Antineutrophil cytoplasmic antibody and/or antiglomerular basement membrane antibody associated crescentic glomerulonephritis in combination with IgG4-related tubulointerstitial nephritis

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Abstract

Objective

Immunoglobulin G4 (IgG4)-related disease (IgG4-RD) is an immune-mediated fibroinflammatory disorder and is characterised by elevated serum IgG4 concentrations and dense lymphoplasmacytic infiltrate rich in IgG4$^+$ plasma cells. IgG4-related tubulointerstitial nephritis (IgG4-TIN) is the most common manifestation of IgG4-related kidney disease (IgG4-RKD). We report four cases of kidney injury with concurrent IgG4-TIN and crescentic glomerulonephritis confirmed by renal pathology.

Methods

The medical charts of four patients were reviewed to collect clinical and laboratory data at the time of diagnosis, treatment and outcomes after 6–36 months. Two of them are cases of IgG4-TIN with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), and the other two cases are rare IgG4-TIN with antiglomerular basement membrane (anti-GBM) glomerulonephritis coexistent with ANCA-positive serum.

Results

Compared with IgG4-TIN, IgG4-TIN combined with AAV or anti-GBM glomerulonephritis is less associated with other organ injuries, and the clinical manifestations, treatment effects and prognosis were consistent with that of crescentic glomerulonephritis.

Conclusion

IgG4-TIN concurrent with anti-GBM glomerulonephritis and positivity in serum has more severe clinical features and a worse renal prognosis than IgG4-TIN coexistent with AVV.

Key words

antineutrophil cytoplasmic antibodies, crescentic glomerulonephritis, IgG4-related disease, tubulointerstitial nephritis

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Introduction

IgG4-RD has been recognised as an immune-mediated fibro-inflammatory disorder and described in nearly every organ system. This disease is characterised by several features: elevated serum IgG4 concentrations; a dense lymphoplasmacytic infiltrate rich in $IgG4^+$ plasma cells; storiform fibrosis; and obliterative phlebitis (1). IgG4-TIN is the most common manifestation of IgG4-RKD (2). The recognised diagnostic criteria for IgG4-RD published in 2011 mainly depends on the increase of serum IgG4 level and the infiltration of $IgG4^+$ plasma cells in the renal tissue, especially the latter is a necessary condition for diagnosis (3).

AAV is multisystem autoimmune diseases potentially involving all organs and systems, characterised by systemic necrotising vasculitis (4). Renal injury in AAV can be characterised by necrotising crescentic glomerulonephritis. The main target antigens of ANCA are myeloperoxidase (MPO) and proteinase 3 (PR3) (4-6).

Anti-GBM disease is a group of autoimmune diseases caused by the deposition of anti GBM antibodies in the organs, and involves the lung and the kidney. Anti-GBM glomerulonephritis is characterised by positive serum resistance to anti-GBM antibody and linear immunofluorescent staining for IgG on the GBM. Diagnosis of anti-GBM glomerulonephritis is made by detection of circulating and renal tissue anti-GBM antibodies. About 30% of patients with anti-GBM antibodies have ANCA detectable in serum (7).

IgG4-RD and AAV are similar in susceptible population, clinical manifestation, organ involvement, laboratory examination and even histopathological features. In recent years, there have been reports of the coexistence of IgG4-RD and AAV, and more and more attention has been paid to the relationship between these two diseases. But few cases of IgG4-TIN associated with anti-GBM glomerulonephritis have been reported. Here, we report four cases of kidney injury with concurrent IgG4-TIN and crescentic glomerulonephritis confirmed by renal pathology, two cases of which are AAV, and other two cases are anti-GBM glomerulonephritis with serum ANCA positivity.

Methods

The medical charts of four patients were reviewed to collect clinical and laboratory data at the time of diagnosis, treatment and outcomes after 6–36 months.

