Rapidly progressive glomerulonephritis caused by overlap syndrome of IgG4-related tubulointerstitial nephritis and myeloperoxidase-antineutrophil cytoplasmic antibody-associated necrotising glomerulonephritis

Sirs,

IgG4-related disease (IgG4-RD) is an immune-mediated systematic fibroinflammatory condition characterised by elevation of serum IgG4 and infiltration of IgG4-positive plasma cells (IgG4-PCs) (1). Although IgG4-RD is often associated with serum IgG4 levels, this finding is neither sensitive nor specific for the diagnosis. In addition, high concentrations of IgG4-PCs within affected organs are not diagnostic of IgG4-RD (1). Thus, the diagnosis of IgG4-RD requires thorough exclusion of potential mimics, such as antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV), polymyalgia rheumatica, infections, and neoplasms (2, 3). We present a case of a 67-year-old man with rapidly progressive glomerulonephritis (RPGN). The pathological kidney findings were typical of both IgG4-RD and AAV, suggesting overlap syndrome.

In September 2015, the patient visited the urology department in our hospital to work-up for the enlarged kidney cysts. Enhanced computed tomography revealed coincidentally multiple low density lesions of the bilateral kidneys and hypertrophic soft tissue around the right common iliac artery (Fig. 1A and 1B). Serum IgG4 level was elevated at 180 mg/dL (normal, <135 mg/dL). Although IgG4-RD was suspected, pathological examination was not performed because of the absence of clinical symptoms or renal disorders.

In March 2016, the patient developed worsening kidney function (serum creatinine (s-Cr) of 4.14 mg/dL) and abnormal urinalysis (urinary protein 2+ and occult blood 3+) identified on periodic visits to the urology department. He was admitted to our department for work-up based on the suspicion of RPGN due to IgG4-RD.

On admission, physical examination demonstrated no specific symptoms. Blood testing showed increased serum IgG and IgG4 levels at 2453 mg/dL (normal, 870-1700 mg/dL) and 378 mg/dL, respectively. Myeloperoxidase (MPO)-ANCA titres were elevated at 280 IU/mL (normal, <3.5 IU/mL) but proteinase 3 (PR3)-ANCA was negative. Urinary test showed 20-29 red blood cells per high power field (HPF) and proteinuria of 1.3 g/day.

Renal biopsy performed on day 2 of hospitalisation, revealing three segmental tuft necrotic glomeruli out of twelve total glomeruli in the specimen (Fig. 1C). The infiltration of plasma cells was found in the tubulointerstitium (Fig. 1D). The fibrous bundles encircled lymphocytes and plasma cells, resembling storiform pattern (Fig. 1E). The number of IgG4-PCs invading in the tubulointerstitium exceeded 50/HPF (Fig. 1F). The patient was diagnosed with RPGN caused by both IgG4 related tubulointerstitial nephritis and MPO-ANCA associated necrotising glomerulonephritis. Extra-renal manifestations associated with IgG4-RD or AAV were not found except for the periarterial involvement.

