30-Year-Old Woman With Dyspnea, Cough, Hemoptysis, and a Cavitary Lung Lesion

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A previously healthy 30-year-old woman presented with a 6-week history of progressive dyspnea on exertion and cough. She also noticed some bright red blood within her sputum. She experienced no improvement with azithromycin as empirical treatment for community-acquired pneumonia and presented to the emergency department.

Her vital signs and physical examination findings were normal. Chest radiography revealed a left upper lobe opacity, which was further characterized as a 7×5×4-cm perihilar cavity on chest computed tomography (CT). She was a smoker and admitted to infrequent binge drinking. She denied prior syncope, aspiration, dental disease, recent travel, illicit drug use, and *Mycobacterium tuberculosis*, occupational, or environmental exposures. She denied weight loss, night sweats, and fevers. Her medical history was only remarkable for donating a kidney to her brother 8 years earlier (for end-stage diabetic nephropathy). She took no regular medications.

1. **Which of the *one* following is the *most likely* diagnosis?**
   a. Lung abscess, secondary to a bacterial infection
   b. Lung abscess, secondary to tuberculosis
   c. Systemic inflammatory disease, such as rheumatoid arthritis
   d. Neoplastic disease
   e. Pulmonary embolus

A cavitary lung lesion is defined as a radiolucent area surrounded by a thick (>4 mm) wall, an area of consolidation, or a mass lesion.[1] The differential diagnosis of focal cavitary lung lesions can be broadly divided into infectious and noninfectious origins. Possible infectious causes include common bacterial pathogens (anaerobic, aerobic, or mixed), mycobacteria (tuberculous or nontuberculous), filamentous bacteria (*Nocardia* and *Actinomyces*), and fungal organisms (endemic mycosis: histoplasmosis, coccidiomycosis, or blastomycosis). A careful microbiological evaluation, including Gram, acid fast, and fungal stains and bacterial, mycobacterial, and fungal nucleic acid amplification testing, and cultures of sputum and bronchial secretions are needed to evaluate most focal cavitary lung lesions. In this otherwise healthy patient with a relatively short antecedent history, as well as a background of infrequent binge drinking, a bacterial lung abscess is the most likely differential diagnosis, pending further diagnostic workup. Endemic or filamentous fungal infections are possible and need to be excluded. Tuberculosis is less likely given the absence of travel or known exposures.

Cavitary lung lesions also occur in systemic inflammatory diseases, such as rheumatoid arthritis or granulomatosis with polyangiitis (GPA), and the presence of extrapulmonary disease manifestations should be assessed in these patients. Serologic testing for rheumatoid factor, anticitrullinated peptide antibodies, and antineutrophil cytoplasmic antibodies (ANCAs) is valuable in the evaluation of rheumatoid arthritis and GPA.[2]

Various neoplasms, such as bronchogenic carcinomas, lymphomas, and metastatic malignant tumors, also frequently cause focal cavitary lung lesions. Bronchoscopy with biopsy of the cavitary lesion should be performed if a malignant tumor is suspected. Lastly, focal cavitary lung lesions are rarely caused by pulmonary infarcts due to septic or pulmonary thromboembolic disease.

The results of sputum microbial stains and cultures, human immunodeficiency virus and fungal serologic testing, purified protein derivative skin testing, and *M tuberculosis* interferon γ release testing were all negative. The ANCA testing revealed low-positive anti—proteinase-3 (PR3) by enzyme-linked immunosorbent assay (1.0 units; reference range, 0-0.9 units). However, the result of ANCA testing by indirect immunofluorescence on ethanol-fixed neutrophils and PR3-transfected human mast cells was negative. Bronchoscopy demonstrated no endobronchial abnormalities, and endobronchial

See end of article for correct answers to questions.

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ultrasonography—guided biopsy of the cavitary lesion revealed acute inflammation with negative microbial stains. Cultures of bronchial secretions yielded *Actinomyces* and *Veillonella* species.

2. Which *one* of the following would be the *best* treatment at this time?

a. Intravenous therapy with penicillin G for 3 weeks
b. Intravenous therapy with penicillin G for 3 months
c. Intravenous broad-spectrum antibiotics for 3 weeks
d. Intravenous broad-spectrum antibiotics for 3 months
e. Surgical referral for refractory lung abscess

On the basis of the available information, the patient was diagnosed as having a mixed bacterial lung abscess. Most cases of lung abscess are due to aspiration of mixed oral flora. In the pre-antibiotic era, anaerobes were found in 90% of lung abscesses at autopsy. They were the only organisms isolated in 50% of cases.[3] Commonly isolated organisms include both anaerobic (*Peptostreptococcus*, *Bacteroides*, *Fusobacterium,* and *Veillonella*) and aerobic (*Streptococcus milleri*, *Staphylococcus aureus,* and *Klebsiella* sp) bacteria.[4] However, given the frequent use of empirical broad-spectrum antibiotics, the diagnostic yield of bacterial cultures remains suboptimal. Consequently, regardless of the bacterial organisms isolated from the respiratory tract, antibiotic treatment for lung abscess generally includes broad-spectrum antibiotics.

