Journal of Investigative Medicine High Impact Case Reports
Volume 9: 1–5

DOI: 10.1177/23247096211013193
journals.sagepub.com/home/hic
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A Rare Case of Double Antibody-Positive Rapidly Progressive Glomerulonephritis: A Therapeutic Challenge

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Abstract

Crescentic glomerulonephritis, also known as rapidly progressive glomerulonephritis, is a syndrome characterized by progressive and rapid deterioration of renal function over the course of weeks to months. Oliguria, hematuria, azotemia, and hypertension are characteristic features of this condition. Crescentic glomerulonephritis is further classified according to the staining pattern on immunofluorescence. In rare instances, a mixed pattern of injury is encountered as in the case of double antibody-positive rapidly progressive glomerulonephritis (RPGN). This case illustrates the challenge in treatment of double antibody-positive RPGN in an elderly female with no previous renal disease. The patient was found to be positive for anti-GBM antibody and MPO-ANCA. Treatment was initially targeted against MPO-ANCA as the biopsy was most consistent with this process; however, the patient failed to respond to treatment and was subsequently transitioned to oral cyclophosphamide directed against anti-GBM disease. In cases of doubly antibody-positive RPGN with anti-GBM disease and ANCA-associated vasculitis, initial treatment should focus on inducing remission of anti-GBM disease as double antibody-positive disease often presents with the aggressive morbidity and mortality seen in anti-GBM disease, and the chronic risk of relapse seen in ANCA-mediated vasculitis.

Keywords

crescentic glomerulonephritis, anti-glomerular basement membrane disease, ANCA-associated vasculitis

Introduction

Crescentic glomerulonephritis (GN) is a syndrome associated with glomerular injury characterized by crescent formation that can be visualized on light microscopy. It is also referred to as rapidly progressive glomerulonephritis (RPGN) due to the rapid deterioration in renal function over the course of weeks to months, which can be fatal if left untreated. The syndrome is characterized by progressive loss of renal function, and signs of nephritic syndrome including azotemia, hematuria, oliguria, and hypertension.[1-3] Crescentic GN can be classified into 3 types. Type 1, anti-glomerular basement membrane (anti-GBM) antibody-mediated disease characterized by linear deposits of immunoglobulin G (IgG) in the basement membrane. Type 2, immune complex-mediated disease, which can be seen in multiple disorders including postinfectious glomerulonephritis, lupus nephritis, IgA nephropathy, and others, whereby granular deposits of immunoglobulins and complement proteins deposit in the glomerulus. Type 3, referred to as pauci-immune due to lack of accentuation on immunofluorescent (IF) staining, which is often seen in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis.[2,4]

In rare instances, mixed patterns of injury can be seen as a consequence of 2 separate processes: anti-GBM disease and ANCA-associated vasculitis, most commonly anti-myeloperoxidase (MPO) ANCA. It is estimated up to one third of patients with anti-GBM antibodies have ANCA antibodies as well.[3] This so-called double antibody-positive RPGN is associated with poor outcomes. Such cases show heterogeneous phenotypic manifestations. Results from a large multicenter study by McAdoo et al[5] revealed double

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Received December 9, 2020. Revised March 25, 2021. Accepted April 3, 2021.

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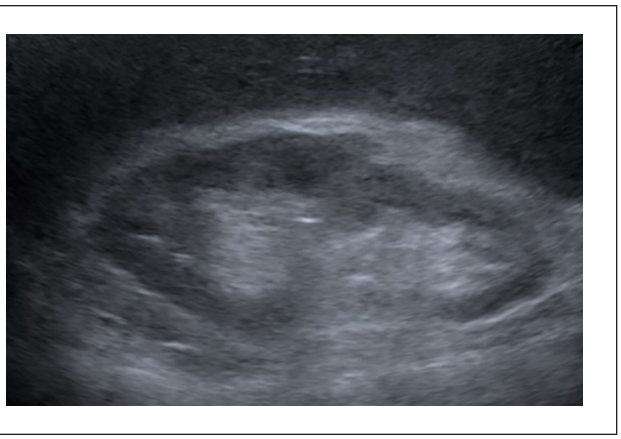

Figure 1. Ultrasound of right kidney, which measures 10.4 × 4.3 × 4.4 cm. There is minor renal cortical thinning asymmetrically involving the mid-pole cortex. The cortex is mildly hyperechoic. No sonographic evidence of calculus or ureteral dilatation.

antibody-positive RPGN cases often follow the aggressive presentation of anti-GBM disease with higher morbidity and mortality, and the chronic risk of relapse seen in ANCA-associated vasculitis.

