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A Case of Glomerulopathy Associated With Monoclonal Glomerular Basement Membrane Antibody

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Received 25 January 2021; revised 11 February 2021; accepted 15 February 2021; published online 24 February 2021

Kidney Int Rep (2021) **6,** 1444–1448; https://doi.org/10.1016/j.ekir.2021.02.028

INTRODUCTION

Classic antiglomerular basement membrane (GBM) nephritis is clinically and pathologically the most aggressive form of glomerulonephritis. Patients typically present with nephritic syndrome and rapidly progressive kidney injury. The pathologic *sine qua non* of anti-GBM nephritis is bright linear polyclonal staining of GBM IgG on immunofluorescence (IF) microscopy. Focal linear staining of distal tubular basement membranes (which express α3, α4, and α5) occurs in more than 50% of the patients. Most cases reveal diffuse crescentic and necrotizing glomerulonephritis on light microscopy.[1] Rarely, anti-GBM nephritis can be characterized by an indolent course, undetectable circulating α3 noncollagenous domain antibodies, and histologically by endocapillary proliferative, mesangial proliferative, or membranoproliferative glomerulonephritis, without crescents or with only focal crescents.[2,3] In this less common presentation, some cases may be due to autoantibodies directed at an antigen other than α3 noncollagenous domain. However, in other cases, the culprit antibody is monoclonal, suggesting a paraprotein-related disease. In a large series of 20 patients with negative anti-GBM enzyme-linked immunosorbent assay (ELISA) serology results and no crescents on light microscopy, 10 patients had polyclonal and 10 had monoclonal IgG linear GBM IF staining.[3] Nephrologists and pathologists need to be aware that linear staining of GBM on IF can be a monoclonal process and may signify a form of monoclonal gammopathy of renal significance. In this article, we present a case of glomerulopathy associated with linear IgG1-kappa GBM reactivity.

CASE PRESENTATION

A 55-year-old woman with a medical history of depression, anxiety, rheumatoid arthritis, basal-cell carcinoma, and hypothyroidism presented to the Nephrology clinic for evaluation of gross hematuria. She had no history of kidney disease. She had been diagnosed with rheumatoid arthritis in her 20s and had been treated with etanercept for many years. She reported that hematuria had been microscopic for the past 7 years before presentation, but for the last 6 months she had noticed gross hematuria, which she described as pinkish in color and at times red colored. She is an active person who runs daily and bikes approximately 50 miles on the weekends. She reported noticing that her urine became red colored after these activities. The patient also complained of an intermittent dull, aching flank pain. She denied any shortness of breath, chest pain, cough, or hemoptysis.

Her home medications included clonazepam, methylphenidate, etanercept, fluoxetine, lithium carbonate, and levothyroxine. No herbal remedies, nonsteroidal anti-inflammatory drugs, or proton-pump inhibitors had been used.

On presentation, she was afebrile, with a blood pressure of 120/85 mm Hg, heart rate of 65 bpm, body mass index of 21.19, and oxygen saturation of 98% on room air. The result of the patient's physical examination was unremarkable.

