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Case Report

Anti-GBM crescentic glomerulonephritis with intensive multinucleated giant cells: a case report

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Abstract: Anti-glomerular basement membrane (anti-GBM) disease is a rare but potentially lethal autoimmune disorder with progressive renal dysfunction in a short time span, which is accompanied with or without pulmonary hemorrhage. Serologic test shows positive anti-GBM antibodies, and extensive crescent formation in the renal biopsy, usually without multinucleated giant cells. Our study presents a case of anti-GBM disease with intensive multinucleated giant cells. We reviewed the literature of relative studies on anti-GBM disease.

Keywords: Crescent glomerulonephritis, anti-GBM antibodies, multinucleated giant cells

Introduction

Anti-glomerular basement membrane (anti-GBM) disease is an autoimmune disorder caused by the circulating antibodies against an antigenic site on type IV collagen in the GBM [1-3]. The disease is manifested with hematuria, active urinary sediment, and progressive renal failure in a short time. When accompanied by pulmonary hemorrhage, it is called as Goodpasture syndrome. The most common renal pathological feature is diffuse crescentic glomerulonephritis with diffuse linear deposits of immunoglobulin G (IgG) along the GBMs [4, 5]. Multinucleated giant cells may be present in the crescents or tubulointerstitial regions. Here, we report a case of anti-GBM disease with intensive multinucleated giant cells (MGCs) in the renal biopsy.

Case presentation

A 91-year-old Chinese male was presented to the emergency department with a 6-day fever, diarrhea and 3-day oliguria. He had a previous history of hypertension for 10 years and nutritional deficiency of anemia for 1 year. He denied having joints pain, purpura, or hemoptysis and was not using any nephrotoxic drugs. He went to the primary care center and was given antibiotic, but his symptoms progressed with remarkable oliguria and acute renal failure. Serum creatinine rose to 1086 μmol/L. He was admitted to the nephropathy ward after hemodialysis once with a temporary catheter in his right femoral vein.

At the time of admission, his vital signs were BP: 140/70, Pulse: 84, R/R: 21 and had intermittent fever. He had a barrel chest with hyperresonant note but had no crackles or wheezing sound. Blood test showed a WBC count of 10040 with no shift, and platelet count of 80000, and hemoglobin 87 g/L. Urine test wasn't done due to oliguria. Other laboratory results showed BUN 40.49 mmol/L (2.9-7.1 mmol/L), creatinine 797.4 μmol/L (53-97 μmol/L), sodium 129 mmol/L (136-145 mmol/L), potassium 5.12 mmol/L (3.5-5.5 mmol/L), albumin 24 g/L (35-55 g/L), cholesterol 2.09 mmol/L (2.4-5.5 mmol/L).

Other tests showed normal complement C3 and C4 levels, negative anti-neutrophil cytoplasmic antibodies (ANCA), antinuclear antibodies (ANA), and hepatitis virus. Procalcitonin was 1.75 ng/ml. Blood erythrocyte sedimentation rate was 90 mm/h. Anti-GBM IgG antibody was positive with a titer of 173.55 RU/mL (<20 RU/mL). Chest CT scan (**Figure 1A**) showed lobe bronchiectasis, interstitial pneumonia and chronic obstructive pulmonary disease. Moxifloxacin

