IgG4-Associated Tubulointerstitial Nephritis: Two Case Reports and a Literature Review

Yi Fang¹, Jun Hou², Fengqing Cai¹, Xiaoqiang Ding¹ and Hong Liu¹

Abstract

IgG4-related systemic disease (IgG4-RSD) is an autoimmune disease that includes a wide variety of lesions. IgG4-RSD is characterized by high levels of serum IgG4, abundant levels of IgG4-positive plasma cells and T-lymphocyte infiltration in various organs. Tubulointerstitial nephritis (TIN) is a major finding when the kidneys are involved and is effectively treated with corticosteroid therapy. We herein describe two cases of IgG4-related TIN. Such cases have rarely been reported in China.

Key words: IgG4, tubulointerstitial nephritis, autoimmune disease


Introduction

The most common causes of tubulointerstitial nephritis (TIN) include infection and drug exposure. In some cases, TIN is secondary to autoimmune diseases such as Sjögren’s syndrome and systemic lupus erythematosus. A novel disease, named IgG4-related systemic disease (IgG4-RSD), was recently reported to be a cause of TIN (1, 2). Although an accumulating number of cases of IgG4-related TIN have been reported in the published literature, few such cases have so far been reported in China.

Case Reports

Case 1

A 65-year-old man was referred to the nephrologists at our hospital with one month history of lower extremity edema, abdominal distension and renal insufficiency. One month prior to his admission, he felt fatigue and shortness of breath during his normal daily activities. He then developed the gradual onset of abdominal distension, anorexia and backaches. He did not take these symptoms seriously until he noted lower extremity edema and foamy urine one week prior to his admission. A urinalysis revealed mild proteinuria (urine protein +) without occult blood or leukocyturia. The serum creatinine level was elevated to 145 μmol/L. The patient had no complaints of dry mouth. No fever, rashes or arthritis were found on examination. The patient’s blood pressure (BP) was within the normal range (130-140/80-85 mmHg). Transient symptoms of ophthalmalgia, dry eyes and bilateral orbital swelling began two months prior to the patient’s admission and were soon relieved by treatment with dexamethasone gutta. The patient’s past history was clear, except for a cholecystectomy 10 years prior to admission. One of his daughters had membranephropathy.

A physical examination revealed the following results: T 36.8°C, P 18/min, R 82/min, BP 130/85 mmHg. Aside from slight lower extremity edema, the remaining physical examination was unremarkable. No swelling of the parotid or submandibular glands was observed.

The laboratory data obtained on admission were as follows: urine protein: 0.49 g/d; urine erythrocytes: negative by dipstick; urine β2 microglobulin: 1.292 mg/L. A full blood count showed a normal level of hemoglobin (124 g/L), and the numbers of RBC, WBC and platelets were all within the normal ranges. The serum creatinine level was 194 μmol/L and the estimated glomerular filtration rate (eGFR) calculated with the MDRD formula was 31.7 mL/min/1.73 m². The fasting blood sugar, 2-hour postprandial blood glucose...
and glycosylated hemoglobin levels were 5.8 mmol/L, 11.0 mmol/L and 6.3%, respectively. The serum levels of free kappa light chains and lambda light chains were 10.50 g/L (normal: 1.38-3.75 g/L) and 5.17 g/L (normal: 0.93-2.42 g/L), respectively. The results of immunofixation electrophoresis and serum tests for cytomegalovirus, herpes simplex virus, Epstein-Barr virus and mycoplasma were all negative. The results of both tumor marker panels and hepatitis virus panels were clear. The results of auto-antibody serology for anti-neutrophil cytoplasmic antibodies (ANCA, PR3 and MPO), anti-glomerular basement membrane, Ro, La, Sm, RNP, Sc170 and Jo1 were all negative. The C3 level was within the normal range. An elevated serum level of rheumatoid factor, a decreased level of C4 and a high anti-nuclear antibody (ANA) titer (1:100) were found (Table 1). The serum albumin (A), globulin (G), IgA and IgE levels were 34 g/L, 58 g/L, 1.14 g/L and 446.0 IU/L (normal: <200 IU/L), respectively. An immunoglobulin subclass analysis of peripheral blood revealed the largest globulin increase to be in the IgG4 subclass, in which a level over 10 times higher than normal was observed (IgG: 37.34 g/L, normal range: 7-16 g/L; IgG4: 20.70 g/L, normal range: 0.03-2 g/L). The results of a bone scan were negative. A daily dose of 80 mg of valsartan was prescribed to reduce the level of protein in the urine. Because of concerns regarding side effects, the patient discontinued azothioprine treatment four weeks later and the dose of methylprednisolone was tapered to a maintenance dose of 4 mg/d for five months. Symptoms of fatigue, abdominal distension, weakness and lower extremity edema were alleviated. The patient’s urine test was negative and the ascites resolved after one month of treatment. After four months of treatment, the serum creatinine level decreased to 84 μmol/L, while the eGFR increased to 79.98 mL/min/1.73 m². Two years later, the patient’s urine test results remained negative. The serum creatinine level fluctuated around 100 μmol/L. The serum levels of albumin, globulin and FBG decreased to 50.9 g/L, 33.9 g/L and 6.0 mmol/L, respectively. Information regarding the serum IgG and IgG4 levels was unavailable at that time. No recurrent episodes of ophthalmalgia, dry eyes, dacyrtrhea or orbital swelling were observed. During the two years of follow-up, the patient felt quite well. The results of a recent abdominal computed tomography (CT) scan were negative.

