CASE REPORTS
MPO-C-ANCA Renal-Limited Vasculitis: A Puzzling Phenomenon

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ABSTRACT

Anti-neutrophil cytoplasmic antibodies (ANCA) are autoantibodies directed against antigens in the cytoplasm of neutrophils and can be used diagnostically to identify different types of systemic vasculitides such as microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), and renal-limited vasculitis (RLV). Two methods are used concomitantly to detect ANCA: indirect immunofluorescence (IIF) and enzyme-linked immunosorbent assay (ELISA). IIF yields either a cytoplasmic (C-ANCA) or peri-nuclear (P-ANCA) pattern with a corresponding antigen identified on ELISA; either proteinase-3 (PR-3) or myeloperoxidase (MPO), respectively. Here, we present a 76 year-old female with a presenting complaint of nausea and emesis, ultimately found to have renal-limited MPO-C-ANCA vasculitis, an unusual IIF and ELISA pairing. The patient presented with lower extremity edema and without nasopharyngeal or pulmonary involvement, complicating the clinical picture for an ANCA-vasculitis. Given other published reports and studies pertaining to this unique finding of C-ANCA with anti-MPO antibodies, we emphasize the importance of using caution while interpreting ANCA results. The diagnosis of vasculitis should be comprehensive and should not solely rely on IIF or physical exam findings.

INTRODUCTION

Anti-neutrophil cytoplasmic antibodies (ANCA) are autoantibodies directed against antigens in the cytoplasm of neutrophils and are important serologic markers for certain autoimmune disorders, particularly small-vessel systemic vasculitis. Two methods are used to detect ANCA: indirect immunofluorescence (IIF) and enzyme-linked immunosorbent assay (ELISA). The IIF staining method uses alcohol-fixed buffy coat leukocytes to detect either cytoplasmic (C-ANCA) or perinuclear (P-ANCA) antibodies. The ELISA technique uses purified specific antigens to detect antibodies to either proteinase-3 (PR-3) or myeloperoxidase (MPO) antigens. The IIF pattern and ELISA result commonly correspond with each other; C-ANCA and P-ANCA patterns on IIF will typically yield antibodies to PR-3 and MPO on ELISA, respectively. Based on serologic ANCA pattern, the patient’s clinical presentation, and pathologic features, ANCA vasculitis is subdivided into four main diseases: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), and renal-limited vasculitis (RLV). Each type of vasculitis corresponds to a characteristic ANCA pattern (Table 1). GPA is typically positive for C-ANCA with specificity.

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for PR-3, whereas MPA and EGPA are usually positive for P-ANCA with specificity for MPO. Renal-limited vasculitis has a P-ANCA pattern on IIF with anti-MPO specificity on ELISA in eighty percent of cases.\(^1\) C-ANCA with anti-MPO specificity has rarely been reported, especially in renal-limited cases.\(^2\) Here, we present a patient with renal-limited vasculitis that revealed a C-ANCA pattern with specificity for anti-MPO.

**CASE REPORT**

A 76 year-old African American female with no reported past medical history presented to the emergency department with a chief complaint of bilateral lower extremity edema, abdominal pain, and a one-week duration of intractable nausea and emesis since returning from vacation in North Carolina and Georgia. She saw her primary care physician earlier in the week and was diagnosed with viral gastroenteritis and given ondansetron for her nausea which provided no relief. In the emergency department, she had an elevated blood pressure of 190/90 mmHg. Pertinent physical exam findings included 2+ pitting edema of the bilateral lower extremities and diffuse abdominal tenderness to palpation. Computed tomography imaging of the chest, abdomen, and pelvis was normal. Labs revealed a hyponatremia (Na\(^+\): 128 mEq/L) as well as a normocytic anemia (hemoglobin: 9.3 g/dL, MCV: 85.5 fL). Her creatinine was elevated at 5.06 mmol/L from a baseline of 1.18 mmol/L. Urine studies revealed trace leukocyte esterase, 2+ protein, and 2+ blood. No bacteria or casts were present. Initially upon admission, the patient’s acute kidney injury was thought to be prerenal in etiology given her persistent nausea, vomiting, resultant dehydration, and a FENa of .8%. Despite receiving 5 liters of intravenous fluids, the patient’s creatinine continued to worsen to 8.2 mmol/L. Of note, the patient remained persistently hypertensive without an underlying diagnosis of hypertension, and was subsequently started on labetalol 100 mg twice daily two days after admission. Her blood pressure immediately improved to 110/66 mmHg. In the setting of a persistent decline in

<table>
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<th>Disease</th>
<th>Typical IIF Pattern</th>
<th>Typical ELISA Pattern</th>
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<tr>
<td>Granulomatosis with Polyangiitis (GPA)</td>
<td>C-ANCA</td>
<td>PR-3</td>
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<td>Microscopic Polyangiitis (MPA)</td>
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<td>Eosinophilic Granulomatosis with Polyangiitis (EGPA)</td>
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<td>Renal-Limited Vasculitis (RLV)(^b)</td>
<td>P-ANCA</td>
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\(^a\)Adapted from *Renal histology in ANCA-associated vasculitis: Differences between diagnostic and serologic subgroups.*\(^1\)

\(^b\)Pattern seen in 80% of renal-limited cases\(^1\)

C-ANCA: Cytoplasmic Anti-neutrophil Cytoplasmic Antibodies
P-ANCA: Perinuclear Anti-neutrophil Cytoplasmic Antibodies
PR-3: Proteinase-3
MPO: Myeloperoxidase

