

Case Report

Atypical anti-glomerular basement membrane disease with IgA nephropathy: a case report

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Abstract: Anti-glomerular basement membrane (anti-GBM) disease is characterized by strong linear IgG staining along GBMs, and accompanied by necrotizing and crescentic glomerulonephritis, along with measurable serum anti-GBM antibodies. Although anti-GBM disease accompanied with other immunocomplexes was discussed previously in some papers, atypical anti-GBM disease combined with IgA deposition in the mesangial was rarely reported. We report a rare case of a 31-year-old female presenting with rapidly progressive glomerulonephritis, who was diagnosed with atypical anti-GBM disease with IgA nephropathy. Therapies with intravenous methylprednisolone, plasmapheresis and cyclophosphamide administration were less effective. This is different from the classic anti-GBM disease. Further studies are needed to characterize the mechanism in these patients and establish optimal therapy.

Keywords: Anti-GBM disease, kidney biopsy, IgA nephropathy

Introduction

Anti-glomerular basement membrane (anti-GBM) disease is characterized by IgG linear deposition along the non-collagenous 1 (NC1) domain of $\alpha 3$ chains of type IV collagen on the GBM. The patient clinically manifests with rapidly progressive glomerulonephritis or pulmonary hemorrhage (Goodpasture syndrome). In a limited number of cases, the coexistence of anti-GBM disease and other immune complex-mediated glomerulonephritis was reported. The present study reports the case of a patient who was diagnosed with anti-GBM disease with IgA nephropathy.

Case report

A 31-year-old female with proteinuria, obvious hematuria, progressive renal impairment, was admitted to our hospital. She denied hemoptysis, skin rash, or joint pain. And physical examination was unremarkable. Laboratory analysis revealed the following values: proteinuria (4 g/24 h), obvious hematuria (1089 cells/ μ l), albumin 32.1 g/L, hemoglobin 104 g/L. And from July 1, 2016 to July 19, 2016, her serum

creatinine (Scr) rose from 114 to 226 μ mol/L. Nuclear antibodies were positive with a speckled (1:100), while antibodies against double-stranded DNA, anti-neutrophil cytoplasmic antibodies (ANCA), complements, anti-GBM antibody (19.7, normal range: 0-20 RU/ml) were negative. Renal ultrasound showed no obstruction, and chest CT did not suggest pulmonary hemorrhage.

Subsequently, a renal biopsy was performed. Light microscopy identified 33 glomeruli with 8 cellular crescents, 1 cellulosifibrous crescents, 4 segmental cellular crescents and 2 glomerular sclerosis (41.9% glomeruli crescents). Immunofluorescence showing bright polytypic linear GBM staining for IgG (IgG++++, IgG1+++), IgG4++), lumpy deposition of IgA (++++), IgM (+++), C3 (+++) in the mesangium (**Figure 1**), and no detectable staining for C4, C1q, Fibrin, HBs, Hbc, IgG2, IgG3, PLA2R. Electron microscopy revealed electron dense deposition in the mesangium.

Based on the aforementioned findings, the diagnosis of atypical anti-GBM disease with IgA nephropathy was confirmed. The patient

