Rapidly Progressive Glomerulonephritis with Delayed Appearance of Anti-Glomerular Basement Membrane Antibody Successfully Treated with Multiple Courses of Steroid Pulse Therapy

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Keywords
Rapidly progressive glomerulonephritis · Delayed appearance of antibody · Anti-glomerular basement membrane antibody · Immunoglobulin G subclass

Abstract
Patients with anti-glomerular basement membrane (GBM) antibody glomerulonephritis typically exhibit rapidly progressive glomerulonephritis (RPGN). The renal outcome as well as the prognosis of this disease is worse than other forms of RPGN such as those from microscopic polyangiitis. Therefore, early therapeutic intervention is essential to improve its prognosis. One month before referral to our hospital, a 54-year-old female attended another hospital because of macrohematuria. At that time, she had proteinuria and macrohematuria with normal renal
function, was negative for anti-GBM antibodies, and was diagnosed with chronic glomerulonephritis. A month later when she was admitted to our hospital, she showed renal insufficiency and was positive for anti-GBM antibodies. Immediately after recognizing the anti-GBM antibody status, plasma exchange and the first course of steroid pulse therapy was started. After 5 days of therapy, renal biopsy confirmed severe crescentic glomerulonephritis in which all the observed glomeruli were involved with cellular crescents. Despite this, she survived without end-stage renal disease after three courses of steroid pulse therapy and seven sessions of plasma exchange. This favorable outcome reflects the repeated analysis of anti-GBM antibodies within a very short period and the rapid therapeutic intervention in addition to the intensive immunosuppressive therapies.

Introduction

Anti-glomerular basement membrane (GBM) disease is characterized by crescentic glomerulonephritis with the pathological finding of linear IgG deposition along the GBM [1]. Immunological findings revealed that specific antibody epitopes are hidden parts of the noncollagenous-1 domain of alpha-3 and -5 chains of type IV collagen, which are occasionally exposed by infection, smoking, and toxic substances [2]. In terms of the pathological pathway, anti-GBM antibody binding induces the accumulation of inflammatory cells and cytokines, resulting in rupture of the GBM. Subsequently, the leakage of fibrin and inflammatory cells outside the Bowman's capsule mediates epithelial cell proliferation and crescent formation.

Clinically, most patients display rapidly progressive glomerulonephritis (RPGN), in which renal failure progresses very rapidly, resulting in end-stage renal disease in two-thirds of patients after 6 months of follow-up despite modern treatments [1]. Therefore, a prompt diagnosis and the immediate initiation of treatment are essential [1]. In this report, we describe a rare case in which we initiated intensive immunosuppressive treatment immediately after recognizing the positive anti-GBM antibody status that had been negative 1 month previously. Renal function was preserved without the need for renal replacement therapies, even though all the observed glomeruli were affected by crescent formation.

Case Report

A 54-year-old female with no medical history noticed dark urine 8 weeks before admission to our hospital, and high fever (>38°C) appeared 2 weeks later. She was admitted to another hospital 4 weeks before referral to our hospital. At that time, she showed macrohematuria and proteinuria (urinary protein/urinary creatinine ratio: Up/Ucr 2.0 g/gCr), and her serum creatinine level was 0.88 mg/dL. She did not have edema and her body weight remained unchanged as before and was 81 kg. Accounting for the creatinine production level estimated by her body weight, her renal function was supposed to be normal. Both anti-GBM (3.2 U/mL; minimal detection level 7 U/mL, BML, Tokyo, Japan) and anti-ANCA antibodies were negative. Antibiotics had no effect on her fever and serum complement levels were normal (C3 195 mg/dL, C4 54.6 mg/dL, CH50 101 U/mL). She was diagnosed with chronic glomerulonephritis and referred to our hospital for renal biopsy.

On admission, her vital signs were as follows: body temperature, 37.1°C; blood pressure, 146/96 mm Hg; heart rate, 81 beats/min; SpO₂, 98% (room air). There was no peripheral
edema and her urine volume was 2,000 mL/day. Other physical examinations including otorhinolaryngology were normal. Chest X-ray and computed tomography showed no alveolar hemorrhage or interstitial pneumonia.

