An Initial Diagnosis of Wegener's Granulomatosis in an 82-Year-Old-Woman

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Wegener's granulomatosis is a small- to medium-vessel vasculitis that manifests as a necrotizing granulomatous disease of the pulmonary and renal systems.[1–3] It is an uncommon and diagnostically challenging disorder that is usually revealed through a combination of clinical criteria, serum cytoplasmic antineutrophilic cytoplasmic antibody (c-ANCA), and histology. Although Wegener's granulomatosis typically presents in the sixth decade, new diagnoses have been reported in the elderly population as well.[1,2,4] Elderly patients with this disease have a distinctive distribution and frequency of organ involvement as compared with younger and middle-aged patients (age, < 60 yr).[4] This article presents the case of an elderly woman with an initial diagnosis of Wegener's granulomatosis and reviews the diagnosis and management of this disease.

CASE PRESENTATION

Initial Presentation and History

An 82-year-old woman presented to the emergency department complaining of vertigo of 2 days' duration. The patient reported that she had sought care from a primary care physician for an upper respiratory tract illness and sinus pain 6 weeks prior to presentation. She was prescribed azithromycin for presumed sinusitis. A chest radiograph performed for persistent symptoms at a follow-up visit 2 weeks later revealed multiple lung masses, and a subsequent computed tomography (CT) scan of the chest confirmed masses in the left upper and lower lobes and scattered nodules in the right lung. Malignancy was suspected, and a CT–guided core biopsy of 1 of the left lung masses demonstrated necrotic tissue. Follow-up CT with contrast and positron emission tomography (PET) were ordered to evaluate progression and characterize the lung masses. The PET scan did not show conclusive uptake in the lesions, which made the diagnosis of malignancy uncertain. Repeat CT scan showed no interval change.

The patient's past medical history was significant for hypertension, hypothyroidism, and hyperlipidemia. Medications included levothyroxine, gemfibrozil, and atorvastatin. The patient denied any recent travel. She had a 45 pack-year history of tobacco use but quit 40 years ago.

Physical Examination

On examination, the patient's vital signs were as follows: temperature, 36.1°C (97°F); blood pressure, 151/72 mm Hg; heart rate, 74 bpm; respiratory rate, 16 breaths/min; and oxygen saturation, 95% on room air. The patient had sustained horizontal nystagmus on right lateral gaze. There was no vertical or rotational nystagmus. She had marked truncal instability as demonstrated by falling to her left side when seated upright. She was unable to stand without support and could not ambulate. Her cranial nerves were intact, and her strength, sensation, and reflexes in all 4 extremities were normal. The remainder of her general physical examination was normal.

Diagnostic Studies

Serum chemistry studies, liver function tests, coagulation studies, and albumin level were normal. The white blood cell count was $15.6 \times 10^3/\mu L$ (normal, $4.5–11.0 \times 10^3/\mu L$), with an eosinophil count of 2370 cells/μL (normal, 0–450 cells/μL). Hematocrit was 37.5% (normal, 35%–45%), and the platelet count was $323 \times 10^3/\mu L$ (normal, $150–450 \times 10^3/\mu L$). Urinalysis demonstrated 3 to 10 red blood cells per high-power field, which was suggestive of glomerulonephritis. The erythrocyte sedimentation rate was 46 mm/hr (normal, 0–20 mm/hr).

Magnetic resonance imaging (MRI) of the brain revealed 2 small dural-based masses, the larger measuring 1.6 × 1.1 × 2.0 cm, along the posterior aspect of the left temporal bone and the left tentorium leaflet with mild associated edema (**Figure 1**). No specific sinus abnormalities were seen. The patient was admitted to the hospital for further evaluation of the masses.