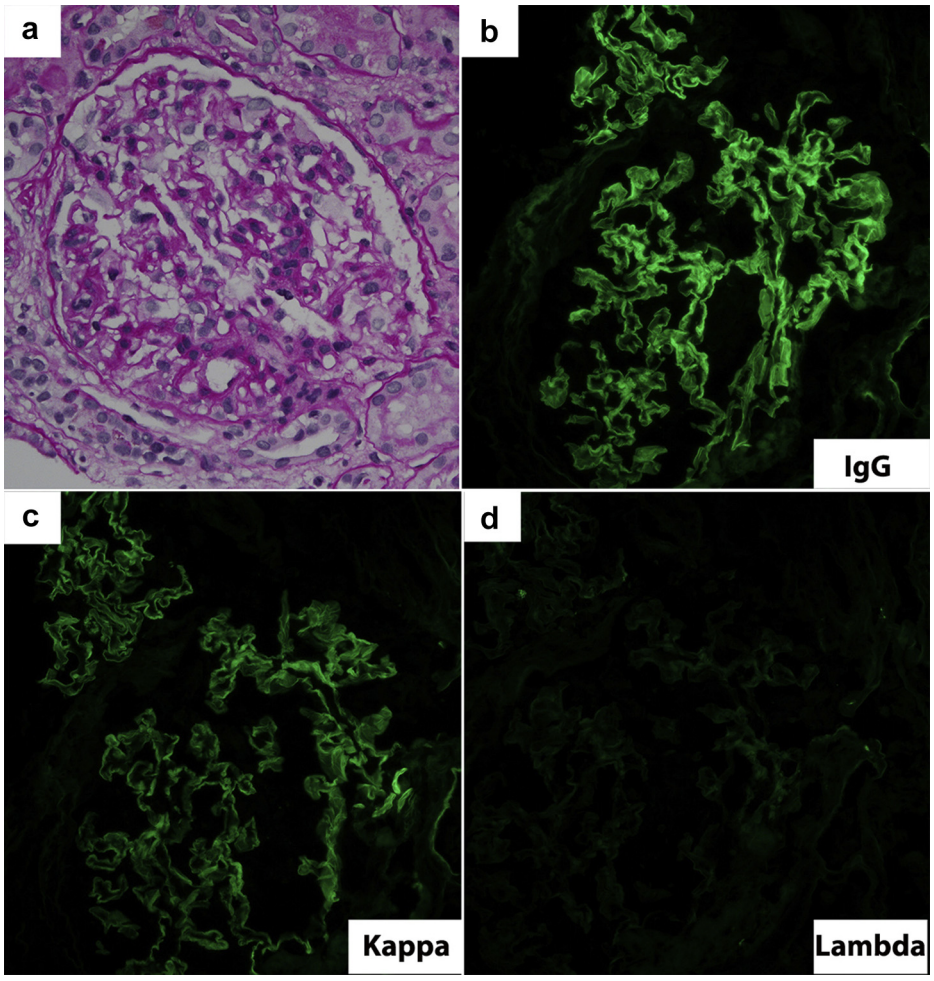

Figure 1. Kidney biopsy findings reveal linear IgG-kappa staining without proliferative glomerulonephritis. (a) Glomerulus reveals mild nonspecific mesangial expansion, without associated endocapillary hypercellularity or crescent formation (PAS stain, 400×). (b–d) Immunofluorescence staining for IgG and kappa-light chains reveals linear distribution along the glomerular basement membranes, whereas lambda light chain is negative (FITC, 400×). FITC, fluorescein isothiocyanate; PAS, periodic acid–Schiff.

Clinical and laboratory data revealed elevated serum creatinine of 1.44 mg/dl (baseline was 1.07 mg/dl), blood urea nitrogen of 23 mg/dl, hemoglobin of 10.0 g/dl, and a low haptoglobin level to <20, with normal platelet count, normal lactate dehydrogenase, and a negative result of the Coombs test. Urinalysis revealed large blood with 158 red blood cells per high power field. Urinary sediment evaluation revealed dysmorphic red blood cells. The urine spot total protein-to-creatinine ratio was 0.5. Viral studies revealed negative results. Further serologic workup for antinuclear antibody, double-stranded DNA antibody, antismith antibodies, antineutrophil cytoplasmic antibody, and anti-GBM antibody revealed negative results. Complement levels were normal. Computed tomography of the abdomen and pelvis was performed, revealing a bladder within normal limits with no evidence of hydronephrosis, nephrolithiasis, or neoplasm. Serum immunofixation revealed a kappa-free light chain concentration of 2.94 mg/dl and a lambda-free light chain concentration of 1.96 mg/dl (ratio 1.5). No monoclonal band was identified in her serum. Bone marrow biopsy performed for evaluation of hemolytic anemia revealed trilineage hematopoeisis with normal maturation and nonspecific findings including a small lymphoid aggregate, a small granuloma, and focal perivascular plasma cells. Bone marrow plasma cells were polytypic by immunohistochemistry.

