

# Atypical Noncrescentic Antiglomerular Basement Membrane Disease With Concurrent Thin Basement Membrane Nephropathy



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## INTRODUCTION

Antiglomerular basement membrane (GBM) disease is caused by circulating autoantibodies against the noncollagenous domain of  $\alpha 3$  chain of type IV collagen ( $\alpha 3$ NC1).<sup>1</sup> Classic anti-GBM disease often presents with rapidly progressive glomerulonephritis (GN) with or without pulmonary hemorrhage.<sup>2</sup> Renal biopsy findings include crescentic GN on light microscopy and bright linear GBM IgG and C3 staining on immunofluorescence (IF).<sup>3</sup> Atypical forms of anti-GBM disease can present as milder noncrescentic GN without pulmonary hemorrhage or in a pulmonary-predominant form without acute kidney injury, and diagnosis often relies on strong linear GBM staining for IgG and C3.<sup>3</sup> It is a rare cause of acute GN with an estimated incidence of fewer than 1 case per million population.<sup>4</sup>

Thin basement membrane nephropathy (TBMN), also known as benign familial hematuria, is among a spectrum of diseases characterized by thin, and structurally abnormal GBM on electron microscopy. TBMN is caused by mutations in the COL4A3 or COL4A4 gene that lead to decreased levels of type IV collagen  $\alpha 3$  and  $\alpha 4$  subunits.<sup>1</sup> GBM thickness can be less than 250 nm compared with the normal range of 300 to 400 nm.<sup>5</sup> TBMN is diagnosed clinically in less than 1% of the population, although the prevalence may be higher, as most patients with TBMN present with isolated persistent hematuria and preserved renal function without other clinical manifestations.<sup>6</sup>

The pathogenesis of both diseases involves subunits of type IV collagen. However, the combined

presentation of anti-GBM disease and TBMN is exceedingly rare. We report the first case of pulmonary-predominant noncrescentic anti-GBM disease with concurrent TBMN.