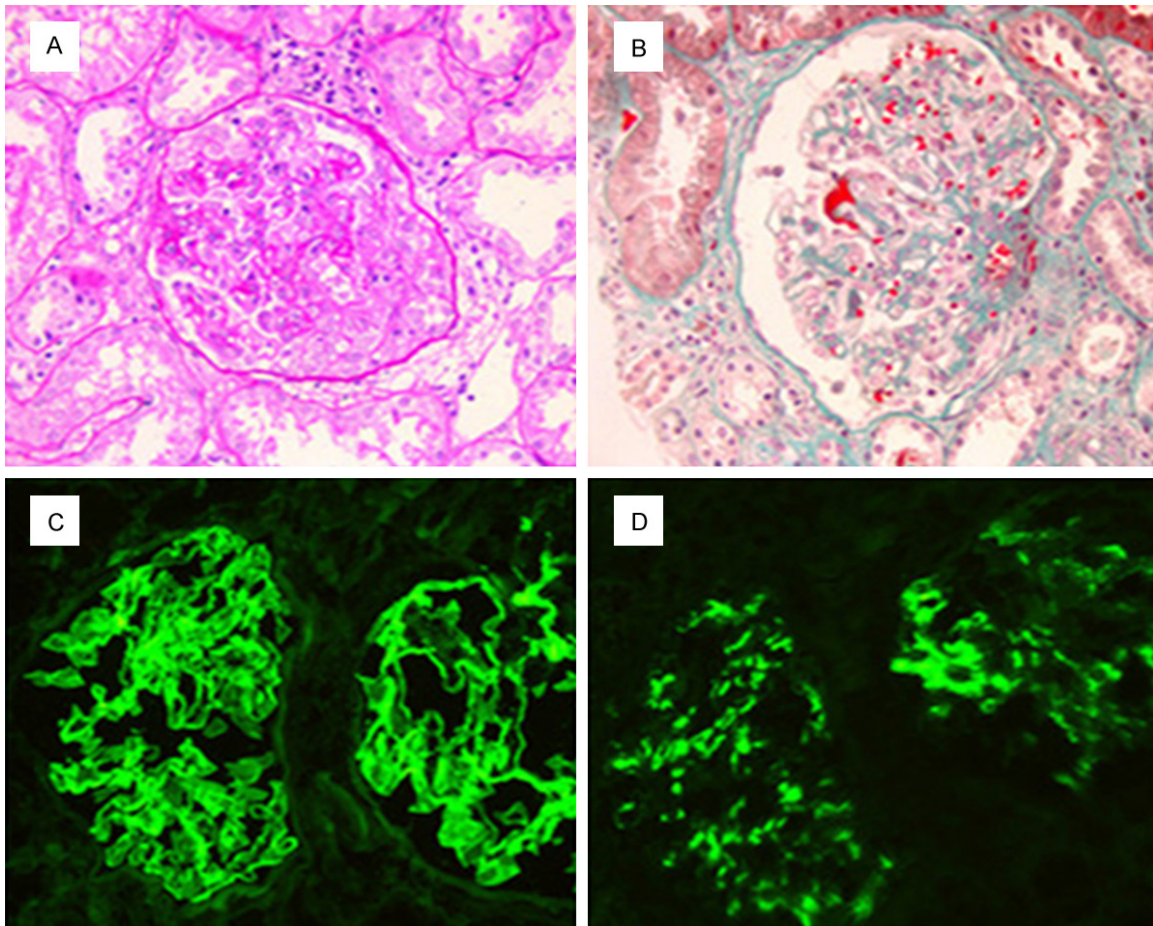


Figure 1. Light microscopy shows hypercellularity with cellularofibrous crescent (A. HE, B. PAS); Immunofluorescence micrographs show bright polytypic linear GBM staining for IgG (+++++) (C), diffuse mesangial staining for IgA (+++++) (D).

received 500 mg/d intravenous methylprednisolone for 3 days, and plasmapheresis for five times, followed by intravenous cyclophosphamide (750 mg/m²/month) and methylprednisolone (40 mg/d) for maintenance monotherapy. After 2 months of therapy, the amounts of anti-GBM antibody decreased to 2.3 RU/ml, while her Scr level remained at 350 μ mol/l, and persistent gross hematuria had been seen (3000 cells/ μ l).

