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Atypical Antiglomerular Basement Membrane Disease With IgG1-κ Staining

Jehan Z. Bahrainwala[1], M. Barry Stokes[2], Afshin K. Hannani[3] and Jonathan J. Hogan[1]

[1]Renal Division, Hospital of the University of Pennsylvania, Philadelphia, PA, USA; [2]Department of Pathology, Columbia University, New York, NY, USA; and [3]Mercer Renal Associates, Trenton, NJ, USA

Correspondence: Jehan Z. Bahrainwala, MD, Renal Electrolyte and Hypertension Division, Hospital of the University of Pennsylvania, 3400 Spruce St., 1 Founders Pavilion, Philadelphia, PA 19104, USA. E-mail: jehan.bahrainwala@uphs.upenn.edu

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INTRODUCTION

Antiglomerular basement membrane (GBM) disease is an autoimmune disease that classically presents as a rapidly progressive crescentic glomerulonephritis, with or without pulmonary hemorrhage, and typically does not relapse.[1] The anti-GBM autoantibodies, typically polyclonal IgG1 and IgG4,[2,3] bind to the non-collagenous 1 domain of the alpha-3 chain of type IV collagen that is present on alveolar and glomerular basement membranes.[2–4] Kidney biopsies in patients with anti-GBM disease reveal a crescentic and necrotizing glomerulonephritis on light microscopy with diffuse linear staining of the glomerular basement membrane for IgG on immunofluorescence (IF) microscopy.[1,4] Anti-GBM antibodies are detectable in the serum of ∼90% of patients using conventional enzyme-linked immunosorbent assays.[4] Atypical anti-GBM disease is a rare entity defined by uncharacteristic histologic features on light microscopy and/or linear GBM staining for an antibody other than the typical polyclonal IgG on IF.[2] Here we describe a case of relapsing, atypical IgG1-κ anti-GBM glomerulonephritis.

CASE PRESENTATION

A 39-year-old African-American woman with a history of morbid obesity and hypertension presented to a hospital 5 years ago with cough, hemoptysis, diarrhea, and emesis. Physical examination was notable for a temperature of 101° F (38.3° C), blood pressure of 142/59 mm Hg, and heart rate of 103 beats per minute; she had no edema and her lungs were clear to auscultation bilaterally. A chest X-ray did not show any infiltrates. She underwent an esophagogastroduodenoscopy and a colonoscopy to further evaluate her gastrointestinal symptoms. Her esophagogastroduodenoscopy test result was unremarkable and her colonic biopsy showed mild-acute chronic ileitis with poorly formed granulomatous inflammation presumed to be autoimmune or infectious in nature. She was also found to have acute kidney injury with a serum creatinine (SCr) level of 3.6 mg/dl (normal range 0.57–1 mg/dl) with an estimated glomerular filtration rate by Modification of Diet in Renal Disease equation of 18 ml/min per 1.73 m^2. Her Scr level peaked at 8.6 mg/dl. Her urinalysis was significant for microscopic hematuria and albuminuria, and a spot urine protein to creatinine ratio was 3.3 g/g (normal range 0–200 mg/g). Anti-GBM (by enzyme-linked immunosorbent assay) and ANCA serologies (by immunofluorescence) were negative. Her C3 level was mildly decreased at 76 mg/dl (normal range 88–201 mg/dl) and her C4 level was mildly elevated at 46 mg/dl (normal range 14–44 mg/dl). Serum protein electrophoresis showed no monoclonal spike, and her serum free light chain levels were normal (κ = 8.6 mg/dl [range 3.3-19.4 mg/dl] and λ = 5.7–26.3 mg/dl).