Case report 1

A 54-year-old Chinese man, who presented with nausea, poor appetite and acute kidney injury was admitted to our hospital. One year prior to admission, the patient was diagnosed with nerve deafness. One month before admission, the patient experienced nausea, poor appetite, and his serum creatinine (SCr) was 146.3umol/L. Two days before hospitalisation, SCr increased to 384.5μmol/L. He suffered from weight loss without hypourocrinia and oedema. The patient had a medical history of diabetes mellitus (Table I). Laboratory tests showed peripheral white blood cells were 6.07×109/L with eosinophils 1.05×10^9/L, and haemoglobin was 77g/L. A microscopic examination of the urine showed 10~15 red blood cells per high power field (RBC/HPF). Urinary protein was 2.38g/d. SCr was 413.0 umol/L, and serum albumin 30.0g/L. The serum levels of IgG and IgG4 were 17.23g/Land 7.32g/L, respectively. A test for serum perinuclear-ANCA (p-ANCA) was positive, and MPO-ANCA level was 168.0IU/mL (Table I). Renal ultrasonography revealed that the length of left kidney was 12.2 cm, and the right kidney 11.8 cm. No abnormality was found in the abdominal computerised tomography scan (CT). A renal biopsy was also performed. Immunofluorescence staining showed IgG (+++-++++) and fibrinogen-related antigen (++) deposition in mesangial and capillary wall. Under light microscopy the specimen contained 16 glomeruli: two of these glomeruli with large cellular crescents, seven with large fibrocellular crescents, two with large fibrous crescents and three with small cellular crescents. Diffuse infiltration of mononuclear cells, plasma cells and occasionally eosino-

Table I. Clinical manifestations of patients.

Patient no.	Case 1	Case 2	Case 3	Case 4
General information				
Gender (M/F)	M	M	M	M
Age (years)	54	56	76	43
Manifestations of renal involvement				
Oedema	N	Y	Y	N
Gross haematuria	N	N	N	N
Hypourocrinia	N	N	Y	Y
Extrarenal manifestations				
Fever (°C)	N	37.8	N	38.4
Weight loss	Y	Y	ND	N
Weakness	Y	Y	Y	Y
Haemoptysis	N	N	N	N

M: male; F: female; N: no; Y: yes; ND: no data.

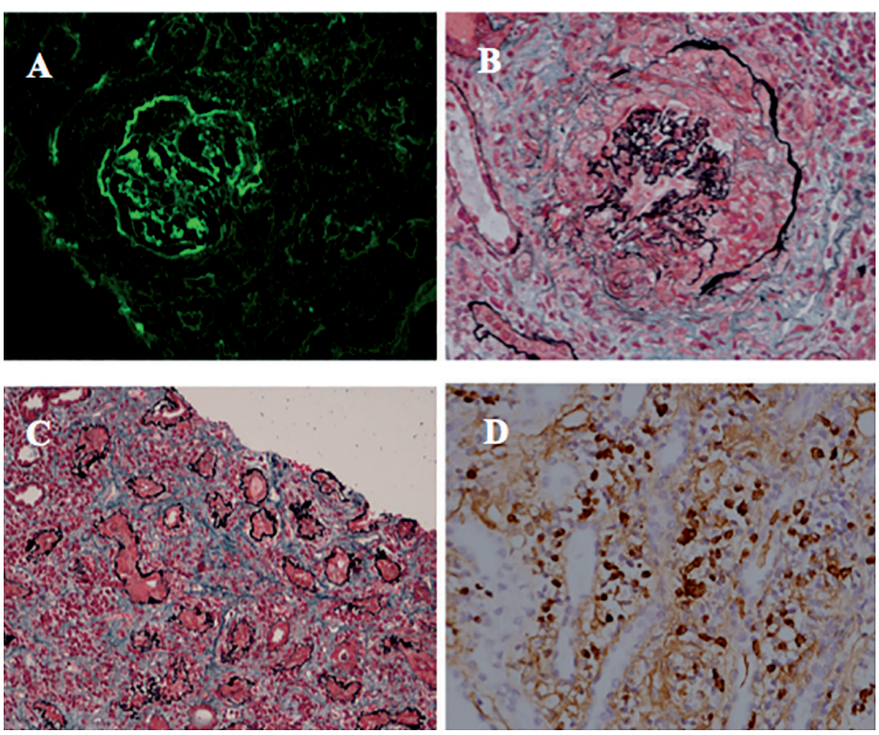

Fig. 1. Pathological findings in the renal biopsy specimen of case 11.
A) Immunofluorescence staining showed IgG deposition in mesangial and capillary wall (×200). **B**) Crescentic glomerulonephritis (PAS+MASSON, ×400). **C**) Interstitial storiform fibrosis (PAS+MASSON, ×200). **D**) IgG4$^+$ plasma cell infiltrates in the renal interstitium (×400).