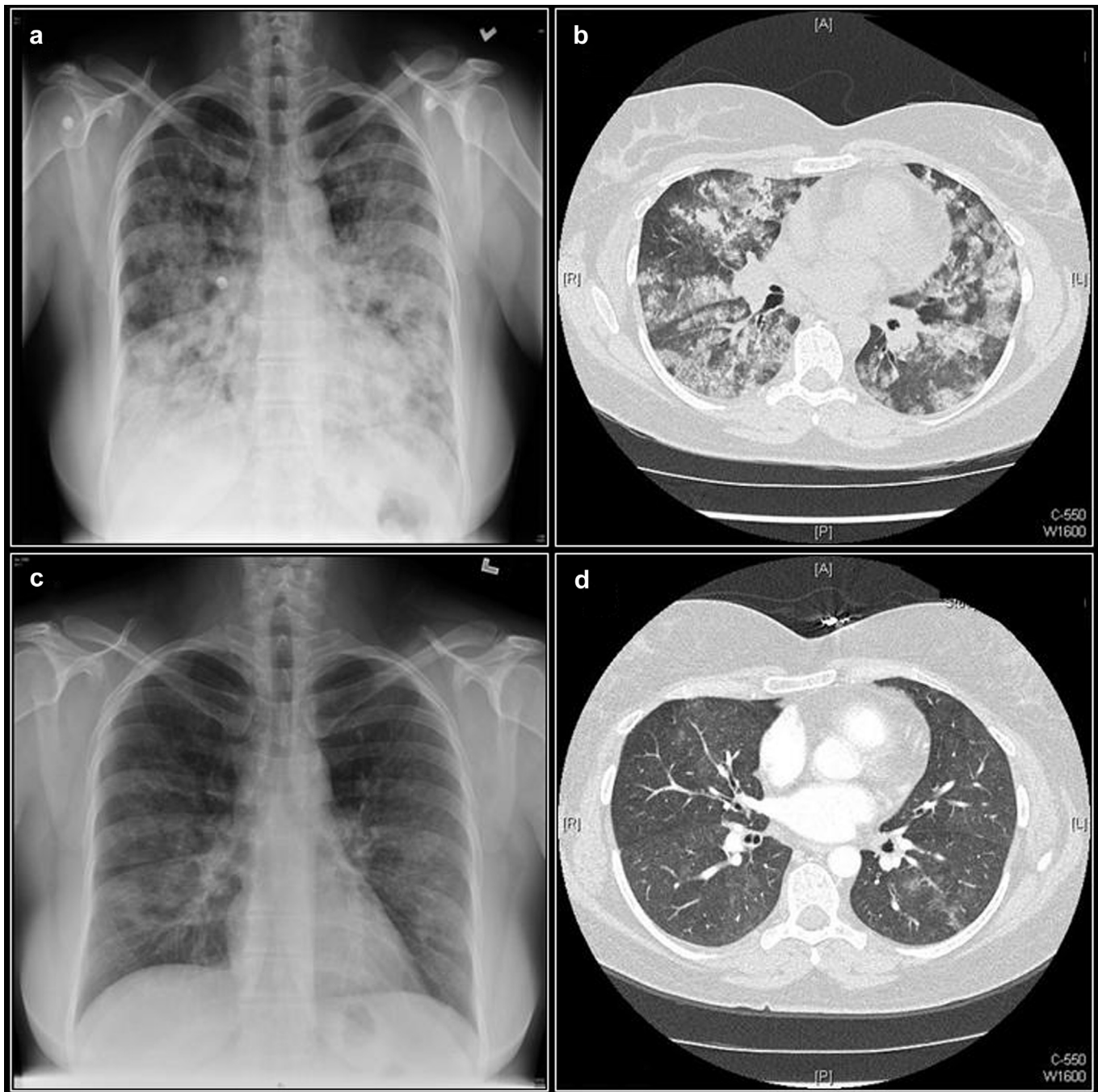
## CASE PRESENTATION

### Clinical History

A 37-year-old white woman presented to the emergency department with a 1-month history of progressive fatigue, dyspnea, and small-volume hemoptysis. She had received multiple courses of antibiotics and a short course of oral prednisone with no improvement. There was no concurrent or preceding rash, arthritis, sinusitis, ocular symptoms, or gross hematuria. Serial chest radiographs during this period showed progressive, symmetrical, bilateral airspace disease (Figure 1a).

Her past medical history was significant for asthma and a 10-pack-year smoking history. She did not report any history of recreational drug use or recent travel, or tuberculosis, chemical, exposure to animal, or sick contact. There was no personal or family history of neurosensory deafness, lenticonus, or renal impairment suggestive of Alport syndrome.

On physical examination, she was afebrile, but was tachypneic with 94% oxygen saturation on room air, and had a blood pressure of 110/60 mm Hg and a heart rate of 104 per minute. Respiratory examination revealed diffuse bilateral rhonchi and inspiratory crackles. The rest of the examination was unremarkable. However, she subsequently required intensive



**Figure 1.** Chest radiograph preceding initial presentation (a) shows bilateral airspace opacities. Computed tomography (lung window) before plasmapheresis (b) shows diffuse, bilateral nodular opacities and consolidation with ground-glass changes consistent with pulmonary hemorrhage. Following plasmapheresis, chest radiograph (c) and computed tomography (lung window; d) demonstrate complete resolution of bilateral opacities and ground-glass changes.

care unit transfer due to worsening dyspnea and increasing oxygen requirements.

Laboratory investigation showed normocytic anemia (hemoglobin 7.7 g/dl), mild leukocytosis (white blood cell count 12,300/ $\mu$ l), and normal creatinine at 0.76 mg/dl. Urinalysis showed 2+ hematuria with 20 to 30 red blood cells per high-power field and red blood cell casts. Perinuclear antineutrophil cytoplasmic antibody (ANCA) was 0.2 U/ml, cytoplasmic ANCA was

0.3 U/ml, and antinuclear antibody was negative. There was no biochemical evidence of coagulopathy. Computed tomography of the chest showed diffuse, bilateral pulmonary nodular opacities and consolidation with ground-glass changes consistent with pulmonary hemorrhage (Figure 1b).

The combined pulmonary and renal manifestations suggested the differential diagnoses that included ANCA-negative vasculitis and anti-GBM disease.

Treatment was initiated empirically due to acute clinical deterioration requiring opti-flow/high-flow oxygen with an  $\text{FiO}_2$  of 60% to 70%. Mechanical ventilation was not required. Respiriology was consulted, and bronchoscopy was considered but deferred due to high procedural risk with no mechanical ventilation support. She received 7 cycles of plasmapheresis, supplemented by corticosteroids. Respiriology suggested broad-spectrum antibiotics coverage for the possibility of superimposed pulmonary infection that cannot be definitively excluded. Cyclophosphamide was considered but deferred due to the patient's young age and potential implication on fertility.

