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CASE REPORT

Atypical Anti-Glomerular Basement Membrane Disease With Diffuse Crescentic Membranoproliferative Glomerulonephritis: Case Report and Review of Literature

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ABSTRACT

Anti-glomerular basement membrane (anti-GBM) disease occurs in fewer than two cases per million population. Patients usually present with features of rapidly progressive glomerulonephritis (RPGN) with or without pulmonary involvement. Anti-GBM disease is classically diagnosed by both demonstrating GBM linear immunofluorescence staining on kidney biopsy and detecting anti-GBM antibodies in serum. More than 90% of patients with anti-GBM disease either become dialysis-dependent or die if left untreated.

Here, we report a 37-year-old man who presented with bilateral lower limb edema, hypertension, acute kidney injury (creatinine of 212 μmol/L), microscopic hematuria, and nephrotic range proteinuria (15 g/day). His kidney biopsy showed diffuse crescentic membranoproliferative glomerulonephritis and bright linear staining of GBM by immunoglobulin G consistent with anti-GBM disease; however, serum anti-GBM antibodies were negative. The patient was diagnosed with atypical anti-GBM disease and treated aggressively with intravenous pulse steroids, plasmapheresis, oral cyclophosphamide, and oral prednisolone with significant improvement in kidney function and proteinuria.

Atypical anti-GBM disease should be considered in patients presenting with RPGN, even in the absence of serum anti-GBM antibodies. Early diagnosis and aggressive treatment in such cases are warranted to prevent irreversible kidney damage as the course of the disease might not be as benign as previously thought.

Keywords: anti-glomerular basement membrane disease, membranoproliferative glomerulonephritis, glomerular crescents, nephrotic-range proteinuria

INTRODUCTION

Anti-glomerular basement membrane (anti-GBM) disease is a rare autoimmune disorder that often presents as rapidly progressive glomerulonephritis (RPGN), with or without pulmonary manifestations.[1] It accounts for 20% of all RPGN cases. Most patients present with both renal and pulmonary diseases (60 – 80%), and 20 – 40% have a renal-limited disease, and less than 10% have only pulmonary disease.[2] Anti-GBM disease can occur at any age, with peak incidence during the third and sixth decades.[3] Prognosis is poor with five-year kidney and patient survival rates of 34% and 83%, respectively.[4] Anti-GBM disease is mostly caused by circulating autoantibodies against cryptic epitopes in the NC1 domain of the alpha-3 chain (a3NC1) of type IV collagen.[5] Of patients, 90% will have detectable serum anti-GBM antibodies using conventional methods.[6] Atypical anti-GBM disease is a rare variant characterized by diffuse linear staining of GBM by immunoglobulin G (IgG) on immunofluorescence microscopy and absence of circulating serum anti-GBM antibodies by enzyme-linked immunosorbent assay (ELISA), Western blot, or indirect immunofluorescence.[5] Although atypical anti-GBM disease was previously thought to have a benign course, progression to end-stage renal disease (ESRD) still occurs in 15 – 32% of cases within a few years of follow-up.[7,8] Here, we report a case of atypical anti-GBM disease with diffuse crescentic membranoproliferative glomerulonephritis.

CASE STUDY

Mr. S, a 37-year-old Sri Lankan man with no significant past medical history of any chronic illness, presented to the emergency department in December 2016 with progressive bilateral lower limb swelling for 10 days. He also reported subjective fever, cough, and dark urine that he developed a few days before hospital presentation. The patient denied chest pain, shortness of breath, orthopnea, hemoptysis, nausea, vomiting, abdominal pain, diarrhea, joint pain, skin rash, or dysuria. His physical examination was notable for a blood pressure of 197/110 mmHg and bilateral pitting lower limb edema without other significant findings.

