Concurrent IgG4-related tubulointerstitial nephritis and IgG4 myeloperoxidase-anti-neutrophil cytoplasmic antibody positive crescentic glomerulonephritis

A case report

Tao Su, MD\textsuperscript{a,b,c,d,*}, Li Yang, MD\textsuperscript{a,b,c,d}, Zhao Cui, MD\textsuperscript{a,b,c,d}, Su-xia Wang, MD\textsuperscript{e}, Ming-hui Zhao, MD\textsuperscript{a,b,c,d,e,f,*}

1. Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a multiorgan immune-mediated systemic disease.\textsuperscript{[1]} Many of the disorders mimic other diseases, making a precise diagnosis difficult. Infiltrates of IgG4-positive plasma cells in tissues and storiform fibrosis are hallmarks of the disease pathology. However, approximately one-third of pauci-immune crescentic glomerulonephritis (GN) patients show moderate to marked infiltration of IgG4+ plasma cells,\textsuperscript{[2]} and immunohistochemical staining for IgG4 or increased serum IgG4 levels are insufficient to differentiate between IgG4-RD and pauci-immune GN. Conversely, cases of IgG4-RD can be associated with other antibodies, such as anti-PLA2R antibody, antineutrophil cytoplasmic antibodies (ANCA) directed to myeloperoxidase (MPO) or proteinase 3 (PR3). Tosovsky et al.\textsuperscript{[3]} reported a case of renal-limited PR3-ANCA-positive vasculitis presenting with pauci-immune crescentic GN and an IgG4-related mediastinal mass. However, no typical features of IgG4-RD were found in the kidney. Whether the PR3-ANCA were specifically of the IgG4 subclass was not investigated.

Here, we report the first case of typical IgG4-related tubulointerstitial nephritis (IgG4-TIN) concurrent with IgG4 MPO-ANCA-positive necrotizing crescentic GN. The presence of...
IgG4 MPO-ANCA in this case may shed light on our understanding of the clinical presentations and pathogenic mechanisms of both IgG4-RD and ANCA-associated vasculitis.

2. Case report

A 42-year-old Chinese man, who was a professional cook and heavy smoker, presented with repeated epigastric pain and acute kidney injury and was admitted to our hospital. One year prior to admission, the patient was diagnosed with acute pancreatitis on the basis of epigastric pain, enlarged pancreas on abdominal computed tomography (CT) scan, and increased serum amylase and lipase. At that time, his C-reactive protein (CRP) level was 79.4 mg/L but serum IgG and IgG4 were in the normal range. Six months before admission, a repeat CT scan revealed a sausage-shaped pancreas, and his serum creatinine was 67 μmol/L, without proteinuria and hematuria. Total IgG was 18.7 g/L, IgG4 was normal at 1.02 g/L, and the IgG4:lgG ratio was 5.4%. CRP was still high at 72.4 mg/L and the erythrocyte sedimentation rate was 87 mm/h. An experimental therapy with prednisone 30 mg/d for 4 weeks helped to relieve epigastric pain. Thus, a diagnosis of autoimmune pancreatitis was made based on sausage-like enlargement of the pancreas in contrast-enhanced CT suggesting diffuse pancreas swelling, increased level of serum IgG, and well response to steroid therapy. Two weeks prior to the current admission, he developed a fever up to 39°C. A magnetic resonance cholangiopancreatography scan disclosed an atrophied body and tail of the pancreas. Ultrasonography revealed normal size and structure of both kidneys. Serum IgG was 25.2 g/L, IgG4 was 1.83 g/L, and the IgG4:lgG ratio had increased to 7.2%. No hypocomplementemia was apparent, with C3 and C4 levels of 0.808 and 0.351 g/L, respectively. The patient’s renal function deteriorated rapidly with serum creatinine 157 μmol/L, urinary red blood cells ∼10 to 15/high-power field, urine albumin to creatinine ratio 125.5 mg/g, and α1-microglobulin 80.5 mg/L. Peripheral white blood cells were 12 × 10⁹/μL with 19% eosinophils, and hemoglobin was 69 g/L. A test for serum perinuclear-ANCA was positive, and MPO-ANCA levels were >200 IU/mL (normal range <201 IU/mL). The patient’s history revealed chronic paranasal sinusitis. The patient was admitted to our hospital and a renal biopsy was performed. Histologic examination showed that most of the infiltrate was CD138-positive plasma cells, and more than 40% were IgG4-positive plasma cells (Fig. 1B). A diagnosis of IgG4-TIN was made, supported by the enriched IgG4-positive plasma cell interstitial infiltration. Interestingly, further analysis revealed that the patient’s serum MPO-ANCA was also predominantly restricted to IgG4 (77.3%), with 22.7% IgG1, and no detectable IgG2 and IgG3 subclasses.

