



## IgG4 Tubulointerstitial Nephritis- A Rare Autoimmune Presentation

Cyndi Odipo, Arshdeep Tindni, Omer Saadat\*

Department of Internal Medicine, Jewish Hospital, Region Cincinnati, Ohio, USA

\***Corresponding author:** Omer Saadat, Department of Internal Medicine, Jewish Hospital. Region Cincinnati, Ohio, USA. Tel: +1-923353900950; Email: omer92osc@gmail.com

**Citation:** Odipo C, Tindni A, Saadat O (2019) IgG4 Tubulointerstitial Nephritis- A Rare Autoimmune Presentation. J Family Med Prim Care Open Acc 3: 131. DOI: 10.29011/2688-7460.100031

**Received Date:** 27 May, 2019; **Accepted Date:** 20 June, 2019; **Published Date:** 27 June, 2019

### Abstract

IgG4 related disease is a recently recognized systemic disease involving multiple organs, including the pancreas, salivary glands, kidneys, lymph nodes, and retroperitoneum. It is characterized by dense infiltration of organs with lymphoplasmacytic cells that leads to fibrosclerosis and elevation in serum IgG4 levels.

We present an 80-year-old Caucasian male with past medical history of DM2, coronary artery disease, hyperlipidemia, hypertension, and cerebral vascular accident with repeated episodes of acute renal failure (AKI). It initially was presumed as due to volume changes, however, that was ruled out with normal blood pressure readings of 119/73 mmHg. The patient's Glomerular Filtration Rate (GFR) ranged from 16 to 24, BUN 33, and Creatinine 2.7 despite treatment with volume resuscitation, discontinuing ACE-inhibitors, and avoidance of NSAIDs. Renal ultrasound studies were negative for obstruction, and urine analysis negative for proteinuria. As time progressed his blood pressure continued to rise in value of 130/67 mmHg, while GFR remained below 25. On renal biopsy the pathology report illustrated chronic tubulointerstitial nephritis with mild mesangial immune complex deposition, a finding that correlates with IgG4-related disease. Congo red stain of the pathology specimen was negative for amyloid deposition, another causal factor for tubulonephritis. Improvement with fatigue and appetite was noted upon starting steroid treatment. Additionally, the GFR improved to an impressive value of 53 with 3 months of treatment.

**Keywords:** Acute renal failure; Fibrosclerosis; IgG4-related disease; Lymphoplasmacytic infiltration; Tubulointerstitial nephritis

### Introduction

Type 1 (IgG4 related) autoimmune pancreatitis is the prototypical form of IgG4-related disease (IgG4-RD). The concept of sclerosing pancreatitis was introduced in 2001 by Hamano, who reported that patients with sclerosing pancreatitis had elevated IgG4 [1]. Sclerosing pancreatitis is a unique form of pancreatitis characterized by infrequent attacks of recurrent pancreatitis, irregular narrowing of the main duct, and swelling of pancreatic parenchyma. It is associated with lymphoplasmacytic infiltration of pancreas and responds well to steroids. Later it was discovered to be a part of a systemic disease involving multiple organs.

IgG4-RD has slight predominance for middle aged, and older males. Most common renal involvement of IgG4-RD manifests as interstitial nephritis. The histological findings include lymphoplasmacytic infiltration of renal interstitial leading to marked inflammation, which, if not controlled results in fibrosis. Patients are more likely to present with acute kidney injury with normal ultrasound findings. Immunohistochemistry of biopsy

demonstrates increased number of IgG4 positive plasma cells.

### Discussion

IgG4-RD is a multisystem disorder, characterized by infiltration of involved organs by IgG4-secreting plasma cells resulting in fibrosclerosis. Findings noted, are tumor like swelling of involved organs, lymphoplasmacytic infiltrate rich in IgG4 positive plasma cells, and variable degree of fibrosclerosis characteristically termed 'storiform' pattern. In addition, elevation in serum concentration of IgG4 is common.