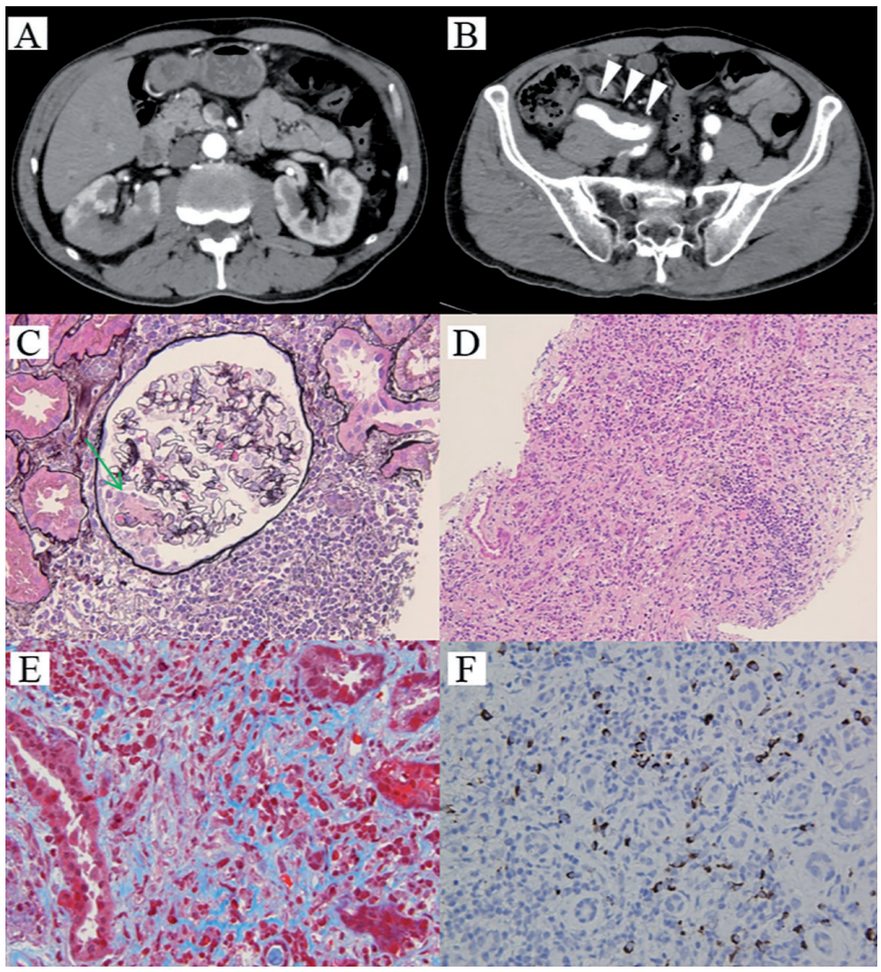

Fig. 1. Image findings of the patient.
(A) Enhanced computed tomography: multiple low density lesions of the bilateral kidneys.
(B) Enhanced computed tomography: hypertrophic soft tissue around the right common iliac artery (arrow heads).
(C) Glomerular tuft necrosis (arrow) (periodic acid methenamine silver stain, original magnification, x40).
(D) Atrophic tubules and infiltrating of mononuclear cells, consisted mainly of plasma cells, in the interstitium (haematoxylin-eosin stain, original magnification, x10).
(E) Fibrous bundles encircling lymphocytes and plasma cells in the interstitium, resembling storiform pattern (masson stain, original magnification, x40).
(F) Immunostaining for IgG4: more than 50 cells positive staining in high power field (original magnification, x40).

He was treated with high dose glucocorticoid and intravenous cyclophosphamide therapies. Three months later, his renal function improved (s-Cr of 1.45 mg/dL). The levels of MPO-ANCA and IgG4 decreased to 1.6 IU/mL and 26.7 mg/dL, respectively. Disease remission has been maintained for one year.

IgG4-RD patients can have MPO- or PR3-ANCA, with or without the concomitant presence of an overt AAV (4). Infiltration of IgG4-PCs can be also observed in AAV (5). In our case, we diagnosed RPGN caused by both IgG4-RD and AAV based not on IgG4 staining alone but on the combination of pathological analysis, serological data, and clinical course. Only five cases of overlap syndrome have been reported (4, 6-9). Just one case, described by Su *et al*., shows concurrent IgG4-related tubulointerstitial nephritis and IgG4-MPO-ANCA positive crescentic glomerulonephritis with mild renal functional disorder (9). These reports suggest IgG4-RD and AAV can overlap each other.

Alba *et al*. reported a case of IgG4-RD with necrotising glomerulonephritis as ANCA negative small-vessel vasculitis (10). Conversely, in our case, the cause of renal involvement was due more likely to AAV than to IgG4-RD because the titre of MPO-ANCA highly increased.

In AAV patients, IgG1 and IgG4 subclasses of MPO-ANCA are predominant (11). IgG4 subclass of PR3-ANCA could stimulate neutrophils to produce numerous superoxide species *in vitro* (12). The function of IgG4-MPO-ANCA is unclear, but effects similar to that of IgG4-PR3-ANCA might be speculated. In our case, the IgG subclass of MPO-ANCA could not be determined; however, IgG4-MPO-ANCA produced by IgG4-PCs might be responsible for RPGN. In conclusion, we experienced a case of RPGN due to two coexisting diseases: IgG4-related tubulointerstitial nephritis and ANCA associated necrotising glomerulonephritis. The pathophysiological relationship between IgG4-RD and AAV should be further investigated.

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