



Case Report

# Multi-Organ Involvement of Immunoglobulin G4-Related Disease

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**Abstract:** Immunoglobulin G4-related disease (IgG4-RD) is a fibroinflammatory condition of unknown etiology, with presumed autoimmune mechanisms. It is characterized by high levels of IgG4 and variable clinical manifestations. It can involve one or multiple organs. Herein, we reported the case of a 62-year-old man with three organs involvement. He initially presented with recurrent jaundice. Laboratory analysis revealed cholestasis, high gamma-globulin levels, renal failure, and proteinuria. Abdominal Magnetic Resonance Imaging (MRI) showed segmental strictures of the left intrahepatic bile ducts and the wirsung duct with an increased volume of the pancreas and diffuse bilateral enlargement of the kidneys. Laboratory tests revealed high IgG4 levels (770 mg/dL). Based on the biological and radiological findings, we have suggested the diagnosis of systemic IgG4-related disease involving bile ducts, the pancreas, and probably the kidneys. Renal biopsy revealed lymphoplasmacytic infiltrate and fibrosis, but no IgG4-positive cell. The patient received corticosteroid therapy with a complete resolution of all symptoms and a rapid normalization of all blood tests. The present case underlines the complexity of IgG4-RD because of its variable clinical presentation. The diagnosis is challenging and should be carefully assessed for possible multi-organ involvement.

**Keywords:** immunoglobulin G4-related disease; autoimmune pancreatitis; cholangitis; steroids



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## 1. Introduction

In recent decades, immunoglobulin G4-related diseases (IgG4-RD) have attracted increasing attention. They are a group of immune-mediated diseases with a variable spectrum of clinical manifestations and common serological markers. This entity is characterized by tissue infiltration by IgG4+ plasma cells and elevated serum IgG4 levels. It can involve multiple organs synchronously or metachronously, with common histopathological features and lead to tissue sclerosis, which can cause irreversible organ damage if untreated [1]. The most affected organs include the pancreas, biliary duct, kidneys, lungs, thyroid, and salivary glands.

IgG4-RD is considered a rare disease and, currently, little is known about its epidemiology. It is threefold more prevalent in male than in female patients. There is little agreement about the diagnostic criteria for systemic IgG4-RD. Up to now, only the criteria for IgG4-related pancreatitis, cholangitis, nephritis, and glandular disease are available. Nevertheless, these criteria are not applicable for the diagnosis of another organ involvement [2,3].

Currently, treatment guidelines are made based on limited data. Many reports have shown that glucocorticoids represent an effective treatment for IgG4-RD, but their long-

term use is still controversial. Herein, we report a case of IgG4-RD with three types of organ involvement, successfully treated with steroids.

We present the following case in accordance with the CARE reporting checklist.

## 2. Case Report

A 62-year-old male patient was referred to our hospital due to recurrent jaundice. His past medical history included cholecystectomy. He had no history of drinking, and no history of liver or biliary diseases. Six months before admission, the patient developed abdominal pain and recurrent jaundice. On admission, physical examination revealed scleral icterus with uniformly jaundiced skin with no evidence of abdominal mass or lymph nodes. Liver function tests showed serum alanine aminotransferase 44 IU/L, aspartate aminotransferase 78 IU/L, cholestasis with high levels of Alkaline phosphatase 196 IU/L, gamma glutamyl transferase 299 IU/L, total bilirubin 87  $\mu\text{mol/L}$ . Prothrombin time and serum tumor markers were within normal limits (carcinoembryonic antigen, 3.3 ng/mL; carbohydrate antigen 19-9, 22.3 U/mL). The other blood tests confirmed a high level of gamma-globulins 33g/dL, elevated serum creatinine 199  $\mu\text{mol/dL}$ , proteinuria 0.6 g/24 h, normal serum, and urinary electrolytes and absence of hematuria. Abdominal ultrasound showed no dilatation of intrahepatic or extrahepatic bile ducts. Abdominal magnetic resonance imaging (MRI) showed segmental strictures of intrahepatic bile ducts, especially in the left liver lobe and of the wirsung duct. The extrahepatic biliary tract was not dilated (Figure 1). There was an increased volume of the pancreas, particularly in the head, with a loss of physiological lobular architecture (Figure 2), and a diffuse bilateral enlargement of the kidneys with mild contrast enhancement (Figure 3).