The patient was finally diagnosed with IgG4-RD based on his history of autoimmune pancreatitis, the IgG4-positive plasma cell-enriched TIN, increased serum IgG4, and the acute systemic process. The findings of pauci-immune necrotizing crescentic GN, periglomerular granulomatosis formation, chronic paranasal sinusitis, MPO-ANCA, and eosinophilia led to a concurrent diagnosis of systemic ANCA-associated vasculitis in the form of eosinophilic granulomatosis with polyangiitis (EGPA). However, considering the dominance of IgG4 ANCA and the criteria of the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides, the systemic vasculitis might also be regarded as a secondary vasculitis associated with IgG4-RD.

The patient received 2 courses of methylprednisolone pulse therapy at 0.5 g/d for 3 consecutive days and then oral prednisone at 1 mg/kg/d with gradual tapering. Intravenous cyclophosphamide was administered at 0.6 g monthly. The patient responded well. His serum creatinine and IgG level decreased (Figs. 2 and 3). After treatment, he showed decreased erythrocyte sedimentation rate (17 mm/h), CRP (2.03 mg/L), and IgG (14.7 g/L), while his serum IgG4 and IgG4:lgG ratio remained high at 1.86 g/L and 22.7%, respectively. A second renal biopsy performed 6 weeks after the initial biopsy revealed normal size and structure of both kidneys. Serum IgG4 and IgG4:lgG ratio remained high at 1.86 g/L and 22.7%. The patient was discharged on oral prednisone 5 mg/d with gradual tapering.

Figure 1. Pathological findings in the renal biopsy specimen. A, Necrotizing crescentic glomerulonephritis. B, IgG4-positive plasma cell infiltrates in the renal interstitium. C, Interstitial storiform fibrosis in the second renal biopsy.
after the first biopsy showed that the majority of glomerular crescents turned to chronic forms, cellular crescents had decreased from 58.4% to 11.4%, and fibrocellular crescents had increased from 41.6% to 81.8%. The density of the IgG4-positive plasma cell infiltrate had also decreased. More importantly, an obvious "storiform" pattern of interstitial fibrosis was present (Fig. 1C). The patient was administered intravenous rituximab at 500 mg, which depleted his CD3- / CD19+ cells from 15.45% to 0.04%. The response was sustained. The serum IgG4 9 months after rituximab administration was 0.16g/L, and CD19+ cells were 3.5%. His serum creatinine at the last visit 1 year later was maintained 124 μmol/L. Regular follow-up is ongoing.

3. Discussion

Here, we presented a case of IgG4-RD, diagnosed by a history of probable autoimmune pancreatitis that responded well to short-term steroid therapy, elevated serum IgG4, and typical pathological features such as abundant renal interstitial IgG4-positive plasma cell infiltration with subsequent occurrences of storiform fibrosis in the second renal biopsy. More importantly, this is the first report of IgG4-TIN concurrent with necrotizing crescentic GN due to IgG4 MPO-ANCA.

Although serum IgG4 is regarded as a sensitive marker of IgG4-RD, it lacks diagnostic specificity. Previous studies have demonstrated that elevated IgG4 and IgG4-positive plasma cell infiltrates can also be observed in patients with diseases such as ANCA-associated vasculitis, allergic disorders, chronic inflammatory diseases, diabetes, idiopathic TIN, membranous GN, and lupus nephritis. Raissian et al. reported that moderate to marked IgG4-positive plasma cell infiltration was observed in 31.7% of patients with pauci-immune vasculitis, especially in MPO-ANCA-associated EGPA or Churg-Strauss syndrome. Tubulointerstitial lesions with abundant IgG4-positive plasma cells were also described in patients with cytoplasmic-ANCA and PR3-ANCA. Sakairi et al. described a male patient with ANCA-negative renal small-vessel vasculitis with IgG4-positive plasma cell infiltration in the tubulointerstitial region. They considered that the severe tubulointerstitial lesions were secondary to renal necrotizing vasculitis and speculated that peritubular capillaritis might contribute to the interstitial lesions in patients with systemic small-vessel vasculitis. In fact, there are similarities between EGPA and IgG4-RD. Yamamoto et al. analyzed serum IgG subclasses in patients with EGPA and found that IgG4 accounted for between 9.35% and 32.62% of total IgG (median 20.15%). They speculated that repeated weak stimulation of unknown origin might induce the production of IgG4 against unidentified target antigens. However, the contribution of IgG4 to the pathogenesis of ANCA-associated systemic vasculitis is not clear.