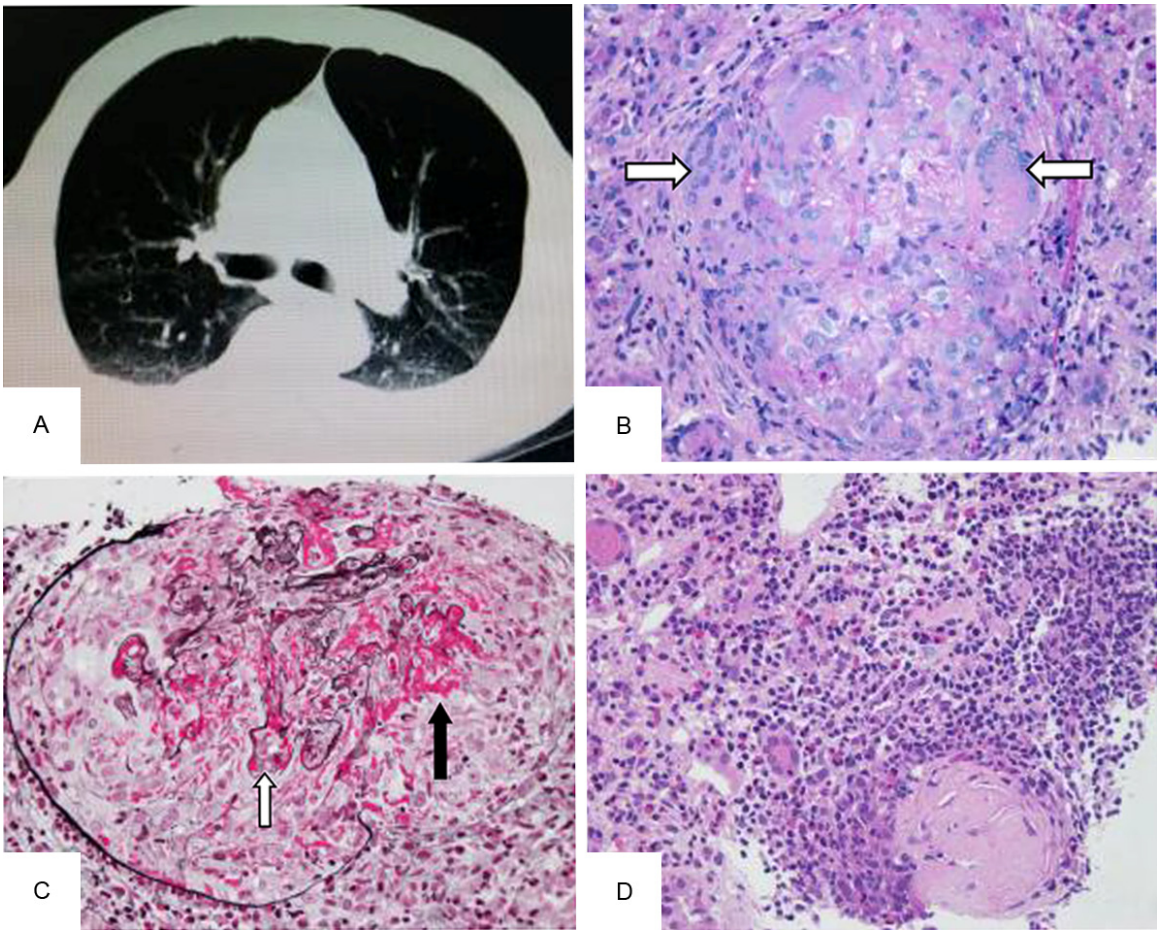

Figure 1. Pathological findings from the renal biopsy. A. Chest CT scan. B. One glomerulus with cellular crescent and several multinucleated giant cells (arrow), also periglomerular edema and inflammation (Periodic acid-Schiff, 400×). C. Crescent with GBM fracture (white arrow) and fibrinoid necrosis (black arrow) (Periodic acid-silver methanamine, 400×). D. Globlally sclerotic glomerulus, diffuse interstitial edema, and marked focal interstitial infiltration of lymphocytes and eosinophils (Hematoxylin-eosin, 200×).

was given. The patient remained oliguric even after undergoing hemodialysis every three days. Renal biopsy was also performed.

Renal biopsy

The tissue was examined by light microscopy (LM), immunofluorescence microscopy (IF) and electron microscopy (EM). For LM, the tissue was fixed in 10% neutral buffered formalin, embedded in paraffin, cut in thicknesses of 2 μm, and stained with hematoxylin-eosin (HE), periodic acid-Schiff (PAS), periodic acid-silver methanamine (PASM), and masson trichrome. IF was performed with IgG, IgA, IgM, C3, C1q, and fibrin.

LM specimen showed renal cortex with 15 glomeruli, 3 of which were globally sclerosed. All of the left 12 glomeruli had cellular crescents with intensive MGCs inside the crescents and fibrinoid necrosis of glomerular capillary tufts. Glomeruli with crescents showed disruption of Bowman's capsule with cells extending to the adjacent of interstitium. Tubular lumina contained casts, and the interstitium was edematous with suffusion inflammatory cells infiltration, including lymphocytes, monocytes, neutrophils, plasma cells, and eosinophils (**Figure 1B-D**). Arteries showed no necrosis. Immunofluorescence staining showed a weakly positive IgM with IgG negative (**Figure 2A**, **2B**). EM specimen showed 1 glomerulus with capillary disruptions, Bowman's capsule disruption and massive cell infiltration in both glomerulus and interstitium. And it was difficult to find the integrity of the glomerulus contour. There were no electron dense immune complex deposits (**Figure 2C**, **2D**).

