ckj

OXFORD

Leading European Nephrology

Clinical Kidney Journal, 2016, vol. 9, no. 1, 97–101

doi: 10.1093/ckj/sfv126
Advance Access Publication Date: 30 November 2015
Exceptional Case

EXCEPTIONAL CASE

Rapidly progressive glomerulonephritis due to coexistent anti-glomerular basement membrane disease and fibrillary glomerulonephritis

Wisit Cheungpasitporn[1], Claudia C. Zacharek[2], Fernando C. Fervenza[1], Lynn D. Cornell[3], Sanjeev Sethi[3], Loren P. Herrera Hernandez[3], Samih H. Nasr[3], and Mariam P. Alexander[3]

[1]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA, [2]Division of Nephrology, Covenant HealthCare, Saginaw, MI, USA, and [3]Division of Anatomic Pathology, Mayo Clinic, Rochester, MN, USA

Correspondence to: Mariam P. Alexander; E-mail: alexander.mariam@mayo.edu

Abstract

Anti-glomerular basement membrane (anti-GBM) disease is a major cause of rapidly progressive glomerulonephritis (RPGN). On the other hand, fibrillary glomerulonephritis (GN) typically presents as proteinuria, hematuria and renal insufficiency, but rarely as RPGN. Without electron microscopy, the diagnosis of fibrillary GN can be missed. We report a 68-year-old white woman who presented with RPGN with kidney biopsy demonstrating diffuse crescentic GN on light microscopy. By immunofluorescence, there was bright linear staining of the GBMs and smudgy mesangial staining for immunoglobulin G, C3, and kappa and lambda light chain. Electron microscopy revealed fibrillary deposits in the GBM and mesangium. A serum test for anti-GBM antibody was positive. To our knowledge, this is the first report of coexistence of fibrillary GN in a patient with anti-GBM disease. Electron microscopy is critical to identify the coexistence of other GN in patients presenting with crescentic GN.

Key words: anti-GBM, anti-glomerular basement membrane disease, crescentic glomerulonephritis, fibrillary glomerulonephritis, rapidly progressive glomerulonephritis

Introduction

Rapidly progressive glomerulonephritis (RPGN) is a clinical syndrome manifested by features of nephritic syndrome and rapid loss of the kidney function over a period of a few weeks to months where the main pathologic finding is a necrotizing and crescentic glomerulonephritis (GN) on kidney biopsy [1]. The general categories of the cause of RPGN are anti-glomerular basement membrane (anti-GBM) disease, pauci-immune crescentic GN [usually antineutrophil cytoplasmic antibody (ANCA)-associated] and immune complex type crescentic GN.

Fibrillary GN (FGN) is an immune complex GN characterized by glomerular staining by immunofluorescence for immunoglobulin G (IgG), complement components, and usually kappa and lambda light chains, and deposition of irregularly oriented, elongated, nonbranching fibrils, 10–30-nm thick, in the GBMs and mesangium [2–5] as seen by electron microscopy; focal

Received: August 31, 2015. **Accepted:** November 1, 2015

tubular basement membrane deposits may be seen as well. Patients with FGN typically present with subnephrotic- or nephrotic-range proteinuria associated with microscopic hematuria, hypertension and progressively worsening renal function [5, 6]. Rarely, FGN can present as RPGN [5, 7–9]. We describe a case of RPGN with kidney biopsy demonstrating both anti-GBM nephritis and FGN. To our knowledge, this is the first report of the coexistence of these two glomerulonephritides.