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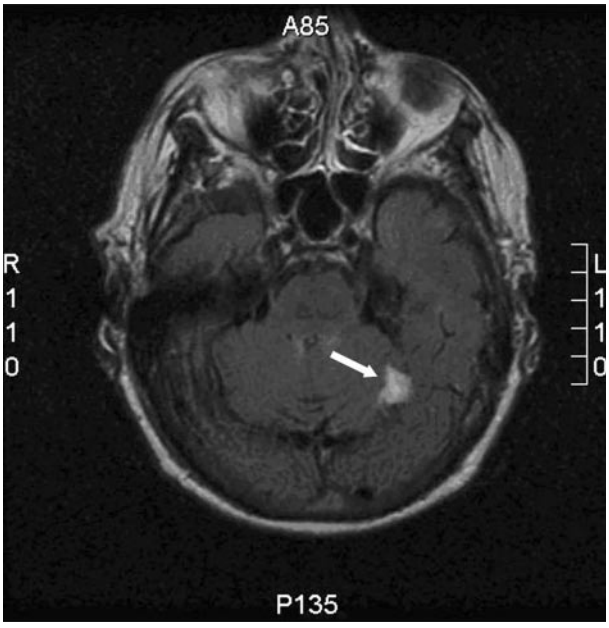

Figure 1. Magnetic resonance imaging scan of the case patient showing a dural-based lesion at the left tentorium leaflet (*arrow*).

Further diagnostic testing included 3 negative sputum smears for acid-fast bacilli and no evidence of urine antigen to *Histoplasma;* serum antibody for coccidioidomycosis was not detectable. Serum cryptococcal antigen was detected at a titer of 1:64. Lumbar puncture demonstrated normal cell count, protein, and glucose with no evidence of cryptococcal antigen, bacteria, fungus, or mycobacteria. The serum c-ANCA assay was positive at 35 U/mL (normal, < 2 U/mL). Antinuclear and antimyeloperoxidase antibodies were undetectable. Levels of angiotensin-converting enzyme and rheumatoid factor were within normal range.

The clinical presentation, chest imaging, and positive c-ANCA assay all pointed to Wegener's granulomatosis. However, the unexpectedly positive serum cryptococcal antigen provided a plausible alternative explanation for her pulmonary masses with substantially different treatment implications. A second serum cryptococcal antigen assay performed on hospital day 6 was negative. The first test was considered a false positive, thus ruling out concomitant cryptococcal disease.

To further characterize the masses, the patient underwent video-assisted thoracoscopic biopsy of the lung on hospital day 8, which demonstrated an irregular necrotic nodule with histiocytic cuffing and peripheral chronic inflammation (**Figure 2**). Adjacent lung tissue showed focal capillaritis and scattered multinucleate giant cells, all features consistent with Wegener's granulomatosis.

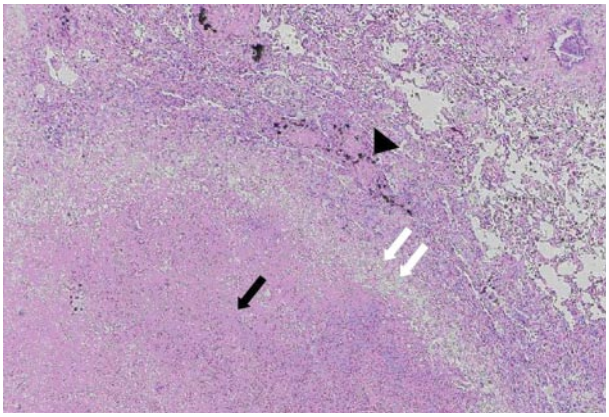

Figure 2. Pathologic specimen showing an irregularly rounded nodule (*black arrow*) with central necrosis and a thin histiocytic rim suggestive of Wegener's granulomatosis (*white arrows*). Occasional airspace hemosiderin-filled macrophages can be seen in adjacent lung tissue (*arrowhead*).

Treatment

After undergoing MRI on hospital day 1, the patient was administered intravenous dexamethasone at a dose of 4 mg every 8 hours for cerebral edema. Within 1 day, the patient's vertigo had decreased considerably and had resolved by hospital day 3. Chest CT demonstrated interval changes of the lung masses, with new nodules in bilateral hilar regions but a decrease in size of 2 of the left upper lobe masses (**Figure 3**). The patient was maintained on a tapering dose of corticosteroids throughout her 2-week hospitalization. Oral cyclophosphamide (1.5 mg/kg/day) was initiated in an outpatient rheumatology clinic 2 weeks after hospital discharge. Three months later, her symptoms had improved significantly and the pulmonary infiltrates had regressed. The dural-based lesions remained unchanged on repeat MRI after treatment, suggestive of a meningioma unrelated to her Wegener's granulomatosis. The patient was referred to a neurosurgery outpatient clinic for follow-up with serial imaging of the meningioma.