The concept of autoimmune pancreatitis was first described by Yoshida in 1995 [2] who reported a case of chronic pancreatitis with an underlying autoimmune etiology. Later in 2001 Hamano reported that patients with sclerosing pancreatitis had high serum IgG4 levels, which helped in distinguishing this disease from other disorders of the pancreas and biliary tract [1]. The pathogenesis for IgG4 related disorder is not well understood, but there is an increasing evidence that it is an autoimmune disease, with an important role of T cells especially CD4+ and T follicular helper cells (Tfh). However, discovery of CD4 cytotoxic T cells appears to be an important phenomenon in understanding its pathogenesis. These cells make products such as granzyme-B and perforin.

They elaborate products such as IL-1, TGF-beta, and interferon gamma, which are important mediators of fibrosis, which is central to the pathophysiology of this condition [3]. Studies additionally indicated pathologic findings of IgG4-RD to involve blood vessels, more specifically veins resulting in obliterative phlebitis; alongside moderate tissue eosinophilia (Jameson L, et al.). Our case study pathology report illustrated diffuse intense interstitial mixed inflammatory infiltrate rich in plasma cells, numerous lymphocytes, and eosinophilia. Immunohistochemical staining for IgG4 highlighted greater than 40 IgG4-positive plasma cells within a focal high power field. Vasculature from the biopsy illustrated arteries with severe intimal fibrosis. Alternatively demonstrating a correlation between clinical manifestation and pathology.

Tubulointerstitial nephritis is the most common renal involvement in IgG4-related disease. Involvement of tubulointerstitial nephritis was first reported in 2004, where a case of autoimmune pancreatitis was complicated with renal dysfunction [4]. The patient had high serum levels of IgG4 immunoglobulins and Circulating Immune Complexes (CICs). Renal biopsy showed infiltration of lymphocytes, predominantly T cells, and plasma cells in the renal interstitium accompanied by fibrosis and tubular atrophy. In addition, the infiltrating plasma cells showed strong immunoreactivity to IgG4.

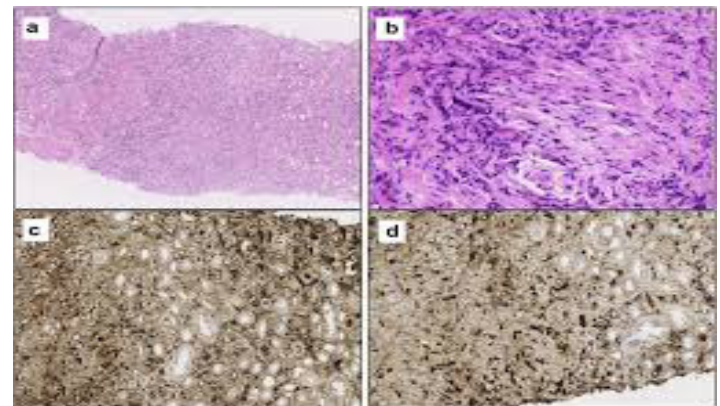
The following criteria are to be met when diagnosing IgG4 related tubulointerstitial nephritis as proposed by Kawano shown in the table below (Table 1) [5].

<b>Histology</b>	Plasma cell rich tubulointerstitial nephritis with greater than 10 plasma cells per hpf Tubular basement membrane immune complex deposits by immunofluorescence or electron microscopy.
<b>Imaging</b>	Small peripheral cortical nodules round or wedge-shaped lesions or diffuse patchy involvement.
<b>Lab Parameters</b>	Elevated serum IgG or IgG4 levels Hypergammaglobulinemia Eosinophilia
<b>Other Organ Involvement</b>	Include autoimmune pancreatitis, sclerosing cholangitis, salivary or lacrimal gland enlargement, lymphadenopathy, inflammatory aortic aneurysm retroperitoneal fibrosis.