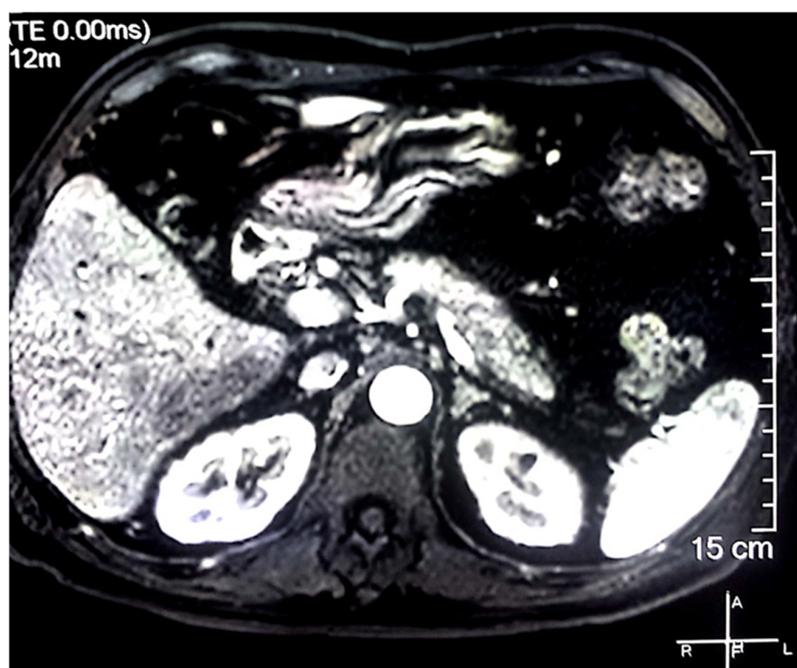


**Figure 1.** Abdominal magnetic resonance imaging (MRI): segmental strictures of intrahepatic bile ducts especially in the left liver lobe and of the wirsung duct. The extrahepatic bile duct was not dilated.

On the basis of these findings, we have discussed other differential diagnosis, including malignancies (pancreatic head cancer and bile duct carcinoma) and inflammatory disorders namely primary sclerosing cholangitis. However, auto-immune disorder with pancreaticobiliary involvement related to IgG4 disease were also suspected.



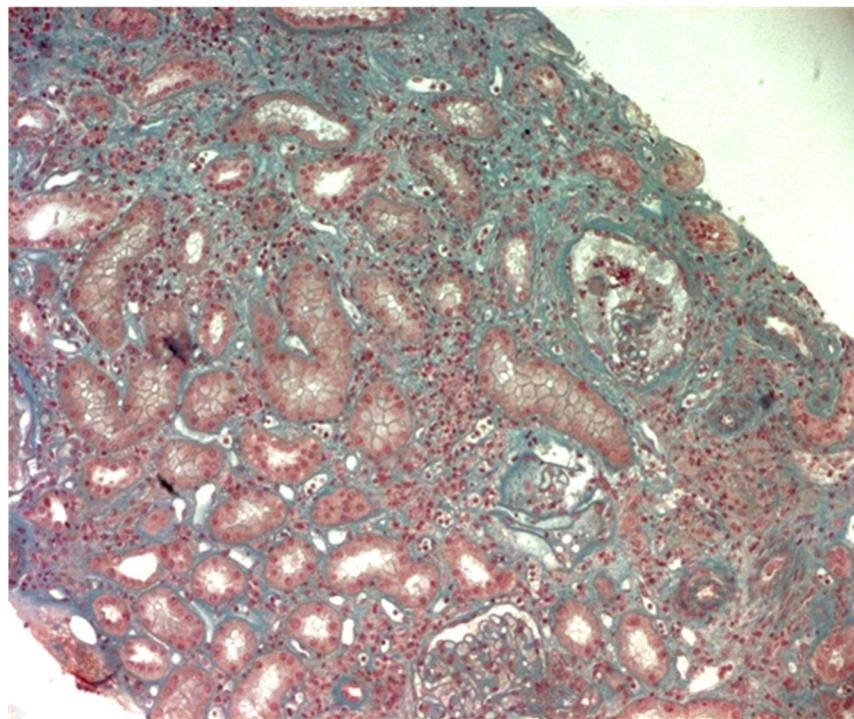
**Figure 2.** Abdominal magnetic resonance imaging (MRI): Segmental strictures in wirsung's duct, an increased volume of the pancreas especially in the head, and loss of physiological lobular appearance.