Discussion

Classic anti-GBM disease classically presents with rapidly progressive glomerulonephritis, while pulmonary hemorrhage occurs in 34% to 62% of patients [1]. On biopsy, most cases show bright polytypic linear GBM staining for IgG by immunofluorescence, and diffuse crescentic and necrotizing GN on light microscopy [2]. However, some patients exhibited nonlinear

IgG deposits, indicating the involvement of immune complex mediated disease. Several studies described the occurrence of other immune complexes in this condition. The coexistence of anti-GBM disease and immune complex-mediated disease such as membranous nephropathy, Schonlein-Henoch nephritis, membranoproliferative glomerulonephritis, and hepatitis B virus associated membranous nephritis were reported [3-5]. It is widely recognized that the combination therapy of plasmapheresis plus corticosteroids and cyclophosphamide had an overall beneficial effect on both patient survival and renal survival for those with typical anti-GBM nephritis [6].

Atypical anti-GBM nephritis is a rare variant of anti-GBM disease characterized by an indolent course, no pulmonary involvement, undetectable circulating anti-GBM antibody, absent or focal crescents, monoclonal antibody-associat-

ed anti-GBM disease involved IgG, IgA, IgM, or light chain only [6, 7]. In the present study, a rare case of anti GBM disease with IgA nephropathy was reported [3, 8, 9].

In this case, we report a patient with proteinuria, obvious hematuria, progressive renal impairment, clinical characteristics in accordance with RPGN. Laboratory analysis indicated no pulmonary involvement, undetectable circulating anti-GBM antibody. And according to the renal biopsy immunofluorescence, bright linear GBM staining for IgG, mesangial staining for IgA, the diagnosis of atypical anti-GBM disease with IgA nephropathy is confirmed. Subsequently, the patient received the standard treatment with intravenous methylprednisolone, plasmapheresis, in combination with cyclophosphamide administration. However, her Scr level remained at 350 $\mu\text{mol/l}$, and persistent gross hematuria had been seen. These limited data suggest that the patients appear irresponsive to conventional immunosuppressive therapy. We speculate that the IgA-mediated glomerulonephritis may have a major pathogenetic role in tissue injury, which is consistent with the literature reported before [9]. However, the association between these two diseases was unclear.

IgA nephropathy is an immune complex-mediated glomerulonephritis defined immunohistologically by the existence of IgA deposits predominantly in the mesangial area, and these immune complexes may lead to renal injury [10]. Anti-GBM disease is characterized by circulating anti-GBM antibodies, normally the NC1 domain of the alpha-3 chain of type IV collagen (α3NC1) [11], and deposition of these antibodies in the renal GBM. Notably, our patients had negative testing for circulating anti-GBM antibody against α3NC1 . As mentioned in an article [7], several possible explanations may support for the negative results: (i) In addition to the classic antibody, autoantibodies against other type IV collagen GBM antigens, including α5NC1 , α4NC1 , and native α345NC1 are frequent, and therefore would not be detected by ELISA or Western blot that use purified or semi-purified α3NC1 antigens; (ii) The autoantibodies could be circulating at low levels. The absence of the classic antibody may have a profound influence on the pathogenesis of the atypical anti-GBM nephritis.

Wang A et al [9] revealed the possibility of increased antigen synthesis, exposure of cryptic epitopes, or capping and shedding of antigen-antibody complexes. Another report study [3] indicated that, the IgA deposits may promote the release of inflammatory mediator, such as IL-1, TNF, and then initiate immunologic inflammatory events resulting in conformational changes of the glomerular basement membrane and exposure of the GBM antigens, thus facilitating anti-GBM antibody generation. It was reasonable to speculate that anti-GBM disease might occur secondary to or simultaneously with the IgA-related immune complex deposition. In short, strong IgA deposition in the renal tissue may have a profound impact on the pathogenesis of this disease, yet the underlying mechanism renders further in depth examination.

In conclusion, we report what is to our knowledge the rare case of atypical anti-GBM nephritis associated with IgA nephropathy, while it showed less effective to the standard treatment. Therefore, an urgent need to make further investigation to identify the characteristics of this rare atypical anti-GBM nephritis should be on the agenda.

Disclosure of conflict of interest

None.

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Atypical anti-GBM disease with IgA nephropathy

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