Table 1. Typical IIF and ELISA Results in Small Vessel Vasculitides\(^a\)
renal function with a BUN/Cr ratio of 11.26, the patient was ultimately started on hemodialysis by hospital day number five. Soon after hemodialysis, her nausea and abdominal tenderness slightly improved. Intrarenal etiologies were appropriately considered and an ANCA panel was ordered for further workup. Serologic ANCA results were positive for C-ANCA (1:640) on IIF and anti-myeloperoxidase antibodies (>100 μ/mL) on ELISA. P-ANCA patterns, atypical P-ANCA patterns, and anti-proteinase-3 antibodies were not present. The erythrocyte sedimentation rate (121 mm/hr) and a C-reactive protein (33.5 mg/L) were also elevated. Anti-nuclear antibodies and anti-glomerular basement membrane antibodies were not present and complement levels were within normal limits. A renal biopsy was obtained and revealed a pauciimmune necrotizing glomerulonephritis with crescent formation, tubulointerstitial nephritis, and confluent cortical coagulative necrosis, typical pathological findings of an ANCA vasculitis (Figure 1). Treatment was initiated immediately with IV methylprednisolone 60 mg daily, plasmapheresis, and IV cyclophosphamide. Two days after initiation of treatment, the patient reported cessation of nausea, vomiting, and fatigue. She regained her appetite as well.

The patient’s symptoms were well controlled with this treatment regimen in addition to hemodialysis three times weekly. She was ultimately discharged home with outpatient dialysis and oral prednisone 60 mg daily for one month. Upon discharge, the patient’s renal function began to improve as her new BUN/Cr ratio was calculated to be 7.25. The lower extremity edema had also resolved. Her anemia in addition to her hypertension remained stable yet persistent. She was discharged on her inpatient blood pressure regimen. The patient’s total length of stay was twenty seven days and she received a total of seven plasmapheresis treatments.

Shortly after discharge, the patient moved to North Carolina to be with her family. Approximately six months later during a follow-up phone call, the patient reported remission of her vasculitis and discontinuation of the medication regimen, including the labetalol for hypertension. However, the patient still requires dialysis due to the residual renal damage inflicted by the vasculitis.

**DISCUSSION**

Our patient’s clinical and serological picture presented a challenge in identifying the final diagnosis. Typically, ANCA serology is paired with specific organ involvement and can assist in accurately identifying the diagnosis. For example, pulmonary involvement is typical in both GPA and MPA, but nasopharyngeal involvement is usually limited to GPA. In our case however, the diagnosis was not as
straightforward as the patient’s vasculitis was renal-limited and the IIF and ELISA results did not correspond with each other as classically described.

On presentation, the patient presented with nausea, emesis, lower extremity edema, hypertension, and notable anemia. She had no pulmonary or nasopharyngeal symptoms. In most instances of ANCA-related vasculitis, nausea and emesis dominate the clinical picture. Physical exam findings can include elevated blood pressure and peripheral edema in up to ten percent of cases, however, up to fifteen percent of patients can be completely asymptomatic. Complete blood count may show a notable anemia, leukocytosis, an elevated ESR and CRP, and/or an elevated creatinine. Urinalysis can show modest proteinuria (1-4 g/dL), microscopic hematuria, and casts. Our patient showed many typical physical exam findings and laboratory characteristics, however, the absence of upper respiratory symptoms typically seen in specific vasculitides complicated the clinical picture for our team.

Furthermore, the discrepancy between the ANCA IIF pattern and ELISA results later on in the clinical course presented an additional challenge. The MPO-C-ANCA type is very unusual and has rarely been reported except in cases of GPA and EGPA. Segelmark et al. have previously reported that antibodies to certain epitopes on MPO can produce a C-ANCA pattern. This phenomenon was proposed by Segelmark et al. to be due to the C-ANCA and P-ANCA epitopes existing simultaneously on the same MPO molecule and that two immunofluorescence patterns occur due to different availabilities of the epitopes in the microenvironment where MPO is present. Likely, this is the reason for our patient’s MPO-C-ANCA serology. MPO-C-ANCA can also be evident in patients with systemic lupus erythematosus (SLE) because the DNA contained within the antigen-binding site of anti-DNA antibodies could bind to the cationic MPO used as substrate antigen in immunoassays. However, this is unlikely in our patient as she had a negative ANA panel. Anti-nuclear antibody (ANA) panels are approximately 99% sensitive in detecting SLE. If negative, it is highly unlikely the patient has SLE.

To conclude, ANCA-related vasculitis can have a complex clinical and laboratory picture. Therefore, we recommend using caution when interpreting laboratory ANCA panels utilizing both IIF and ELISA. As of 2017, the international consensus statement on testing and reporting antineutrophil cytoplasmic antibodies (ANCA) recommends high-quality immunoassays for PR3-ANCAs and MPO-ANCAs as the preferred method for the diagnostic evaluation of patients without the need for IIF. Hopefully, these new recommendations will further improve diagnosis of systemic vasculitides and eliminate IIF and ELISA discrepancies. Our case of MPO-C-ANCA renal-limited vasculitis represents a unique phenomenon that should remind clinicians to be cautious and thorough when interpreting and reporting ANCA results. The diagnosis of an ANCA-related vasculitis should be comprehensive and should not solely rely on IIF results or physical exam findings.

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REFERENCES


