Case Report

SAGE Open Medical Case Reports

SAGE Open Medical Case Reports
Volume 11: 1–5

DOI: 10.1177/2050313X231189767
journals.sagepub.com/home/sco
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Anti-GBM disease with positive serum anti-GBM antibodies but negative IgG deposition: A case report

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Abstract

Anti-glomerular basement membrane antibodies are significantly specific for detecting anti-glomerular basement membrane disease. These antibodies are typically targeted against the non-collagenous (NC1) domain of the alpha 3 chain of type IV collagen and, to a lesser extent, the α4(IV) or α5(IV) chains, which create a triple-helical structure in the glomerular basement membrane. The modification of the hexameric structure of NC1 (α3(IV)) results in the exposure of new epitopes, leading to an immune reaction and the subsequent deposition of linear antibodies along the glomerular basement membrane, culminating in crescentic glomerulonephritis. Anti-glomerular basement membrane antibodies that are positive are believed to be pathogenic and capable of binding to the glomerular basement membrane in vivo, particularly in the context of rapidly progressive glomerulonephritis. Herein, we present a patient with positive serum anti-glomerular basement membrane antibodies but negative IgG deposition. The current findings are significant for raising physicians' awareness of the probable errors in detecting anti-glomerular basement membrane antibody disease as a possible cause of irreversible kidney failure.

Keywords

Anti-glomerular basement membrane antibodies, IgG deposition, glomerulonephritis, anti-GBM disease, crescentic glomerulonephritis

Date received: 13 April 2023; accepted: 7 July 2023

Introduction

Anti-glomerular basement membrane (anti-GBM) disease is a classic autoimmune small vessel vasculitis. It is described by the presence of pathogenic autoantibodies aimed against the non-collagenous (NC) domain of the α3 chain of type IV collagen,[1,2] which is exclusively found in the basement membranes of the glomerulus, alveoli, choroid plexus, eye, cochlea, and testis. Nevertheless, the disease almost always manifests with the involvement of glomerular capillaries, and to a lesser extent, pulmonary alveoli. Other organs are spared due to the limited access of the circulating antibodies to the tissue basement membrane.[3] Although the severity of the disease varies among individuals, it could result in advanced glomerular injury and therefore irreversible kidney failure.[4] The diagnosis is initially formulated by serological detection of the circulating anti-GBM antibodies and later confirmed by immunohistopathology. Regarding histological findings, a crescent is made up of proliferating epithelial cells that line the Bowman capsule and infiltrating macrophages.[5]

Anti-GBM antibodies are highly specific for this condition. Therefore, detecting anti-GBM antibodies with related clinical manifestations of glomerulonephritis can be considered a diagnostic way of this disease.[6] Enzyme immunoassays, fluorescence assays, and western blotting are different antibody detection methods.[3] Direct immunofluorescence

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for detecting deposited antibodies is a gold standard for anti-GBM disease diagnosis. Also, crescent formation as a histopathological indication of this disease can be observed in renal biopsy as another diagnostic way.[3,7]

In this study, we aimed to present an atypical case of anti-GBM disease which was detected and confirmed by serologic testing and biopsy. However, deposited antibodies were not observed while testing.

Case presentation

A 58-year-old woman, a resident of the province of Isfahan, Iran, presented with the chief complaint of dyspnea. She also had diabetes and hypertension detected 4 years ago and had been followed up ever since. Her serum creatinine (Cr) has maintained an approximate level of 0.9 mg/dl during this period. Last month, a sudden increase of serum creatinine up to 8 mg/dl was detected. Therefore, she received dialysis three times due to her symptoms, including fluid overload and drowsiness. In sonography, both kidneys were observed with normal size and her serum was positive for the anti-GBM antibody. Then she was referred to a referral hospital where more diagnostic tests were carried out. At that time, her platelet count was 90,000. According to her thrombocytopenia and anemia, a peripheral blood smear was required to evaluate the pancytopenia state. The results revealed hypochromic and microcytic erythrocytes with anisopoikilocytosis. Polychromasia was seen and leukocytes were normal in the count with granulocytic predominancy. Moderate thrombocytopenia was detected. The repeated serologic study also showed elevated anti-GBM antibodies. The brownish color of the urine revealed gross hematuria.

The patient underwent an ultrasound-guided renal biopsy to evaluate proteinuria and hematuria and found a definite diagnosis. The biopsy consisted of two pieces of cortical tissue containing 45 glomeruli. Ten of them were globally sclerosed and the others showed mesangial expansion with an increase in cellularity. Twenty-one of the glomeruli showed cellular to fibrocellular crescent formation and endocapillary proliferation. Three of them showed capsular rupture. Also, nine glomeruli with segmental sclerosis, adhesive to the Bowman capsule, and three fibrous crescents were observed. The tubules showed a simplification of their lining with proteinaceous casts in their lumen and about 10%–20% atrophic changes. There was proportional fibrosis of the interstitium lymphocytic infiltration in the scarred and non-scarred areas making tubulitis. The arterioles were unremarkable. Five interlobular arteries showed subintimal fibrosis and large arteries were not sampled. Active lesions included mesangial proliferation in all, 21 glomeruli with cellular to fibrocellular crescent formation and endocapillary proliferation, and 3 ruptured capsules of glomeruli in favor of severe activity of the disease. Chronic lesions included 9 segmentally and 10 globally sclerosed glomeruli with 1 fibrous crescent. Consequently, diffuse crescentic glomerulonephritis (GN) was detected by biopsy (see Figures 1 and 2). Despite elevated anti-GBM antibodies, expected linear immunoglobulin G (IgG) deposition in immunofluorescence microscopy was not detected. The immunofluorescent study was repeated two times in two runs of testing and control polyvalent antisera was present in every run of the test. Based on the serological detection of anti-GBM antibodies, along with the