Case report

Clinical history and initial laboratory data

A 68-year-old woman was admitted with progressive weakness and altered mental status. Approximately 2 weeks prior to admission, the patient was diagnosed with an upper respiratory tract infection and was prescribed a 7-day treatment course with trimethoprim/sulfamethoxazole. Her respiratory symptoms improved. However, she developed progressive generalized weakness, nausea and altered mental status and was brought to the hospital for evaluation. Her past medical history was significant for diabetes mellitus type 2 on diet control, rheumatoid arthritis in remission, dyslipidemia and gastroesophageal reflux disease. Medications included pravastatin and ranitidine. The patient was a former smoker. There was no family history of kidney disease. Physical examination was unremarkable except for 1+ pitting edema in the lower extremities. Serum creatinine (Cr) was increased at 4.0 mg/dL (353.6 µmol/L) from a baseline Cr of 1.0 mg/dL (88.4 µmol/L; estimated glomerular filtration rate, 59 mL/min/1.73 m^2 calculated by the four-variable Modification of Diet in Renal Disease Study equation) obtained 3 months prior. Urinalysis showed 10–15 red blood cells per high-power field and 3+ proteinuria. Urine protein to creatinine ratio was measured at 2.8 g/g. Urine eosinophils were present (>5%). Serologic test results for anti-nuclear antibody, anti-double-stranded DNA antibody, rheumatoid factor, cryoglobulinemia, hepatitis B and C, and ANCA were negative by both enzyme-linked immunosorbent assay and indirect immunofluorescence; serum C3 and C4 levels were normal. Serum protein electrophoresis and immunofixation showed no monoclonal proteins. Renal ultrasound showed normal renal size and echogenicity bilaterally. The presence of eosinophiluria raised the possibility of trimethoprim/sulfamethoxazole (TMT/SMT)-induced acute interstitial nephritis. Thus, TMT/SMT was discontinued and the patient was treated conservatively without corticosteroids. However, renal function continued to deteriorate with Cr of 5.1 mg/dL at Day 2 of hospital admission. At that time, an anti-GBM IgG antibody test was positive at 272 units/mL (reference range 0–19 units/mL). A chest X-ray revealed no pulmonary infiltration. A kidney biopsy was performed.

Kidney biopsy

Light microscopic evaluation showed two small cores of renal cortex including a small portion of medulla. The sample included seven glomeruli, two of which were globally sclerosed. Four glomeruli (57%) showed crescents, including two cellular crescents, one fibrocellular and one fibrous crescent. No necrotizing lesions were identified. The uninvolved glomeruli showed mild mesangial matrix expansion with periodic acid–Schiff positive and silver negative material. No significant mesangial or endocapillary hypercellularity was noted. There was minimal thickening of peripheral capillary loops.

Tissue submitted for immunofluorescence studies contained one glomerulus, which showed linear GBM staining and segmental smudgy mesangial staining with IgG (2–3+), C3 (2+), and kappa (2+) and lambda (2+) light chains. Fibrinogen stained glomerular crescents. IgG subclass staining was attempted, but additional sections lacked glomeruli.

Ultrastructural studies showed an expanded mesangial matrix with several areas of electron-dense to intermediately dense deposits. On higher magnification, these deposits were composed of randomly oriented fibrils, measuring mean thickness of 19 nm, range 14–25 nm. The GBMs were thickened. Fibrils were also seen within segments of glomerular capillary loops within thickened basement membranes. Podocytes showed moderate to severe foot process effacement. No tubular basement membrane deposits were seen. Representative light, immunofluorescence and electron microscopy findings are shown in Figure 1.

Diagnosis

Kidney, needle biopsy: (i) anti-GBM disease; (ii) FGN.

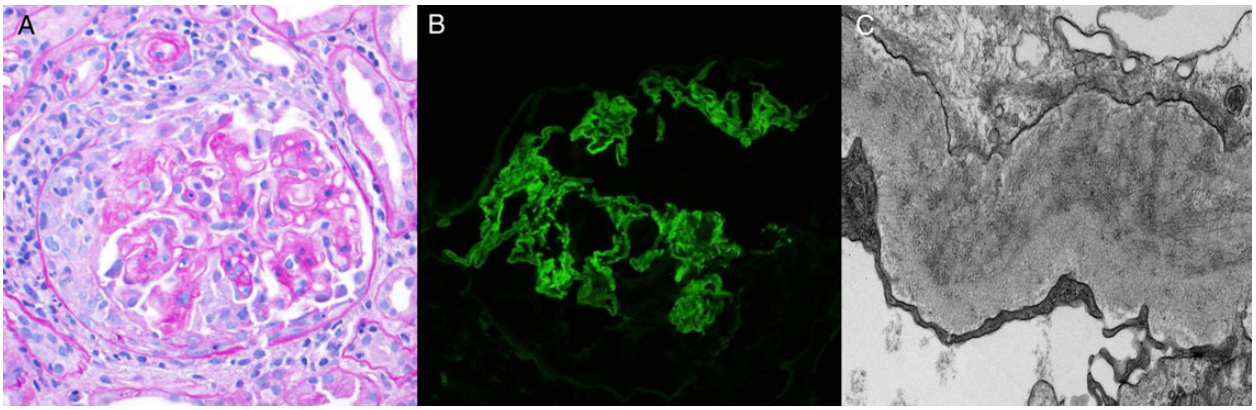

Fig. 1. Representative kidney biopsy findings showing FGN with anti-GBM disease. (**A**) Glomerulus with cellular crescent and mild mesangial matrix expansion. Associated interstitial inflammation is noted (periodic acid–Schiff, 40×). (**B**) Immunofluorescence staining with IgG demonstrates linear GBM staining as well as segmental smudgy mesangial staining. (**C**) Electron microscopy shows randomly oriented nonbranching fibrils distributed within mesangium as well as within the peripheral capillary loops.

