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Case Report Open Access

Anti-Glomerular Basement Membrane Disease Accompanied by Membrano Proliferative Glomerulonephritis: A Case Report

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Abstract

Anti-glomerular basement membrane disease is characterized by autoimmunity to antigenic sites on type IV collagen of the glomerular basement membrane. The majority of patients present with rapidly progressive glomerulonephritis and alveolar hemorrhage. The occurrence of anti- glomerular basement membrane disease and other types of glomerulonephritis, such as membranous nephropathy, IgA nephropathy and antineutrophil cytoplasmic antibodies associated vasculitis, is not uncommon. Herein, we describe a patient who presented with worsening kidney function, hemoptysis, and detectable circulating anti-glomerular basement membrane disease antibodies in serum. A kidney biopsy revealed the classical pathological finding of anti-glomerular basement membrane disease, with linear deposition of IgG along the glomerular basement membrane and diffuses extracapillary crescentic sclerosing glomerulonephritis. Likewise, the biopsy revealed a membranoproliferative pattern with abundant C3 deposition. Subsequently, the patient was diagnosed with anti-glomerular basement membrane disease and the rare concurrent existence of membranoproliferative glomerulonephritis. The patient's clinical course was unusual for the anti-glomerular basement membrane disease, with slower progressive decline in renal function and nephrotic range proteinuria. Unfortunately, the presence of membranoproliferative glomerulonephritis did not change the prognosis and the patient lost his renal function irretrievably despite immunosuppressive treatment.

Keywords: Anti-glomerular basement membrane; Goodpasture's disease; Membranoproliferative glomerulonephritis; Rapidly progressive glomerulonephritis; Nephrotic syndrome; Immune-complex glomerulonephritis

Introduction

Anti-glomerular basement membrane (anti-GBM) is characterized by autoantibodies specific to the carboxyl terminal, non-collagenous (NC1) domain of type IV collagen chain, α3 (IV) NC1 [1,2]. Type IV collagen is an essential component of all glomerular basement membranes (GBM). Anti-GBM disease, also known as Goodpasture's disease, frequently manifest as nephritic syndrome (rapidly progressive glomerulonephritis), with or without pulmonary hemorrhage [3]. The majority of patients has circulating anti-GBM antibodies in their serum and diffuse crescentic glomerulonephritis with diffuse linear deposition of IgG on renal biopsy [4]. Frequently, renal involvement is severe compared with other causes of nephritic syndrome, and most patient progress to end-stage renal disease (ESRD) despite early diagnosis and aggressive treatment. The association of anti-GBM disease and ANCA-associated vasculitis is not uncommon [5]. Likewise, concurrent occurrence of anti-GBM disease with other types of glomerulonephritis such as membranous and IgA nephropathy and Henoch-Schonlein purpura have been described in several case studies [6-11]. Membranous nephropathy is the most commonly reported immune-complex glomerulonephritis that accompanies anti-GBM disease. However, anti-GBM disease accompanied by membranoproliferative glomerulonephritis is rare and a limited number of case reports have evaluated the possible underlying pathological mechanism and clinical significance [12-15]. This report describes the unusual clinical presentation of anti-GBM disease with coexistent membranoproliferative glomerulonephritis pattern on renal biopsy.

Case Report

A 28-year-old male presented to the nephrology clinic of our institution with a 3-month history of progressive lower limb edema and dark-colored urine. He denied having any shortness of breath, fever, hemoptysis, or skin rashes. Four weeks prior to his presentation, he had experienced influenza-like illness.

He smoked 10-15 cigarettes daily for 10 years and was not taking any medications. Initial investigations revealed nephrotic-range proteinuria (3.8 g/day), renal impairment with serum creatinine 239 μ mol/L, and urine analysis demonstrated more than 50 RBC/HP, with 65% dysmorphic red blood cells (RBCs).

Serological testing for antinuclear antibodies (ANA), anti-double strand DNA antibodies, anti-neutrophil cytoplasmic antibodies (ANCA), and complements C3 and C4 were all negative. Serum anti-GBM antibodies were positive by standard enzyme-linked immunosorbent assay (ELISA).

Upon admission his chest radiograph was normal and ultrasonography revealed normal-size kidneys with enhanced cortical echogenicity.