philic cells were observed in the tubulointerstitium. Characteristic storiform pattern could be observed in the renal interstitium, and immunohistochemistry for IgG4$^+$ plasma cells more than 10 per high power field (/HP) (Fig. 1). The final diagnosis was IgG4-TIN and ANCA-associated necrotising crescentic glomerulonephritis. The patient received methylprednisolone pulse therapy at 0.5/d for 3 consecutive days and then oral prednisone at 40mg/d with gradual tapering. Treatment with cyclophosphamide (CTX) was given simultaneously and the total amount was 9 grams. After 1 month of treatment, SCr decreased to 201 μmol/L and was maintained 213 μmol/L at 3 year later (Table III).

Case report 2

A 56-year-old Chinese man who presented with weakness and acute kidney injury was admitted to our hospital. One year prior to admission, the patient began to feel weak. Two weeks before admission, the level of SCr was 216umol/L. One week before hospitalisation, he developed a fever of 37.8°C. He suffered from weight loss without hypourocrinia and oedema. The patient had no previous medical history (Table I). Laboratory tests showed that the peripheral white blood cells were 11.65×10^9/L with eosinophils 2.43×10^9/L, and haemoglobin was 75g/L. A microscopic examination of the urine showed 10~15 RBC/HPF. Urinary protein was 1.1g/d. The serum level of creatinine was 274.7 umol/L, albumin 27.6g/L, Hs-CRP 41.29mg/L, IgG 32.4g/L and IgG4 4.26g/L, respectively. P-ANCA in serum was positive, and the level of MPO-ANCA was 95.3IU/mL (Table II). Renal ultrasonography revealed that the length of the left kidney was 10.4 cm, and the right kidney 11.1 cm. A renal biopsy was also performed. No positive findings were found in immunofluorescence staining. Under light microscopy, 16 glomeruli could be seen in the specimen, among which there were 2 glomeruli with large cellular crescents, 6 with large fibrocellular crescents, 2 with large fibrous crescents and 1 with small cellular crescents. Diffuse infiltration of mononuclear cells, plasma cells and eosinophilic cells were observed in the tubulointerstitium. An obvious storiform pattern of interstitial fibrosis was present. In immunohistochemical staining, we found that the number of IgG4$^+$ plasma cell/HP were more than ten. Fibrinoid necrosis was showed in some small arteries (Fig. 2). The finally pathologic diagnosis was IgG4-TIN and ANCA-associated necrotising crescentic glomerulonephritis. The patient received methylprednisolone pulse therapy of 0.5/d for 3 consecutive days and then oral prednisone at 50 mg/d. Treatment with CTX was given simultaneously. After 1 week of treatment, the level of SCr decreased to 224μmol/L (Table III). The patient returned to his hometown and received treatment.

Case report 3

A 76-year-old Chinese man who presented with oedema, oliguria and acute kidney injury was admitted to our

Table II. Laboratory data of patients.