Pretreatment serum anti-GBM antibody against  $\alpha 3\text{NC1}$  was drawn, but required referral to an external laboratory. The result became available after completion of plasmapheresis, and the pretreatment anti-GBM antibody index was mildly elevated at 1.1 (normal  $<1$ ). A renal biopsy was performed 1 week after completion of plasmapheresis for definitive diagnosis.

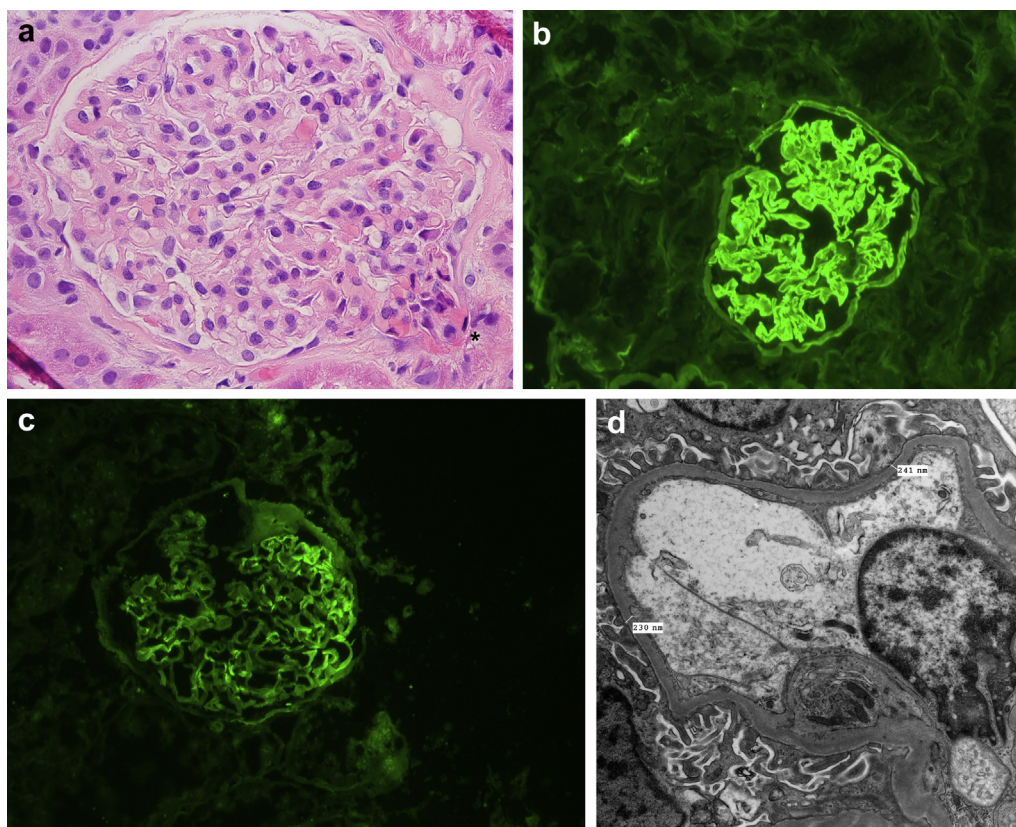
### Kidney Biopsy

The renal biopsy contained 6 glomeruli, none of which was globally sclerosed. One glomerulus displayed

early segmental fibrinoid necrosis of 1 tuft (Figure 2a). The remaining glomeruli were unremarkable with minimal increase in mesangial matrix and no cellular crescents. The glomerular capillary walls were delicate and wrinkled. Groups of red blood cells were seen within the urinary space. The tubulointerstitium was well preserved with mild interstitial fibrosis and tubular atrophy affecting  $<20\%$  of the tissue. There was mild arteriolar hyalinosis and moderate arterial sclerosis.

Direct IF study showed strong linear staining for IgG (3+) (Figure 2b), C3 (2+), and kappa and lambda along the GBM. There was no significant staining for IgA, IgM, or C1q. Indirect IF on control tissue incubated with the patient's serum showed mild linear IgG staining along the GBM. Direct IF study for IgG subclasses showed linear staining for IgG4 along the GBM (Figure 2c), and mild linear staining for IgG1. Direct IF study for type IV collagen  $\alpha 3$  and  $\alpha 5$  chains showed appropriate linear GBM staining.