Laboratory investigations showed white blood cells (WBC) 8100/μL, hemoglobin 10.4 g/dL, platelets 240,000/uL, blood urea nitrogen 7.2 mmol/dL, creatinine 212 μmol/dL, albumin 12 g/dL, urine WBC 42 cells/HPF, urine red blood cell 681 cells/HPF, and 24-hour urine protein 15 g/day. Renal ultrasound and chest X-ray were both unremarkable. All viral and immunologic workups were negative, including anti-GBM antibodies (two samples),

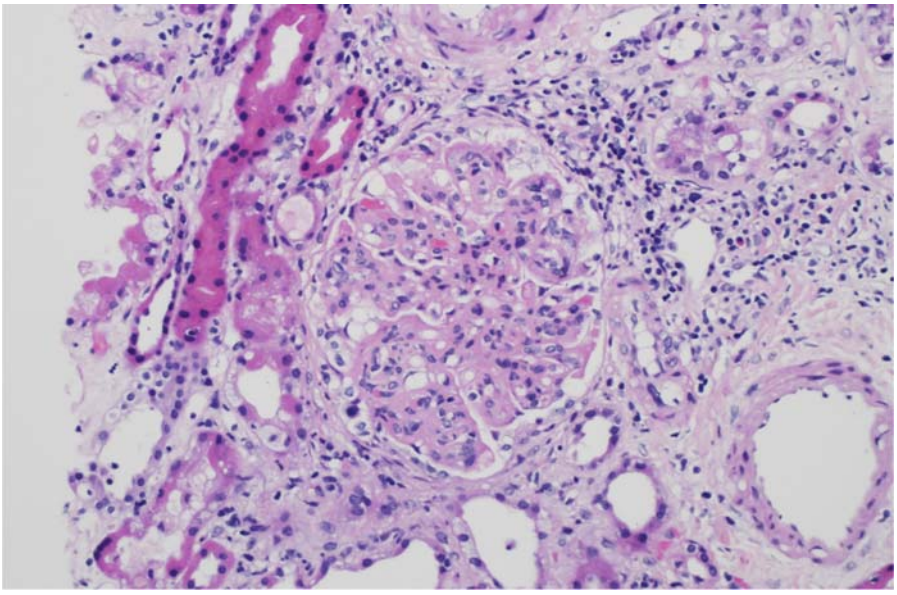

Figure 1. Hematoxylin and eosin stain 400×, endocapillary proliferation, and expanded mesangium with increased cellularity.

antinuclear antibodies, antineutrophil cytoplasmic antibodies, and complement 3 and 4 (C3 and C4) levels. Creatinine continued to increase, and kidney biopsy was conducted on the second day of admission for suspicion of RPGN. The light microscopy of kidney tissue showed 12 glomeruli, and none of which was globally sclerosed. There was a diffuse proliferation in the glomeruli with increased mesangial cellularity and matrix with seven glomeruli showing crescents. There was also mild acute tubular injury, interstitial inflammation, and interstitial fibrosis. Direct immunofluorescence studies showed three glomeruli with bright linear GBM staining for IgG (3+) and C3 (2+). There was also linear staining in some tubular membranes for IgG (2+). Kidney tissue was also sent to Mayo clinic for electron microscopy (EM), which showed similar proliferative features with no immune complex, fibrillation, or paraprotein-related deposits in GBM, mesangial regions, or tubular interstitial compartment. Kidney biopsy findings are shown in the figures below (Figures 1 – 3).

The patient was diagnosed with diffuse crescentic membranoproliferative glomerulonephritis due to atypical anti-glomerular basement membrane disease. His serum creatinine peaked at 270 mmol/L by the third day of admission and then started to trend down with the initiation of immunosuppression. Given the presence of diffuse crescents on kidney biopsy, the patient was treated aggressively with intravenous methylprednisolone 500 mg for five days, daily plasma exchange (eight sessions in total), oral cyclophosphamide 150 mg/day, and oral prednisolone. The patient completed a 6-month course of oral cyclophosphamide and a 16-month course of oral prednisolone in total. The patients' creatinine improved gradually and reached 142 mmol/dL at three months of treatment. Now, 12 months posttreatment completion, the patient's creatinine is 116 μmol/L, and his 24-hour urine protein is 1.5 g/day with no hematuria.

DISCUSSION

Atypical anti-GBM is a rare variant of anti-GBM disease characterized by diffuse linear staining of GBM by IgG on immunofluorescence microscopy and absence of serum anti-GBM antibodies.