A renal biopsy (Figures 1-3) revealed findings consistent with rapidly progressive glomerulonephritis (RPGN) secondary to anti-GBM disease with membranoproliferative glomerulonephritis.

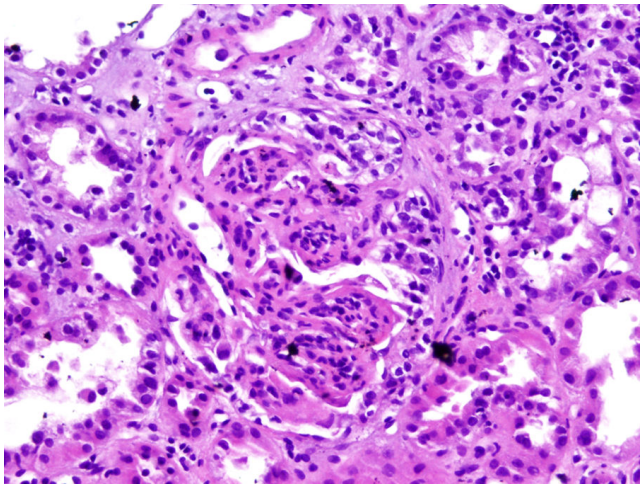

Figure 1: A glomerulus showing a membranoproliferative pattern with a fibro cellular crescent (H&E, 200X).

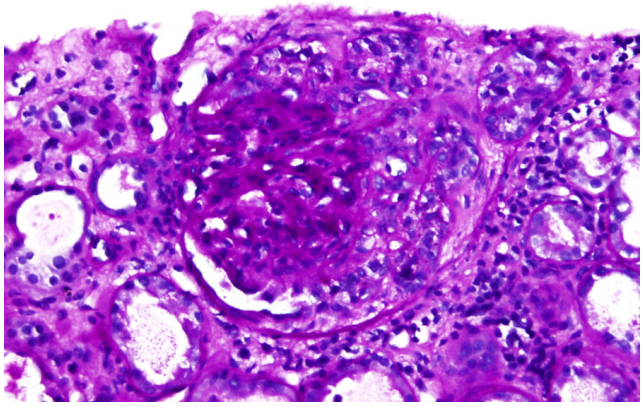

Figure 2: A glomerulus showing cellular proliferation and mesangial matrix expansion with a crescent (PAS, 200X).

Immunofluorescence study showed linear staining of the GBM for IgG (2+) along with segmental coarse granular staining for C3 (3+) along the GBM and in the mesangium (Figures 4 and 5).

IgM was positive (2+) in the collapsed segments. Negative results were obtained for IgA and C4 while C1q was unavailable. Electron microscopy demonstrated cellular crescents with segmental collapse in two of the three glomeruli examined. The intact glomerulus showed endothelial and mesangial cell proliferations with few neutrophilic infiltrates. Observed also were mesangial cell interpositioning with double-contouring of the glomerular basement membrane, a few dense deposits in the mesangium, rare sub endothelial deposits, and one small subepithelial hump (Figures 6 and 7).

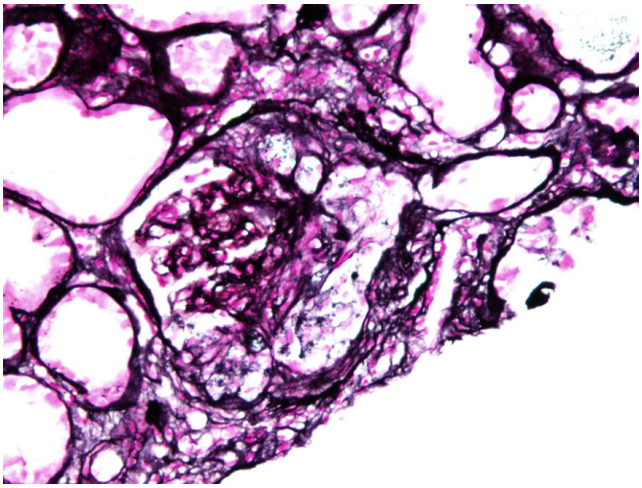

Figure 3: A glomerulus showing an increase in the mesangial matrix, disruption of the glomerular basement membrane, and double-contour with a fibro cellular crescent (JMS, 200X).