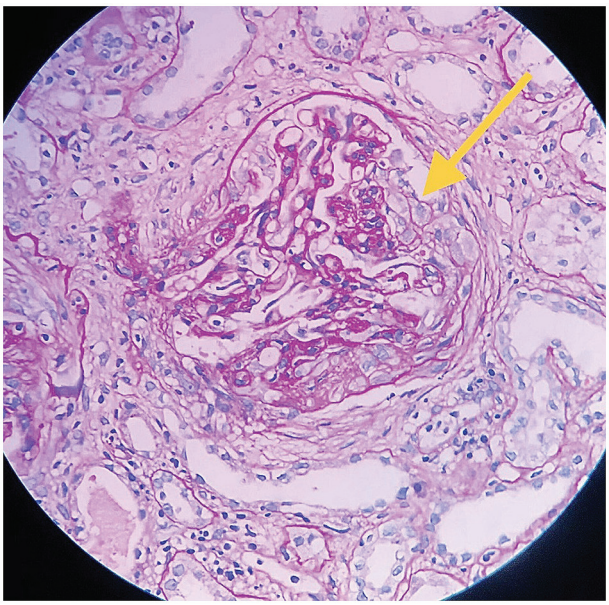

Figure 1. Atrophic proximal tubules and a glomerulus (arrow) with a cellular crescent, composed of a proliferation of parietal epithelial cells; Periodic Acid Schiff staining x400.

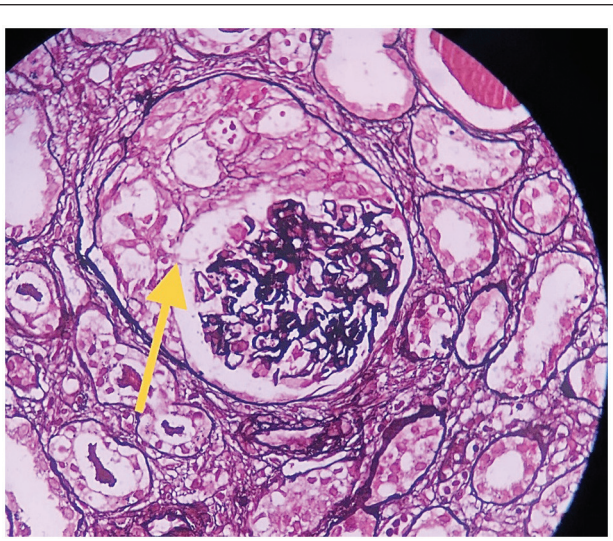

Figure 2. Atrophic proximal tubules and a glomerulus (arrow) with a fibrocellular crescent composed of a proliferation of parietal epithelial cells of Bowman capsule admixed with fibrin and fibrous matrix; Jones staining, x400.

Table 1. Changes in the patient's serum creatinine (Cr) and blood urea nitrogen (BUN) in the hospital stay days were reported daily from the first day to the last day of hospitalization.

Cr (mg/dl)	3.1	3.6	4.0	4.7	2.9*	4.0	5.0	5.1	4.1	4.3	4.2	4.1	4.0	4.1	3.8	3.6
BUN (mg/dl)	26	33	33	43	22	35	59	73	69	76	78	74	75	72	67	59

*After dialysis.

related immunohistopathological findings, the anti-GBM disease was speculated. Subsequently, we planned a treatment approach with cyclophosphamide and plasmapheresis (five times), which resulted in a significant decrease in serum Cr level (Table 1). Due to the patient's positive response to the aforementioned treatments, chronic dialysis was not required.

Regarding differential diagnosis, systemic lupus erythematosus was ruled out due to negative results on antinuclear antibodies (ANA) and anti-dsDNA (double-stranded deoxyribonucleic acid). Due to the negative results of the antineutrophilic cytoplasmic antibody (ANCA) test, ANCA-associated glomerulonephritis was excluded.

Because of the concurrent involvement of renal and pulmonary systems in about 50% of patients with the anti-GBM disease,[8] a comprehensive pulmonary exam along with a chest X-ray was performed, which did not detect simultaneous pulmonary involvement.

