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Renal limited ANCA-positive vasculitis: a rare manifestation of a rare disease

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Abstract

Pauci-immune crescentic glomerulonephritis is the most common variant of rapidly progressive glomerulonephritis, accounting for approximately 80% of total cases. Most of the cases are associated with the presence of anti-neutrophil cytoplasmic antibody (ANCA) and are usually referred to as ANCA-associated vasculitis. A 68-year-old male with no previous renal history presented with complaints of shortness of breath, cough, and bilateral leg swelling for 2 weeks. Initial workup was significant for creatinine elevated at 2.9 mg/dL, blood urea nitrogen at 65 mg/dL, and glomerular filtration rate of 27 mL/min. Further workup was unremarkable for any significant abnormality. Subsequently patient's kidney function worsened, and temporary hemodialysis was started. Kidney biopsy was performed, which later came back significant for necrotizing arteritis, multifocal, with focal necrotizing and crescentic glomerulonephritis, pauci-immune type. High-dose corticosteroids were administered, and good clinical response was noticed. This is a very rare case of renal limited pauci-immune crescentic glomerulonephritis with annual incidence of 7 to 10 cases per million every year in the United States. The absence of involvement of other organs makes our case even rarer. Mortality is as high as 90% in untreated patients and aggressive therapy with glucocorticoids and cyclophosphamide or rituximab are the mainstay of treatment. The presence of significant renal impairment in the absence of other organs involvement in our patient makes it a very unique presentation of ANCA-positive vasculitis.

Keywords

renal limited vasculitis, pauci-immune, anti-neutrophil cytoplasmic antibody

Introduction

Pauci-immune crescentic glomerulonephritis (PICGN) is the most common type of primary rapidly progressive glomerulonephritis (RPGN). It is usually associated with presence of circulating anti-neutrophil cytoplasmic antibody (ANCA) and are known as ANCA-associated vasculitis. PICGN is often part of a systemic disease with involvement of multiple organs including skin, ear, nose, kidneys, and lungs. Disease limited to kidneys is called as renal limited vasculitis. In this article, we present a rare case of biopsy-proven renal limited vasculitis; pauci-immune type in a 68-year-old male who presented with acute renal failure requiring dialysis.

Case History

A 68-year-old Caucasian male presented with complaints of shortness of breath, cough, and leg swelling for past 2 weeks. His past medical history included ventricular tachycardia and a recently treated community-acquired pneumonia. He denied any orthopnea, paroxysmal nocturnal dyspnea, history of congestive heart failure, recent sick contacts, tick bites, or travels. Vital signs included blood pressure of 130/78 mm of Hg, heart rate of 78 beats per minute, respiratory rate of 16 breaths per minute, and oxygen saturation of 96%. On physical examination, he was alert, awake, and oriented to time, place, and person. Complete physical examination was unremarkable other than bilateral inspiratory crackles and 2+ pitting edema up to the level of mid shin. Initial laboratory workup included creatinine of 2.9 mg/dL, blood urea nitrogen of 65 mg/dL, glomerular filtration rate of 27 mL/min, and marked proteinuria. Complete blood count, electrolytes, magnesium, and phosphorus were within normal limits. Renal ultrasound did not show any hydronephrosis or obstructive

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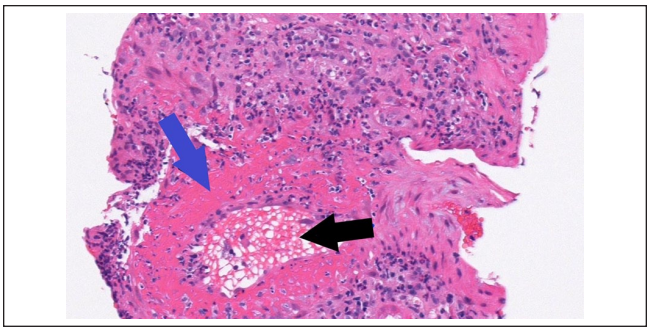

Figure 1. Photomicrograph of necrotizing crescentic glomerulonephritis showing glomerulus with crescentic glomerulonephritis (blue arrow) and compression of capillary loops (black arrow).

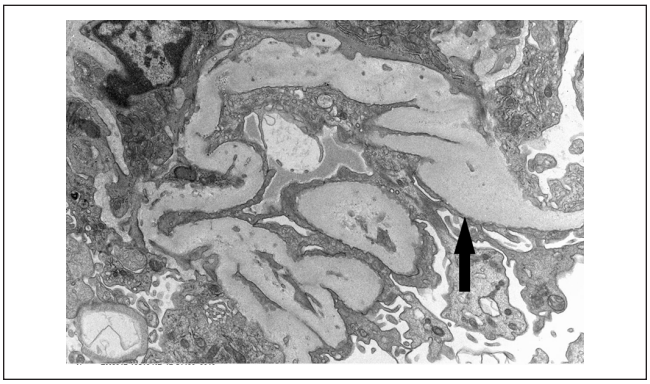

Figure 2. Photomicrograph of kidney biopsy on electron microscopy showing markedly thickened basement membrane (black arrow).

uropathy. In the successive days his creatinine went up to 4.5 mg/dL, potassium 6.5 mg/dL, phosphorus 4.8 mg/dL, and became oliguric. Right internal jugular hemodialysis catheter was placed, and dialysis was initiated. Patient was scheduled for kidney biopsy and autoimmune workup was obtained. C-ANCA came back remarkably elevated at 1:1640 and myeloperoxidase antibody at >8. Antinuclear antibody, proteinase 3 antibody, anti-glomerular basement membrane antibodies, complement levels, β-2 microglobin, serum protein electrophoresis, urine protein electrophoresis, hepatitis panel, and lyme titers were unremarkable. Kidney biopsy was performed, which came back significant for necrotizing arteritis, multifocal, with focal necrotizing and crescentic glomerulonephritis, pauci-immune type (Figures 1 and 2). More than 50% of glomeruli were involved. Induction therapy with high-dose glucocorticoids plus either rituximab or cyclophosphamide was discussed with him. He agreed to high-dose glucocorticoids only and was adamant to be transferred to a bigger tertiary care center for another opinion. Therefore, pulse dose methylprednisolone 1 g per day was initiated without rituximab or cyclophosphamide and transfer was arranged. Significant improvement in his kidney function was observed in the next few days before his transfer.