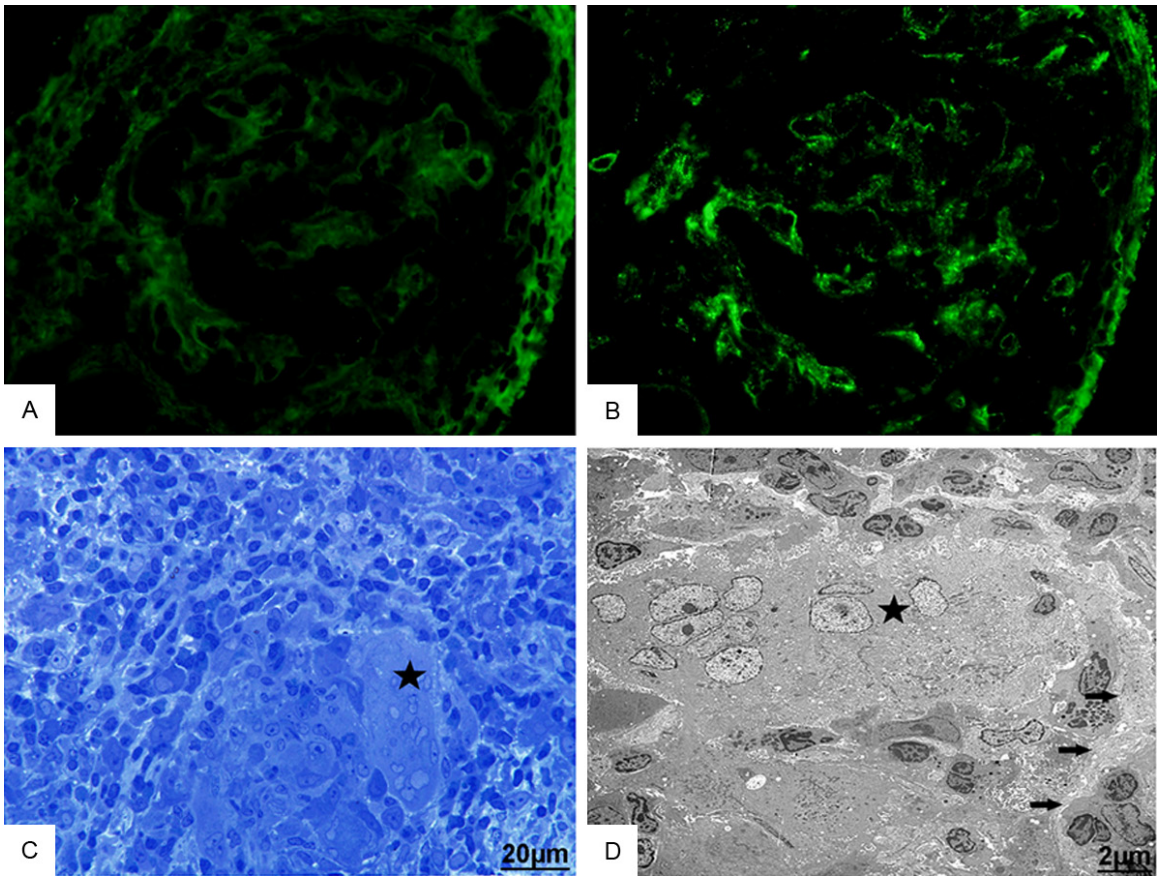

Figure 2. Immunofluorescence microscopy shows negative staining for IgG (A) and weakly positive staining for IgM (B) in the mesangium and a few loops (400×). (C) Semithin section shows one glomerulus with Bowman's capsule disruption and a multinucleated giant cell (asterisk), with inflammatory cells infiltration in the interstitium (Toluidine Blue staining, 600×). Bar = 20 μm. (D) Electron microscopy shows the debris of Bowman's capsule (arrows) and a multinucleated giant cell (asterisk). No dense deposit is detected in the glomerulus (1800×). Bar = 2 μm.

The clinical presentation and laboratory findings were consistent with anti-GBM disease. But unfortunately, because of his family economic condition and bad prognosis, the patient gave up the ongoing therapy, including plasmapheresis and immunosuppressive therapy.

Discussion

Anti-GBM disease was first reported by Goodpasture in 1919 with an autopsy case of rapidly progressive glomerulonephritis with pulmonary hemorrhage [4]. In 1958, Stanton and Tang reported another 9 patients and named the disease as Goodpasture syndrome [5]. In 1967, anti-GBM antibody was proved to be associated with Goodpasture syndrome [1]. Researchers found that anti-GBM antibody could also result in glomerulonephritis without pulmonary hemorrhage. So this kind of glomerulonephritis with or without pulmonary hemorrhage was denominated as anti-glomerular basement membrane disease [6]. The incidence of anti-GBM disease is about 1 case per-million per year. It accounts for approximately 10%-20% of all cases of crescentic glomerulonephritis, and about 1%-5% of all renal biopsy cases [7]. The age distribution is bimodal, 20-30 years and 60-70 years. The prevalence of the disease is higher in younger aged men and women in the older age subgroups [8]. The exact cause of the anti-GBM disease is still unknown, but due to certain behaviors and environmental factors, individuals are believed to put at a higher risk. Such exposure include: smoking; infection (influenza A2); organic solvents or hydrocarbons (glue or solvent sniffing); cocaine inhalation; metal dusts; and lymphocyte-depletion therapy (alemtuzumab) [9-15].

