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## IgG4-related disease; a unifying entity

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### ABSTRACT

IgG4-related disease (IgG4-RD) is characterized by dense lymphoplasmacytic infiltration of different organs and elevated serum IgG4 level. The disease involves different organs including pancreas, kidney, aorta, lung, thyroid, salivary and lacrimal glands. IgG4-RD mimics malignancies, infectious and inflammatory disorders. Many disorders previously regarded as isolated, single-organ diseases such as autoimmune pancreatitis type 1, Mikulicz disease, and Riedel thyroiditis are connected within the spectrum of IgG4-RD. Chronic interstitial nephritis (CIN) is the main type of renal involvement. Membranous nephropathy is another renal picture of IgG4-RD. Multiple, hypo-dense, cortical, round and wedge-shape lesions are the main renal ultrasound features. IgG4-RD during its inflammatory phase successfully responds to glucocorticoid therapy. Here we presented a case of IgG4-RD and then reviewed the existing literature.

#### Implication for health policy/practice/research/medical education:

Chronic interstitial nephritis is the main type of renal involvement in IgG4-related disease (IgG4-RD). Membranous nephropathy is another renal picture of IgG4-RD. Multiple, hypo-dense, cortical, round and wedge-shape lesions are the main renal ultrasound features.

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### Introduction

IgG4-related disease (IgG4-RD) is a fibro-inflammatory condition characterized by dense lymphoplasmacytic infiltration of different organs and elevated serum IgG4 level. The disease involves pancreas, kidney, biliary tree, aorta, lung, meninges, peripheral nerve, cranial nerves, thyroid, salivary and lacrimal glands (1). The lymphoplasmacytic infiltrates of IgG4-RD are rich in IgG4-positive plasma cells. Pancreas, submandibular and lacrimal gland are the most affected organs (1). In 2003 Kamisawa for the first time noticed the prescience of multi-organ involvement in some patients with autoimmune pancreatitis and described the condition (2). IgG4-RD affect the middle-aged to elderly person with male to female predominance of three to one. Disease evolves over a period of months or years. Weight lost, fatigue, musculoskeletal symptoms are frequent symptoms. Compression of peripheral and cranial nerve some times are the main clinical presentation (3). Xerostomia of IgG4-RD is less severe than Sjögren's syndrome and improves after immunosuppressive therapy. Up to 40% of patients

with IgG4-RD has allergic features such as atopy, eczema and asthma. Undiagnosed or untreated cases of IgG4-RD lead to chronic pancreatitis, cryptogenic cirrhosis, honeycomb lung disease or end-stage renal disease (ESRD) (1,2).

IgG4-RD has a protean face and mimics malignancies, infectious and inflammatory disorders. Many disorders previously regarded as isolated, single-organ diseases such as Mikulicz disease, Küttner tumor and Riedel thyroiditis are connected to the spectrum of IgG4-RD (1). Here we describe a case of IgG4-RD.

A 78-year-old female was referred to our outpatient clinic for further evaluation of elevated serum creatinine level. She had a past medical history of recurrent swelling of both eyelids since four years. Patient also had lower extremity edema developed since 2 years ago. Pathologic examination of the kidney biopsy was compatible with membranous nephropathy. Treatment with corticosteroid was started, however she did not follow her medical work up properly. She had a long history of xerostomia and exophthalmia. Since one year ago, epigastric pain was added to her

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clinical picture. Upper gastrointestinal endoscopy did not reveal any pathologic finding. In her ophthalmologic examination bilateral elastic swollen non-painful lacrimal glands were detectable. Non painful bilateral enlarged submandibular glands were another noticeable finding on physical exam. Laboratory assessments revealed; fasting blood glucose was 167 mg/dL, serum creatinine was 2 mg/ dL. Additionally serum urea of 43 mg/ dL, serum calcium; 9.2 mg/ dL, serum phosphorus; 5.2 mg/ dL, plasma hemoglobin; 12 g/ dL and hematocrit of 38% was detected. Accordingly serum sodium; 139 mEq/L, serum potassium; 4.7 mEq/ L, ESR; 65 mm/h, CRP; 2+ was detected too. Urinalysis was negative for hematuria, but leukocyturia was detectable. Study of 24 hours urine collection revealed proteinuria of 1200 mg. Serum amylase was 83 IU/L (up to 100) and serum lipase was 37 IU/L (up to 60). Total alkaline phosphatase levels were 332IU/L (100-290). In abdominal ultrasound examination, liver, hepatic bile ducts, gall bladder, portal vein and spleen had normal appearance. Heterogeneous appearance without any mass lesion was detectable in ultrasound examination of pancreas. The sizes of left kidney and right kidney were 98 mm and 105 mm, respectively. A contrast enhanced CT scan study of abdomen revealed a hypo-dense lesion 15 × 11 mm in head of pancreas without any calcification. Another two hypo-dense lesions, 16 × 11 mm and 11 × 19 mm were detected in right and left adrenal glands respectively. CT scan study of liver was normal. Cortical cysts were detectable in both kidneys (Figure 1). Ascites and para-aortic lymphadenopathy was not detectable. Further laboratory examination for antinuclear and anti-SSA/SSB antibodies, ANCA antibodies and RF antibody all were negative. Serum IgG4 was 1870 mg/dL (normal 8-140 mg/dL) which was compatible with IgG4-RD in our patient.

