

## Progressive multi-organ expression of immunoglobulin G4-related disease: A case report

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### Abstract

A 63-year-old Caucasian man presented with a cholestatic syndrome, renal failure and arthralgias. A laboratory examination revealed high immunoglobulin G (IgG) and IgG4 levels (5.95 g/L; normal range: 0.08-1.4 g/L), pointing to a diagnosis of systemic IgG4-related disease, with definite radiological evidence of biliary and pancreatic expression, and plausible renal, articular, salivary and lacrimal glands involvement. Due to the rarity of the condition, there are currently no random control trials to point to the optimal therapeutic approach. The patient has been on steroid therapy with the subsequent introduction of azathioprine, with a complete resolution of all symptoms, a rapid reduction to normalization of all blood tests, and a complete regression of the radiological picture. Our experience underlines the complexity of IgG4-related disease and its variable and sometimes progressive presentation, while pointing out the need for a careful and complete assessment for possible multi-organ involvement.

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**Key words:** Immunoglobulin G4 related-disease; Auto-immune cholangitis; Autoimmune pancreatitis; Renal failure

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### INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) is a recently recognized disease<sup>[1]</sup> with a presumed autoimmune pathogenesis, characterized by high levels of IgG4 and a good response to immunosuppressive therapy<sup>[2]</sup>. Its clinical pattern is variable and may present with single organ expression (pancreatitis, cholangitis, sialadenitis, dacryoadenitis, nephritis, inflammatory pseudotumor and retroperitoneal fibrosis; other organs may occasionally be affected) or with multi-organ involvement<sup>[3,4]</sup>. All these localizations of IgG4-RD have a homogenous histological pattern, *i.e.*, lymphoplasmacytic infiltration with abundant IgG4-positive cell and storiform fibrosis. The etiology remains unknown, although a modified Th2 response with activation of regulatory T cells and overexpression of transforming growth factor beta and interleukin-4, 5, 10, 13 could be involved<sup>[5]</sup>. We report a patient with an insidious onset of IgG4-RD who proceeded to a full multi-organ expression.

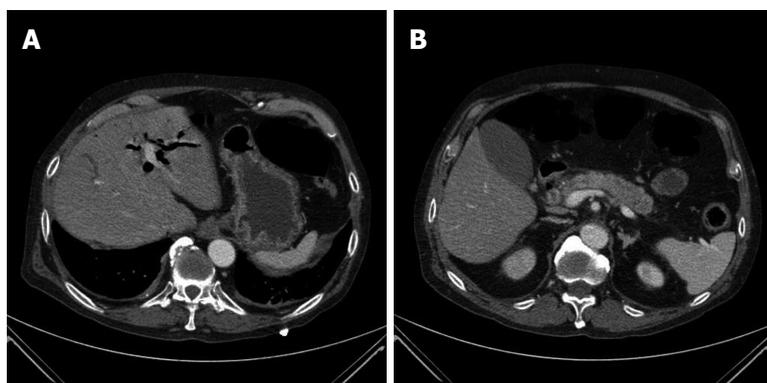
### CASE REPORT

A 63-year-old Caucasian man was admitted to our unit in July 2011 for a cholestatic syndrome of 4 mo duration. His medical history included heavy smoking (about 50 cigarettes/d) and an active consumption of 6 alcohol units/d, a previous diagnosis of "rheumatoid arthritis"

**Table 1** Laboratory tests at onset and during follow-up

Parameter	Normal range	Values					
		March 2011	April 2011	July 2011 (admission)	August 2011 (4 <sup>th</sup> week of follow-up)	October 2011 (12 <sup>th</sup> week of follow-up)	March 2012 (36 <sup>th</sup> week of follow-up)
Alkaline phosphatase (U/L)	40-129	401	190	490	97	83	74
GGT (U/L)	8-61	380	91	506	32	25	21
Bilirubin total/direct (mg/dL)	< 1	6.3/5.98	1/0.8	4.5/4.3	0.7/0.2	0.5/0.1	0.4/0.1
Amylase (U/L)	28-100	210	66	230	85	99	76
Lipase (U/L)	13-60	121	60	130	50	58	36
AST (U/L)	< 37	56	30	110	16	15	20
ALT (U/L)	< 41	64	35	130	19	13	19
Creatinine (mg/dL)	0.67-1.17	1.7	1.65	2	1.1	1	1.1
Gamma-globulins (g/dL)	0.67-1.56	-	-	2.94	1.09	1.5	1.45
IgG4 (g/L)	0.08-1.4	-	-	5.95	1.2	-	-

GGT: Gamma-glutamyltransferase; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; IgG4: Immunoglobulin G4.



**Figure 1** Computed tomography scans of the abdomen performed on admission. A: Dilatation of intrahepatic bile ducts; B: Dilatation of extrahepatic bile ducts with wall thickening and contrast enhancement in the arterial phase of distal common bile duct and increased volume of the pancreas with loss of physiological lobular appearance.

treated with intermittent steroid therapy for several years, a histological diagnosis of interstitial nephritis three years before, and no history of allergic disease. In March 2011, at the onset of jaundice, he had been admitted to another hospital. At that time, cholestatic tests [total/direct bilirubin 6.3/5.98 mg/dL, alkaline phosphatase  $3 \times$  upper limit of normal (ULN), gamma-glutamyltransferase (GGT)  $6 \times$  ULN] and pancreatic enzymes (amylase and lipase  $2 \times$  ULN) were raised (Table 1). Abdominal ultrasound (US) and computed tomography (CT) scans of the abdomen revealed a dilatation of the intrahepatic and extrahepatic biliary tract, without evidence of gallstones or biliary sludge, and an increased volume of the pancreas with loss of the physiological lobular appearance. A diagnosis of obstructive jaundice secondary to chronic pancreatitis was made and a plastic endoprosthesis was placed in the common bile duct by endoscopic retrograde cholangiopancreatography. During the following weeks, a progressive reduction of biochemical markers of cholestasis occurred (Table 1).