DISCUSSION

This patient's initial presentation with upper respiratory tract illness and sinusitis, nodular pulmonary infiltrates, hematuria, and c-ANCA assay results is typical of Wegener's granulomatosis, an uncommon disease that can be diagnostically challenging because many conditions in the differential diagnosis are far more common in clinical practice. The distinctive aspect of this case is the late age of disease onset. The mean age at diagnosis of Wegener's granulomatosis is 55 years, although diagnosis in older patients is documented in the literature.[1,2,4]

In the case patient, the positive serum cryptococcal antigen, which initially raised concern about disseminated cryptococcal disease, was negative on repeat testing. The literature suggests that current serum cryptococcal assays are approximately 97% sensitive and 93% to 100% specific.[5] Some potential causes of false-positive assays include contamination by disinfectants, soaps, talc from latex gloves, and surface condensation from agar.[6] Rheumatoid factor and other serum macroglobulins have also been noted to cause false-positive results in some patients.[7]

WEGENER'S GRANULOMATOSIS

Wegener's granulomatosis is a systemic vasculitis of medium and small arteries, arterioles, and veins that manifests as a necrotizing granulomatous disease of the upper respiratory tract, lungs, and kidneys.[1–3] It is an uncommon disorder with an estimated prevalence of 3 in 100,000 persons.[8] Approximately 2300 new cases are diagnosed in the United States each year. Between 80% and 97% of patients are white, and there is an equal distribution between the sexes.[1,8]

Clinical Features

More than 90% of patients with Wegener's granulomatosis present with upper respiratory tract and/or pulmonary symptoms.[1,8] The spectrum of upper respiratory disease manifestations includes sinus pain, epistaxis due to friable mucosa, persistent rhinorrhea, or nasal ulcers.[1,8] Less commonly, patients may present with stridor due to subglottic stenosis. Although vertigo may be seen in Wegener's granulomatosis, vertigo in this case was attributed to the patient's meningioma.

The lungs are affected in approximately 80% of Wegener's granulomatosis cases.[8] The bronchi, pulmonary parenchyma, and occasionally the pleura may be involved, presenting as cough, hemoptysis, dyspnea, or pleuritis. Chest radiograph typically reveals bilateral nodular infiltrates, which may be fixed or migratory. Other findings include solitary nodules, cavitary lesions, and diffuse alveolar hemorrhage.[1,8,9] Hilar lymphadenopathy is usually absent in Wegener's granulomatosis and when present should prompt consideration of alternative diagnoses, including malignancy, sarcoidosis, or infection.[2,9]

Glomerulonephritis develops in approximately 80% of patients with Wegener's granulomatosis. It may present subtly with microscopic hematuria (as was seen in the case patient), proteinuria, or acute renal failure.[1,8] Renal disease is often the most serious complication of Wegener's granulomatosis and should be monitored closely.

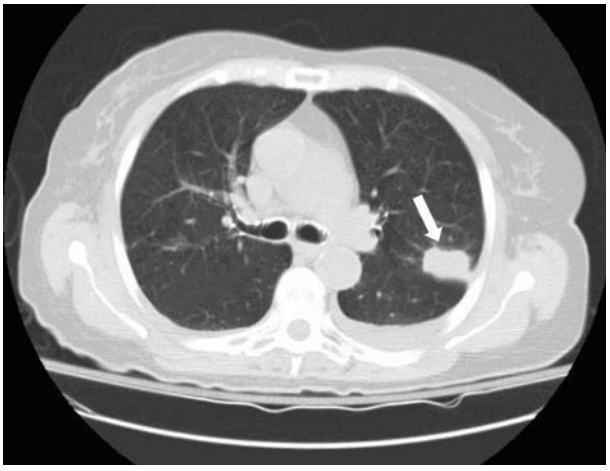

Figure 3. Computed tomography scan demonstrating a dense consolidated left upper lobe lung nodule (*arrow*).

Consideration of the brain masses in the case patient served as a reminder to the clinicians that neurologic involvement may be a feature of Wegener's granulomatosis, especially in elderly patients.[2,4,10,11] Peripheral neuropathy, particularly mononeuropathy multiplex, has been frequently described in Wegener's granulomatosis.[10] CT and MRI findings in neurologic Wegener's granulomatosis include dural enhancement and thickening, infarcts, or nonspecific white matter changes.[11–13] In this case, the repeat MRI ultimately led to an unrelated diagnosis (meningioma) rather than central nervous system Wegener's granulomatosis.