Electron microscopy of 4 glomeruli revealed homogeneous thinning of GBM (mean thickness 237.7 nm) due to reduction of the lamina densa with segmental areas showing trilaminar substructure



**Figure 2.** Renal biopsy findings. Light microscopy (a) shows a glomerulus exhibiting an early segmental lesion with fibrinoid necrosis but no cellular crescents (\*) (hematoxylin-eosin stain,  $\times 40$  field). Direct IF shows strong linear IgG staining (b) along the GBM. Indirect IF using patient's serum shows mild linear IgG4 staining (c) along the GBM on control tissue glomerulus. Electron microscopy demonstrates homogeneous thinning of GBM (d) due to diminished lamina densa ( $\times 10,000$  magnification).

without splitting or lamination of the GBM (Figure 2d). The podocyte foot processes were well preserved.

### Clinical Course

The patient showed excellent response to plasmapheresis, with complete resolution of hemoptysis, stabilization of hemoglobin level, and significant improvement of dyspnea and oxygen requirement. Follow-up chest imaging confirmed resolution of pulmonary hemorrhage (Figure 1c and 1d). Serum anti-GBM antibody index decreased to less than 0.2 after plasmapheresis. Cyclophosphamide was not added, considering the atypical biopsy result, satisfactory response to plasmapheresis and corticosteroid, as well as concern regarding patient compliance. She was discharged home in stable condition but was eventually lost to follow-up 18 months later. Genetic testing for mutations in *COL4A3* and *COL4A4* gene to confirm TBMN was not completed, as the patient declined further follow-up. The renal biopsy finding along with the clinical history strongly supports the diagnosis of TBMN even in the absence of genetic testing. Her clinical findings and laboratory investigation results are summarized in Table 1.

### DISCUSSION

We believe this is the first report of pulmonary-predominant, noncrescentic anti-GBM disease presenting in a patient with TBMN. The clinical presentation of hemoptysis and hematuria raised the differential diagnoses of systemic diseases with pulmonary-renal involvement that included anti-GBM disease and ANCA-mediated vasculitis. Negative serum ANCA, direct IF findings of strong linear GBM IgG and C3 staining from the renal biopsy, and indirect IF findings of anti-GBM IgG in the patient serum strongly support the diagnosis of anti-GBM disease. We acknowledge that her renal biopsy contained a limited amount of renal cortex with 6 glomeruli. Therefore, although only 1 glomerulus contained an early segmental necrotizing lesion, a histologically more significant focus of glomerulonephritis or crescentic lesions cannot be completely excluded.

However, her preserved renal function and the absence of crescentic lesion on biopsy suggested a variant form of anti-GBM disease that differs from the usual presentation of rapidly progressive GN with diffuse necrotizing and crescentic GN in classic anti-GBM disease. It is recognized that atypical forms of anti-GBM disease can have a milder clinical course with undetectable circulating anti-GBM antibodies, no pulmonary hemorrhage, and a wide range of glomerular findings on renal biopsy.<sup>3</sup> Another rare variant of

**Table 1.** Summary of clinical parameters and laboratory investigation findings and results

Clinical parameters and laboratory investigations	Findings and results
Clinical presentation	Hematuria, hemoptysis, dyspnea, progressive fatigue
Chest imaging (pretreatment)	
Serial chest radiograph	Progressive, symmetrical bilateral airspace disease
Computed tomography	Diffuse, bilateral nodular opacities and consolidations with ground-glass changes
Clinical laboratory tests	
Serum creatinine	0.76 mg/dl (67 μmol/l)
pANCA	Negative (0.2 U/ml)
cANCA	Negative (0.3 U/ml)
Urine microscopy	Red blood cell casts
Pretreatment serum anti-COL4α3 antibody	Borderline positive (1.1)
Posttreatment serum anti-COL4α3 antibody	Negative (<0.2)
Renal biopsy	
Light microscopy	One glomerulus with small segmental necrotizing lesion
Immunofluorescence	Strong linear IgG (3+), C3 (2+), kappa (2+), and lambda (2+) staining along the GBM Negative staining for type IV collagen α3 and α5 chains
Electron microscopy	Homogeneous thinning of GBM with reduction of the lamina densa without lamination or splitting
Serum anti-GBM antibody study	
Indirect immunofluorescence	Positive for IgG, and subclass IgG4

cANCA, cytoplasmic antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane; pANCA, perinuclear antineutrophil cytoplasmic antibody.

anti-GBM disease presents with pulmonary-predominant symptoms including dyspnea, cough, and alveolar hemorrhage that are very similar to our case.<sup>7</sup> Many of these patients are active smokers who present with normal serum creatinine and would maintain independent renal function throughout their disease course.<sup>7,8</sup> Serum anti-GBM antibody (against α3 [IV]) characteristically positive in classic anti-GBM disease can be low or undetectable in a significant proportion of these atypical variants of anti-GBM disease.<sup>3,7,8</sup> The diagnosis often relies on strong diffuse linear GBM staining for IgG and C3 by IF.