Case 2

A 55-year-old man was admitted due to a 3-week history of renal insufficiency accompanied by new-onset hypertension. Three months prior to admission, he experienced the sudden onset of weakness in the left extremities accompanied by commissural distortion. He also felt numbness in the left limb. A CT scan and magnetic resonance imaging (MRI) indicated a lacunar infarction, an acute right basal ganglia infarction and maxillary sinusitis; however, no swelling of the lacrimal glands was observed. The patient’s symptoms were somewhat alleviated by anti-coagulation therapy. One month after the stroke, the patient was found to have high BP. The highest value of BP measured was 170/100 mmHg. Valsartan was prescribed and the BP was soon under good control. Three weeks before his admission, the patient presented with lower extremity edema and an increased serum creatinine level of 130 μmol/L. No obvious changes in weight, daily urine output or any other accompanying symptoms such as fever, anorexia, skin rashes, arthralgia, dry eyes or dry mouth were observed. A physical examination showed no abnormal signs, except for reduced muscle tension on the left side. The patient did not exhibit either parotid or submandibular gland swelling. The laboratory data obtained on admission were as follows: urine pro-

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<th>Table 1. Patients’ Laboratory Tests</th>
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<td>Case</td>
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Figure 1. Renal biopsy of case 1. A: Structure of glomeruli was generally in the normal state (Hematoxylin and Eosin (HE) staining, 20×magnification), B: Dense infiltration of inflammatory cells in the renal interstitium (HE staining, 10×magnification), C: Ponderous irregular wool-like collagen fibers deposition in renal interstitium, with dense infiltration of inflammatory cells (PAM stain, 20×magnification), D: IHC stain: Dense infiltration of IgG4 positive cells in the interstitium (40×magnification).

Protein: 0.65 g/d; urine microalbumin: 216.6 mg/d; urine β2-MG: 1.082 mg/L; Hb: 132 g/L; Plt: 391×10^9/L; WBC: 9.13×10^9/L; N: 33.5%; E: 34.2%; BUN: 7.1 mmol/L; Scr: 125 μmol/L; UA: 513 μmol/L; eGFR: 52.64 mL/min/1.73 m²; FBG: 4.3 mmol/L; 2h BG: 8.0 mmol/L; HbA1c: 5.3%; anticardiolipin antibodies: 20.7 RU/mL (normal <12 RU/mL); serum kappa light chains: 17.41 g/L (1.38-3.75 g/L); lambda light chains: 6.22 g/L (0.93-2.42 g/L). The results of serology tests of ANA, anti-dsDNA, ANCA (PR3 and MPO) were negative. The serum levels of C3, C4, high sensitive C-reactive protein (hs CRP) and rheumatoid factor were 0.36 g/L (normal range: 0.79-1.52 g/L), 0.01 g/L (normal range: 0.16-0.38 g/L), 4.2 mg/L (normal range: 0-3 mg/L) and 20 U/L (normal: <14 U/L), respectively. The serum levels of A, G, IgA, IgE, IgG and IgG4 were 26.0 g/L, 85.0 g/L, 1.32 g/L, 26 U/L, 55.97 g/L and 50.80 g/L, respectively. In the hepatitis marker panel, only HBsAg was positive. The serum tumor markers were negative (-) (Table 1).