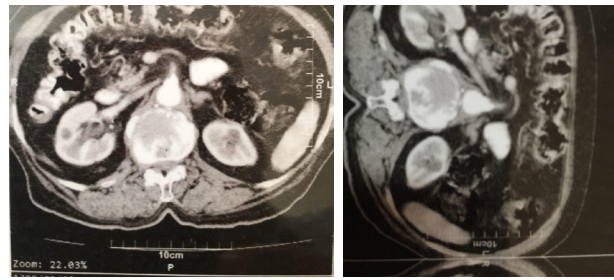
### Organ involvement

Histopathology of IgG4-RD is similar across the different organs (4). The three central histopathology features of IgG4-related disease in any involved organs are; lymphoplasmacytic infiltration, storiform fibrosis, and alliterative phlebitis. Necrosis and granulomata formation are not typical findings (5). Accumulation of IgG4-positive plasma cells of involved organs is a disease hallmark, and is detectable even when serum IgG4 concentration is normal.

The first organ that leads us to understand the histopathology of IgG4-RD was autoimmune pancreatitis type 1. Lymphoplasmacytic infiltration and sclerosis are detectable in this condition (1,2).

Non-tender lymphadenopathy in cervical, supraclavicular, submandibular, and axillary regions are detectable in some patients with IgG4-RD. Hilar, mediastinal, para-aortic and retroperitoneal lymphadenopathy are another type of lymph node involvement in these patients.

Thoracic aorta involvement by aneurysmal formation has been reported in patients with IgG4-RD. In contrast to



**Figure 1.** Cystic lesion in right kidney.

giant-cell and Takayasu's arteritis - which mainly affect the aortic branches - IgG4-RD involves the aortic trunk. IgG4-RD is the main cause of idiopathic retroperitoneal fibrosis (5,6). Destructive bone lesions similar to granulomatous polyangiitis and peripheral-nerve involvement with perineural mass lesions have been reported in patients with IgG4-RD (7).

Pituitary involvement with anterior and posterior hormone deficiencies has been reported in IgG4-RD. Sjögren's syndrome, sarcoidosis, granulomatosis with polyangiitis, Castleman's disease, lymphomatoid granulomatosis, and idiopathic interstitial pneumonitis have the overlapping pictures with IgG4-RD. Primary sclerosing cholangitis and multi-centric Castleman's disease are associated with mild tissue infiltration of IgG4 positive plasma cells (6,8). Chronic pancreatitis and cholangiocarcinoma should be considered in the differential diagnosis of IgG4-RD. Riedel's thyroiditis and fibrosing Hashimoto's thyroiditis are also in the range of IgG4-RD (9).

### Renal involvement

Chronic interstitial nephritis (CIN) is the main type of renal involvement. Less common pictures include glomerular lesions such as membranous nephropathy and vasculitis (5,10). Patients often present with low-grade proteinuria and progressive kidney failure. Renal biopsies usually show extensive tubular atrophy, and storiform interstitial fibrosis.

Clinical renal involvement occurs in 15% of patients with IgG4-RD (1) and CIN is the primary source of renal dysfunction (11). Membranous nephropathy is another renal feature of IgG4-related disease. However, IgG4 antibody against podocytes phospholipase A 2 receptor (PLA2-R) does not exist in this condition (12). Prominent proteinuria is the main clinical picture in this condition (12). Clinical picture of renal involvement in IgG4-RD is a slowly progressive renal failure leading to ESRD in late adulthood (1). In the cases of diffuse kidney enlargement, lymphoma should be considered in the differential diagnosis (1,5). Drug-induced tubulointerstitial nephritis, idiopathic membranous glomerulonephritis, pauci-immune necrotizing glomerulonephritis, sarcoidosis and Sjögren's syndrome should be considered in the differential

diagnosis of renal involvement in IgG4-RD (1,5). CIN in general has less symptoms. In the cases of allergic interstitial nephritis extra-renal symptoms such as fever, skin rash, arthralgia, and peripheral eosinophilia do not exist in most of the times. Conditions such as atheroembolic renal disease particularly in elderly should be considered in the differential diagnosis of interstitial nephritis (13). Karyomegalic interstitial nephritis is a rare, adult-onset disease causes of ESRD. It is characterized by enlarged proximal tubular cells nuclei. The underlying pathogenesis of karyomegalic interstitial nephritis is defective DNA repair (14,15).