A kidney biopsy was performed (Figure 1). Light microscopy showed 9 glomeruli with segmental endocapillary hypercellularity with intracapillary leukocytes and segmental glomerular basement membrane duplication, 3 glomeruli with cellular crescents and segmental fibrinoid necrosis, patchy interstitial edema, and moderate to severe interstitial inflammation. There was no significant interstitial fibrosis and tubular atrophy and the vessels were normal. IF microscopy revealed bright diffuse linear staining of the glomerular basement membrane with IgG1 (2+) and kappa (2+) light chain. There was focal staining of tubular basement membranes and no staining of Bowman capsule basement membrane. There was staining of the glomerular capillary wall and mesangium with C3 (2+). There was no detectable staining for IgG2, IgG3, IgG4, IgM, IgA, C1, or lambda light chain. The IF was negative for albumin. Electron microscopy was significant for 20% foot process effacement and no electron

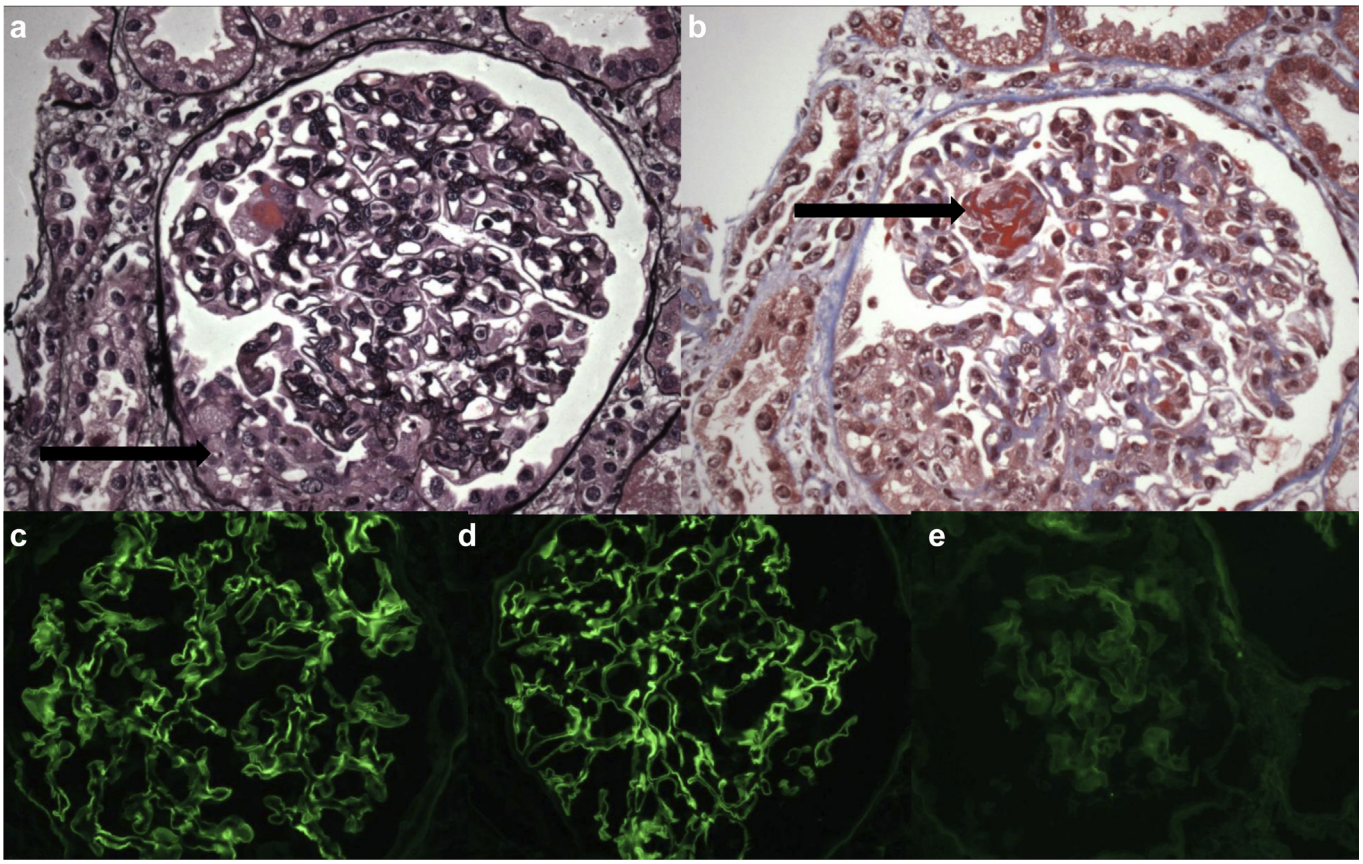

Figure 1. Histologic findings in the initial biopsy specimen. (a) Light microscopy shows a glomerulus with cellular crescent (black arrow) (Jones silver methenamine stain, original magnification x 400). (b) The same glomerulus shows segmental fibrinoid necrosis (black arrow) (trichome stain, original magnification x 400). Immunofluorescence stains (all magnifications x 400) show staining of glomerular basement membranes for (c) IgG1, (d) kappa light chain, and (e) negative light chain lambda staining.

dense deposits were present. She was treated with induction therapy with pulse methylprednisolone (1 g i.v. daily for 3 days) followed by oral prednisone 60 mg/d, plasma exchange therapy for 4 sessions, and oral cyclophosphamide (150 mg/d) for 6 months. Her prednisone therapy was tapered to off to the point at which at 6 months she was started on maintenance therapy with azathioprine that was discontinued after 1 year. At that time, her SCr level was 1.2 mg/dl (normal range 0.57–1 mg/dl), her urine protein to creatinine ratio was 55 mg/g (normal range 0–200 mg/g), and her microscopic hematuria had resolved. She continued to receive amlodipine and valsartan for hypertension.

Four years after her initial presentation, she was admitted to a hospital for shortness of breath, productive cough, sinus congestion, emesis, and gross hematuria. On physical exam, she was afebrile, her blood pressure was 134/86 mm Hg, her pulse oximetry was 92% on room air, and her heart rate was 83 beats per minute. The remainder of the examination was unremarkable. Her SCr level on presentation was 2.9 mg/dl (normal range 0.57–1 mg/dl), and her urinalysis was significant for proteinuria and hematuria; microscopy