In this case, strong linear GBM IgG and C3 IF staining were crucial to establish the diagnosis in the absence of crescents. Other conditions with linear GBM IgG staining, including diabetic nephropathy were unlikely in the absence of hyperglycemia and characteristic renal biopsy findings of diabetic nephropathy, such as diffuse or nodular glomerulosclerosis. In addition, the direct IF staining of IgG and C3 would have been much weaker in diabetic nephropathy.<sup>9</sup> The positive anti-GBM IgG by indirect IF and the elevated serum anti-GBM antibody before plasmapheresis indicates the presence of a circulating autoantibody

against  $\alpha 3(\text{IV})$ , which further supports the diagnosis of anti-GBM disease.

The possibility of classic anti-GBM disease with excellent treatment response was considered, as her biopsy was obtained after completion of plasmapheresis that can effectively remove anti-GBM antibodies, complement proteins, and immune complexes from the circulation.<sup>10</sup> Corticosteroids before plasmapheresis may also have attenuated the immune response. However, the preserved renal function before plasmapheresis was not consistent with classic anti-GBM disease.

Classic anti-GBM disease has been shown to have IgG subtype restrictions in both circulating serum anti-GBM antibody and GBM IgG deposits, with IgG1 and IgG3 being the predominant subclasses respectively.<sup>11,12</sup> A distinct subgroup of 4 patients with IgG4 predominance in circulating anti-GBM antibody have been reported.<sup>13</sup> All patients in this subgroup were relatively young women who presented with pulmonary hemorrhage and had preserved renal function at follow-up after treatment.<sup>13</sup> The patient demographics, clinical presentation, and the IgG subclass restriction are very similar to the present case. Most commercially available enzyme-linked immunosorbent assays for anti-GBM antibody are sensitive and specific for IgG1 and IgG3, and therefore may yield falsely negative results in IgG4-predominant cases.<sup>14</sup> This may at least in part explain the slightly elevated pretreatment serum anti-GBM antibody level disproportional to the severity of her pulmonary symptoms.

It is exceedingly rare to see any form of active anti-GBM disease presenting in patients with abnormally thin GBM, including TBMN and different variants of Alport syndrome. Patients with diffuse thinning of GBM can have reduced amount of  $\alpha 3(\text{IV})$  in their GBM.<sup>15</sup> This offers a plausible explanation to the milder renal manifestation in this case, as the extent of renal damage was likely limited by the attenuated amount of target epitopes on the GBM.

A small number of patients with Alport syndrome have been shown to develop anti-GBM disease in their allograft following transplantation.<sup>1</sup> The pathogenesis is related to the development of alloantibodies against  $\alpha 3\text{NC1}$  and other epitopes in the allograft that would have been absent in native tissues of patients with Alport syndrome.<sup>1,16</sup> The clinical course of posttransplant anti-GBM disease in Alport syndrome is highly aggressive and nearly always results in graft loss.<sup>16,17</sup> Patients with TBMN, however, usually have preserved renal function and rarely require transplantation. As result, a similar phenomenon has not been observed in TBMN.<sup>17</sup>

Isolated cases of linear IgA, IgM, IgG, and/or C3 staining along the GBM have been reported in patients with TBMN with no active pulmonary or renal

symptoms and no detectable circulating anti-GBM antibody.<sup>18,19</sup> Possible explanations to this staining can be attributed to exposed antigen by abnormally thin GBM that would be normally be concealed, nonspecific IgG binding along the GBM as can be seen in diabetes or lupus, or autoantibodies against uncommon collagen subunits not recognized by commercially available assays.<sup>9,20–23</sup>

In conclusion, we present a rare case of non-crescentic pulmonary-predominant anti-GBM disease with concurrent TBMN. The atypical clinical presentation and biopsy findings of 2 superimposed pathologic diagnoses are further complicated by preceding empirical treatment, which presented a unique diagnostic challenge. It highlights the importance of integrating clinical, radiological, and pathological information to arrive at the correct diagnosis. Further studies are required to explore the association between these 2 rare diseases and to elucidate the long-term follow-up data.