Mesoamerican nephropathy happens in Central American male patients who are working in sugar cane fields. Repeated episodes of severe dehydration and rehydration have been proposed as underlying mechanism (16). Chronic environmental exposure to aristolochic is the underlying cause of Balkan nephropathy, and interstitial nephritis should be considered as a common picture of this disease (17,18).

### Pathogenesis

Normally IgG4 accounts for less than 5% of the total serum IgG in healthy persons. IgG4 molecule has a weak binding affinity to complement component and low ability to activate the complement pathway. The Fab arm exchange happens during IgG4 molecule processing down-regulates the antigens binding and immune complexes formation (1,19).

Various species of bacteria through stimulation of innate immunity are the primary trigger for IgG4 production. Stimulation of toll-like receptor ligand induces IgG4 and interleukin-10 production by mononuclear cells (20). Both humoral and cell-mediated immunity are involved in the pathogenesis of IgG4-RD (20). T helper type2 (Th2) cytokines contribute to eosinophilia, serum IgG4 and IgE elevation and fibrosis (1).

Memory CD4-positive T cells are sustained through antigen-presenting B cells. In a positive feedback loop T helper cells also sustain the development of B cells germinal centers. This explains why B-cell depletion is an important therapeutic element (5). Elevated proportion of CD4+CD25 regulatory T cells is another immunologic feature of IgG4-RD (21).

### Diagnosis

Measurement of serum IgG4 level is the first diagnostic test and its elevated levels is found in majority of IgG4-RD (5). Elevated levels of IgG4, six to eight fold of normal (~0.86–1.35 g/L) are highly diagnostic. However elevated serum IgG4 level is not sufficient for diagnosis, but in presence of clinical symptoms it is highly suggestive. Increased ratios of IgG4 to total IgG (>10%) are also helpful, especially when total IgG4 concentrations is not elevated (22). Elevated serum IgG4 concentrations correlate with multi-organ involvement (23). Milder

elevation of IgG4 is common in some conditions that mimic the IgG4-RD including bronchiectasis, Sjögren's syndrome, granulomatosis with polyangiitis, and eosinophilic granulomatosis with polyangiitis (formerly known as Churg-Strauss syndrome) (24,25). Malakoplakia that represents with renal impairment and renal mass mimics renal cell carcinoma and IgG4-RD (26).

Kidney ultrasound examination most commonly reveals multiple hypo-dense, cortical lesions that are detectable in 40% of patients with IgG4-RD renal involvement. Bilateral renal enlargement has been reported in 20% of patients. Poorly defined round lesions, wedge-shaped lesions and thickening of renal pelvis are other ultrasound findings (5). Lymphoma, metastatic tumors, embolic lesions and pyelonephritis should be considered in differential diagnosis of those pictures (5,27). Pulmonary nodules, pleural thickening, and interstitial lung disease are reported findings in patients with IgG4-RD. Thickening of bronchovascular bundle shows the tendency of lymphoplasma cell infiltrations to track along the bronchi and blood vessels (5). Gallium scintigraphy and fluorodeoxyglucose positron emission tomography (PET) are helpful in identifying the renal and extra-renal lesions and monitoring the disease activity (28).

Diagnosis is based on a combination of clinical, serologic, imaging and histologic findings (19,30). Tissue biopsy is the gold standard for diagnosis. However imaging is an important part of diagnostic approach and in some circumstances they are diagnostic. Tissue diagnosis is important for patients who do not have pancreatic involvement (28). When histologic study is unavailable, diagnosis of the kidney involvement is based on the radiologic features (28). In late stages of disease, histologic diagnosis is hampered by advanced fibrosis (10).

### Treatment

IgG4-RD during its inflammatory phase successfully responds to glucocorticoid therapy. Therapeutic approach includes a starting dose of 0.6–1.0 mg/kg/daily prednisolone, tapered or discontinued over 2 to 3 months. Azathioprine, mycophenolate mofetil, methotrexate and B-cell depletion with rituximab are another proposed treatment (5,29,30).

### Conclusion

The nomenclature for IgG4-RD continues to evolve. Identification of specific antigens and immune cells that ignite the disease remains to be elucidated. According to insufficient conscious about the disease, its epidemiology is unknown. Awareness about the disease is needed because it is treatable in its earlier stages (5).

### Authors' contribution

MRA handled the patient. KA prepared the primary draft. MRA conducted final edition. All authors read and signed the final manuscript.



### Conflicts of interest

The authors declare that they have no competing interests.

### Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors. Informed consent was obtained from the patient for publication as a case report.

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