MPO or PR3-specific ANCA is generally regarded as a specific serological marker for vasculitis. However, recent studies suggest that some patients with IgG4-RD are ANCA positive. Della-Torre et al. described a 51-year-old woman showing manifestations of granulomatosis with polyangiitis, serum IgG4 PR3-ANCA, and IgG4-RD involving the lacrimal gland, but not the kidney. MPO-ANCA-positive IgG4-RDs have also been described, mainly involving hypophysitis, otitis media, rhinosinusitis, and pachymeningitis. The case reported here is complex because of the mixed but typical pathological changes of the kidney resulting from concurrent IgG4-TIN and MPO-ANCA-associated necrotizing crescentic GN. Neither IgG4-related disease nor ANCA-associated vasculitis alone could explain the spectrum of disease manifestations, since pancreatitis is rare in systemic vasculitis and extensive crescent formation is also uncommon in IgG4-TIN.

The 4 subclasses of human IgG have different biological functions. IgG4 is thought to induce less severe inflammation than other subclasses due to its inability to activate complement or engage Fcγ receptors on proinflammatory phagocytes, such as macrophages and polymorphonuclear neutrophils. IgG4 production is currently believed to result mainly from a combination of sustained antigenic challenge and the effects of T-cell regulatory factors. To our knowledge, a number of environmental substances, for example high silica exposure, increase risk of ANCA-associated vasculitis (AAV). The affected TH2 cells produce IL-4 and B-cell growth factor, which stimulate the production of IgG1 and IgG3. IL-4 can also induce polymorphonuclear neutrophil degranulation and mononuclear macrophage fusion into giant cells, leading to granuloma formation. IL-4 also plays a role in class switching from IgG1 to IgG4. Elevated Th2 cytokines, such as IL-4, IL-5, IL-10, and IL-13, are associated with allergic manifestations, eosinophilia, and fibrotic progression. Finally, recent studies have shown that IgG4 is the major class of autoantibodies against the phospholipase A2 receptor in idiopathic membranous nephropathy and that IgG4 is linked to allergic disorders.

In patients with primary ANCA-associated systemic vasculitis, the offending antibodies are predominantly IgG1 and IgG4. IgG3 ANCA may act as complement-fixing antibodies and are closely associated with renal involvement. By contrast, IgG4 ANCA is less effective, and its pathogenic role in renal necrotizing lesions remains unclear. Holland et al. found that IgG4 isolated from cytoplasmic-ANCA-positive patients could stimulate neutrophils by coligation of PR3 with constitutively expressed Fcγ receptors, providing a possible clue to the pathogenic mechanism of the ANCA IgG4 subclass. Immunoglobulins are mainly produced by mature plasma cells. Patients with IgG4-RD display diffuse infiltration of IgG4-producing plasma cells in the renal interstitial. It is reasonable to speculate that this IgG4 might recognize target autoantigens and thus induce a secondary inflammatory response. We can hypothesize that, in our patient, IgG4 MPO-ANCA produced by infiltrating IgG4-positive plasma cells might be responsible for the necrotizing crescentic GN. However, the mechanism by which this might occur needs further study.
Corticosteroid and cyclophosphamide are effective treatments for the majority of cases of both IgG4-RD and ANCA-associated vasculitis, but a small percentage of patients have refractory phenotypes. Although our patient responded to combination corticosteroid and cyclophosphamide therapy, his serum IgG4 remained high and the repeat renal biopsy revealed chronic IgG4-RD. Therefore, we added rituximab, which effectively depleted his peripheral CD19+ B cells and he has remained in clinical remission throughout follow-up. Whether this treatment depleted the IgG4-RD. Therefore, we added rituximab, which effectively depleted his peripheral CD19+ B cells and he has remained in clinical remission throughout follow-up. A number of reports have suggested that rituximab, a monoclonal antibody targeting CD20+ B cells, may benefit patients with IgG4-RD. Indeed, rituximab demonstrates good long-term efficacy and safety in other autoimmune diseases, including rheumatoid arthritis and ANCA-associated vasculitis. In our patient, a single injection of rituximab successfully depleted his peripheral CD19+ B cells and he has remained in clinical remission throughout follow-up.

4. Conclusions
In conclusion, we report a rare case of IgG4-RD with concurrent IgG4-TIN and IgG4 MPO-ANCA-associated necrotizing crescentic GN. This not only raises the difficulty in differentiation diagnosis of the 2 separate diseases, but also reveals that IgG4-RD and AAV share a common etiology and pathogenesis.

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