Discussion

Diagnosing the anti-GBM disease requires a holistic medical approach. Besides reviewing the patient's symptoms and medical history, serological detection of anti-GBM antibodies and immunohistopathological analysis of the kidney biopsy specimen are fundamental.[9] Anti-GBM antibody detection in conjunction with glomerulonephritis is the mainstay of the diagnosis.[6] These antibodies are demonstrated in serum with enzyme-linked immunosorbent assay in approximately 90% of patients. Another hallmark of the anti-GBM disease is continuous linear immunoglobulin (especially IgG) deposition along GBMs which is detected by immunofluorescence microscopy. In kidney biopsy, tissue injury usually manifests as diffuse crescentic glomerulonephritis. Regarding their signs and symptoms, most patients present with significantly elevated serum Cr and hematuria.[10]

A systematic review and meta-analysis reported that the sensitivity and specificity of anti-GBM antibody detection in diagnosing anti-GBM disease were 93% and 97%, respectively.[11] In another study, Qu et al.[12] claimed that IgG deposition was detected among all patients with anti-GBM disease. Large biopsy series suggest that 95% of patients will have evidence of crescent formation on kidney biopsy, and that in 80% of patients $>$50% of glomeruli will be affected.[3]

Regarding its immunopathogenesis, the GBM contains type IV collagen molecules which are composed of triple-helical protomers (α3, α4, and α5 chains). The NC part of the α3 chain was defined as the target of immune response in anti-GBM disease. The clinical pattern of this disease shows the restricted expression of this antigen to GBM. In native GBM, two autoantibody epitopes within the autoantigens are often sequestered in the quaternary structure of the NC part of α3, α4, and α5 chains.[3] Sera of patients with anti-GBM disease react to NC part of α3(IV) chain. Additionally, there are antibodies directed against α4 and α5 chains in serum as well as upon elution from renal tissue. In 1967, Lerner et al. transferred these antibodies from the renal tissue of patients suffering from the anti-GBM disease to nonhuman primates. This process led to the presentation of crescentic GN in them, which clarifies the pathogenic potential of these antibodies.[13,14]

The main reason for not seeing a deposition in this patient is not clear yet. Reviewing the literature, the absence of linear binding in vivo is intriguing. The antibodies' capacity to bind fixed primate kidney and collagenase-digested human GBM, however, implies that a conceivable explanation for this lack may be attributed to the patients not having the requisite epitope to facilitate antibody binding. Due to the aforementioned quaternary structure of the α3(IV) hexamers, antigenic epitopes might be expressed with cryptic nature. Although autoantibodies might be able to bind some monomer-containing hexamers, they do not bind those containing dimers (D-hexamers) and monomers (M-hexamers) together.[15] Some studies suggested that alternations in the proportion of D- and M-hexamers might prevent antibody binding due to the consequent lack of exposure of appropriate M-hexamers to GBM.[16,17] There is still a question as to how the immune response to α3(IV) was generated at first which might have involved some degradation of GBM. Noticeably, an experimental model has been delineated, wherein T cell-mediated anti-GBM damage is instigated in the absence of antibody deposition, which can provide a potential disease mechanism.[18]

Another reason could be due to the limited amount of affected glomeruli, which were possibly not included in the biopsied tissue.

As mentioned before, ANCA-associated GNs were ruled out in this case. However, co-presentation with anti-GBM and ANCA antibodies is rare. A large cohort study claimed that double-positive patients manifest a longer duration of symptoms before diagnosis, a greater tendency to recover, as well as much more evidence of chronic injury in renal biopsy in comparison with patients with the anti-GBM disease. However, general patient survival was similar in both groups. Another noticeable point is after a

follow-up of approximately 5 years, no disease relapses were observed in single-positive anti-GBM patients but half of the survived double-positive patients experienced relapses.[19]

Exploring literature, there were some atypical presentations of this disease reported in some studies. For instance, two studies reported two different cases of anti-GBM disease with IgG deposition; however, serological examination revealed negativity for anti-GBM antibodies and kidney biopsy showed cellular crescents.[20,21]. Yao et al.[22] reported another atypical case with rapidly progressive glomerulonephritis diagnosed with the anti-GBM disease with IgA nephropathy. Bulanova et al.[23] presented a case of a young man without renal failure and with isolated hematuria as the only renal manifestation. Herein, we presented another atypical presentation of anti-GBM disease with positive anti-GBM antibody in serum but negative IgG deposition.

Conclusion

The present study's discoveries shed light on the fact that a subset of patients may exhibit anti-GBM antibodies that do not bind to their own GBM. This finding carries significant implications for clinical diagnosis, indicating that obtaining histological confirmation of kidney injury via anti-GBM antibodies is necessary, since nonbinding GBM antibodies may be linked to noteworthy renal recovery. As a suggestion, it is best to consider all aspects of diagnostic ways when one of them seems to be against the clinical manifestations. In this way, physicians can better counsel the patients and manage their condition.

Author's contributions

K.K.: Drafting the article, reviewing literature, and revision. E.K.N. and A.N.: Review and editing the article. F.M.: Supervision and editing the article.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

Consent statement

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

Ethics approval

Our institution does not require ethical approval for reporting individual cases or case series.

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