In this patient, *Actinomyces*, a branching (filamentous), gram-positive bacillus, and *Veillonella,* a gram-negative anaerobic coccus, both part of the normal intestinal and oral flora, were isolated from the respiratory tract. Penicillin G represents the first-line therapy for both of these organisms. Nevertheless, given the limited yield of bacterial cultures and the polymicrobial nature of these infections, broad-spectrum antibiotic therapy is indicated for this patient. Treatment options include clindamycin and β-lactam antibiotics with anaerobic coverage, such as amoxicillin-clavulanic acid or carbapenems. Metronidazole is not preferred for treating lung abscesses. It has little activity against actinomyces and the microaerophilic streptococci commonly found in abscesses. There is no established duration of antibiotic therapy. Therapy is typically continued until there is notable or total radiologic response, usually for several months. Surgical resection is infrequently needed for patients without radiologic and/or clinical improvement despite appropriate antibiotic therapy or to manage complications such as major hemoptysis.

The patient was prescribed outpatient intravenous ertapenem therapy. After an initial radiologic and clinical improvement, her abscess cavity did not decrease further after 3 months of treatment. In addition, her fever and cough returned after the transition from intravenous to oral antibiotic therapy. Consequently, she underwent surgical resection of her refractory lung abscess. Unfortunately, because of the hilar location of the lesion, she required a left pneumonectomy. The initial pathology was interpreted as an abscess cavity. All stains and cultures were negative, and antimicrobial therapy was discontinued.

Six weeks later she experienced recurrent fevers and abdominal pain. Repeated chest CT demonstrated the expected postoperative changes but no new abnormalities. Abdominal CT revealed 2 complex cavitary mass lesions—in the left pelvis involving the iliac artery and in the right kidney. Blood and urine culture results were negative, and the lesions progressed despite the reinitiation of empiric broad-spectrum antibiotic therapy. She subsequently underwent complex multispecialty abdominal surgery for decortication of both lesions and vascular bypass of the compressed left iliac artery. The results of cultures and microbial stains remained negative. Histopathologic analysis of the renal lesion demonstrated extensive areas of geographic necrosis, numerous neutrophilic microabscesses, and necrotizing granulomatous inflammation. In addition, pauci-immune crescentic glomerulonephritis was present within the renal parenchyma.

3. Which *one* of the following tests would be *most helpful* in confirming the clinically suspected diagnosis in this patient?

a. Repeated ANCA testing
b. Repeated bronchoscopy with biopsy
c. Repeated *M tuberculosis* interferon γ release testing
d. Repeated fungal serologic testing
e. Angiotensin-converting enzyme level

The lack of clinical response to broad-spectrum antimicrobial therapy and negative

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results from cultures of surgically removed tissue suggest a noninfectious inflammatory process. Histopathologic changes of geographic necrosis, neutrophilic microabscesses, and necrotizing granulomatous inflammation, the presence of crescentic glomerulonephritis, and the previously low-positive PR3-ANCA test result are highly suggestive of GPA. On the basis of these observations, ANCA testing, which usually involves a stepwise approach, should be repeated in this patient. The PR3- and myeloperoxidase (MPO)-ANCAs are measured using an antigen-specific assay, such as an enzyme-linked immunosorbent assay. If PR3- and/or MPO-ANCAs are detected, the sample is further evaluated by indirect immunofluorescence staining of ethanol-fixed neutrophils. The staining pattern is generally categorized as cytoplasmic or perinuclear ANCA. Positive PR3-ANCA results are typically associated with a cytoplasmic ANCA pattern, whereas MPO-ANCAs result in a perinuclear ANCA pattern. The diagnostic sensitivity and specificity of a combined positive PR3-ANCA result and cytoplasmic ANCAs for GPA are excellent (73% and 99%, respectively).[2]

There are 2 major classification systems for the vasculitides. The American College of Rheumatology criteria, published in 1990, require the presence of 2 or more of the following 4 criteria: nasal or oral inflammation, an abnormal chest radiograph finding (nodules, fixed infiltrates, or cavities), an abnormal urinalysis result (microscopic hematuria), and evidence of granulomatous arterial or perivascular inflammation on biopsy. The presence of 2 or more criteria has a sensitivity of 88% and specificity of 92% for diagnosing GPA. The Chapel Hill Consensus criteria, published in 1994, were created for the purposes of identifying pathologic differences among the different vasculitides. These criteria defined GPA as a granulomatous inflammation involving the respiratory tract with a vasculitis of small to medium vessels. Neither system includes the presence of ANCAs as a requirement to fulfill the disease definition. Given her cavitary lung lesion and biopsy-proven granulomatous disease, our patient met criteria for GPA under the American College of Rheumatology classification and fulfilled the Chapel Hill Consensus Conference definition of GPA. Consequently, a diagnosis of GPA was established.