She displayed renal dysfunction (blood urea nitrogen, 27 mg/dL; serum creatinine, 1.62 mg/dL), and had persistent macrohematuria and proteinuria (Up/Ur 3.06 g/gCr). Her hemoglobin level was 9.4 g/dL, and C-reactive protein (CRP) level was 13.98 mg/dL. As RPGN was highly suspected at this point, we repeatedly measured anti-GBM antibodies on the first day of admission and obtained a positive result (52.6 U/mL; minimal detection level 3 U/mL, SRL, Tokyo, Japan) on the third hospital day. We also repeatedly measured anti-ANCA antibodies (MPO and PR3) and confirmed these were negative. At that time, she had further increase in serum creatinine level (1.62 mg/dL to 2.00 mg/dL). Immediately after recognizing the anti-GBM antibody-positive status, we started methylprednisolone pulse therapy (1 g/day for 3 days) and plasma exchange (seven sessions for 3 weeks) (Fig. 1). We treated this patient with plasma exchange using 5% albumin instead of fresh-frozen plasma as volume replacement, which is associated with fewer adverse reactions than plasma exchange using fresh-frozen plasma as previously described [3]. Also, we adjusted the frequency of plasma exchange (less than 3 sessions per week) and kept the patient’s fibrinogen level to more than 200 mg/dL to avoid hemorrhagic complication.

On the eighth hospital day, we performed renal biopsy to confirm crescentic glomerulonephritis. Renal biopsy specimens included 16 glomeruli of which six were global sclerosis and four were segmental sclerosis; cellular crescents were present in all glomeruli with or without glomerular sclerosis (Fig. 2a and b). Inflammatory cell infiltration was detected in over 50% of the renal interstitium with moderate to severe interstitial fibrosis and tubular atrophy (Fig. 2c and d). Linear IgG deposits were detected along the glomerular capillaries, which was compatible with anti-GBM glomerulonephritis (Fig. 2e). To gain further insight into IgG deposition on GBM, we examined IgG subclass in the glomeruli. As shown in Figure 2f–i, IgG1 subclass is predominant in the glomeruli. We also confirmed IgG4 is negative in the glomeruli. Indeed, her HbA1c (NGSP) level is 6.7% on admission to our hospital. Her diabetes vintage was unclear, because she had never received a health checkup. However, she did not have any diabetic neuropathy including autonomic neural dysfunction as well as diabetic retinopathy. Furthermore, light microscopic examination of renal biopsy did not show any diabetic change in the vessels (hyalinosis) and glomeruli (mesangial expansion). In this case, linear IgG deposition on GBM (Fig. 2e–i) was not associated with diabetic nephropathy, in which faint linear IgG deposition on GBM is sometimes observed. During steroid treatment, she did not require any anti-diabetic drugs or insulin.

After the first course of steroid pulse therapy, macrohematuria, high fever, and elevated CRP were temporarily improved. However, with the daily administration of 40 mg oral prednisolone, macrohematuria appeared again and the patient’s body temperature and CRP were gradually elevated within 2 weeks (Fig. 1). From the 16th hospital day, she was repeatedly treated with a second course of steroid pulse therapy (1 g/day for 3 days), and the dose of oral prednisolone administration was increased to 60 mg/day. These abnormalities were rapidly reversed after the second course of steroid pulse therapy, but again relapsed with 2 weeks of oral prednisolone (Fig. 1). From the 30th hospital day, a third course of steroid pulse therapy (500 mg/day for 3 days) was performed, and the patient responded rapidly. She was successfully treated with oral prednisolone with cyclophosphamide after the third steroid pulse therapy. The titer of anti-GBM antibody and serum creatinine was gradually decreased from 87.3 U/mL and 6.33 mg/dL to 12.2 U/mL and 3.01 mg/dL, respectively, at the time of discharge.
(Fig. 1). Thirteen months after discharge from our hospital, she remained stable on renal function and negative anti-GBM antibody status (<2.0 U/mL) with the daily administration of 10 mg oral prednisolone. She did not have hematuria (1–4/HPF) nor overt proteinuria (Up/Ucr 0.37). Her serum creatinine level was 2.95 mg/dL, which was comparable with the level at the time of discharge.

Discussion

Anti-GBM disease has a worse renal prognosis than other forms of RPGN [4]. Previous reports showed that a decrease in renal function at diagnosis, the percentage of crescent formation in glomeruli, and the anti-GBM antibody titer are important risk factors for renal prognosis [4–8]. In terms of renal dysfunction at diagnosis, oliguria [8] and/or serum creatinine >500 µmol/L (>5.7 mg/dL) [5, 8] and more than 30% [4] or 75% [8] crescent formation were reported to be associated with poor renal prognosis. Indeed, Levy et al. [5] found that all patients who underwent immediate dialysis and had 100% crescent formation could not recover from dialysis dependence. The titer of the anti-GBM antibody is a good predictor of renal prognosis when patients are not initially dialysis dependent [6]. Because the level of renal dysfunction at diagnosis is associated not only with renal but also life prognosis, a rapid diagnosis and initiation of therapy are effective strategies at improving prognosis [6, 7]. In the present case, the patient survived without end-stage renal failure following the early initiation of immunosuppressive therapy, even though all glomeruli showed crescent formation.