An imageology examination revealed the presence of chronic inflammatory lesions in the left lower lobe on chest X-ray. An enhanced abdominal CT scan showed bilateral diffuse nephromegaly with multiple cystic lesions in the left kidney, while the pancreas, liver, gallbladder and bile ducts were negative. A bone marrow biopsy identified erythrocytes, granulocytes and megakaryocytes in the hematopoietic tissue. Mild cellular hyperplasia was found in all three of these cell types, especially in the karyocytes. Cell distribution/orientation profiles showed normal results. The proportion of eosinophils was slightly increased. No hyperplasia of plasmocytes leukocytes was observed.

A renal biopsy revealed five sclerotic glomeruli. Dense infiltration of plasma cell-dominant inflammatory cells was identified in the renal interstitium. A small number of eosinophil granulocytes was found. Widespread, severe interstitial fibrosis accompanied by patchy collagen deposition was observed. The intima of the arterioles was found to be thickened and fibrotic. Immunofluorescence showed only C3 deposition in a finely granular pattern along the capillary walls. IHC revealed dense infiltration of IgG4-positive plasma cells into the interstitium (>50/phf) (Fig. 2).

The patient received oral prednisone (20 mg tid) and azothioprine (50 mg qd) as the initial dose of immunosuppressive therapy. His symptoms were completely relieved one week after immunosuppressive treatment was initiated. At the end of the first month of treatment, the Hb level increased to 154 g/L and the proportion of peripheral eosino-
Figure 2. Renal biopsy of case 2. A: Glomerular sclerosis, with diffuse infiltration of inflammatory cells in renal interstitium, predominantly lymphocytes and plasma cells, with a few eosinophilic cells (Hematoxylin and Eosin staining, 20×magnification), B: Ponderous collagen fibers deposition in renal interstitium, with dense infiltration of inflammatory cells (Masson stain, 20×magnification), C: Ponderous irregular wool-like collagen fibers deposition in renal interstitium, with dense infiltration of inflammatory cells (PAM stain, 20×magnification), D: Renal ICH: IgG4 positive cells >50/phf (40×magnification).

Discussion

Early in 1961, Sarles et al. (3) first reported a case of sclerotic pancreatitis accompanied by hypergammaglobulinemia, which was recognized to be a new type of autoimmune disease. In 1995, Yoshida et al. (4) named this disease autoimmune pancreatitis (AIP). In patients with AIP, the serum IgG4 levels are frequently significantly elevated and tissue infiltration with IgG4-secreting plasma cells and various extrapancreatic lesions are present. Therefore, a novel clinicopathological entity, IgG4-related sclerosing disease or IgG4-related systemic disease (IgG4-RSD), was proposed and AIP was determined to be a subset of IgG4-RSD that involved pancreatic lesions (5, 6). IgG4-RSD has been identified in nearly every organ system, including the liver, gallbladder and organs outside the gastrointestinal tract such as the salivary glands, lacrimal glands, breasts, lungs, adrenohypophysis, retroperitoneum, lymph nodes and aorta (2, 7, 8). Although there are accumulating numbers of cases of IgG4-RSD, the number of patients with IgG4-related nephropathy is comparatively small. In 2004, Takeda et al. (9) first reported a case of AIP-related TIN diagnosed with a renal biopsy. More than 30 cases have been reported since (Table 2 (9-27)). For the 37 cases listed in Table 2, the average patient age is 65.76 ± 9.53 years. 30 men (86.49%) are included and almost all of the patients showed elevated serum levels of IgG and IgG4 (only one patient receiving hydrocortisone therapy had a normal IgG4 level (23)). Twenty-two of 30 (73.33%) and 21 of 30 (70.0%) patients had low serum C3 and C4 levels, respectively. The percentage of patients with positive ANA and positive RF test results were 57.58% (19/33) and 40.0% (10/25), respectively. 58.33% (20/36) of the patients had a pretreatment Scr value over 1.5 mg/dL (133 μmol/L). The patients with TIN alone presented with common clinical features of renal tubulointerstitial lesions and demonstrated either no proteinuria or only slight proteinuria (Table 2). Of the 27 cases of TIN alone, only one patient had mild proteinuria with a daily urine protein level of 1.5 g. Five patients had urine protein + results as
Table 2. Clinical Features of IgG4 Related TIN