Patient no.	Case 1	Case 2	Case 3	Case 4
Urinary RBC (/HP)	8-15	5-10	ND	full
Urinary protein (g/d)	2.38	1.1	ND	0.57 (urinary volum 500ml)
Urinary α1-MG (mg/L)	211.1	88.6	ND	98.1
HGB (g/L)	77	73	93	87
SCr (μmol/L)	413	274.4	824.2	905.5
IgG (g/L)	17.23	32.47	14.04	15.89
IgG4 (g/L)	7.32	4.26	2.32	2.19
p-ANCA	Pos	Pos	Neg	Pos
MPO (U/ml)	168	121.1	2.7	114.1
c-ANCA	Neg	Neg	Pos	Neg
PR3 (U/ml)	2.0	2.0	62.6	2.0
Anti-GBM antibody	Neg	Neg	Pos	Pos
ANA	Neg	Neg	Neg	Neg
hsCRP (mg/L)	36.95	35.79	35.79	36.93
RF (U/ml)	121.6		145.9	10.1
Serum C3 (mg/L)	1.39	1.31	0.78	1.21
Serum C4 (mg/L)	0.48	0.15	0.16	0.28

RBC: red blood cell; α1-MG: α1- microglobulin; HGB: hemoglobin; SCr: serum creatinine; IgG: Immunoglobulin G; p-ANCA: perinuclear-antineutrophil cytoplasmic antibody; c-ANCA: cytoplasmic-antineutrophil cytoplasmic antibody; Anti-GBM antibody: Antiglomerular basement membrane antibody; ANA: antinuclear antibody; hsCRP: high sensitivity C-reactive protein; RF: rheumatoid factor; Pos: positive; Neg: negative.

hospital. Ten days prior to admission, the patient had oedema of both lower limbs, and the urine volume decreased gradually. Six days before admission, the patient progressed rapidly to anuria and required dialysis. The patient had a medical history of pulmonary emphysema (Table I). After admission the urine analysis could not be obtained because of anuria. Laboratory tests showed peripheral white blood cells were 10.30×10^9/L with eosinophils 0.11×10^9/L, and haemoglobin was 85g/L. SCr was 824.2 umol/L, and serum albumin 24.8g/L. The serum levels of IgG and IgG4 were 14.04g/L and 2.32g/L, respectively. Anti-GBM antibody was positive with the level of 160.5IU/ml (normal <20IU/mL). The result of the laboratory test for cytoplasmic-ANCA (c-ANCA) in serum was positive, and the level of PR3-ANCA was 60.7IU/mL (Table II). Renal ultrasonography revealed that the length of the left kidney was 12.3 cm and the right kidney 12.8 cm. A renal biopsy was performed. Immunofluorescence examination showed that IgG (++-+++) and C3 (++) linear deposition in capillary wall. Under light microscopy the specimen contained 16 glomeruli, among which there were fifteen glomeruli with large cellular crescents, and one with ischaemic sclerosis. Diffuse infiltration of mononuclear cells, plasma cells and eosinophilic cells were observed in the tubulointerstitium. The immunohistochemistry showed that IgG $^+$plasma cells more than 10/HP (Fig. 3). The final diagnosis was IgG4-TIN and anti-GBM glomerulonephritis coexistent with ANCA. The patient refused treatment for economic reasons and died (Table III).

Case report 4

A 43-year-old Chinese man, who presented with fever, weakness and acute kidney injury was admitted to our hospital. Twenty days prior to admission, the patient had a fever of 38°C. SCr increased from 351μmol/L to 565μmol/L within two days and the urine volume decreased gradually to 400 ml/d. The patient had no previous medical history (Table I). After admission the patient was treated with haemodialysis. Laboratory tests showed that the peripheral white blood cells were 8.73×10^9/L with eosinophils 0.4×10^9/L, and haemoglobin was 87g/L. A microscopic examination of the urine sediment showed full RBC/HPF. Urinary protein was 0.57g/d (urine volume was only 400ml). Scr was 905.5umol/L, and serum albumin 25.7g/L. The serum levels of IgG and IgG4 were 15.89g/L and 2.19g/L, respectively. Anti-GBM antibody in serum was positive with the level of 103IU/ml. P-ANCA in serum was positive, and the level of MPO-ANCA was 114.1IU/mL (Table II). Renal ultrasonography revealed that the length of the left kidney was 11.2 cm and the right kidney was 12.6 cm. A renal bi-