There is a considerably higher mortality rate in elderly patients with Wegener's granulomatosis versus younger patients (54% versus 19%, respectively),[4] and the possibility of vasculitis should not be overlooked in the geriatric population. Attributing multisystem disease to age-related decline or undocumented infection is a potential diagnostic pitfall in these patients. Elderly patients have a distinctive distribution and frequency of organ involvement compared with younger and middle-aged patients (age < 60 yr).[4] Elderly patients are less likely to have upper respiratory tract symptoms but are more likely to have renal insufficiency (64% versus 35%) and pulmonary infiltrates (73% versus 54%) at presentation. In addition, the incidence of neurologic involvement in the elderly is approximately 4 times greater than in younger patients (27% versus 6%, respectively).[4]

Diagnosis

The differential diagnosis of Wegener's granulomatosis is broad and includes malignancy, pulmonary infections, and other small-vessel vasculitides presenting with pulmonary-renal syndromes, such as Churg-Strauss

syndrome, microscopic polyangiitis, and Goodpasture's disease. It is distinguished from these conditions through a combination of clinical features, serum c-ANCA assay, and tissue biopsy. The American College of Rheumatology criteria for diagnosing Wegener's granulomatosis include nasal or oral inflammation, an abnormal chest radiograph, an abnormal urinary sediment, and granulomas on biopsy. Demonstration of 2 or more of these criteria is 88% sensitive and 92% specific in distinguishing Wegener's granulomatosis from other forms of vasculitis.[3] However, these clinical criteria were created to differentiate among categories of systemic vasculitis, particularly for research studies, and were not intended for use in routine clinical practice given the low prevalence of Wegener's granulomatosis in the general population.

Newer diagnostic modalities include serologic tests such as c-ANCA (also known as anti-proteinase 3 antibody). This antibody is produced by T cells in response to neutrophil cytoplasmic antigen. A meta-analysis showed that the sensitivity and specificity of this test are approximately 66% and 98%, respectively, although utility is dependent on the clinical context and pretest probability.[14] Although most patients with Wegener's granulomatosis are c-ANCA positive, a negative test does not rule out the disease, as c-ANCA may not be present in more limited or inactive forms of the disease.[14]

Despite consensus clinical criteria and advances in serologic testing, the diagnosis of Wegener's granulomatosis should be made with tissue biopsy, especially when considering the potential toxicity of treatments. Histology will show necrosis, caseating granulomas, and vasculitis.[1] If there is clinical evidence of inflammation, biopsy of the lung or kidneys is most helpful in making the diagnosis, whereas biopsy of the upper respiratory tract is diagnostic in a minority of specimens.[2]

Treatment

Treatment of Wegener's granulomatosis includes 3 phases: induction of remission, maintenance, and treatment of relapse. Induction treatment is usually 1.5 to 2 mg/kg/day of oral cyclophosphamide and 1 mg/kg/day of prednisone for 3 to 6 months or until remission occurs. Follow-up imaging may be helpful in assessing treatment response. Remission is often followed by maintenance therapy with methotrexate, which is usually tapered after 12 months depending on the patient's clinical course. In patients with glomerulonephritis and known renal dysfunction, azathioprine is usually substituted for methotrexate.[15] Relapse is usually treated with cyclophosphamide and steroids.[15] Response to treatment is often followed by clinical assessment of inflammation and organ involvement based on scoring systems such as the Birmingham Vasculitis Activity Score.[15] Ninety percent of untreated patients will die within 2 years, but with treatment approximately 75% achieve complete remission and 80% are alive at 8 years.[1] Even with treatment, however, there is significant morbidity from chronic renal insufficiency, hearing loss, nasal deformities, and medication toxicities.

CONCLUSION

Wegener's granulomatosis is a rare disease that typically presents with a constellation of pulmonary, upper respiratory tract, and renal abnormalities, although other organ systems, particularly the central nervous system, may be affected. Although it typically presents in the sixth decade of life, onset may occur in the elderly as well. Wegener's granulomatosis–related mortality rates are often higher in this population, so careful consideration of this diagnosis should be made when the appropriate clinical findings are present. **HP**

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