was not performed. Her serologic workup was again negative for anti-GBM (by enzyme-linked immunosorbent assay) and ANCA (by immunofluorescence) antibodies (p-ANCA titer $<$ 1:20, c-ANCA titer $<$ 1:20, antimyeloperoxidase antibody $<$9 U/ml, and antiproteinase-3 $<$3.5 U/ml). Serum protein electrophoresis, serum immunofixation, and serum kappa/lambda free light chain showed no evidence of a paraprotein. Her serum Ig studies were IgG 1340 mg/dl (range 650–2000 mg/dl), IgA 141 mg/dl (range 50–500 mg/dl), and IgM 99 mg/dl (range 40–270 mg/dl). A computed tomography scan of her chest without i.v. contrast was unremarkable.

Her renal ultrasound showed kidneys with normal size and echotexture. She underwent a second kidney biopsy that again demonstrated focal necrotizing and crescentic glomerulonephritis on light microscopy with 20% interstitial fibrosis and tubular atrophy and mild arteriosclerosis. Immunofluorescence was significant for linear IgG1-κ GBM staining. A cystoscopy test was negative. Due to concern that the IgG1-κ represented a monoclonal gammopathy of renal significance, she was referred to hematology for evaluation of a clonal B cell or

plasma cell clone. Peripheral blood flow cytometry showed no overt immunophenotypic evidence of a clonal lymphoproliferative disorder. A bone marrow biopsy and aspirate smear were also performed. Microscopic examination of the aspirate smear demonstrated normocellular marrow with trilineage hematopoiesis. Flow cytometry on the bone marrow aspirate demonstrated unremarkable T cells, precursor B cells, natural killer cells, and polytypic B cells. There was no morphologic or immunophenotypic evidence of a B cell lymphoproliferative disorder, nor an expansion of plasma cells. She was treated with pulse i.v. steroids followed by oral prednisone at 60 mg daily and rituximab 1000 mg i.v. biweekly for 2 doses. Her prednisone therapy was tapered off across 3.5 months due to significant weight gain, and mycophenolate mofetil was started at 500 mg twice daily. During the next 4 months, her SCr level decreased to 1.6 mg/dl (normal range 0.57–1 mg/dl), with a urine protein to creatinine ratio of 162 mg/g (normal range 0–200 mg/g). She received a second rituximab course (1 dose of 1000 mg i.v.) 6 months after her initial dose. Six months after this dose, while taking mycophenolate mofetil 500 mg twice daily, her Scr level is stable at 1.6 mg/dl with an estimated glomerular filtration rate by Modification of Diet in Renal Disease equation of 46 ml/min per 1.73 m^2. Her urine protein to creatinine ratio is 0.2 g/g and her urinalysis continues to show microscopic hematuria. She has not had recurrence of pulmonary or gastrointestinal symptoms.