Clinical follow-up

The patient was initiated on treatment with intravenous pulsed methylprednisolone 500 mg daily for 3 days followed by prednisone 60 mg daily and oral cyclophosphamide 100 mg/day. However, kidney function continued to deteriorate with Cr of 5.8 mg/dL and the patient developed hyperkalemia at 5.8 mmol/L (reference range 3.6–5.2 mmol/L). On hospital Day 5, the patient was started on hemodialysis. Following plasmapheresis, her circulating levels of anti-GBM IgG antibodies were reduced to 173 and 70 units/mL after the first and second sessions, respectively. On Day 7, the patient developed thrombocytopenia, oral candidiasis and urinary tract infection with sepsis. The patient was treated with levofloxacin, and plasmapheresis was discontinued. The patient was treated with cyclophosphamide for 3 months. Prednisone was gradually tapered to 10 mg daily. At 4 months following diagnosis, the patient remained on dialysis.

Discussion

Anti-GBM disease is an autoimmune disorder resulting from circulating antibodies against an antigen intrinsic to the alpha 3 chain of type IV collagen in the GBM [10]. Emerging evidence has demonstrated that autoreactive T cells may also play an important role in the development of anti-GBM disease [11, 12]. Anti-GBM disease is a well-known cause of RPGN. In contrast, patients with FGN typically present with proteinuria and progressive loss of kidney function [5, 6]. Nevertheless, cases of FGN presenting as RPGN have been reported [5, 7, 8, 13, 14]. The diagnosis of FGN requires the pathognomonic histologic finding of the deposition of irregularly oriented, elongated, nonbranching microfibrils 10–30-nm thick in the mesangium and along the capillary walls on electron microscopy [5, 6], with negative staining by Congo red.

The kidney biopsy findings of FGN on light microscopy are variable and include diffuse mesangial hypercellularity and matrix expansion that may be seen with other types of GN [7, 13, 14]. Less commonly, light microscopy may show crescents [5, 7, 8, 15]. Immunofluorescence microscopy is positive for mesangial polyclonal IgG and C3 staining with weaker, less often granular and irregular, capillary wall staining [7, 14, 16]; ~10% of FGN cases show monotypic IgG. The texture of the immunofluorescence staining is typically smudged without distinct linearity or granularity [13]. However, the extensive fibrillary deposits of IgG can lead to a pseudolinear staining along the GBMs, similar to that seen in anti-GBM disease [3, 16]. For this reason, there have been several reported cases of FGN presenting as crescentic GN with linear IgG staining of the glomerular capillary walls mimicking anti-GBM disease [5, 7, 8, 17] (Table 1). However, in these cases of crescentic FGN, serum anti-GBM antibodies were consistently absent [2–5]. In the present case, the highly elevated anti-GBM levels in the serum together with immunofluorescence microscopy showing both linear GBM and smudgy mesangial staining for IgG and C3, along with fibrillary deposits by electron microscopy, confirmed the coexistence of two distinct pathological processes: anti-GBM disease and FGN.