**Table 1:** Diagnostic criteria for diagnosing tubulointerstitial nephritis proposed by Kawano.

Upon review renal histology is heavily relied on and fundamental to the correct diagnosis. Three characteristic features examined are, Interstitial lymphoplasmacytic infiltrate with dominant IgG4 positive plasma cells, the ratio of IgG4 positive/IgG positive plasma cells over 40%, and obliterative phlebitis. In lymphocyte rich infiltrate, T lymphocytes are the predominant ones and numerous eosinophils may be seen in some cases. Clinical and laboratory features of IgG4-related tubule interstitial nephritis may

emulate findings similarly triggered by other causal factors such as, Systemic Lupus erythematosus, Sjogren syndrome, or Anti-Neutrophil Cytoplasmic Antibody (ANCA) associated vasculitis due to these conditions being autoimmune. In turn, reinforcing confirmatory diagnosis via clinical and histological features being paramount (Figure 1).



**Figure 1:** a) showing fibrosis and dense inflammatory infiltrate rich in plasma cells and eosinophils. b) depicting storiform fibrosis c) IgG stain d) IgG4 stains showing greater than 30 IgG4 plasma cells.

Clinical presentation of Acute Renal Failure (AKI) is associated with elevated creatinine, proteinuria, and edema. Moreover, extra renal features occur due to compression of ureters from retroperitoneal fibrosis in turn leading to electrolyte imbalance, acute renal failure, and other associated complications [6].

Although the optimal treatment for the IgG4 related disease has not been established, glucocorticoids has proven to be the first line of treatment for remission induction in active IgG4-RD, because of rapid clinical response. Initiating treatment with Prednisone 40 mg/d with tapering to discontinuation, or maintenance dose of 5 mg/d in 2-month period is an advised protocol (Jameson L, et al.). However, some experts state that a combination of glucocorticoids and immunosuppressive agents may be needed in a few patients, as glucocorticoid monotherapy may not be able to control the disease and the potential risk of toxicities with long-term glucocorticoid use [3]. Few patients with advanced fibrosis in IgG4-RD may respond poorly to steroid therapy, hence the degree of fibrosis affecting clinical outcome. To add on, individuals with relapsing or glucocorticoid-resistance, disease may benefit from steroid sparing treatment with Rituximab, a monoclonal antibody therapy. Its effect against Tumor Necrosis Factors (TNF) leads to dramatic decline in serum IgG4 concentrations through preventing repletion of short-lived plasma cells, along with B-cell depletion via negating CD4+ T-cell function [7].

## Conclusion

IgG4-RD occurs in middle-aged and elderly men. It is a multisystemic disease that involves multiple organs, which exhibit different manifestations of the disease from inflammation due to

lymphoplasmacytic infiltrate. Acute renal failure is noted as a result of IgG4 positive plasma cell infiltrate within the tubulointerstitial area leading to nephritic signs and symptoms. To manipulate the clinical adversity and disease progression, early clinical and laboratory diagnosis in combination with treatment has proven prudent.

## References

1. Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, et al. (2001) High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med* 344: 732-738.
2. Yoshida K, Toki F, Takeuchi T, Watanabe S, Shiratori K, et al. (1995) Chronic pancreatitis caused by an autoimmune abnormality. Proposal of the concept of autoimmune pancreatitis. *Dig Dis Sci* 40: 1561-1568.
3. Moutsopoulos HM, Fragoulis GE, Stone JH (2019) Overview of IgG4 related diseases. Pathogenesis and clinical manifestations of IgG4-related disease. Up To Date.
4. Uchiyama-Tanaka Y, Mori Y, Kimura T, Sonomura K, Umemura S, et al. (2004) Acute tubulointerstitial nephritis associated with autoimmune-related pancreatitis. *Am J Kidney Dis* 43: e18-e25.
5. Kawano M, Saeki T, Nakashima H, Nishi S, Yamaguchi Y, et al. (2011) Proposal for diagnostic criteria for IgG4-related kidney disease. *Clin Exp Nephrol* 15: 615-626.
6. Evans RDR, Cargill T, Goodchild G, Oliveira B, Rodriguez-Justo M, et al. (2019) Clinical Manifestations and Long-term Outcomes of IgG4-Related Kidney and Retroperitoneal Involvement in a United Kingdom IgG4-Related Disease Cohort. *Kidney International Reports* 4: 48-58.
7. Stone JH (2019) IgG4-Related Disease. In: *Harrison's Principles of Internal Medicine*, 20e. Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, et al. (Eds.). McGraw-Hill, New York, NY, USA.