DISCUSSION

Cases of atypical anti-GBM disease are rare and are defined by unique features on kidney biopsy compared with typical anti-GBM disease.[4] Here we report a case of relapsing IgG1-κ anti-GBM disease that presented as acute kidney injury and extrarenal symptoms. No circulating antibodies were detected, and her SCr level and extrarenal symptoms improved with immunosuppression. Our case is unique in the presence of both a relapsing course and extrarenal (i.e., gastrointestinal and pulmonary) symptoms with disease activity.

To our knowledge, this is only the third reported case of IgG1-κ anti-GBM disease.[2,5] Coley *et al.*[5] described the first case of IgG1-κ anti-GBM nephritis in a 53-year-old man who presented with renal insufficiency, hematuria, and proteinuria. A kidney biopsy showed endocapillary proliferative glomerulonephritis with no crescents, and linear staining for IgG1-κ on IF. No circulating autoantibodies were detectable. The patient's renal function improved with immunosuppression (prednisone and cyclophosphamide, then mycophenolic acid) but relapsed 9 years later with concomitant symptoms of an upper respiratory infection, and a repeat kidney biopsy showed the same findings in addition to glomerulosclerosis and tubulointerstitial scarring. He again responded to immunosuppression (rituximab).

A second patient with IgG1-κ anti-GBM disease is described in a retrospective case series by Nasr *et al.*[2] composed of 20 patients with atypical anti-GBM disease (defined by linear Ig GBM staining on IF but without the classic crescentic phenotype). Restricted light chain staining on IF was observed in 50% of cases. The specific details for patients with IgG1-κ are not presented, but as a whole, these patients had a more chronic disease course, better 1-year survival, no detectable circulating antibodies, and no pulmonary involvement compared with those with typical anti-GBM disease.

Because classic anti-GBM tends to have a monophasic course, immunosuppression is usually tapered off over a period of months after clinical and serologic remission.[6] However, the possible relapsing nature of IgG1-κ anti-GBM disease, as noted in our case and that of Coley *et al.*,[5] raises the question of how to chronically manage this disease. We treated our patient initially using standard therapies for classic anti-GBM disease. After relapsing, she was treated with rituximab to minimize her cumulative cyclophosphamide exposure, and additional rituximab and mycophenolate mofetil were added as steroid-sparing agents for maintenance immunosuppression. Of note, no relapses were described in the series by Nasr *et al.*,[2] but rare cases of relapsing atypical anti-GBM disease, but without IgG1-κ staining, have also been described.[4]

The pathogenesis of atypical anti-GBM disease and why these antibodies are not detected on routine testing is not understood. It is possible that the pathogenic antibodies produced by our patient are directed against an antigen other than the alpha-3 chain of type IV collagen, or that there is lower or transient antibody production making it undetectable by standard tests.[1,2,5,7] The light-chain restriction observed on IF leads to the hypothesis that monotypic anti-GBM disease is a paraprotein process resulting from a lymphoproliferative disorder. However, as in our patient, no associated B or plasma cell clone has been identified in the atypical anti-GBM literature. It is possible that this entity is a monoclonal gammopathy of renal significance, because the detection a clonal cell population has been variable with these disorders as well.

CONCLUSION

We have described a case of IgG1-κ anti-GBM disease notable for its relapsing course and the presence of extrarenal symptoms. Further work is needed to

elucidate the mechanism underlying this unique entity and appropriate treatment strategies to address relapses.

DISCLOSURES

All the authors declared no competing interests.

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