Kidney Biopsy

A kidney biopsy was performed owing to a worsening kidney function and persistence of hematuria. The biopsy result revealed nonspecific changes in the glomeruli, with mild segmental mesangial expansion by matrix and no significant glomerular hypercellularity. In particular, crescents were not found. There was no significant interstitial inflammation or tubular changes. Chronic changes were overall mild. On IF microscopy, there was 3+ linear GBM staining for IgG and kappa-light chains, whereas lambda light

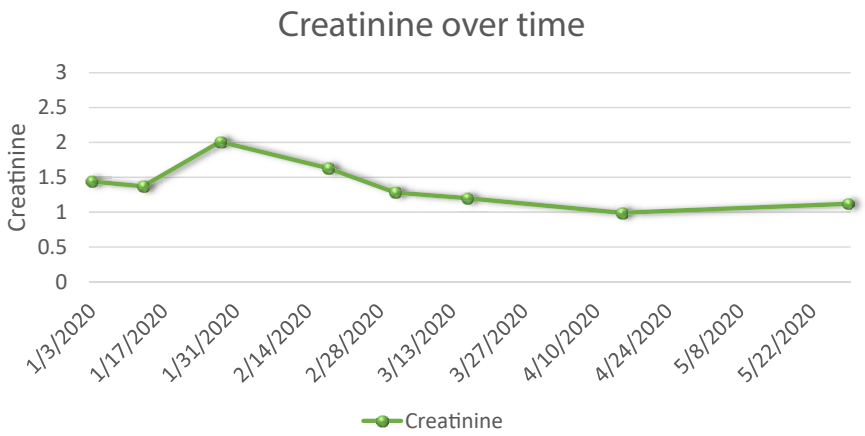

Figure 2. Graph revealing creatinine trends over time in relationship to presentation, biopsy examination, and treatment initiation.

chains, IgA, IgM, and C3 were negative in the glomeruli. On subclass IgG staining (Supplementary Figure S1A-D), only gamma 1 was found to have linear GBM reactivity whereas other subclasses were negative. One glomerulus was found on electron microscopy, and extensive foot process effacement was noted with GBM wrinkling and focal endothelial cell swelling. No electron-dense deposits were noted in the mesangium or along the capillary walls. Representative images are found in Figure 1.

Clinical Course

A diagnosis of glomerulopathy with IgG1-kappa linear GBM reactivity was made. Given no evidence of hematologic or solid malignancy, and the lack of crescentic disease, the patient was treated with oral steroids at a dose of 1 mg/kg, followed by slow taper and rituximab weekly for 1 month at a dose of 375 mg/m^2. There was a significant improvement in kidney function and gross hematuria (Figure 2). The patient completed 3 doses of rituximab; the fourth dose was not given as the patient developed COVID-19. She was admitted with COVID-19 and experienced protracted fever but ultimately recovered without antibody formation. The rheumatoid arthritis of the patient was well controlled while on rituximab, but after 6 months from her last dose of rituximab, she developed a recurrence of synovitis. Etanercept was not resumed owing to its potential malignancy concerns; so she was started on low-dose methotrexate, which has controlled her symptoms for now. Though methotrexate can rarely lead to methotrexate-associated lymphoproliferative disorder, it was deemed safe by the hematology service because monoclonal gammopathy of renal significance is caused by a monoclonal immunoglobulin secreted by a nonmalignant B-cell clone. That said, this does not exclude the possibility of development of future hematologic disease, and these patients require close monitoring. After 10 months of receiving the final dose of rituximab, the patient's creatinine remains stable at 1.16 mg/dl with no detectable proteinuria or gross hematuria.

DISCUSSION

Anti-GBM disease is a rare but typically severe form of glomerulonephritis. The disease is associated with pathogenic antibodies against the noncollagenous domain of the α-3 chain of type 4 collagen.[1] Rapidly progressive kidney injury with crescentic changes in the glomeruli and linear IgG IF reactivity along GBM is found on kidney biopsy.[2] Other forms of glomerulonephritis with anti-GBM IF have been described as atypical anti-GBM disease; these tend to be clinically less aggressive, characterized by nondetectable anti-GBM autoantibodies by the standard ELISA technique, and not associated with overt proliferative or necrotizing disease on a kidney biopsy.3 In many cases, atypical antibodies are monoclonal, making them subsets of cases monoclonal gammopathies of renal significance and more specifically "monoclonal gammopathies of glomerular basement membrane significance."