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<thead>
<tr>
<th>Case</th>
<th>Age/Gender</th>
<th>Urine Protein (g/dL)</th>
<th>IgG (mg/dL)</th>
<th>IgG4 (mg/dL)</th>
<th>IgE (IU/mL)</th>
<th>Extrarenal Injury</th>
<th>Renal Biopsy</th>
<th>Treatment</th>
<th>Pre-treatment Scr</th>
<th>Post-treatment Scr</th>
<th>Reference</th>
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<td>1-25</td>
<td>40-76y</td>
<td>1.5</td>
<td>19.30</td>
<td>221</td>
<td>9/13</td>
<td>AIP (n=10)</td>
<td>TIN</td>
<td>PSL</td>
<td>13/25</td>
<td>1.5mg</td>
<td>Improved</td>
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<td>8.841</td>
<td>4,630</td>
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<td></td>
<td>26</td>
<td>55/male</td>
<td>1,800</td>
<td>127</td>
<td>none</td>
<td>RPF</td>
<td>TIN</td>
<td>Hydrocortisone</td>
<td>1.57</td>
<td>1 (18 m)</td>
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<td>27</td>
<td>83/male</td>
<td>1.5</td>
<td>8,100</td>
<td>1,750</td>
<td>1,295</td>
<td>RPF, Sa, Ly</td>
<td>TIN</td>
<td>Rituximab</td>
<td>30</td>
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<td>68/male</td>
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<td>4,661</td>
<td>1,120</td>
<td>335</td>
<td>Sa, La, Ly, Lu,P</td>
<td>TIN+ endocap</td>
<td>PSL50</td>
<td>1.75</td>
<td>1.55 (1m)</td>
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<tr>
<td>29</td>
<td>60/male</td>
<td>+/-</td>
<td>5,188</td>
<td>305</td>
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<td>Sa, Ly</td>
<td>TIN+ mesPGN</td>
<td>PSL50</td>
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<td>0.9 (1 m)</td>
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<td>30</td>
<td>56/male</td>
<td>+/-</td>
<td>5,680</td>
<td>1,920</td>
<td>248</td>
<td>La, Sa, Ly</td>
<td>TIN+ mesPGN</td>
<td>PSL50</td>
<td>0.9</td>
<td>0.9 (1 m)</td>
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<tr>
<td>31</td>
<td>62/male</td>
<td>+/-</td>
<td>8,194</td>
<td>704</td>
<td>none</td>
<td>Sa, AIP, Ly</td>
<td>TIN+ pulse+</td>
<td>PSL30</td>
<td>1.3</td>
<td>1.1 (1m)</td>
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<td>32</td>
<td>78/male</td>
<td>1.4/2+</td>
<td>3,731</td>
<td>1,860</td>
<td>Sa, AIP</td>
<td>TIN+ MN</td>
<td>PSL20</td>
<td>6.17</td>
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<td>33</td>
<td>83/male</td>
<td>2.3/3+</td>
<td>3,144</td>
<td>924</td>
<td>32</td>
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<td>TIN+ MN</td>
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<td>1.39 (1m)</td>
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<td>34</td>
<td>64/male</td>
<td>0.35/-</td>
<td>3,060</td>
<td>617</td>
<td>none</td>
<td>Sa</td>
<td>TIN+ MN</td>
<td>PSL40</td>
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<td>1.212</td>
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<td>PSL40</td>
<td>3.4</td>
<td>2.4 (7m)</td>
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<td>36</td>
<td>80/male</td>
<td>0.4/22(HIP)</td>
<td>3,450</td>
<td>553</td>
<td>none</td>
<td>AIP</td>
<td>TIN+ PSL</td>
<td>5.6</td>
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<td>37</td>
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<td>4,359</td>
<td>1,100</td>
<td>537</td>
<td>Ly</td>
<td>TIN+ MPGN</td>
<td>PSL30</td>
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<td>27</td>
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others 1: Ly n=6, Lu n=5, Lan=3, Mikulicz’s disease n=2, idiopathic thrombocytopenia n=2
others 2: 1 patients was treated with prednisone at 60mg/d, the other 3 received intravenous pulse PSL treatment