Discussion

RPGN is a rare clinical syndrome manifested by progressive loss of renal function and features of glomerular disease on urinalysis including proteinuria, hematuria, and erythrocytes casts. It is most commonly characterized by extensive crescent formation on histopathology.[1] Primary RPGN is divided into PICGN, anti-glomerular basement membrane glomerulonephritis, and immune complex glomerulonephritis on immunopathology grounds. PICGN is the most common variant of RPGN, accounting for almost 80% of cases. The estimated annual incidence is approximately 7 to 10 cases per million people per year in the United States.[2] In approximately 85% to 90% of patients with PICGN, systemic ANCA is found giving them another name of ANCA-associated vasculitis. Moreover, myeloperoxidase antibodies are elevated in 80%, whereas proteinase 3 antibody is elevated in 20% of patients.[3,4] Normal reference ranges might vary depending on the laboratory but myeloperoxidase antibody levels 0 to 9 units/mL and proteinase 3 antibody 0 to 3.5 units/mL are considered normal by our laboratory. PICGN is more common in White population with equal predilection in both males and females.[5,6]

Several diagnostic criteria have been proposed to standardize the classification of PICGN including the American College of Rheumatology criteria, Chapel Hill Consensus Conference criteria, and European Medicines Agency algorithm.[7] PICGN is usually part of systemic vasculitis involving different organs like ear, nose, throat, skin, and lungs. In certain number of cases disease is limited to kidney and are often referred as renal limited vasculitis.[8] ANCA antibodies are implicated in the pathogenesis of PICGN. ANCA are specific for proteins in the cytoplasm of neutrophils and monocytes including myeloperoxidase and proteinase 3 initiating an immune response resulting in necrotizing crescentic glomerulonephritis.[9]

Common clinical features would include fatigue, fever, weight loss, arthralgias, rhinosinusitis, cough and dyspnea, urinary abnormalities (an active urine sediment) with or without renal insufficiency, purpura, and neurologic dysfunction. Patients with renal limited vasculitis usually present with hematuria, proteinuria, and acute renal insufficiency requiring dialysis in some cases as seen in our patient. A positive ANCA test strongly suggests the diagnosis of vasculitis, but false-positive and false-negative results may be seen. Therefore, in all suspected cases with positive ANCA tissue biopsy should be performed to confirm the diagnosis. In renal limited vasculitis kidney biopsy shows diffuse necrotizing and crescentic glomerulonephritis usually pauci-immune type.[10] ANCA-positive vasculitis usually present with multiple organs involvement more prominently the

upper respiratory system. The presence of significant renal impairment with absence of involvement of other organs in our patient makes it a very unique presentation of ANCA-positive vasculitis.

Treatment of ANCA-associated vasculitis consists of 2 main components including induction of remission and maintenance of remission, both with immunosuppressive therapy. High-dose corticosteroids are usually combined with cyclophosphamide or rituximab to achieve induction of remission.[11,12] According to one study, initial treatment with corticosteroids and cyclophosphamide has been found to decrease mortality significantly.[13] In patients with nonsevere non-organ-threatening disease, methotrexate in combination with glucocorticoids might be used as an alternative.[14] Historically plasma exchange in general has demonstrated no overall benefit in most cases of ANCA-associated vasculitis with some exceptions including severe active renal disease and concurrent anti-glomerular basement membrane autoantibody disease.[15] More recent studies like PEXIVAS trial (plasma exchange and glucocorticoids in severe ANCA-associated vasculitis) and MEPEX trial (methylprednisolone vs plasma exchange) also failed to demonstrate improvement in mortality with plasma exchange therapy.[16,17] Several factors like severity of the disease, presence of life-threatening organ damage, and comorbid conditions should be considered before initiation of therapy.

The major causes of mortality in patients with ANCA-associated vasculitis are complications from underlying renal failure, cardiovascular complications, and adverse effects of aggressive immunosuppression therapy, for example, infections. Mortality could be as high as 90% in untreated patients but has significantly declined since aggressive immunotherapy has been added to the treatment regimen.[18] Several risk factors like worsening kidney function at the time of presentation, presence of pulmonary hemorrhages, and life-threatening organ damage are associated with worse outcome. Nonfatal adverse outcomes including risk of malignancy, glucocorticoid toxicity, and progressive organ failure are also reported.

Conclusion

Renal limited ANCA-associated vasculitis is a rare rheumatologic disease of grave significance. Patients usually present with acute renal insufficiency with or without requiring hemodialysis. ANCA with myeloperoxidase or proteinase 3 antibodies are elevated in most cases, but kidney biopsy is required to establish diagnosis. Aggressive immunosuppressive therapy with glucocorticoids in combination with cyclophosphamide or rituximab are the mainstay of treatment. Mortality in untreated cases approaches 90%. Treatment toxicity, risk of malignancy, and fatal infections are the greatest challenges and would be a great area of study for future studies. Early diagnosis and prompt treatment with induction therapy is critical as untreated renal limited vasculitis can progress to widespread systemic involvement and can be fatal.

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Verbal informed consent was obtained from the patient for their anonymized information to be published in this article.

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