In the case series by Troxell and Houghton[4], 5 cases were presented with atypical manifestations of anti-GBM disease. All 5 cases had linear glomerular capillary wall IF staining, 4 cases were polyclonal and 1 revealed IgG3-lambda IF restriction. Furthermore, 4 of these cases had a mild clinical course and no lung involvement. The treatment was adjusted individually, but in summary, all 5 patients received steroid regimen, 4 of the 5 patients received plasmapheresis, and 2 patients received additional cyclophosphamide. The patient with IgG3-lambda–restricted deposition disease was a renal transplant recipient and was successfully treated with plasmapheresis, steroids, and a single dose of rituximab.[4]

Olivier *et al.*[5] has described a 53-year-old woman who presented with rapidly worsening serum creatinine and whose biopsy examination revealed linear staining along GBMs by monotypic IgG1-kappa. Serum

Table 1. Atypical anti-GBM disease: literature review

Author	Monotypic	Age	Gender	Pretreatment creatinine	Immunofluorescence	Treatment	Post treatment creatinine	Outcome	
								Patient	Kidney
Troxell and Houghton[4]	Yes/1 case	68	Male	1.2 mg/dl	IgG3-lambda monotypic	PLX/IVIG/steroids/ rituximab	1.0 mg/dl	Alive	Persistent kidney dysfunction
Nasr *et al.*[3]	Yes/10 cases	51	Male	1.2 mg/dl	Lin GBM IgG (3+) and lambda (3+)	Tacrolimus	1.3 mg/dl	Alive	Persistent kidney dysfunction
		77	Male	1.6 mg/dl	Lin GBM and focal TBM for IgG (3+) and lambda (3+)	Prednisone	ESRD	Expired	ESRD
		57	Male	3.5 mg/dl	Lin GBM and focal TBM IgG (2+) and lambda (2+)	None	2.8 mg/dl	Alive	Persistent kidney dysfunction
		49	Female	1.0 mg/dl	Lin GBM and focal TBM IgG (3+) and lambda (3+)	None	0.9 mg/dl	Alive	Persistent kidney dysfunction
		59	Female	1.9 mg/dl	Lin GBM IgG (3+) and lambda (3+)	Pred/CYC	2.0 mg/dl	Alive	Persistent kidney dysfunction
		19	Male	1.7 mg/dl	Lin GBM IgG (3+) and kappa (3+)	Pred/MMF/Bort/CYC/ rituximab/tacrolimus	ESRD	Alive	ESRD
		61	Male	2.6 mg/dl	Lin GBM IgG (3+) and lambda (3+)	Prednisone	1.8 mg/dl	Alive	Persistent kidney dysfunction
		69	Female	0.9 mg/dl	Lin GBM IgM (3+) and kappa (1+)	Dexa/Bort	0.7 mg/dl	Alive	Persistent kidney dysfunction
		64	Male	1.1 mg/dl	Lin GBM IgM (3+) and kappa (2+)	N/A	N/A	N/A	N/A
		63	Male	2.6 mg/dl	Lin GBM IgA (2+), lambda (3+)	N/A	N/A	N/A	N/A
Olivier *et al.*[5]	yes	53	Female	2.4 mg/dl	IgG1-kappa monotypic	PLX/steroids/CYC	1.3 mg/dl	Alive	Kidney function returned to baseline
Coley *et al.*[6]	yes	53	Male	3.0 mg/dl	IgG1-kappa monotypic	IV steroids/CYC, followed by MFA	1.9 mg/dl	Alive	Persistent kidney dysfunction
Bonilla *et al.*	Yes	55	Female	1.44 mg/dl	IgG1-kappa monotypic	Pred/rituximab	1.16 mg/dl	Alive	Kidney function returned to baseline

Bort, bortezomib; CYC, cyclophosphamide; Dexa, dexamethasone; ESRD, end-stage renal disease; GBM, glomerular basement membrane; Ig, immunoglobulin; IV, intravenous; IVIG, intravenous immunoglobulin; IF, immunofluorescence; MFA, mycophenolate acid; MMF, mycophenolate mofetil; N/A, nonavailable; PLX, plasmapheresis; Pred, prednisone; TBM, tubular basement membrane.