Rupture of GBM has been well known to cause the exudation of fibrin in the urinary space, leading to crescent formation [19]. In anti-GBM disease, which has recently been considered as an autoimmune 'conformeropathy' [20], the quaternary structure of the alpha 345 noncollagenous-1 hexamer that forms GBM undergoes a conformational change resulting in an exposure of pathogenic epitopes on the α-3 and α-5 subunits and development of a pathogenic autoantibody anti-GBM response. The GBM rupture with subsequent crescentic GN can occur due to these anti-GBM antibodies against the α-3 chain of type IV collagen in the GBM [10]. In patients with FGN, the accumulation of intra-membranous fibrils may result in the rupture of GBM leading to the development of crescents as described in glomerular crescents in renal amyloidosis cases [19, 21]. It is possible that fibril accumulation disrupts the GBM exposing the cryptogenic Goodpasture antigen. Anti-GBM nephritis typically shows a diffuse necrotizing and crescentic GN on renal biopsy, with all of the crescents of the same 'age' (in the absence of ANCA) [22]. The current case showed a histologic picture somewhat different from typical anti-GBM nephritis: while there were diffuse crescents by light microscopy, the crescents ranged from cellular to fibrocellular to fibrous, indicative of different 'ages' and a more prolonged clinical course prior to presentation with renal insufficiency. This histologic feature is an indication of a glomerular disease concurrent with anti-GBM nephritis; in this case, FGN was concurrent.

In contrast to the well-known finding of positivity of ANCA, especially anti-myeloperoxidase-ANCA, in 30–38% of patients with anti-GBM disease [23, 24], the presence of circulating anti-GBM IgG antibody in patients with FGN has been demonstrated only in one other recent case [18] (Table 1). Momose *et al.* [18] described a patient who presented with acute kidney injury and positive serum anti-GBM antibody; renal biopsy showed thrombotic microangiopathy and ultrastructural features of FGN. Proliferative GN pattern and global sclerosis were described on light microscopy of 17 glomeruli. Unfortunately, immunofluorescence analysis was not performed in their case. In addition, diffuse necrotizing and crescentic GN was not noted, and so the authors could not conclude the existence of anti-GBM nephritis concurrent with FGN.

It is unclear whether the current case reflects an incidental coexistence of two uncommon GNs. Electron microscopy examination is not always performed in kidney biopsy specimens for patients presenting with RPGN [25, 26], and therefore, coexisting FGN may be missed and underreported. It is also possible that pre-existing deposition of fibrils in fibrillary GN may result in exposure of the cryptic antigen in anti-GBM disease, a required step in the development of anti-GBM nephritis [27, 28]. Anti-GBM disease has been described in several conditions that may predispose to exposure of cryptic GBM antigens, including infection, inhaled hydrocarbons, cocaine use, smoking and lithotripsy [29, 30]. Similarly, anti-GBM nephritis may occur superimposed on membranous GN, which may result in cryptic GBM antigen exposure [31]. In addition to antigen exposure, genetic factors such as human leukocyte antigen (HLA)-DR15 and DR4 have also played an important role for an increased risk of developing anti-GBM disease [32].

Although there are no controlled trials to guide treatment for FGN, high-dose glucocorticoids and cyclophosphamide have been used as treatment for FGN with crescentic GN [5, 9]. Its prognosis, however, is poor, and all reported cases of FGN with the clinical presentation of RPGN required renal replacement therapy and remained dialysis dependent [5, 8, 9, 18]. Plasmapheresis in conjunction with prednisone and cyclophosphamide have been recommended for the treatment of anti-GBM disease except in patients who are dialysis dependent at presentation with 100% crescents in kidney biopsy (correlated with poor kidney survival) and do not have pulmonary hemorrhage [33]. In our case presentation of coexistent anti-GBM disease with FGN, the patient received plasmapheresis in addition to treatment with cyclophosphamide and corticosteroids. Unfortunately, plasmapheresis was discontinued due to thrombocytopenia

Table 1. Characteristics and kidney biopsy findings of patients with FGN with or without anti-GBM antibody presenting as RPGN