Treatment approaches for crescentic GN are targeted to the underlying pathophysiology. A 3-pronged treatment approach consisting of plasma exchange (PLEX), corticosteroids, and immunosuppression is favored for anti-GBM disease. Cyclophosphamide is considered to be first-line treatment; however, there has been reported success with rituximab maintenance therapy following pulse cyclophosphamide induction therapy for anti-GBM disease.[6] Rituximab in combination with corticosteroids is the treatment of choice for inducing remission in patients with ANCA-associated vasculitis due to a favorable side effect profile.[4] In 2010, Jones et al[7] compared rituximab plus cyclophosphamide to conventional cyclophosphamide followed by azathioprine for induction therapy for ANCA-associated renal vasculitis. Both groups received glucocorticoids. The results of the rituximab versus cyclophosphamide in ANCA-associated renal vasculitis (RITUXVAS) trial demonstrated rituximab was not superior to cyclophosphamide.[7] A similar study by Stone et al[8] evaluated rituximab plus placebo cyclophosphamide compared with placebo rituximab plus cyclophosphamide. Both groups received the same glucocorticoid regimen. The results showed rituximab was noninferior to cyclophosphamide for achieving remission in ANCA-associated vasculitis.[8] Importantly, both of these trials showed no difference in adverse events between the 2 groups.

In this article, we present a case of double antibody-positive RPGN in a patient who failed initial induction therapy targeting ANCA-associated vasculitis, and later responded to oral cyclophosphamide targeting anti-GBM disease.

Case Presentation

A 76-year-old female was referred to the hospital by her primary care physician for evaluation of abnormal laboratory findings. The patient was found to have worsening renal function on routine laboratory tests with a creatine of 3.5 g/dL and her baseline around 1.2 g/dL. She reported vague symptoms over the past 2 months including malaise, fatigue, and some upper respiratory congestion. She was recently diagnosed with Eustachian tube dysfunction. She took approximately six 200 mg ibuprofen tablets during this time but denied a history of chronic nonsteroidal anti-inflammatory use. She denied any change in urination including increased frequency, hesitation, burning on urination, or foamy urine or hematuria. She did admit to chronic, intermittent diarrhea, which she attributed to irritable bowel syndrome. She denied any skin rashes or arthralgias.

The patient's medical history included hypertension, hypothyroidism, and hyperlipidemia. Her medications included losartan-hydrochlorothiazide 50 to 12.5 mg daily, levothyroxine 125 μg daily, and simvastatin 40 mg nightly. Her family history was remarkable for coronary artery disease in her mother. There was no history of kidney disease in the family. She was a former tobacco user, and denied alcohol or illicit drug use.

On physical examination, the patient was cooperative and in no acute distress. Her blood pressure was elevated at 171/94 mm Hg. Cardiopulmonary examination was normal. There were positive bowel sounds and her abdomen was not distended or tender to palpation. There was no costovertebral angle or suprapubic tenderness. The rest of the examination was unremarkable. A complete blood count was remarkable for hemoglobin 9.8 g/dL with a mean corpuscular volume of 88.4 fL. A basic metabolic panel was remarkable for blood urea nitrogen 68 mg/dL and creatinine 4.26 mg/dL. A urinalysis revealed 100 mg/dL protein, large blood, 10 to 20 white blood cells/high-power field, and 50 to 75 red blood cells/high-power field without casts or bacteria. A spot urine protein-creatinine ratio returned 1157.9 mg protein/g creatinine.