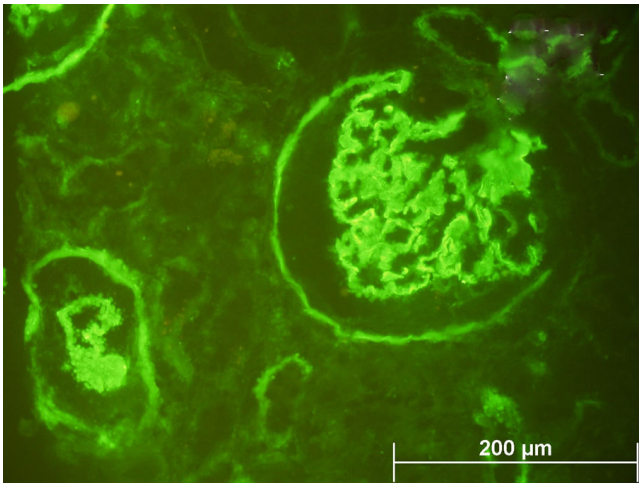

Figure 4: Linear IgG staining (2+) along the glomerular basement membrane (direct immunofluorescence 250X).

One week after admission, hemoptysis, respiratory insufficiency, severe renal impairment, and anemia needing transfusions were documented. Treatment with plasmapheresis, methyl prednisone (intravenous pulse 1 g/3 days followed by oral prednisone 1 mg/kg/day) and oral cyclophosphamide 2 mg/kg/day were initiated. Furthermore, the patient required urgent hemodialysis for volume overload and resistant hyperkalemia.

One month later, hemoptysis subsided but the patient remained dialysis-dependent. Oral prednisone was tapered down and cyclophosphamide was continued for the next 6 weeks. Anti-GBM antibodies were not detectable throughout the treatment period.

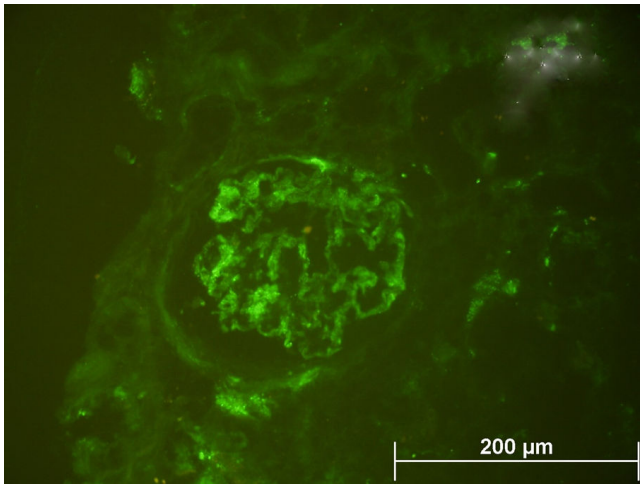

Figure 5: Segmental coarse granular staining of C3 along the capillary loops and the mesangium (direct immunofluorescence 250X).

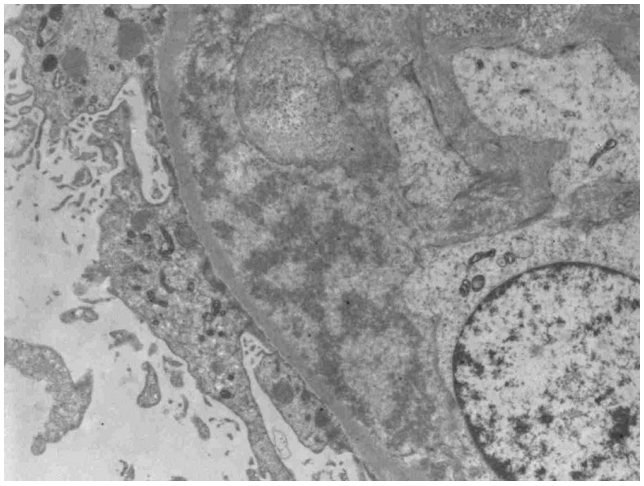

Figure 6: Transmission electron micrograph showing sub endothelial deposits with mesangial cell interposition (uranyl acetate and lead citrate, 5800X).