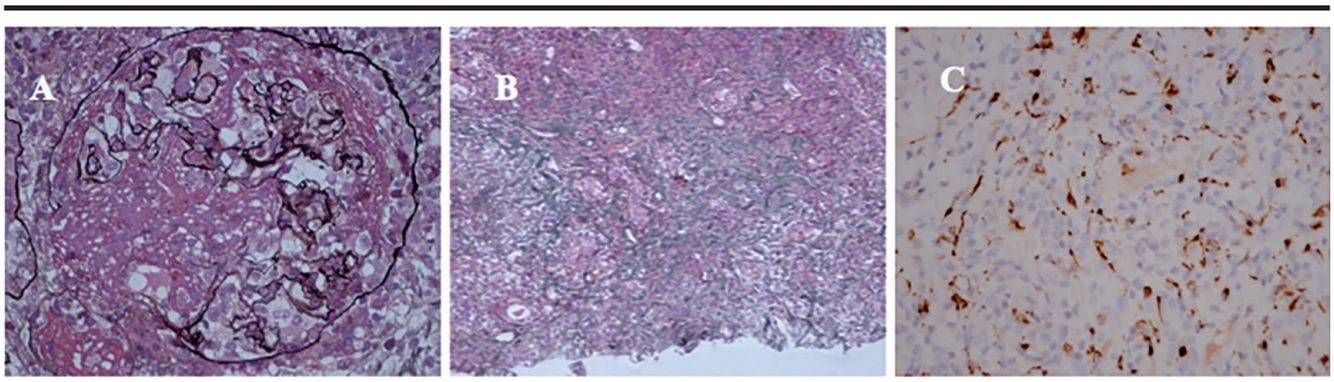

Fig. 2. Pathological findings in the renal biopsy specimen of case 2.
A) Crescentic glomerulonephritis (PAS+MASSON, ×400). **B**) Interstitial storiform fibrosis (PAS+MASSON, ×200). C) IgG4+ plasma cell infiltrates in the renal interstitium (×400).

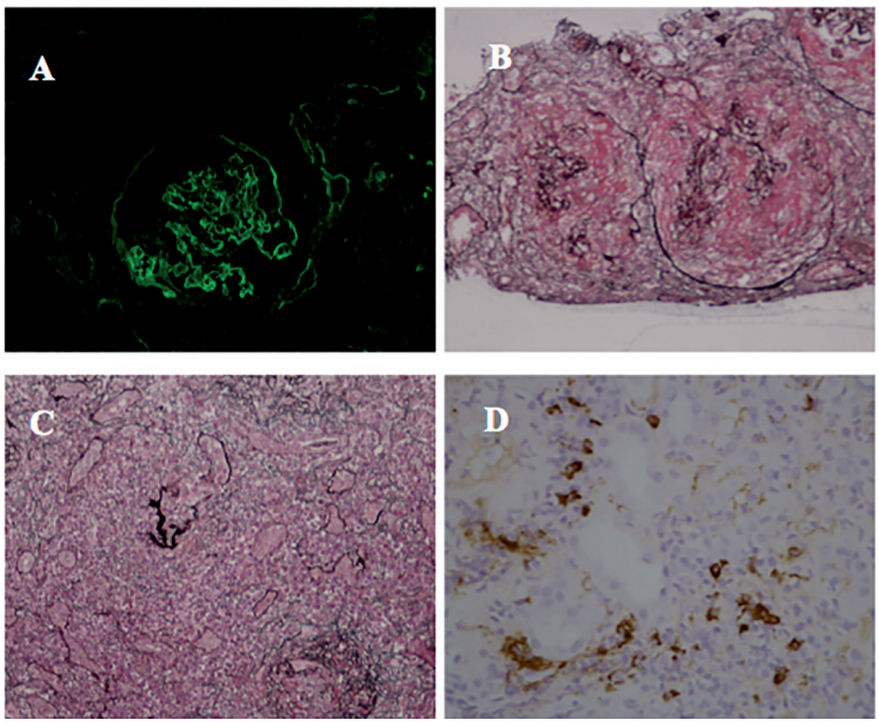

Fig. 3. Pathological findings in the renal biopsy specimen of case 3.
A) Immunofluorescence for IgG shows linear deposition in capillary wall (×200). **B**) Crescentic glomerulonephritis (PAS+MASSON, ×400). **C**) Diffuse infiltration of lymphocyte, mononuclear cells, plasma cells infiltration in the tubulointerstitium (PAS+MASSON, ×200). **D**) IgG4+ plasma cell infiltrates in the renal interstitium (×400).

