JAMA Diagnostic Test Interpretation

Clinical Significance of a Positive Antineutrophil Cytoplasmic Antibody (ANCA) Test

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A 67-year-old woman with a history of idiopathic pulmonary fibrosis was admitted to the hospital for new onset of cough with blood-streaked sputum, which followed several months of weight loss, anorexia, nausea, vomiting, and abdominal pain. She reported no occurrence of fever, rashes, oral ulcers, Raynaud phenomenon, chest pain, dyspnea on exertion, paresthesia, or joint concerns. On examination, her temperature was 36.9° C, blood pressure was 134/81 mm Hg, pulse was 110/min, and oxygen saturation level was 91% breathing room air. She appeared dyspneic, had no heart murmur, and had diffuse crackles especially at the lung bases and 2+ pitting edema of the legs without jugular venous distension. No rashes, synovitis, or focal neurological deficits were found. Laboratory evaluation showed a hemoglobin level of 7.5 g/dL from a baseline of 10.4 g/dL (reference range, 11.6-15.2 g/dL); a creatinine level of 6.5 mg/dL from a baseline of 1.2 mg/dL (reference range, 0.6-1.2; SI conversion to μmol/L, multiply by 88.4); and normal white blood cell count, platelets, and lactate. Urinalysis showed the presence of red blood cells but no protein. Chest x-ray showed new bilateral opacities. Computed tomographic imaging of the chest showed moderate stable fibrosis with multiple ground-glass opacities in the left lung. Based on these results, additional studies were performed (**Table**).

HOW DO YOU INTERPRET THESE TEST RESULTS?

A. The patient has pneumonia with sepsis.

B. The patient has systemic lupus erythematosus.

C. The patient has microscopic polyangiitis.

D. The patient has antiglomerular basement membrane disease (Goodpasture syndrome).

Table. Clinical Laboratory Test Results

Laboratory Test	Prior to Hospitalization	Day of Admission	Reference Range
Antinuclear antibody, titer	1:80	1:40	<1:40
Rheumatoid factor, IU/mL	<10	98	<25
Antiglomerular basement membrane, AU/mL	Not tested	1	0-19
Cytoplasmic ANCA, titer	<1:20	<1:20	<1:20
Perinuclear ANCA, titer	1:160	1:320	<1:20
Myeloperoxidase antibody, U	63	92	<21
Proteinase 3 antibody, U	<21	<21	<21
Erythrocyte sedimentation rate (Westergren method), mm/h	Not tested	>100	0-22
C-reactive protein, mg/L	7	92	<8
C3 complement, μg/mL	Not tested	1190	760-1650
C4 complement, μg/mL	Not tested	310	140-460

Abbreviation: ANCA, antineutrophil cytoplasmic antibody.

SI conversion factor: To convert C-reactive protein to nmol/L, multiply by 9.524.

Answer

C. The patient has microscopic polyangiitis.

Test Characteristics

Antineutrophil cytoplasmic antibodies (ANCAs) are directed toward the cytoplasmic components of neutrophils and monocytes.[1] ANCA-associated vasculitis, characterized by presence of ANCAs, includes granulomatosis with polyangiitis (formerly Wegener granulomatosis syndrome), microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss granuloma syndrome).[2] Although ANCAs to several antigenic targets have been identified, ANCAs to proteinase 3 and myeloperoxidase have been associated with ANCA-associated vasculitis.[3,4]

ANCA testing is facilitated using indirect immunofluorescence (IIF) or antigen-specific enzyme-linked immunosorbent assay (ELISA).[3] Results of IIF are reported as a titer and by staining pattern as perinuclear ANCA (associated with microscopic polyangiitis), cytoplasmic ANCA (associated with granulomatosis with polyangiitis), or atypical ANCA (not associated with ANCA-associated vasculitis). ELISA testing quantitatively evaluates presence of antibodies to myeloperoxidase or proteinase 3.