There are multiple explanations for having negative serology in atypical anti-GBM disease that include the following: (I) antibodies might be directed against α4NC1 of type IV collagen instead of α3NC1, therefore not detected by conventional assays. (II) Antibodies might be deficient in provoking inflammation, IgG4 instead of IgG1, which are weak and have no capacity to fix complement. (III) There are low levels of antibodies in the circulation due to high avidity for glomeruli.[9,10]

The first case of atypical anti-GBM disease was reported in the literature in 1993.[11] The patient presented with proteinuria and hematuria but had normal kidney function, and his or her kidney biopsy showed focal crescents (less than 50% of glomeruli involved) with no membranoproliferative features, unlike our patient who presented with

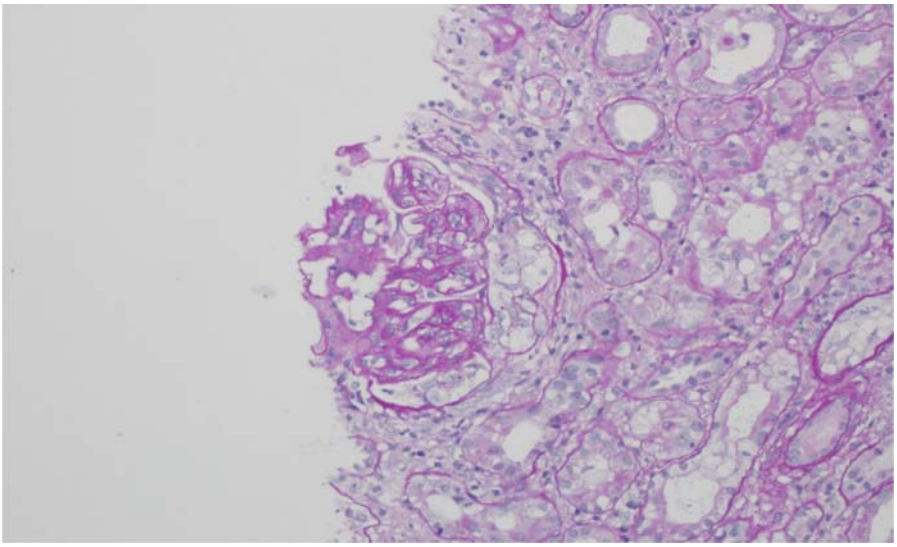

Figure 2. Periodic acid – Schiff stain 400×; cellular crescent in a glomerulus.

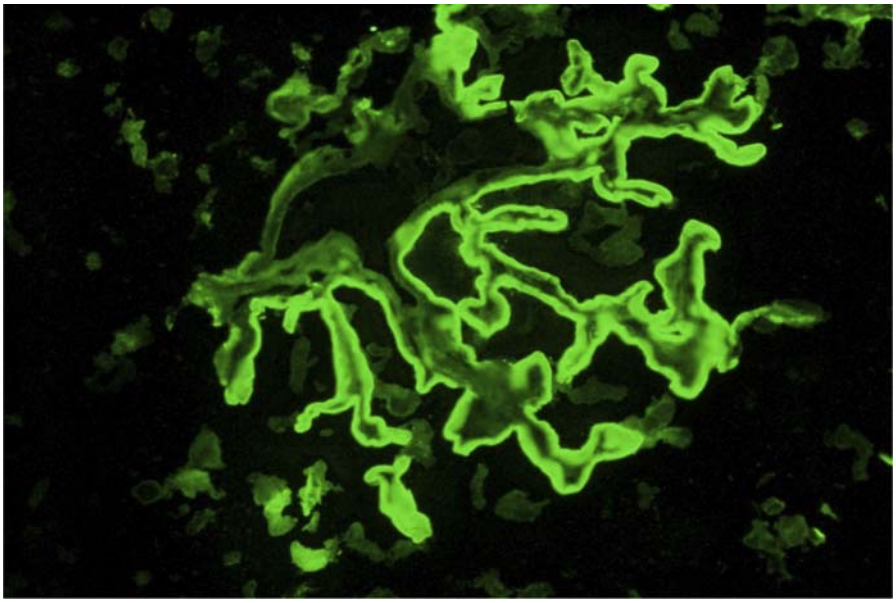

Figure 3. Immunofluorescence staining for immunoglobulin G showing diffuse strong linear staining pattern.

RPGN and found to have diffuse crescentic membranoproliferative GN (greater than 50% of glomeruli involved). In 2016, Nasr et al.[7] reported the largest case series of 20 patients with atypical anti-GBM disease. Our patient shared several features with Nasr et al.'s case series such as hypertension, nephrotic syndrome, mildly impaired kidney function, undetectable anti-GBM antibody, absence of pulmonary involvement, and absence of immune-complex deposition and fibrils in EM. However, none of the 20 patients in that case series had diffuse crescents on kidney biopsy.

