucocorticoids is not a preferred induction therapy because it has been less effective in achieving and maintaining disease remission than when combined with another immunosuppressive agent.[2] In addition, GPA with renal involvement is associated with increased mortality if treated with glucocorticoids alone.[3] Prolonged high-dose glucocorticoid therapy is also associated with many adverse effects including glucose intolerance, development of cushingoid features, emotional lability, cataracts, glaucoma, osteoporosis, and immunosuppression. In less severe cases of GPA in which major organ involvement such as glomerulonephritis or DAH has not occurred, methotrexate can be considered. However, it should not be used for induction in this case given our patient's high disease activity and organ dysfunction.

The combination of high-dose glucocorticoids and cyclophosphamide has historically been the preferred treatment of ANCA-associated vasculitis presenting with renal involvement or pulmonary capillaritis. This combination has improved remission rates and survival.[4] More recently, the combination of high-dose glucocorticoids and rituximab, a monoclonal anti-CD20 antibody, has emerged as a promising alternative therapy to treat ANCA-associated vasculitis. One landmark trial found that induction with a single course of rituximab was comparable to cyclophosphamide for achieving disease remission and was as effective as continuous conventional immunosuppressive therapy for the induction and maintenance of remissions over the course of 18 months.[5,6] Rituximab has become an alternative to cyclophosphamide because it is not associated with cyclophosphamide's treatment-related toxicities such as cystitis, bladder cancer, blood dyscrasias, and infertility. The most common adverse reactions of rituximab are infusion related, including angioedema, bronchospasm, chills, dizziness, fever, headache, and hypertension or hypotension. Less common serious adverse effects of rituximab include cytopenias, particularly neutropenia. Although plasma exchange may serve as an adjunctive therapy for severe cases of ANCA-associated vasculitis, its role as a primary therapy has not been investigated.[7] Intravenous immunoglobulin is not an appropriate induction therapy for GPA, and there is insufficient evidence to support its use as an adjunctive therapy as well.[8]

After treatment with a combination of high-dose glucocorticoids and rituximab, the patient's condition quickly improved, and he was eventually able to be dismissed from the hospital.

5. Which *one* of the following tests has the *greatest* predictive value for future disease flares?

a. PR3-ANCA positivity
b. B-cell counts
c. c-ANCA/p-ANCA titers
d. Creatinine value
e. Hemoglobin level

Recent evidence has documented that most patients—86%—achieve remission within the first 6 months after induction therapy with either rituximab or cyclophosphamide and high-dose glucocorticoids.[9] However, almost half—42%—do not remain disease free within 6 months of cessation of corticosteroid therapy. In the study by Miloslavsky et al,[9] 91% of patients who experienced a flare or

uncontrolled disease had PR3-ANCA positivity. B-cell counts and c-ANCA/p-ANCA titers were not found to be predictive of disease flare. The creatinine and hemoglobin levels have also not been found to correspond with disease activity. Importantly, despite the fact that patients with persistently positive or increasing PR3-ANCA levels are at higher risk for disease relapse compared with PR3-ANCA–negative patients, an increase in PR3-ANCA or the conversion from a negative to a positive PR3-ANCA level is not an accurate predictor of disease relapse for most individual patients with GPA.[10]

Since his hospitalization, the patient has done remarkably well and has been closely monitored by pulmonary and nephrology outpatient services.

DISCUSSION

Diffuse alveolar hemorrhage often presents a diagnostic challenge. Clinical presentations range from asymptomatic radiologic findings to life-threatening respiratory failure.[10] Prompt diagnosis and management are necessary for survival when respiratory failure is present, making early recognition essential. Presentation of DAH frequently includes cough, dyspnea, fever, and chest pain.[10] Concurrent progressive anemia is also supportive of the diagnosis. It is important to note that hemoptysis is not consistently present.[1] In addition, imaging studies reveal an alveolar filling process that is often nonspecific and changes throughout the course of the disease.[10] Imaging may reveal a diffuse, focal, or patchy distribution of pulmonary involvement.[1] Therefore, a strong clinical suspicion must be present.

Once DAH is suspected, the primary objective is stabilization of the patient. This may require respiratory support through oxygen supplementation or intubation. Blood transfusion is also frequently required in severe cases. The diagnosis of DAH is confirmed through bronchoscopy with bronchoalveolar lavage that has progressively bloodier return with each lavage aliquot. Hemosiderin-laden macrophages are also commonly present but not necessary for diagnosis because bloody return may precede this finding.[10] Evaluation of the coagulation cascade should be completed as well. A goal international normalized ratio of less than 1.5 and platelet count of more than 50,000/μL should be maintained through administration of platelet transfusions, vitamin K, and/or fresh frozen plasma.[10]

After initial stabilization and diagnosis, an underlying cause must be sought. Diffuse alveolar hemorrhage is a clinical syndrome that results from a vast array of pathologic processes. These processes consist of 3 main categories: pulmonary capillaritis, bland pulmonary hemorrhage (capillary stress failure), and diffuse alveolar damage.[1] The clinical presentation guides the next steps in evaluation. Concurrent renal involvement in patients with DAH suggests the presence of a systemic disorder.[10] These pulmonary-renal syndromes include GPA, MPA, anti-GBM antibody disease, and SLE.[10]