**Figure 3.** Abdominal magnetic resonance imaging (MRI): Mild contrast enhancement of the kidneys with a diffuse bilateral enlargement.

Further immunological tests revealed elevated serum levels of IgG4 770 mg/dL (NV = 135 mg/dL) pointing to a diagnosis of IgG4-related pancreatitis and cholangitis according to the Asian diagnostic criteria. Since we suspected an association with IgG4-related kidney disease, a renal biopsy was accomplished. Histological analysis of renal

specimen demonstrated interstitial inflammation with dense lymphoplasmacytic infiltrate and fibrosis, but immunostaining for IgG4 did not reveal any infiltration of plasma cells by IgG4+ (Figure 4). According to the standards proposed by the Japanese Society of Nephrology, the diagnosis of IgG4-related kidney disease is clear. Therefore, IgG4-related kidney disease was diagnosed based on clinical, serological, and histological findings. The oral dose of prednisolone given to patients was 0.6 mg/kg per day for four weeks associated to Azathioprine at the dose of 2.5 mg/kg/day. After four weeks of management, we noticed a marked general improvement, with regression of jaundice and a rapid decrease of alkaline phosphatase, gamma glutamyl transferase, bilirubin, and serum creatinine levels. Then, the prednisolone dose was gradually reduced within 12 weeks to a maintenance dose of 5 mg/d. At 6-month follow-up, laboratory analysis showed complete normalization of gamma-globulins and IgG4 levels with the disappearance of proteinuria. In the next three years, no further recurrence occurred.



**Figure 4.** Inflammatory cells are mainly made of plasma cells and lymphocytes (HE×200).

### 3. Discussion

Our 62-year-old patient presented with recurrent jaundice and abdominal pain associated to cholestatic liver function tests, proteinuria and renal failure. Further investigations revealed a marked elevation of total serum immunoglobulin G4 (IgG4) with diffuse enlarged pancreas and radiological signs suggestive of cholangitis. These findings led to the diagnosis of multi-organ expression of IgG4-related disease with involvement of the pancreas, bile ducts, and probably the kidneys.

Recently, IgG4-RD has been recognized as a systemic inflammatory condition of unknown cause [4]. The possible involvement of IgG4 in sclerosing lesions was first suggested by Hamano et al. who described high serum IgG4 concentrations in subjects with autoimmune pancreatitis [5]. Kamisawa et al. reported abundant IgG4-positive plasma cells in extrapancreatic lesions in patients with autoimmune pancreatitis, suggesting that IgG4-related pathology is not limited to the pancreas [6]. Therefore, IgG4-related sclerosing lesions have been identified at various anatomical sites and the term of IgG4-RD was used to better describe this systemic condition [7,8]. The pancreas and bile ducts were the most commonly affected gastrointestinal localizations in IgG4-RD. However, since his first description, every organ system has been reported to be affected, including lungs,

thyroid, lymph nodes, central nervous system, liver, gall bladder, heart, skin, small intestine, esophagus, colon and prostate [9–16]. In our case, three organs were involved: the pancreas, bile ducts, and kidneys. Multiorgan involvement may be evident at initial diagnosis, as was the present case, but usually evolves metachronously over months to years.