Table III. Treatment and prognosis of patients.

Patient no.	Case 1	Case 2	Case 3	Case 4
Therapy	Methylprednisolone 0.5g 3times prednisone 50mg/d CTX 50mg/d	methylprednisolone 0.5g 3times prednisone 50mg/d CTX 50mg/d	n.	prednisone 40mg/d
Prognosis	Renal function partial recovery	Renal function partial recover	died	hemodialysis

CTX: cyclophosphamide.

opsy was performed. Immunofluorescence examination showed linear deposition of IgG (++-+++) and C3 (++) in the capillary wall and Bowman's capsule wall. Under light microscopy the renal specimen contained 13 glomeruli, among which there were 11 glomeruli with large cellular crescents, and 1 with ischaemic sclerosis. Diffuse infiltration of lymphocyte, mononuclear cells, plasma cells and infiltration of a few eosinophilic cells were observed in the tubulointerstitium. The immunohistochemistry showed that IgG4+ plasma cells/HP were more than ten (Fig. 4). The final diagnosis was IgG4-TIN and anti-GBM glomerulonephritis coexistent with ANCA. The patient refused plasma exchange treatment for economic reasons and received prednisone treatment of 40 mg/d. Renal function was not restored and the patient has remained with a maintenance dialysis therapy till now (Table III).

Discussion

We have presented four cases of IgG4-TIN, finally diagnosed by typical pathological features and elevated serum IgG4. In case 1 and case 2, the findings of crescentic glomerulonephritis and serum ANCA positivity led to a coordinated diagnosis of AAV. In case 3 and case 4, although these patients' serum presented double positive for ANCA and anti-GBM antibody, the final diagnosis was of anti-GBM glomerulonephritis coexistent ANCA, as the immunofluorescence examination of the kidneys showed the linear deposition of IgG in glomerular capillary wall. According to the diagnostic criteria for IgG4-TIN, we identified the diagnosis of case 1 and case 2 where IgG4-TIN combined with AAV, and case 3 and case 4 where the rare disease of IgG4-TIN combined with anti-GBM glomerulonephritis with ANCA-positive antibodies.

In 2010, Yamamoto *et al*. (8) firstly reported five patients with Churg-Strauss syndrome (CSS) with MPO-ANCA positive presenting with elevated IgG4 in serum. In three of these patients, the pathological results of renal biopsy revealed infiltration of IgG4+ plasma cells in renal tissue. The authors proposed that IgG4+ plasma cells may be involved in the pathogenesis of CSS, but it was necessary to have a further research on the relationship between IgG4-RD and CSS. Since then, many reports have been published on medium to large numbers of IgG4+ plasmacytes infiltrated seen in the affected tissues of AAV patients. In 2011 Raissian *et al*. (3) reported that specimens of ANCA-associated pauci-immune glomerulonephritis, moderate to severe IgG4+ plasma cells infiltration could be observed in the renal tissue. In 2013 Chang *et al*. (9) reported increased IgG4+ plasmacytes in sinonasal, orbital/periorbital or renal biopsies of AAV patients. Therefore, the authors even considered that AAV should be excluded before the diagnosis of IgG4-RD. In 2015 Alba *et al*. reported a patient with ANCA-negative small-vessel systemic vasculitis involving muscle, peripheral nerve and focal segmental necrotising glomerulonephritis in the context of IgG4-RD diagnosed on the basis of elevated serum IgG4 and histologically consistent sign in renal biopsied tissues. Further studies are necessary to determine the relationship of vasculitis and IgG4-RD (10).