Serologic evaluation is the next step in diagnosis. Testing for complement levels, anti–double-stranded DNA, antinuclear antibodies, ANCA panel including immunofluorescence (c-ANCA and p-ANCA) and enzyme-linked immunosorbent assay (PR3 and MPO-ANCA), antiphospholipid antibodies, and anti-GBM antibodies should be obtained.[10] Other laboratory tests to consider include coagulation studies, measurement of creatinine level, anti–cyclic citrullinated peptide antibodies, rheumatoid factor, and creatinine kinase value, urinalysis with urinary sediment measurement, and a drug screen.[10] Current diagnostic criteria require confirmation through histologic evaluation via biopsy. However, biopsy carries a high risk to the patient and has variable diagnostic yield.[10] Therefore, it has been proposed that diagnosis may be established through serologic evaluation alone, avoiding the need for more invasive testing.[10] In particular, serologic testing is accurate in establishing a GPA or MPA diagnosis. Testing of c-ANCA/PR3 has a sensitivity of 91% and specificity of 99% in acute cases of GPA.[11] If the results of serologic evaluation are equivocal, then tissue biopsy of affected organs is used to establish the diagnosis.

Granulomatosis with polyangiitis is a systemic inflammatory disease with multiorgan involvement. In the United States, the incidence of GPA is approximately 13 to 30 cases per million persons per 5-year period.[12,13] It is characterized as a small-vessel vasculitis that classically involves the upper and lower airway and kidneys. Upper respiratory tract symptoms can include sinusitis, otitis media, and epistaxis. Lower respiratory tract symptoms include cough, wheezing, pleuritic pain, and hemoptysis. Renal involvement in the form of necrotizing pauci-immune glomerulonephritis is also commonly present. However,

Mayo Clin Proc. ■ May 2015;90(5):e47-e52 ■ http://dx.doi.org/10.1016/j.mayocp.2014.09.013
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clinicians should also be aware that this disease is often not limited to the "classic" organ system triad but may involve the nervous, cutaneous, musculoskeletal, cardiovascular, and gastrointestinal systems.

The initial presentation of GPA can be diagnostically challenging even to the most apt and experienced clinicians. Although DAH may be the initial presenting symptom, such as in our case, more frequently patients present with more indolent constitutional symptoms. These symptoms may include low-grade fevers, anorexia, and weight loss. Symptoms and clinical findings such as chronic cough, dyspnea, or sinusitis are also often present and are frequently misinterpreted as infectious etiologies, such as a pneumonia or bacterial sinusitis. Consideration of the whole patient and clinical suspicion are essential for the diagnosis.

After establishing the diagnosis of GPA, the goal of therapy is 2-fold: (1) induce disease remission and (2) prevent relapse. To achieve induction, traditional therapies with cyclophosphamide and high-dose glucocorticoids have been the preferred treatments given their success in most patients. More recently, rituximab has been reported to be an effective alternative because it does not have the treatment-related toxicities of cyclophosphamide.[5,6]

Although most patients respond positively to induction therapy, GPA is a chronic recurring disease for many. Therefore, patients often require prolonged immunosuppressive therapy. Beyond the disease itself, management of an immunosuppressed patient must be undertaken. Patients should be tested for tuberculosis before initiation of therapy with an immunosuppressive agent such as cyclophosphamide or rituximab. Firm guidelines regarding prophylaxis for *Pneumocystis* pneumonia in patients without human immunodeficiency virus infection are lacking; however, such prophylaxis should be considered in these patients after carefully weighing the risk of the prophylactic regimens against the potential risks of development of this infection and the high associated mortality.[14,15] A dual-energy x-ray absorptiometry scan is often performed at baseline, and calcium and vitamin D are prescribed with prolonged glucocorticoid use.[16]

This case emphasizes the diagnostic challenges of DAH as well as GPA. Initially, pneumonia was diagnosed and treated. The patient's chronic symptoms of fatigue, nasal congestion, maxillary sinus pressure, cough with scant hemoptysis, diffuse arthralgias, and low-grade fevers were indicative of an underlying systemic disease even before presentation with respiratory distress. However, awareness of the diagnostic challenges of GPA and DAH are necessary to recognize these conditions. His physicians were initially influenced by the focal findings on chest radiography and his symptoms of dyspnea. Continued deterioration of his condition alerted his astute physicians to an alternative diagnosis. At this time, further evaluation was completed and other symptoms were considered. Ultimately, the correct diagnosis was reached and appropriate management was implemented.

ACKNOWLEDGMENTS

We thank Dr Ulrich Specks for his expertise and insightful comments and suggestions on the submitted manuscript.

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CORRECT ANSWERS: 1. e. 2. b. 3. c. 4. c. 5. a

Mayo Clin Proc. ■ May 2015;90(5):e47-e52 ■ http://dx.doi.org/10.1016/j.mayocp.2014.09.013
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