The patient's losartan-hydrochlorothiazide was held on admission and she was started on amlodipine 10 mg daily. In light of minimal proteinuria, decision was made to treat conservatively with intravenous (IV) fluid hydration with normal saline at 125 mL/h and daily monitoring of renal indices. The patient was without uremic symptoms, hyperkalemia, or acidosis to warrant dialysis. Anti-neutrophil antibody returned negative and serum complement levels were within normal limits. MPO-ANCA returned positive with a titer of 188.0 (normal <1.0) and IgG anti-GBM antibody was positive at 4.6 (normal <1.0). A bilateral renal ultrasound demonstrated minor cortical thickening without evidence of perinephric fluid collection, hydronephrosis, or ureteral dilatation (Figure 1).

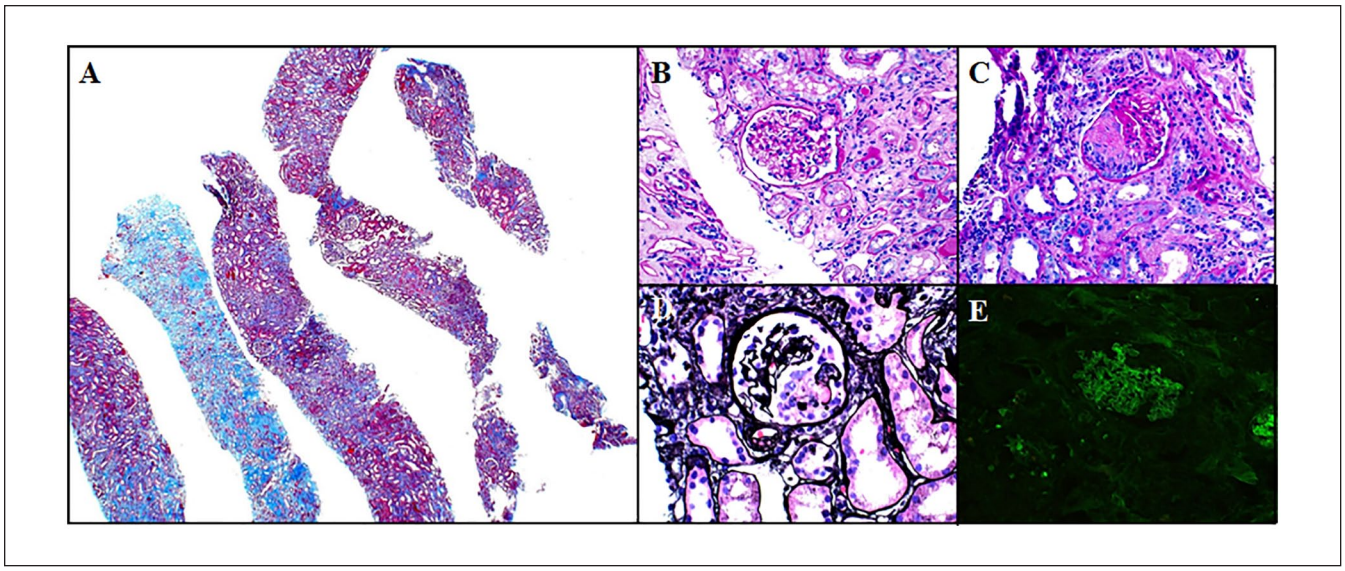

Figure 2. Renal biopsy specimen. Trichrome stain of the kidney biopsy revealing approximately 30% scarring (A). Hematoxylin and eosin stain showing collapsing glomeruli with associated increase in size of Bowman's space (B and C). Extravasation of fibrin into Bowman's can be appreciated (C). Jones Silver stain highlighting the basement membrane (D). Immunofluorescent staining shows linear deposits of immunoglobulin G in the basement membrane (E).