Discussion

This report describes a patient who presented initially with renal impairment, nephrotic-range proteinuria, and features suggestive of glomerulonephritis. Shortly after admission, the patient's clinical course deteriorated with worsening renal function and pulmonary hemorrhage. The diagnosis of anti-GBM disease was made after demonstration of anti-GBM antibody positivity in serum and presence of the classical crescent sclerosing glomerulonephritis with IgG deposition along the GBM. In addition, there was an incidental finding of membranoproliferative pattern with significant (+3) coarse segmental C3 staining along the GBM and mesangium. Other diseases that display a membranoproliferative pattern, such as infection, malignancy, and autoimmune disease were ruled out. This is not the first report to describe the co-existence of anti-GBM disease with other types of immune complex glomerulonephritis. In a case series, Cui et al. [12] estimated the prevalence of immune complex glomerulonephritis and anti-GBM disease in a Chinese cohort to be 28.0%. However, anti-GBM disease with membranoproliferative glomerulonephritis is very rare and there are only 4 reports in the literature that described their clinical picture and possible pathological existence [12-15].

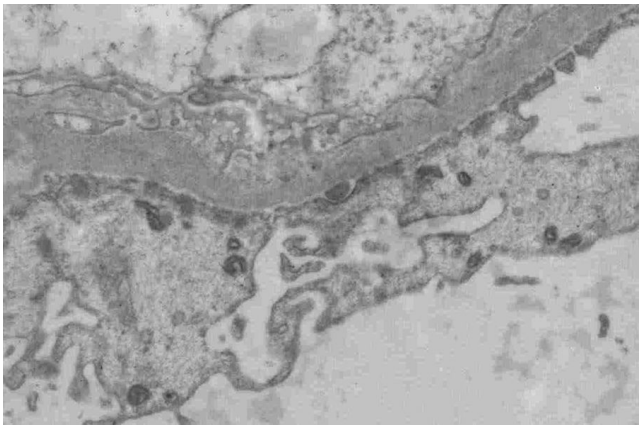

Figure 7: Transmission electron micrograph showing small sub endothelial humps deposits (uranyl acetate and lead citrate, 13500X)

Existing reports did not identify unique clinical, pathological or laboratory features for anti-GBM disease accompanied by membranoproliferative glomerulonephritis. However, nephrotic syndrome with mild progressive renal impairment has been described in previous reports of anti-GBM disease with proliferative glomerulonephritis and could consider this presentation as a distinguishable feature for anti-GBM disease accompanied by membranoproliferative glomerulonephritis [12,15]. Considering this clinical presentation, it is reasonable to hypothesize that in this patient, membranoproliferative glomerulonephritis preceded the onset of anti-GBM disease. The likely pathological mechanism underlying the course of immune complex-glomerulonephritis with exposure of GBM antigens might subsequently lead to the production of anti-GBM antibodies, as supported by animal model studies [16]. Moreover, several case reports describe membranous nephropathy evolved to anti-GBM disease [17,18]. On the other hand, progression of anti-GBM disease to membranous nephropathy has been documented in several reports [19-21]. This was demonstrated in experimental studies, where it was reported that anti-GBM disease and glomerular-bound anti-GBM antibodies might alter the GBM permeability and predispose it to the deposition of different molecules with particular affinity for these antibodies [22]. Whether anti-GBM disease occurs secondary or prior to immune-complex glomerulonephritis, the pathogenesis is due to an autoimmune process in the GBM (localized) and the association of immune complex glomerulonephritis and anti-GBM disease is definitely not coincident. Unfortunately, previous reports confirmed that this association did not seem to lead to a favorable prognosis [23]. In our patient, despite the uncommon clinical presentation for anti-GBM disease, he was initiated on intense immunosuppressive treatment once the diagnosis was reached. Extra-

renal manifestation subsided and anti-GBM antibody titers were undetectable; however, he remained hemodialysis-dependent.

Conclusion

This is one of the few reports that describe the coexistence of anti-GBM disease and membranoproliferative glomerulonephritis. The exact pathological mechanism might involve multiple unrelated or interrelated autoimmune responses at the level of the GBM. The sub-acute clinical course, accompanied by the presence of membranoproliferative glomerulonephritis, should not delay the early initiation of aggressive immunosuppressive therapy as there is a narrow window for effective treatment.

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