Repeated chest CT did not reveal any new pulmonary processes; therefore, repeated bronchoscopy with biopsy would not be indicated. However, reevaluation of the prior lung pathology in light of the additional information is essential. It too demonstrated geographic necrosis, neutrophilic microabscesses, and necrotizing granulomatous inflammation, adding further support to the clinical diagnosis of GPA. Repeating the *M tuberculosis* interferon γ release assay, performing more fungal serologic tests, or measuring an angiotensin-converting enzyme level would not be helpful in this patient.

The results of repeated ANCA testing for PR3-ANCA by enzyme-linked immunosorbent assay (2.5 units; reference range, 0-0.9 units; previously 1.0 unit) and cytoplasmic ANCA by indirect immunofluorescence were now clearly positive (1:8), and a diagnosis of GPA was established.

4. Which *one* of the following statements is *true* in regard to the cause of the GPA in this patient?

a. Single-nucleotide polymorphisms in the gene encoding PR3 are found in approximately 90% of cases of GPA
b. Special stains frequently demonstrate organisms within the necrotizing granulomas of GPA
c. The upper airway of patients with GPA is commonly colonized with *S aureus*
d. Therapy with azithromycin may decrease the number of exacerbations in GPA patients
e. ANCA seroconversion is only seen with the vasculitides

The pathogenesis of GPA remains unclear, and GPA is classified as an idiopathic small vessel vasculitis. Multiple genetic, environmental, and immunologic factors have been associated with the development of GPA. However, no definite causal genetic or environmental exposure has been identified. Multiple single-nucleotide polymorphisms have been identified in PR3, but none of these is routinely associated with GPA. Microbial stain results are typically negative for the necrotizing granulomas associated with GPA. In this patient, the cavitary lung lesion and positive culture results for *Actinomyces* and *Veillonella* from within the lesion, in conjunction with a clinical and radiologic response to

appropriate antibiotic therapy, are highly suggestive of a lung abscess. Interestingly, over time the patient's therapeutic progress stalled, and the disease progressed despite surgical site control and antimicrobial therapy, indicating a transition to a noninfectious inflammatory process.

Infections are not uncommonly reported before the initial presentation or exacerbations of GPA cases. Patients with GPA are more likely to carry *S aureus* in their nasal passages than age-matched controls. These carriers are at higher risk for disease flares, and therapy with a combination of trimethoprim and sulfamethoxazole may prevent these events. The putative mechanisms for the benefit of trimoxazole-sulfamethoxazole remain speculative. Azithromycin has some anti-inflammatory properties and has been found to reduce exacerbations in patients with cystic fibrosis, follicular bronchiolitis, and chronic obstructive pulmonary disease but not in GPA. Several systemic infections, including bacterial endocarditis, may mimic the clinical presentation of GPA and cause ANCA seroconversion. Consequently, it is crucial to exclude systemic infections before establishing a diagnosis of GPA.

5. **Which *one* of the following would be the *most appropriate* next step in managing this patient's GPA?**
   a. Because the disease has been resected, observe and repeat imaging in 1 month
   b. Immunosuppression with prednisone alone
   c. Immunosuppression with prednisone and cyclophosphamide
   d. Immunosuppression with prednisone and methotrexate
   e. Immunosuppression with prednisone and rituximab (anti-CD20 chimeric antibody)

The goal of immunosuppressive therapy in GPA is to treat acute inflammation and prevent irreversible organ damage and mortality. The mortality of untreated severe GPA approaches 90% at 2 years; however, combination therapy with prednisone and cyclophosphamide improves long-term survival to closer to 80%.[5] Consequently, once a diagnosis of GPA has been established, it should be treated promptly and aggressively. Selection of optimal treatment regimen for GPA is based on disease extent (nonsevere disease [limited] vs severe), stage (remission induction vs remission maintenance), and patient-specific risk of treatment-associated adverse effects. Our patient is a young woman of childbearing age who needs remission induction therapy for a new diagnosis of severe GPA (given the pauci-immune glomerulonephritis). Despite the crucial role of corticosteroids in controlling acute inflammation in patients with GPA, the long-term effects of corticosteroid monotherapy are suboptimal. Historically, combination therapy with high-dose corticosteroids tapered during 3 to 6 months in combination with 3 to 6 months of either oral or pulsed intravenous cyclophosphamide was considered the standard of care for these patients.[5] However, the use of cyclophosphamide has been associated with major acute and chronic adverse events. Patients frequently develop severe leukopenia in the short term, which has been associated with a high risk of severe, potentially life-threatening acute infections or acute hemorrhagic cystitis. Long-term adverse effects of cyclophosphamide include an increased risk for hematologic and solid malignant tumors, including bladder cancer, and irreversible infertility.