The patient's creatinine improved to 3.48 mg/dL with IV fluid hydration but remained persistently elevated. As such, a renal biopsy was obtained and the patient was started on methylprednisolone 500 mg IV daily. PLEX was initiated for the positive anti-GBM antibody. Further immunomodulation was deferred until the results of the biopsy were available to guide therapy. Light microscopy of the renal specimen revealed glomerular crescent formation with associated fibrinoid necrosis of the tufts on a background of minimal (10% to 20%) interstitial fibrosis and early tubular atrophy (Figure 2). IF staining showed mild linear accentuation of the tuft by IgG. Based on pathologic and serologic data, the patient was diagnosed with double antibody-positive crescentic GN with clinical and histological features favoring ANCA-associated vasculitis as the primary disease process. After 4 days of "pulse-dose" steroids, the patient was transitioned to oral prednisone 60 mg daily. Based on the biopsy results and a creatinine below 5 mg/dL, treatment was selected to target ANCA-associated vasculitis consisting of induction therapy with IV rituximab 375 mg/m^2 once weekly and IV.

Cyclophosphamide 15 mg/kg every 2 weeks with plans for 4 weeks of therapy as outlined in the RITUXVAS protocol with rituximab to continue as maintenance therapy. IV cyclophosphamide was given first followed by IV rituximab 4 days later. Additionally, she was started on pantoprazole 40 mg daily for gastrointestinal prophylaxis and trimethoprim-sulfamethoxazole DS 800/160 three times weekly for pneumocystis pneumonia prophylaxis. The prednisone was tapered to 40 mg daily after 5 days. Despite 8 PLEX treatments, prednisone, and IV cyclophosphamide and rituximab, the patient's creatinine remained elevated at 3.22 mg/dL 7 days after initiation of immunomodulatory therapy. A repeat anti-GBM antibody level increased to 5.5. Given the increase in anti-GBM antibody level and the failure to respond to the current therapy, the treatment was revised to target anti-GBM disease. The patient was started on oral cyclophosphamide 100 mg daily, while continuing oral prednisone 40 mg daily, and rituximab was discontinued. PLEX was continued daily for a total of 14 treatments. A repeat anti-GBM antibody level was undetectable 4 days after initiating the new regimen. Cyclophosphamide was decreased to 50 mg daily due to a decrease in platelet count with a nadir of 128×10^3/μL. Anti-GBM antibodies and ANCAs were monitored every week for 4 weeks followed by every 3 months. We are happy to report 3 months into treatment with oral cyclophosphamide and a slow prednisone taper, her creatinine stabilized between 1.8 and 2.1 g/dL and her anti-GBM antibody levels remain undetectable. This regimen will be continued for another 3 months before refocusing treatment on ANCA-associated vasculitis.

Discussion

This case recapitulates the urgency in diagnosis and the potential challenges in the treatment of RPGN. The condition is associated with a high mortality rate if not diagnosed and treated urgently. In cases of double antibody-positive disease, there is an overlap syndrome with phenotypic features of both entities. In our case, the histopathology favored ANCA-associated renal vasculitis as the primary disease state; however, the patient did not respond to conventional

therapy targeting this disease. One study showed nearly 10% of patients with ANCA-associated renal vasculitis failed rituximab therapy.[9] The lack of response to treatment in this case was thought to be an indication the patient's primary pathological process was anti-GBM disease despite the histopathologic findings and serology favoring ANCA-mediated vasculitis as the predominant disease process. One explanation is the low titers of anti-GBM antibodies at the time of diagnosis may be suggestive of early identification of disease or less severe disease.[5] The initial significance of ANCA disease at time of diagnosis remains unclear. Treatment approaches for double antibody-positive disease should focus on induction therapy targeted against anti-GBM disease followed by maintenance therapy targeted against ANCA-mediated vasculitis.

The mechanism and clinical significance of double antibody-positive disease remains unclear. Some authors opine that ANCA-mediated renal vasculitis may play a role in the development of anti-GBM antibodies by triggering endothelial injury and exposure of collagen epitopes.[10,11] Usually, ANCA-associated renal vasculitis has a more insidious onset compared with anti-GBM disease, and as such, the level of scarring that correlates with chronicity of disease is often less severe in the latter. The histopathological findings in this case correlate with severe glomerulosclerosis; however, there was minimal tubulointerstitial scarring that has been shown to be an important prognostic indicator.[12] Berden et al[13] developed a glomerular classification scheme for ANCA-associated GN categorizing glomerular involvement as focal, crescentic, mixed, or sclerotic, the latter of which carries the highest risk of incomplete renal recovery and mortality. This classification system, however, is not appropriate for double antibody-positive disease or other overlap syndromes.[13]