Typically, the anti-GBM antibody titer is also a good indicator of disease activity [4, 9], but occasionally it cannot be detected in the early stages of disease [10–12]. In these cases, delays in appearance of anti-GBM antibodies in serum varied from 4 to 11 weeks [10–12]. In two out of three cases, only lung involvement was initially evident and the positive antibody status was associated with the onset of renal involvement [10, 12]. Therefore, a delay in appearance of anti-GBM antibodies in serum mostly is associated with delayed renal involvement. Another important issue about detecting anti-GBM antibody is immunoglobulin G (IgG) subclass. Basically, IgG subclass of anti-GBM antibody is IgG1, as previously reported [13]. However, anti-GBM antibody using enzyme linked immunosorbent assay (ELISA) reveals negative or borderline results in some cases with IgG2- and/or IgG4-restricted autoantibodies [14, 15]. Ossman et al. [15] reported that these patients could be confirmed by IgG4 anti-GBM ELISA or kidney biopsy and had relatively favorable renal outcome despite having severe alveolar hemorrhage in most cases [14, 15]. In the present case, anti-GBM antibody ELISAs performed by different companies are basically the same. The epitopes of both assays are exactly the same, recombinant human noncollagenous domain 1 of type IV collagen of the alpha-3 chain, but the minimal detection levels of the assays are different (7 U/mL from BML, 3 U/mL from SRL). Also, the predominant subclass was IgG1, and IgG4 was negative, the same as usual cases. Putting together these results, we reached the clear conclusion that firstly negative antibody changed to positive subsequently. Despite having significant renal involvement (macrohematuria and proteinuria), the present case was initially negative for anti-GBM antibody at the time of stable renal function but became positive for the antibody after a rapid deterioration in renal function. This indicates that a negative antibody status can be seen with renal involvement and can change to a positive one even within a month.

Immunohistological analysis of a renal biopsy is the definitive means of diagnosing anti-GBM antibody disease. However, it usually takes time to obtain the results of this analysis, and it is not always possible to perform a renal biopsy depending on the patient’s condition. In our
case, we tested the anti-GBM antibody status of the patient repeatedly over the course of a month and so could initiate intensive immunosuppressive therapy earlier than by performing a renal biopsy. This approach resulted in a favorable outcome in this case. Therefore, repeatedly testing the antibody status is recommended for patients in whom RPGN is highly suspected.

In summary, anti-GBM antibody glomerulonephritis rarely mimics chronic glomerulonephritis with normal renal function and negative antibody status in the very early stage of this disease and this negative antibody status can become positive within a month. Repeatedly testing the anti-GBM antibody status in a very short interval enabled us to initiate prompt intervention. As a result, the patient survived without end-stage renal disease after very intensive immunosuppressive therapies including three courses of steroid pulse therapy and seven sessions of plasma exchange, despite having 100% crescent formation in all the observed glomeruli.

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Statement of Ethics

Informed consent was obtained from all individual participants included in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee at which the studies were conducted and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors. The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

S.T., M.E., and T.N. conceived and designed the research; S.T., M.E., K.F., K.T., K.T., and T.N. performed the treatment; K.U, Y.M., and A.T. performed the histological diagnosis; M.E. and S.T. drafted the manuscript; S.T., M.E., S.H., Y.M., A.T., K.F., K.T., T.N., and T.K. edited and revised the manuscript.
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Fig. 1. Clinical course after the onset of anti-GBM glomerulonephritis. PSL, prednisolone; CRP, C-reactive protein.
Fig. 2. Histological findings from renal biopsy. a Periodic acid-Schiff (PAS) staining image of a low-power field (magnification ×10). b PAS staining of a high-power field (magnification ×20). All the glomeruli were involved by “cellular” crescents (black arrows), which suggested that all the crescents were formed very recently. c Masson trichrome staining image (magnification ×10). d Periodic acid methenamine silver staining (magnification ×10). White arrows indicate interstitial fibrosis and tubular atrophy. Inflammatory cell infiltration was detected in over 50% of the renal interstitium with moderate to severe interstitial fibrosis and tubular atrophy. e Immunostaining for immunoglobulin G (IgG) of a frozen section (magnification ×20). f-i Immunostaining for IgG subclass. IgG1 is positive (f), IgG2 and -3 are borderline positive (g, h), and IgG4 is negative (i).