ANCA testing by IIF has a higher sensitivity compared with ELISA, which has higher specificity for the diagnosis of ANCA-associated vasculitis. In a cross-sectional study, the overall sensitivity for IIF testing alone was 67% and specificity was 93%; for ELISA alone, overall sensitivity was 55% and specificity was 96%; and for combined

IIF and ELISA, overall sensitivity was 52% and specificity was 99% for ANCA-associated vasculitis.[5] The low sensitivity of ANCA may be related to the cross-sectional nature of this study with inclusion of treated patients with ANCA-associated vasculitis as well as patients with inactive disease (which can turn ANCA negative).[5] When evaluating large cohorts of patients with ANCA-associated vasculitis, ANCA positivity occurred in patients with granulomatosis with polyangiitis (>90%), patients with microscopic polyangiitis (>72%), and patients with eosinophilic granulomatosis with polyangiitis (≈31%), which suggests good sensitivity of ANCA for granulomatosis with polyangiitis and microscopic polyangiitis but not for eosinophilic granulomatosis with polyangiitis.[6-8]

Consensus guidelines recommend using IIF as a screening test followed by confirmation of a positive result using ELISA.[9] An ELISA confirmation is important because positive perinuclear ANCA and cytoplasmic ANCA (typically without antigen specificity to myeloperoxidase or proteinase 3) have been reported in other autoimmune diseases (especially perinuclear ANCA in inflammatory bowel disease), infections (tuberculosis, endocarditis), and cancer.[3,5] Cocaine-induced vasculitic syndromes have also been described with antigen specificity of ANCA to human neutrophil elastase.[3] The majority of patients with granulomatosis with polyangiitis have proteinase 3–ANCA and those with microscopic polyangiitis have myeloperoxidase–ANCA.[3]

The prevalence of ANCA-associated vasculitis is low, approximately 46 to 184 per million people.[10] The estimated likelihood ratio for ANCA-associated vasculitis with a positive IIF and ELISA is 82.00 and with a negative test is 0.48.[5] Given the low prevalence of ANCA-associated vasculitis, testing in clinical situations that are not suggestive of this condition will result in false-positive results. The approximate Medicare midpoint reimbursement for an ANCA screening using IIF is $28 and using ELISA is $21.23.

Application of Test Results to This Patient

The patient's presentation is concerning for a pulmonary-renal syndrome (alveolar hemorrhage and glomerulonephritis). Differential diagnosis includes systemic lupus erythematosus, antiglomerular basement membrane disease, and ANCA-associated vasculitis; therefore, testing for these conditions was pursued. Normal complement levels with negative immunofluorescence using renal biopsy make systemic lupus erythematosus unlikely. A negative test result for antiglomerular basement membrane disease excludes it as a diagnosis. Although sepsis can cause multiorgan involvement, the normal lactate level, lack of leukocytosis, and overall clinical picture were not suggestive of sepsis. The presence of perinuclear ANCA and myeloperoxidase positivity is suggestive of ANCA-associated vasculitis.

What Are Alternative Diagnostic Testing Approaches?

Histopathologic confirmation remains the criterion standard for diagnosis of ANCA-associated vasculitis. Additional diagnostic evaluation should include bronchoscopy with bronchoalveolar lavage to rule out infection and confirm alveolar hemorrhage. To definitively evaluate the cause of acute kidney failure, a biopsy should be performed. If the clinical presentation is consistent with ANCA-associated vasculitis and biopsy is not possible, ANCA positivity can be used as a surrogate marker for the diagnosis.

Patient Outcome

The patient underwent bronchoscopy, which confirmed alveolar hemorrhage without infection, and the patient also underwent a kidney biopsy, which showed pauci-immune crescentic glomerulonephritis. She received treatment with pulse-dose methylprednisolone, plasmapheresis, and rituximab. The patient's renal function improved and she continues monotherapy with rituximab.

Clinical Bottom Line

- Antineutrophil cytoplasmic antibodies (ANCA) testing is useful for the diagnosis of ANCA-associated vasculitis in patients with its symptoms and should be performed in patients with pulmonary-renal syndrome.
- False-positive ANCA can be seen in other autoimmune diseases, cancer, and infections.[8]
- Some patients with ANCA-associated vasculitis, especially those with eosinophilic granulomatosis with polyangiitis (≤70%), may have negative ANCA test results.
- Whenever possible, histologic confirmation of vasculitis should be pursued.

ARTICLE INFORMATION

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Section Editor: Mary McGrae McDermott, MD, Senior Editor.

Conflict of Interest Disclosures: Both authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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