Until recently, atypical anti-GBM disease was thought to have a relatively benign course. However, Liang et al.[8] reported that 32% of patients with atypical anti-GBM progressed to ESRD. Of patients, 16% had lung involvement, and 21% had diffuse crescents. However, none of the patients with diffuse crescents had diffuse membranoproliferative features. Of patients, 53% received immunosuppression. Another two cases of aggressive atypical anti-GBM disease with diffuse crescentic GN that progressed to ESRD despite immunosuppressive treatment were also reported.[12,13] Taken all together, these cases highlight the importance of early diagnosis and treatment of atypical anti-GBM disease as the course of the disease might not be as benign as previously thought.

To the best of our knowledge, only one case of RPGN due to atypical anti-GBM disease with diffuse crescentic membranoproliferative GN was reported in the literature.[13] However, this patient progressed to ESRD despite immunosuppressive treatment, unlike our patient whose kidney function improved following immunosuppression.

CONCLUSION

We aimed in this case report to highlight the fact that despite the high sensitivity of ELISA in detecting serum anti-GBM antibodies, atypical anti-GBM disease cannot be ruled out without performing a kidney biopsy in patients presenting with RPGN picture. Given that atypical anti-GBM is not always a benign disease, early diagnosis and immunosuppressive treatment should be considered to prevent irreversible renal damage.

REFERENCES

1. Pusey CD. Anti-glomerular basement membrane disease. *Kidney Int*. 2003;64(4): 1535 – 1550.

2. Hellmark T, Segelmark M. Diagnosis and classification of Goodpasture's disease (anti-GBM). *J Autoimmun*. 2014;48-49:108 – 112.

3. Hudson BG, Tryggvason K, Sundaramoorthy M, Neilson EG. Alport's syndrome. *Goodpasture's syndrome, and type IV collagen. N Engl J Med.* 2003; 348(25):2543 – 2356.

4. Van Daalen EE, Jennette JC, McAdoo SP, Pusey CD, Alba MA, Poulton CJ, et al. *Predicting outcome in patients with anti-GBM glomerulonephritis. Clin J Am Soc Nephrol.* 2018;13(1):63 – 72.

5. Pedchenko V, Bondar O, Fogo AB, Vanacore R, Voziyan P, Kitching AR, et al. Molecular architecture of the Goodpasture autoantigen in anti-GBM nephritis. *N Engl J Med.* 2010;363:343 – 354.

6. Troxell ML, Houghton DC. Atypical anti-glomerular basement membrane disease. *Clin Kidney J.* 2016;9(2):211 – 221.

7. Nasr SH, Collins AB, Alexander MP, Schraith DF, Herrera Hernandez L, Fidler ME, et al. The clinicopathologic characteristics and outcome of atypical antiglomerular basement membrane nephritis. *Kidney Int*. 2016;89(4):897 – 908.

8. Liang D, Liang S, Xu F, Zhang M, Li X, Tu Y, et al. Clinicopathological features and outcome of antibody-negative anti-glomerular basement membrane disease. *J Clin Pathol.* 2019;72(1):31 – 37.

9. Rosales IA, Colvin RB. Glomerular disease with idiopathic linear immunoglobulin deposition: a rose by any other name would be atypical. *Kidney Int*. 2016;89(4):750 – 752.

10. Balasubramaniyan T, Dhanapriya J, Dineshkumar T, Maasila AT, Arivazhagan S, Rajasekar D, et al. Atypical anti-glomerular basement membrane disease superimposed on IgA nephropathy. *J Integr Nephrol Andril.* 2017;4(1):26 – 28.

11. Knoll G, Rabin E. Burns BF. Antiglomerular basement membrane antibody-mediated nephritis with normal pulmonary and renal function. *A case report and review of the literature. Am J Nephrol.* 1993; 13(6):494 – 496.

12. Adapa S, Konala VM, Hou J, Naramala S, Agrawal N, Dhingra H, et al. Seronegative atypical anti-glomerular basement membrane crescentic glomerulonephritis. *Ann Transl Med.* 2019;7(11):246.

13. Sporinova B, McRae SA, Muruve DA, Fritzler MJ, Nasr SH, Chin AC. A case of aggressive atypical anti-GBM disease complicated by CMV pneumonitis. *BMC Nephrol.* 2019;20(1):29.