determined using a dipstick test. The remaining patients were protein negative or had less than 0.3 g of daily urine protein. Most of the patients were hematuria negative, except for four patients who had slight microscopic hematuria (urine erythrocyte +). However, when TIN was accompanied by glomerular injuries, substantial proteinuria or overt hematuria was observed. Performing a CT scan is important in order to detect renal injuries. Twenty-six of the 37 patients were found to have various imageological abnormalities using CT scans. Forty AIP patients in Takahashi’s study had undergone either renal CT scanning or renal MRI (28), and 35% of these patients were found to have renal injuries. The major imageological findings in IgG4-related nephropathy are: nodular lesions in the cortex; round lesions in the renal cortex, well-circumscribed or not; wedge-shaped, well-circumscribed lesions in the renal cortex; diffuse low-dense patching lesions revealed by CT scan; and an extrarenal presentation of perirenal fibrosis and soft masses in the renal sinus. The use of contrast during CT scans is mandatory. Triantopoulou et al. (29) reported that 38.8% of AIP patients have abnormal CT images when contrast exposure is necessary. Although imaging tests are very helpful, diagnosing IgG4-related nephropathy is primarily dependent on renal biopsies. Additionally, the renal toxicity of contrast medium should be considered. The pathological patterns of TIN, including dense infiltration of IgG4-positive plasma cells into renal tissue, were observed in both of our cases. Unlike general chronic interstitial nephritis, IgG4-related TIN involves more severe interstitial fibrosis, as seen in Case 2, in particular. In Case 2, the normal structures of the kidneys were damaged almost completely because of the accumulation and deposition of massive amounts of collagens. Tubulo-interstitial lesions sometimes co-exist with glomerular disease in the setting of IgG4-related nephropathy. Among the 37 published cases, 10 (27.02%) involved concurrent glomerulitis, in which membranous nephropathy is most commonly observed (Table 2).

As a component of IgG4-RSD, TIN may be associated with other organ damage. Sialadenitis is the most common extrarenal manifestation of IgG4-RSD (20/37, 54.1%), followed by AIP (15/37, 40.5%), lymphadenopathy (12/37, 32.4%), dacyrrhynthis (6/37, 16.2%) and lung injury (6/37, 16.2%). Occasionally, hepatic inflammatory pseudotumors (18), idiopathic thrombocytopenia (26) and prostatitis (30) may also be present. In Case 1, the patient exhibited transient symptoms of ophthalmalgia, dry eyes, dacyrrhynthis and bilateral orbital swelling two months prior to his admission. These symptoms were soon relieved by treatment with dexamethasone gutta. We should have performed a cranial CT scan and other important tests before initiating steroid treatment, as this contributed to our initially poor recognition of a systemic disease. However, since no recurrent episodes of dacyrrhynthis, dry eyes or ophthalmalgia were observed after oral immunosuppressive treatment was initiated, we presume that orbital soft tissue might have been involved in this case. In Case 2, the patient had no past history of hypertension; however, the onset of stroke symptoms and maxillary sinusitis was observed. It may be possible that the brain and nasal sinuses are involved in IgG4-RSD in a way that causes episodes of stroke and sinusitis; however, there...
is not adequate or strong evidence to verify this presumption and no related cases have been reported. Even in Case 2, the maxillary sinusitis healed quickly after steroid therapy was initiated.