Methotrexate is not indicated for remission induction therapy in patients with severe GPA. However, it effectively induces remission in nonsevere disease and can be used for remission maintenance therapy. On the basis of the results of a recent clinical trial demonstrating the noninferiority of B-cell depletion therapy with the humanized anti-CD20 antibody rituximab in combination with corticosteroids compared with cyclophosphamide in severe GPA, the Food and Drug Administration approved rituximab as the first-line agent for remission induction therapy of GPA.[6] Rituximab has a more favorable adverse effect profile, especially in younger patients. Our patient was successfully treated with high-dose corticosteroids and rituximab therapy (375 mg/m^2 for 4 doses in weekly intervals).

DISCUSSION

Granulomatosis with polyangiitis (Wegener granulomatosis) is a small vessel vasculitis, part of the spectrum of ANCA-associated vasculitides, which also includes microscopic polyangiitis, eosinophilic GPA (Churg-Strauss syndrome), and renal-limited vasculitis. It is

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a rare disease, with an incidence of approximately 3.0 per 100,000 persons in the United States.[7]

Clinical presentation of GPA is highly variable and can include constitutional symptoms (eg, fever, arthralgias, malaise, anorexia, and weight loss) and organ-specific symptoms (eg, hemoptysis, cavitary lung nodules or masses, sinusitis, hematuria, palpable purpura, and mononeuritis multiplex). The most commonly affected organs are the upper and lower respiratory tract and the kidneys.

The cause of GPA remains poorly defined and is likely multifactorial, involving genetic, environmental, and immunologic factors. In the case described, an antibiotic-responsive polymicrobial lung abscess preceded the clinical development of GPA and ANCA seroconversion. It is possible that the prior infection triggered the autoimmune process. Chronic smoldering inflammation (in our case due to polymicrobial infection with *Actinomyces* and *Veillonella* sp) may result in persistent neutrophil activation, autoantigen presentation (PR3), and the subsequent generation of ANCA targeting PR3. Interestingly, although low-grade chronic inflammation is relatively common, the development of vasculitis is rarely seen, indicating that host and pathogen-specific factors likely contribute to the development of autoimmunity.

The association between GPA and *S aureus* is well established. Commonly, *S aureus* colonizes patients with GPA and represents an independent risk factor for disease relapse (relative risk, 7.2).[8] The chances of developing vasculitis may be further augmented through immune activation by *S aureus* superantigens. Associations among other infective agents have been much less frequently reported.

Whereas ANCAs represent a valuable diagnostic marker, their role in the disease pathogenesis remains controversial. Putative mechanisms include neutrophil activation followed by release of proteolytic enzymes and reactive oxygen species, mediated by binding of ANCAs to the PR3 on activated neutrophils. Over time, ANCA-mediated neutrophil activation may result in damage to vascular endothelium and surrounding tissues.

Active GPA needs to be treated promptly and aggressively with high-dose corticosteroids in conjunction with other immunosuppressive agents. Severe (ie, life or organ threatening) disease is treated with either rituximab or cyclophosphamide, whereas nonsevere disease may be treated with methotrexate. The successful induction of remission is typically based on the comprehensive clinical assessment of all organ manifestations and systemic symptoms. To help with this assessment, clinical scoring systems, such as the Birmingham Vasculitis Activity Score for GPA, have been developed to measure disease activity. Aggressive therapy results in disease remission in approximately 90% of patients. Once remission is achieved, the goal of therapy becomes remission maintenance. Preferred medications for maintenance therapy are azathioprine and methotrexate, which have similar safety and efficacy profiles.[9] In contrast, a recent study demonstrated mycophenolate mofetil to be less efficacious.[10] Recent retrospective case series also suggest a potential role of rituximab for remission maintenance therapy, and an international, prospective randomized controlled trial is being developed.

Despite remission maintenance therapy, 30% to 60% of patients will experience disease relapses.[5] Risk factors for relapse include persistent ANCA positivity, upper respiratory tract and lung involvement, and airway colonization with *S aureus*. To assess for relapse, patients are monitored closely, approximately every 3 to 4 months, on disease remission. At these visits, patients undergo history, physical examination, urinanalysis with microscopy (to assess for hematuria), chest radiography (to assess for new pulmonary nodules), and a comprehensive laboratory evaluation measuring serum creatinine, electrolytes, complete blood cell count, liver function, sedimentation rate, C-reactive protein, and B cells in patients treated with rituximab. Even though ANCA testing is frequently performed, increases of ANCA levels are poor predictors of relapses in patients treated with conventional immunosuppression.[11]

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

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