As this case illustrates, double antibody-positive RPGN can present a significant treatment challenge. Patients may be less likely to respond to treatment and more likely to experience relapse than individuals with single antibody positivity. Clinicians should be wary of ambiguous biopsy reports in the case of double antibody-positive disease. Regardless of what IF staining shows, the mere presence of anti-GBM positivity should be the focus of treatment initially. Further investigations are necessary to elucidate the mechanism of this rare disease process and to optimize treatment strategies.

Author Contributions

SB and AS performed the physical examination, and ordered and interpreted laboratory data and the kidney biopsy. SB and AS were major contributors in writing the manuscript. All authors were involved in editing the manuscript and approved the final manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethics Approval

The case series was evaluated by Sarasota Memorial Hospital Institutional Review Board and was deemed to not meet the definition of human subject research under the purview of the institutional review board according to federal regulations.

Informed Consent

Written informed consent was obtained from the patient for publication of this case.

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References

1. Arimura Y, Muso E, Fujimoto S, et al. Evidence-based clinical practice guidelines for rapidly progressive glomerulonephritis 2014. *Clin Exp Nephrol*. 2016;20:322-341. doi:10.1007/s10157-015-1218-8
2. Moroni G, Ponticelli C. Rapidly progressive crescentic glomerulonephritis: early treatment is a must. *Autoimmun Rev*. 2014;13:723-729. doi:10.1016/j.autrev.2014.02.007
3. Smith C, Dhaliwal G, Saint S, Farkash EA, Garg P. Double trouble. *N Engl J Med*. 2019;381:1854-1860. doi:10.1056/NEJMcps1810654
4. Cancarevic I, Malik BH. Use of rituximab in management of rapidly progressive glomerulonephritis. *Cureus*. 2020;12:e6820. doi:10.7759/cureus.6820
5. McAdoo SP, Tanna A, Hrušková Z, et al. Patients double-seropositive for ANCA and anti-GBM antibodies have varied renal survival, frequency of relapse, and outcomes compared to single-seropositive patients. *Kidney Int*. 2017;92:693-702. doi:10.1016/j.kint.2017.03.014
6. Touzot M, Poisson J, Faguer S, et al. Rituximab in anti-GBM disease: a retrospective study of 8 patients. *J Autoimmun*. 2015;60:74-79. doi:10.1016/j.jaut.2015.04.003
7. Jones RB, Tervaert JWC, Hauser T, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med*. 2010;363:211-220. doi:10.1056/NEJMoa0909169
8. Stone JH, Merkel PA, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med*. 2010;363:221-232. doi:10.1056/NEJMoa0909905
9. Geetha D, Specks U, Stone JH, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis with renal involvement. *J Am Soc Nephrol*. 2015;26:976-985. doi:10.1681/ASN.2014010046
10. Uto K, Yanagi S, Tsubouchi H, Matsumoto N, Nakazato M. Successful treatment of steroid-refractory double-positive ANCA and anti-GBM disease with combination of plasma exchange and immunosuppression: a case report and literature review. *Respir Med Case Rep*. 2018;25:242-246. doi:10.1016/j.rmcr.2018.09.016

11. Srivastava A, Rao GK, Segal PE, Shah M, Geetha D. Characteristics and outcome of crescentic glomerulonephritis in patients with both antineutrophil cytoplasmic antibody and anti-glomerular basement membrane antibody. *Clin Rheumatol*. 2013;32:1317-1322. doi:10.1007/s10067-013-2268-5
12. Sethi S, Fervenza FC. Standardized classification and reporting of glomerulonephritis. *Nephrol Dial Transplant*. 2019;34:193-199. doi:10.1093/ndt/gfy220
13. Berden AE, Ferrario F, Hagen EC, et al. Histopathologic classification of ANCA-associated glomerulonephritis. *J Am Soc Nephrol*. 2010;21:1628-1636. doi:10.1681/ASN.2010050477