Patients with IgG4-related TIN respond to steroid therapy. Both of our cases showed marked improvements in renal function shortly after steroid therapy was initiated. Although no guidelines exist for treating IgG4-related TIN, most nephrologists would choose prednisolone, based on experience, at an initial daily dose of 30-60 mg (0.6 mg/kg/d) for the first one to two months and then taper off the dose to a maintenance dose within six to 12 months (1, 31, 32). There is a high probability of relapse if steroids are tapered off too quickly (31, 32). For some critically ill patients, pulse corticosteroid therapy followed by oral steroid treatment is recommended (1, 11, 22). No reports have so far been published regarding the efficacy of combined therapy with steroids and other immunosuppressants. One case report describes a patient with tuberculosis infection who recovered significantly after receiving rituximab treatment (21).

The nature and pathogenesis of IgG4-related TIN remain elusive. Being the least common of the four subclasses of IgG, the production of IgG4 could be increased very substantially under long-term exposure to some antigens. For example, the serum IgG4 levels of beekeepers and patients under desensitization treatment are much higher than those observed in the general population (33). Compared to IgG1, IgG4 has weaker inter-chain bonds, thus making it incapable of fixing complements or activating immune responses (34). Despite being thought of as an “anti-inflammatory” immunoglobulin, IgG4 is found at high levels in patients with IgG4-RSD. The roles of IgG4 and its corresponding antigens in the pathogenesis of IgG4-related diseases remain unknown. Autoimmune or allergic mechanisms have been discussed (35-37). The increased peripheral blood count of eosinophils in Case 1 and the renal infiltration of eosinophils in Case 2 suggest that allergic reactions might play a role in the pathogenesis of IgG4-RSD, even in patients without histories of allergies or exposure to allergens. Additionally, IgG4-related TIN may have concurrent glomerular diseases. Membranous nephropathy (MN), another IgG4-dominant disease (10, 23-25) is most commonly observed in patients with IgG4-related TIN. In Case 1, the patient’s daughter had been diagnosed with idiopathic membranous nephropathy. The correlation between these two diseases is worthy of further investigation. Cases of IgG4-related TIN are rarely reported in China, which might be attributed to the poor recognition of IgG4-RSD. There are some limitations associated with this case report. In Case 1, we missed the evaluation of systemic disease early in the disease stage, which contributed to our poor recognition of IgG4-RSD. The patient refused to undergo a systemic CT scan, as he felt quite well after receiving steroid treatment. He underwent an abdominal CT scan only, which showed no abnormal findings. Additionally, we did not perform a biopsy on any other organs suspected to be involved in the disease process. These limitations might have prevented us from identifying the exact number of organs affected and the true clinical patterns involved in each case of IgG4-SD in China.

Hopefully, with a better recognition of IgG4-SD in the future, early diagnosis and intervention may be achieved in patients with IgG4-SD.

IgG4-related systemic disease is a novel autoimmune disease that involves multiple organs and is characterized by hyperglobulinemia, hypocomplementemia and elevated serum levels of IgG4/IgE. Serologic tests usually reveal a positive ANA result and a negative extractable nuclear antigen (ENA) result. TIN is the most common histopathologic pattern involving the kidneys. Renal manifestations are usually characterized by renal insufficiency, mild proteinuria and slight microscopic hematuria. Sometimes patients may present with serious proteinuria or gross hematuria when TIN is concurrent with glomerular disease. Renal immunolabeling shows numerous IgG4-positive plasma cell infiltrations with peritubular and glomerular subepithelial IgG4 deposition. Finally, most patients respond well to steroids.

The authors state that they have no Conflict of Interest (COI).

References