In recent years, it has been reported that AAV and IgG4-RD are two coexistent diseases. Tosovsky *et al*. (11)

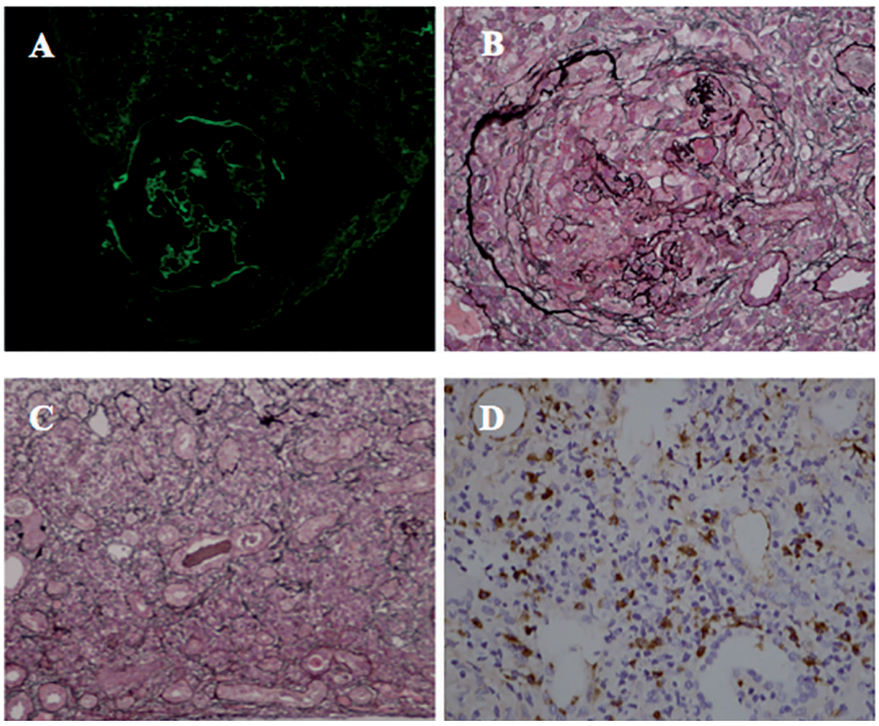

Fig. 4. Pathological findings in the renal biopsy specimen of case 4.
A) Immunofluorescence for IgG shows linear deposition in capillary wall (×200). **B**) Crescentic glomerulonephritis (PAS+MASSON, ×400). **C**) Diffuse infiltration of lymphocyte, mononuclear cells, plasma cells infiltration in the tubulointerstitium (PAS+MASSON, ×200). **D**) IgG4$^+$ plasma cell infiltrates in the renal interstitium (×400).

reported one case of PR3-ANCA associated glomerulonephritis with IgG4-related mediastinal masses, with two diseases diagnosed by renal biopsy and mediastinal mass biopsy, respectively. Because there were biological and histological features of both IgG4-RD, as well as AAV, the possible diagnosis of IgG4-RD and AAV coexistent in the same patient was hypothesised. Su *et al*. (12) described a patient with renal biopsy showing IgG4-TIN and necrotising crescentic glomerulonepritis, with MPO-ANCA positive in serum. Other than kidney injury, the patient presented autoimmune pancreatitis secondary to IgG4-RD, and chronic paranasal sinusitis secondary to AAV. The final diagnosis of the patient was IgG4-TIN coexistent with ANCA-associated glomerulonephritis. At the same time, the author analysed the IgG subclass of MPO-ANCA and found that the subclass of IgG4 accounted for 77.3%, hence they speculated that IgG4 MPO-ANCA produced by infiltrating IgG4$^+$plasma cells might be responsible for the necrotising crescentic glomerulonephritis. A European retrospective multicentre observational study was conducted on 18 patients who presented with typical histological and serological characteristics of AAV and IgG4-RD. According to the current diagnostic criteria of these two diseases, the authors considered that "overlap syndrome" constituted AAV and IgG4-RD. They speculated that the possible pathogenesis was pathophysiological similarities between AAV and IgG4-RD. A common pathophysiological pathway could involve T follicular helper (Tfh) cells which were shown to be increased in both diseases and polarised towards Tfh-2 subtype, enhancing IgG4$^+$ plasma cell polarisation, but further evidence is needed (13).