anti-GBM antibodies were negative by ELISA. The patient was treated with plasmapheresis, corticosteroids, and cyclophosphamide, which was later changed to mycophenolate mofetil owing to hemorrhagic cystitis. The patient's renal function improved and remained stable at 3 months follow-up.[5]

Coley *et al*.[6] have reported the case of a 53-year-old man with decreased kidney function after an upper respiratory tract infection. He was also found with microscopic hematuria and non-nephrotic range proteinuria. Serum anti-GBM antibodies were not detected. Kidney pathology revealed mild diffuse endocapillary proliferative and exudative glomerulonephritis with multifocal GBM breaks. IF revealed an intense diffuse linear staining of GBM for IgG1 kappa. He was treated with cyclophosphamide and corticosteroids as an induction regimen, followed by mycophenolate acid for maintenance therapy, and his creatinine levels remained stable for 9 years.[6]

The largest case series has been reported by Nasr *et al*.[3]; they described 20 patients with indolent progressive kidney damage, often presenting with hematuria, proteinuria, and mild kidney injury. On kidney biopsy examination, these patients had bright diffuse linear GBM staining for IgG, with monoclonal restriction in half the patients but without features of crescentic glomerulonephritis on light microscopy. Serum anti-GBM antibodies were not detected by ELISA in these patients. Treatment regimen for these 20 patients was individualized; 13 patients received corticosteroids as part of a regimen or as monotherapy in 2 patients. Furthermore, 1 patient who achieved complete remission was treated with mycophenolate mofetil. There were 6 patients who received cyclophosphamide as part of the immunosuppression regimen, 2 patients who received rituximab, and 2 patients who also had plasmapheresis treatment.

Table 2. Teaching Points

1.	Monoclonal or polyclonal linear GBM reactivity on a kidney biopsy may occur in patients with a mild form of glomerulonephritis and undetectable serum anti-GBM antibodies.
2.	Monoclonal forms may present as a "monoclonal gammopathy of renal significance."
3.	Rituximab and steroids can lead to a good response but targeting the underlying clone may be more appropriate

GBM, antiglomerular basement membrane.

We propose that patients with monoclonal disease be categorized separately from other patients with the so-called typical anti-GBM disease and that these patients be considered to have a form of monoclonal gammopathy of renal significance. Table 1 summarizes all 14 published cases of monoclonal linear GBM deposition, including the case presented here. A total of 64% patients were male with a mean age of 59 years. The average creatinine at presentation was 1.86 mg/dl. Steroids were the most used medication (in 57% of the cases), and only 2 patients received plasma exchange. Furthermore, 7 of the 14 cases were lambda restricted and 7 were kappa restricted. There were 2 patients who progressed to end-stage kidney disease of whom 1 expired. Moreover, 2 patients experienced a return to baseline kidney function, but the rest were left with residual chronic kidney disease.

In our case, the patient presented with a mild clinical course, with hematuria and mild kidney injury, and no detectable serum anti-GBM antibodies by ELISA. On kidney biopsy examination, there was linear monoclonal IgG1-kappa reactivity along GBM. No overt endocapillary proliferative changes or cellular crescents were found. Treatment was unconventional; owing to lack of typical serum anti-GBM antibodies by ELISA, plasmapheresis was not performed, and a decision was made to start the patient on prednisone at a dose of 1 mg/kg daily along with rituximab. Nephrologists should be aware that monoclonal linear reactivity of GBM can be found on kidney biopsy in patients with hematuria, acute kidney injury, and negative anti-GBM serologies; with close follow-up and individualized treatment, they may have favorable outcomes. A summary of learning points can be found in Table 2.

DISCLOSURE

KJ reports having served as a consultant for Astex Pharmaceuticals and Natera. The remaining authors declared no competing interests.

PATIENT CONSENT

Consent was received from the patient.

SUPPLEMENTARY MATERIAL

Supplementary file (PDF)

Figure S1. (A–D) Immunofluorescence staining for IgG subclasses reveals linear staining for gamma-1 along the glomerular basement membranes, while the staining for other subclasses gamma 2, 3, and 4 is negative (FITC, 400×).

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