Case	Age (years)	Gender	Anti-GBM antibody	Light microscopy	Immunofluorescence	Electron microscopy
Reported cases of FGN presenting as crescentic GN with linear IgG staining of the glomerular capillary mimicking anti-GBM disease						
1 [5]	61	Female	Negative	Cellular crescents in 3 of 10 glomeruli, acute tubular injury and mild to moderate mononuclear interstitial infiltrate.	Linear, nearly global glomerular capillary wall staining for IgG (3+), C3 (3+) and albumin (1+).	Fibril deposition in the GBM.
2 [7]	50	Male	Negative	Cellular crescent formation with collapse of the capillaries in 12 of 17 glomeruli, interstitial nephritis and acute tubular injury.	Prominent linear and pseudolinear staining of the capillary walls for IgG and prominent staining for fibrin in glomeruli with areas of fibrinoid necrosis.	Fibrils predominantly in the subepithelial areas of the capillary walls.
3 [8]	59	Male	Negative	Cellular crescents and fibrinoid necrosis of glomerular tuft in 7 of 19 glomeruli, moderate interstitial infiltrates along with tubular injury.	4+ linear deposits of IgG with 2+ confluent deposits of C3 along segmental mesangial and capillary loops.	Nonbranching fibrils measuring 16 nm in diameter electron-dense deposits in the glomerular mesangium and capillary walls.
4 [17]	55	Male	Negative	Cellular crescents in ~30% of the glomeruli. The interstitium was infiltrated with lymphocytes and neutrophils.	3+ linear staining of the GBM with IgG, C3, and kappa and lambda light chains.	Abundant, fairly straight, nonbranching fibrils with mean diameter of 26 nm in the thickened GBM and expanded mesangial regions.
Reported cases of FGN presenting as crescentic GN with positive anti-GBM antibody						
1 [18]	54	Male	Positive	Proliferative GN pattern and global sclerosis were described on light microscopy of 17 glomeruli. Renal arterioles, both afferent and efferent, showed extensive endothelial cell edema and swelling. Renal tubules were atrophic.	Immunofluorescence was not performed.	Extensive and dense extracellular deposition of fibrillar components, larger in diameter than amyloid fibers and aggregated to form large bundles.
Our case presentation	68	Female	Positive	4 of 7 glomeruli (57%) showed crescents, including two cellular crescents, one fibrocellular and one fibrous crescent.	Linear GBM staining and segmental smudgy mesangial staining with IgG (2–3+), C3 (2+), and kappa (2+) and lambda (2+) light chains.	Randomly oriented fibrils, measuring mean thickness of 19 nm, range 14–25 nm, within mesangium as well as within the peripheral capillary loops.

and sepsis, and the patient remained dialysis dependent at 4-month follow-up despite treatment with immunosuppressive treatment.

In summary, we present a case of coexistent anti-GBM disease with FGN presenting as RPGN. To the best of our knowledge, this has not previously been reported.

Authors' contribution

All authors were involved and approved the final manuscript.

Conflict of interest statement

None declared.