IgG4-TIN concurrent with anti-GBM glomerulonephritis is rare. In 2011 Houghton *et al*. (14) reported five cases of necrotising and crescentic glomerulonephritis with active interstitial inflammation for the presence of IgG4$^+$ plasma cells in renal biopsy samples. In one case, the linear deposits of IgG could be observed in the glomerular capillary under immunofluorescence, and positive both for MPO-ANCA and an anti-GBM antibody in serum. In our report, case 3 and case 4 were IgG4-TIN concurrent with anti-GBM glomerulonephritis, and ANCA-positive meanwhile. It has been known that about 30% of patients with anti-GBM antibodies also have ANCA detectable in their serum (7, 15). However, the relationship between IgG4-TIN, anti-GBM antibody and ANCA in the pathogenesis is not clear, it is necessary to make a further observation in more cases.

IgG4-RKD often associated with other organ injuries (16). In fact, it is reported that only 5.4% of IgG4-RKD without other organ involvement (17). In our study we found that all cases do not have other organ injury secondary to IgG4-RD except for renal. AAV is also a disease of multiple organ involvement, however, in our cases of IgG4-TIN with AAV, case 1 had neurogenic deafness only, and case 2 had paranasal sinusitis. Neither case was associated with the injuries of important organs such as the lung. In anti-GBM disease, pulmonary haemorrhage often occurred concurrently with glomerulonephritis. However, in our case of 3 and 4, there was only renal injury without lung involvement.

IgG4-TIN is clinically characterised by tubulointerstitial damage without prominent haematuria and proteinuria. In our study, all cases of IgG4-TIN also presented prominent clinical manifestations of crescentic glomerulonephritis, such as haematuria, proteinuria and rapid progression of renal function. In clinical, anti-GBM glomerulonephritis with both positivity of anti-GBM antibody and ANCA, which has a worse renal prognosis than AAV (7, 15, 18). Likewise, compared with case 1 and 2, case 3 and 4 with anti-GBM antibody positivity showed a higher level of SCr and a faster deterioration of renal function, in line with the clinical manifestations of anti-GBM glomerulonephritis.

IgG4-TIN has a favourable response to steroid treatment, even in cases with deteriorated renal function (16, 17, 19, 20). AAV can be involved with life-threatening organ injury, so when IgG4-RD is coexistent with AAV, the treatment aimed at AAV should be selected. The therapy including corticosteroid

and cyclophosphamide are effective for the majority of cases of both IgG4-RD and AAV. In case 1, after treatment with prednisone combined with cyclophosphamide, the renal function improved, the level of IgG4 in serum also decreased to normal and ANCA was negative. In the treatment course of IgG4-RD and AAV, the disease easily relapses during the period of corticosteroid reduction and maintenance (18). It is reported that rituximab therapy was effective for relapsing or refractory patients with IgG4-RD and AAV (21, 22). IgG4-RD coexistent with anti-GBM glomerulonephritis is rarely reported. Because anti-GBM disease can lead to severe fatal alveolar haemorrhage, the therapy should be aimed at anti-GBM disease. In our cases, the prognosis of the patients is mainly determined by the severity and type of crescentic glomerulonephritis, and is significantly worse than that of patients diagnosed with IgG4-TIN only.

Conclusion

In conclusion, we report two cases of IgG4-TIN coexistent with AAV, and the other two cases are the rare disease of IgG4-TIN coexistent with anti-GBM glomerulonephritis and ANCA positive. The clinical manifestations of these patients were consistent with the characteristics of crescent glomerulonephritis, however, they had no other important organ injury secondary to IgG4-RD. Treatment should be aimed at crescentic glomerulonephritis; the response for treatment and prognosis with the kidney are also closely accorded (correlated?) with the characteristics of crescentic glomerulonephritis. Compared with patients of IgG4-TIN coexistent with AAV, patients of IgG4-TIN coexistent with anti-GBM glomerulonephritis have more severe clinical manifestations and a poor prognosis. However, more cases should be collected for further research on the clinical and diagnostic features of these combined diseases.

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