Anti-GBM disease is a rare and lethal autoimmune disorder which is mediated by anti-GBM antibodies against the non-collagenous domain of the α3 chain of type IV collagen (α3 [IV] NC1) in the vascular basement membranes [1-3]. The main epitopes are EA and EB, defined at amino acid residues 17-31 and 127-141 [16]. Clinical symptoms include acute nephritic syndrome with renal dysfunction, oliguria or anuria. Serologic test shows that anti-GBM antibodies are positive. In one-third of patients, ANCA, predominantly myeloperoxidase-ANCA, are positive as well [17-19]. The renal pathological characteristics are formation of crescents which is ≥50% glomeruli and linear deposition of IgG antibodies along the GBMs. Fibrinoid necrosis and focal destruction of Bowman's capsule often accompany in the LM.

The unique finding in this case was the intensive MGCs in the crescents by LM. MGC has large volume with multiple nuclei in a ring-like or horseshoe-shaped arrangement in the cytoplasm. In general, it is formed by the differentiation and fusion of monocyte-macrophage cells in the microenvironment of granuloma [20]. Adverse reactions to medications are probably the most common cause. Other causes include foreign bodies, mycobacterial or fungal infections, sarcoidosis, and ANCA-related glomerulonephritis. MGCs of periglomerular interstitial inflammation have been documented before. Rutgers and co-workers examined the renal biopsies from 46 myeloperoxidase proteins (MPO)-ANCA positive patients, 13 positive for anti-GBM antibody and 10 positive for both. Periglomerular granulomatous inflammation was observed in only MPO-ANCA positive and double positive patients (11% and 40%), not in those with anti-GBM-mediated chronic glomerulonephritis [21]. Bajema's team reported periglomerular granulomas in approximately 10% of 157 renal biopsy specimens from patients with ANCA-associated systemic vasculitis [22]. While some experts commented that, MGCs act as a common marker in anti-GBM disease but not ANCA-related glomerulonephritis [23]. But MGCs rarely occurred in the crescent. Besides, there was no typical linear IgG positive in the immunofluorescence, but showed only a weakly positive IgM. The exact mechanisms of these phenomena need further research.

Till now, mechanisms of anti-GBM disease are still being researched. Cui Z and co-workers have identified natural autoantibodies against GBM in normal human sera [24], and proved that anti-GBM natural antibodies can recognize the same major epitopes as anti-GBM antibodies from patients with anti-GBM disease [25]. Besides, complement activation also contributes to the injury and outcome of kidney in human anti-GBM disease [26]. Chen and co-workers proposed that intramolecular epitope spreading might occur before the onset of human anti-glomerular basement membrane disease [27]. Anti-GBM disease has a relatively poor prognosis. By using the pulse steroids, plasmapheresis, oral corticosteroids and cyclophosphamide, patient survival rate was about 85% and 40% progressing to ESRD. Syeda's team reviewed 6 patients who were treated with a combination of prednisone, plasmapheresis, and rituximab. The result of this treatment was that all the patients except one recovered the renal function and remained dialysis independent, and the anti-GBM antibody level remained undetected in all patients [28]. In China, a retrospective survey estimated the effects of 3 different treatment regimens: plasmapheresis plus immunosuppression, steroids plus cytotoxic agents, and steroids only [29]. Follow-up at 1 year showed renal survival rates of 25.0%, and patient survival rates of 72.7% which were similar to the reports from Hong Kong [30] (70%) and Japan [31] (76.7% at 6 mo). Immunoadsorption (IA) can reach up to a 50% renal survival and 90% patient survival [32]. Double filtration plasmapheresis (DFPP) plus immunosuppressive therapy can also achieve similar patient survival and renal survival results as similar to IA [33]. What regretful was that our patient gave up any therapy. However, even if he accepted active therapies, the outcome may not be as good because of his age and clinical symptoms. A two-center cohort proved that oligoanuria during diagnosis was the strongest predictor of mortality, and that age was the only other independent predictor of survival [34].

This case was diagnosed with anti-GBM disease. Renal biopsy showed predominant crescent formation, with particularly intensive multinucleated giant cells inside crescents. This granuloma-like phenomenon was rare, and the

cause of severe inflammation reaction was unclear. Future studies are still warranted.

Disclosure of conflict of interest

None.

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