There is not enough data to determine the global incidence and prevalence of IgG4-RD because it is relatively a novel disease entity and often underdiagnosed or missed especially for patients with low IgG4 titers [1]. IgG4-RD usually occurred in middle-aged or older patients, with male predominance, particularly in IgG4-related pancreatitis (AIP) [7].

Although the diagnostic criteria for AIP have been developed, standardized international diagnostic criteria for systemic IgG4-RD have not yet been fully established, and the presence of many clinical situations mimicking IgG4-RD can lead to an over-diagnosis of the disease. The current best diagnosis of IgG4-RD depends on the comprehensive and organ-specific diagnostic criteria of subjects suffering from IgG4-related pancreatitis, sclerosing cholangitis and kidney disease [17]. The comprehensive diagnostic (CD) criteria for systemic IgG4-RD were first proposed by Umehara et al. [18]. The IgG4-RD CD-criteria included three main items, categorizing subjects as having definite, probable, or possible IgG4-RD (Table 1) [1]. One limitation of these criteria is that they may not be applicable if the organs involved are difficult in taking biopsy specimens such as the pancreas. To overcome this problem, specific Japanese societies for various organs have established diagnostic criteria for the IgG4-RD of these specific organs [18]. Patients, who could not respond to these CD criteria, could be diagnosed by applying organ-specific criteria, including those for IgG4-pancreatitis (AIP), IgG4-sclerosing cholangitis (IgG4-SC), and IgG4-kidneys related Disease (IgG4-RKD) (Table 2) [19–21]. Herein, according to CD criteria, the diagnosis of IgG4-RD was definite because he fulfilled the following criteria (1), (2) and (3i) [18]. The majority of patients with IgG4-RKD have similar lesions identified in multiple other organs. Tubulointerstitial nephritis is the most common renal manifestation; glomerular lesions may also be observed, with eventually renal function impairment. Elevated IgG or IgE levels as well as hypocomplementemia are the frequently observed serologic features of IgG4-RKD. Serum IgG4 elevation (>135 mg/dL) is the most, but not entirely, specific marker for the diagnosis [21]. Imaging findings are variable from small nodules to bilateral diffuse abnormalities. Renal pelvis and perirenal adipose tissue could be affected along with the renal parenchyma [21]. Histological features included dense lymphoplasmacytic infiltration, storiform or “bird’s eye” fibrosis and IgG4-positive plasma cell infiltration [21]. In our case, despite the absence of infiltrating IgG4-positive plasma cells in histologic findings of the renal biopsy, the diagnosis of IgG4-RKD was strengthened by the complete clinical and biochemical remission after steroid therapy. IgG4-RD is responsive to immunosuppressive agents and timely recognition of the disease is clinically important to prevent irreversible complications and organ damage if undiagnosed until advanced stages. Since there were no clear recommendations for optimal therapeutic approach, glucocorticoids were considered as the first line therapy of IgG4-RD patients. Broad treatment targets consist of the induction of remission and prevention of relapse.

**Table 1.** Comprehensive diagnostic criteria for systemic IgG4-related Disease.

1. Clinically: characteristic diffuse/localized swelling or masses in single or multiple organs
2. Hematologically: an elevated serum IgG4 level (>135 mg/dL)
3. Histologically: (i) marked lymphoplasmacytic infiltration and fibrosis; (ii) infiltration of IgG4+ plasma cells with a ratio of IgG4/IgG cells of more than 40% and more than 10 IgG4+ cells/ high power field
1 + 2 + 3 as “definite”
1 + 3 as “probable”
1 + 2 as “possible”