References

1. Couser WG. Rapidly progressive glomerulonephritis: classification, pathogenetic mechanisms, and therapy. *Am J Kidney Dis* 1988; 11: 449–464
2. Iskandar SS, Falk RJ, Jennette JC. Clinical and pathologic features of fibrillary glomerulonephritis. *Kidney Int* 1992; 42: 1401–1407
3. Fogo A, Qureshi N, Horn RG. Morphologic and clinical features of fibrillary glomerulonephritis versus immunotactoid glomerulopathy. *Am J Kidney Dis* 1993; 22: 367–377
4. Alpers CE. Immunotactoid (microtubular) glomerulopathy: an entity distinct from fibrillary glomerulonephritis? *Am J Kidney Dis* 1992; 19: 185–191
5. Sharma P, Kuperman M, Racusen L *et al*. Fibrillary glomerulonephritis presenting as rapidly progressive glomerulonephritis. *Am J Kidney Dis* 2012; 60: 157–159
6. Pronovost PH, Brady HR, Gunning ME *et al*. Clinical features, predictors of disease progression and results of renal transplantation in fibrillary/immunotactoid glomerulopathy. *Nephrol Dial Transplant* 1996; 11: 837–842
7. Sethi S, Adeyi OA, Rennke HG. A case of fibrillary glomerulonephritis with linear immunoglobulin G staining of the glomerular capillary walls. *Arch Pathol Lab Med* 2001; 125: 534–536
8. Nilajgi S, Killen JP, Baer R *et al*. Fibrillary glomerulonephritis: presenting as crescentic glomerulonephritis causing rapidly progressive renal failure. *NDT Plus* 2011; 4: 413–415
9. Mahajan S, Kalra V, Dinda AK *et al*. Fibrillary glomerulonephritis presenting as rapidly progressive renal failure in a young female: a case report. *Int Urol Nephrol* 2005; 37: 561–564
10. Pusey CD. Anti-glomerular basement membrane disease. *Kidney Int* 2003; 64: 1535–1550
11. Wolf D, Hochegger K, Wolf AM *et al*. CD4+CD25+ regulatory T cells inhibit experimental anti-glomerular basement membrane glomerulonephritis in mice. *J Am Soc Nephrol* 2005; 16: 1360–1370
12. Zou J, Hannier S, Cairns LS *et al*. Healthy individuals have Goodpasture autoantigen-reactive T cells. *J Am Soc Nephrol* 2008; 19: 396–404
13. Rosenstock JL, Markowitz GS, Valeri AM *et al*. Fibrillary and immunotactoid glomerulonephritis: distinct entities with different clinical and pathologic features. *Kidney Int* 2003; 63: 1450–1461
14. Nasr SH, Valeri AM, Cornell LD *et al*. Fibrillary glomerulonephritis: a report of 66 cases from a single institution. *Clin J Am Soc Nephrol* 2011; 6: 775–784
15. Guerra G, Narayan G, Rennke HG *et al*. Crescentic fibrillary glomerulonephritis associated with hepatitis C viral infection. *Clin Nephrol* 2003; 60: 364–368
16. Alpers CE, Rennke HG, Hopper J Jr *et al*. Fibrillary glomerulonephritis: an entity with unusual immunofluorescence features. *Kidney Int* 1987; 31: 781–789
17. Odioemene N, Rogers T, Doran J. Fibrillary glomerulonephritis masquerading as anti-GBM disease. *Am J Kidney Dis* 2014; 63: A84
18. Momose A, Nakajima T, Chiba S *et al*. A case of fibrillary glomerulonephritis associated with thrombotic microangiopathy and anti-glomerular basement membrane antibody. *Nephron Extra* 2015; 5: 30–38
19. Nagata M, Shimokama T, Harada A *et al*. Glomerular crescents in renal amyloidosis: an epiphenomenon or distinct pathology? *Pathol Int* 2001; 51: 179–186
20. Pedchenko V, Bondar O, Fogo AB *et al*. Molecular architecture of the Goodpasture autoantigen in anti-GBM nephritis. *N Engl J Med* 2010; 363: 343–354
21. Masutani K, Nagata M, Ikeda H *et al*. Glomerular crescent formation in renal amyloidosis. A clinicopathological study and demonstration of upregulated cell-mediated immunity. *Clin Nephrol* 2008; 70: 464–474
22. Kambham N. Crescentic glomerulonephritis: an update on Pauci-immune and anti-GBM diseases. *Adv Anat Pathol* 2012; 19: 111–124
23. Hellmark T, Niles JL, Collins AB *et al*. Comparison of anti-GBM antibodies in sera with or without ANCA. *J Am Soc Nephrol* 1997; 8: 376–385
24. Levy JB, Hammad T, Coulthart A *et al*. Clinical features and outcome of patients with both ANCA and anti-GBM antibodies. *Kidney Int* 2004; 66: 1535–1540
25. Collan Y, Hirsimaki P, Aho H *et al*. Value of electron microscopy in kidney biopsy diagnosis. *Ultrastruct Pathol* 2005; 29: 461–468
26. Sabir S, Mubarak M, Ul-Haq I *et al*. Pattern of biopsy proven renal diseases at PNS SHIFA, Karachi: a cross-sectional survey. *J Renal Inj Prev* 2013; 2: 133–137
27. Turner N, Mason PJ, Brown R *et al*. Molecular cloning of the human Goodpasture antigen demonstrates it to be the alpha 3 chain of type IV collagen. *J Clin Invest* 1992; 89: 592–601
28. Borza DB, Hudson BG. Molecular characterization of the target antigens of anti-glomerular basement membrane antibody disease. *Springer Semin Immunopathol* 2003; 24: 345–361
29. Xenocostas A, Jothy S, Collins B *et al*. Anti-glomerular basement membrane glomerulonephritis after extracorporeal shock wave lithotripsy. *Am J Kidney Dis* 1999; 33: 128–132
30. Iwamoto I, Yonekawa S, Takeda T *et al*. Anti-glomerular basement membrane nephritis after extracorporeal shock wave lithotripsy. *Am J Nephrol* 1998; 18: 534–537
31. Troxell ML, Saxena AB, Kambham N. Concurrent anti-glomerular basement membrane disease and membranous glomerulonephritis: a case report and literature review. *Clin Nephrol* 2006; 66: 120–127
32. Phelps RG, Rees AJ. The HLA complex in Goodpasture's disease: a model for analyzing susceptibility to autoimmunity. *Kidney Int* 1999; 56: 1638–1653
33. KDIGO GN Work Group. KDIGO clinical practice guideline for glomerulonephritis. *Kidney Int Suppl* 2012; 2: 139–274