## DISCLOSURE

All the authors declared no competing interests.

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## REFERENCES

1. Hudson BG, Tryggvason K, Sundaramoorthy M, et al. Alport's syndrome, Goodpasture's syndrome, and type IV collagen. *N Engl J Med*. 2003;348:2543–2556.
2. Jennette JC, Falk R, Bacon P, et al. 2012 revised international chapel hill consensus conference nomenclature of vasculitides. *Arthritis Rheum*. 2013;65:1–11.
3. Nasr SH, Collins AB, Alexander MP, et al. The clinicopathologic characteristics and outcome of atypical anti-glomerular basement membrane nephritis. *Kidney Int*. 2016;89:897–908.
4. Bolton WK. Goodpasture's syndrome. *Kidney Int*. 1996;50:1753–1766.
5. Haas M. Alport syndrome and thin glomerular basement membrane nephropathy: a practical approach to diagnosis. *Arch Pathol Lab Med*. 2009;133:224–232.
6. Savige J, Rana K, Tonna S, et al. Thin basement membrane nephropathy. *Kidney Int*. 2003;64:1169–1178.
7. Lazor R, Bigay-Game L, Cottin V, et al. Alveolar hemorrhage in anti-basement membrane antibody disease: a series of 28 cases. *Medicine*. 2007;86:181–193.

8. Serisier DJ, Wong RC, Armstrong JG. Alveolar haemorrhage in anti-glomerular basement membrane disease without detectable antibodies by conventional assays. *Thorax*. 2006;61:636–639.
9. Westberg NG, Michael AF. Immunohistopathology of diabetic glomerulosclerosis. *Diabetes*. 1972;21:163–174.
10. Stojkovski L. Plasmapheresis in treatment of acute oligoanuria in crescentic glomerulonephritis. *Artif Organs*. 1998;22:827–830.
11. Segelmark M, Butkowski R, Wieslander J. Antigen restriction and IgG subclasses among anti-GBM autoantibodies. *Nephrol Dial Transplant*. 1990;5:991–996.
12. Qu Z, Cui Z, Liu G, et al. The distribution of IgG subclass deposition on renal tissues from patients with anti-glomerular basement membrane disease. *BMC Immunol*. 2013;14:19.
13. Ohlsson S, Herlitz H, Lundberg S, et al. Circulating anti-glomerular basement membrane antibodies with predominance of subclass IgG4 and false-negative immunoassay test results in anti-glomerular basement membrane disease. *Am J Kidney Dis*. 2014;63:289–293.
14. Glasscock R. Atypical anti-glomerular basement membrane disease: lessons learned. *Clin Kidney J*. 2016;9:653–656.
15. Pettersson E, Törnroth T, Wieslander J. Abnormally thin glomerular basement membrane and the Goodpasture epitope. *Clin Nephrol*. 1990;33:105–109.
16. Browne G, Brown PA, Tomson CR, et al. Retransplantation in Alport post-transplant anti-GBM disease. *Kidney Int*. 2004;65:675–681.
17. Ierino FL, Kanellis J. Thin basement membrane nephropathy and renal transplantation. *Sem Nephrol*. 2005;25:184–187.
18. De Caestecker M, Hall C, MacIver A. Atypical anti-glomerular basement membrane disease associated with thin membrane nephropathy. *Nephrol Dial Transplant*. 1990;5:909–913.
19. Rogers PW, Kurtzman NA, Bunn SM, et al. Familial benign essential hematuria. *Arch Intern Med*. 1973;131:257–262.
20. Butkowski RJ, Wieslander J, Wisdom BJ, et al. Properties of the globular domain of type IV collagen and its relationship to the Goodpasture antigen. *J Bio Chem*. 1985;260:3739–3747.
21. Gallo GR. Elution studies in kidneys with linear deposition of immunoglobulin in glomeruli. *Am J Pathol*. 1970;61:377.
22. Koffler D, Agnello V, Carr R, et al. Variable patterns of immunoglobulin and complement deposition in the kidneys of patients with systemic lupus erythematosus. *Am J Pathol*. 1969;56:305.
23. Charytan D, MacDonald B, Sugimoto H, et al. An unusual case of pulmonary-renal syndrome associated with defects in type IV collagen composition and anti-glomerular basement membrane autoantibodies. *Am J Kidney Dis*. 2005;45:743–748.