**Table 2.** Diagnostic criteria for IgG4-related kidney disease.

1. Presence of some kidney damage, as manifested by abnormal urinalysis or urine marker(s) or decreased kidney function with either elevated serum IgG level, hypocomplementemia, or elevated serum IgE level
2. Abnormal renal radiologic findings: a. Multiple low-density lesions on enhanced computed tomography b. Diffuse kidney enlargement c. Hypovascular solitary mass in the kidney d. Hypertrophic lesion of renal pelvic wall without irregularity of the renal pelvic surface
3. Elevated serum IgG4 level (IgG4 $\geq$ 135 mg/dL)
4. Histologic findings in the kidney a. Dense lymphoplasmacytic infiltration with infiltrating IgG4-positive plasma cells [10/high power field (HPF) and/or IgG4/IgG-positive plasma cells (40%) b. Characteristic fibrosis surrounding nests of lymphocytes and/or plasma cells
5. Histologic findings in extra-renal organ(s): Dense lymphoplasmacytic infiltration with infiltrating IgG4-positive plasma cells [10/HPF and/or IgG4/IgG-positive plasma cells 40% in extra-renal organ(s) Definite: 1 + 3 + 4 a, b 2 + 3 + 4 a, b 2 + 3 + 5 1 + 3 + 4 a + 5 Probable: 1 + 4 a, b 2 + 4 a, b 2 + 5 3 + 4 a, b Possible: 1 + 3 2 + 3 1 + 4 a 2 + 4 a

The initial dosage of prednisolone may vary according to different guidelines. The Mayo Clinic recommends a standard initial dose of 40 mg per day of oral prednisolone, for 4 weeks [22]. However, the Japanese consensus statement on treatment and prognosis of IgG4-related pancreatitis recommends an induction dose of oral prednisolone of 0.6 mg/kg per day. This dose should be administered for 2–4 weeks and then gradually tapered. Most patients treated with this dose showed a favorable response in a few weeks [7]. In case of multiorgan involvement, patients have also shown good and rapid response rates to glucocorticoids especially for IgG4-RKD [20]. Patients presenting with obstructive jaundice should be considered for biliary stenting. Nevertheless, most cases of IgG4-SC are often associated with type1 AIP, both of which showing a favorable response to steroid therapy with complete resolution of jaundice without stenting [3].

To prevent relapse, a maintenance dose of 2.5–5.0 mg/d of corticosteroids is recommended by the Japanese guidelines. Treatment of relapsing IgG4-RD was effectively achieved with corticosteroids. The subsequent introduction of azathioprine, to maintain a complete clinical, biochemical and radiological response is recommended as well. If corticosteroids are not effective, the diagnosis of IgG4-RD should be reviewed, before considering other immunosuppressive agents as a second-line treatment such as calcineurin inhibitors and mycophenolate mofetil or rituximab [23]. At present, rituximab, a monoclonal anti-CD20 antibody, has been proved to be highly effective in inducing remission in patients with recurrent or refractory IgG4-RD. It is now incorporated in the new guidelines for the second-line treatment of IgG4-RD [24,25]. Disease remission was reported in 67–83% of patients treated with rituximab even in the absence of concomitant glucocorticoid treat-

ment. The most frequently used induction regimens consisted either of four doses of 375 mg/m<sup>2</sup>/week or two doses of 1000 mg at an interval of 14 days. The optimal regimen of rituximab administration was not fully defined, and it was suggested that fixed dosing interval of every 6 months can eventually prevent relapse [26].

To date, THE clinical outcome and prognosis of patients with IgG4-RD is not well established.

Clinical relapse and treatment failure were reported to be significantly associated with a higher risk of death. Diabetes mellitus and biliary obstruction, associated inflammatory aortic aneurysms or idiopathic retroperitoneal fibrosis, development of cirrhosis and portal hypertension, were the main disorders significantly associated with the unfavorable prognosis of IgG4-RD [27].

#### 4. Conclusions

In conclusion, we report a case of IgG4-RD involving three organs, the pancreas, bile ducts, and the kidneys, with a favorable response to glucocorticoids. Only a few cases with extensive multiorgan involvements have been reported in the literature. Regrettably, universal criteria for IgG4-RD have not yet been recognized, and consequently, the IgG4-RD diagnosis remains confusing. As clinical presentation and pathological features depend on the organ involved, detailed diagnostic criteria for each organ are needed.

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#### Abbreviations

IgG4-RD	Immunoglobulin G4-related disease
AIP	IgG4-related pancreatitis
CD	comprehensive diagnostic
IgG4-SC	IgG4-sclerosing cholangitis

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