In July 2011, he was admitted to our unit for recurrence of jaundice and elevated markers of cholestasis.

Physical examination on admission was unremarkable, except for mild bilateral submandibular and lacrimal glands swelling. Laboratory tests showed hyperbilirubinemia (direct/total 4.5/4.3 mg/dL), alkaline phosphatase  $3 \times$  ULN, GGT  $10 \times$  ULN, aspartate aminotransferase and alanine aminotransferase  $3 \times$  ULN, pancreatic amy-

lase and lipase  $2 \times$  ULN, gamma-globulins  $3 \times$  ULN, and creatinine 2 mg/dL (Table 1). Anti-hepatitis C virus and hepatitis B surface antigen and non organ specific auto-antibodies (antinuclear antibodies, anti-mitochondrial antibody, smooth-muscle antibodies, liver kidney microsomal antibody, liver cytosolic-1) were negative. Abdominal US revealed a hypoechoic lesion of 2.3 cm in the uncinata process of the pancreas, dilatation of intrahepatic and extrahepatic bile ducts (up to 9 mm for the common bile duct) and of Wirsung's duct (4 mm), with no gallstones or biliary sludge. CT scans of the abdomen showed an increased volume of the pancreas, especially in the head, loss of physiological lobular appearance, dilatation of intrahepatic and extrahepatic bile ducts, with wall thickening and contrast enhancement in the arterial phase of distal common bile duct (Figure 1), and a diffuse bilateral enlargement of the kidneys. The patient declined to have a liver and/or pancreatic biopsy performed.

IgG4 levels were 5.95 g/L (normal range: 0.08-1.4 g/L), pointing to a diagnosis of IgG4-related pancreatitis and possibly cholangitis. Suspecting the coexistence of IgG4-related kidney disease (IgG4-RKD), the etiology of renal failure was re-evaluated. Laboratory tests confirmed a creatinine value of 2 mg/dL, normal serum and urinary electrolytes, the absence of proteinuria and hematuria, and normal values of immunoglobulin free light chains in serum and urine. It was not possible to reassess the previous renal biopsy, performed elsewhere.



**Figure 2** Magnetic resonance imaging, performed at the 12<sup>th</sup> week of follow up, showed a resolution of the radiological picture, with persistence of minimal dilation of the left biliary branch.

In view of the mild bilateral submandibular and lacrimal glands swelling and the worsening of previously present xerostomia and xerophthalmia, a salivary flow test and Schirmer's test were performed, showing a deficiency of both salivary and lacrimal secretion. Tests for anti-Sjögren syndrome A and B antibodies and anti-extractable nuclear antibodies were negative. A biopsy of the salivary glands showed the absence of lymphocyte and plasma cell infiltration.

Finally, the previous diagnosis of rheumatoid arthritis was ruled out because of no involvement of small joints, a normal X-ray of the hand, negative serology (rheumatoid factor and anticitrullinated peptide antibody) and normal acute-phase reactants (C-reactive protein and erythrocyte sedimentation rate).

The patient was given oral prednisone (0.6 mg/kg per day for 4 wk, then tapered over a period of 12 wk to a maintenance dose of 10 mg/d). After the first 4 wk, there was a marked general improvement, with regression of xerophthalmia and xerostomia and a rapid reduction to normalization of aminotransferases, alkaline phosphatase, GGT, bilirubin, creatinine, amylase, lipase, gamma-globulins and IgG4 levels (Table 1).

At the 12<sup>th</sup> week of follow up, abdominal US was negative and magnetic resonance imaging showed a resolution of the radiological picture, with persistence of minimal dilation of the left biliary branch (Figure 2).

Considering the coexistence of diabetes and osteoporosis, the dose of prednisone was reduced to 5 mg/d and azathioprine 1.5 mg/kg per d added as a glucocorticoid-sparing agent. At the 36<sup>th</sup> week of follow-up, abdominal US and biochemical tests were persistently normal (Table 1) and the patient is currently asymptomatic.

## DISCUSSION

IgG4-RD may involve several organs, including the pancreas, biliary duct, salivary glands, kidneys, lungs, retroperitoneum and lymph nodes. The peculiarity of our patient lies in the progression towards a systemic multi-organ expression of the disease.

Diagnostic criteria for systemic IgG4-RD are not fully established. To date, only the criteria for IgG4-related pancreatitis, cholangitis, nephritis and glandular disease are available. However, they are not suitable for the diagnosis of other organ involvement. In this case, the diagnosis of pancreatitis was confirmed by both Asian diagnostic criteria<sup>[6]</sup> and HISORt criteria for autoimmune pancreatitis<sup>[7]</sup>. Diagnosis of IgG4-related cholangitis was confirmed by HISORt criteria for IgG4-associated cholangitis<sup>[8]</sup>. Liver and/or pancreatic biopsies were not performed; they cannot be deemed essential for diagnosis, since two out of three for Asian diagnostic criteria and two out of five for HISORt criteria were satisfied. For evidence of renal damage and CT-documented enlargement of the kidneys in a context of an IgG4-RD, the etiology of renal failure was also re-evaluated. According to the criteria proposed by the Japanese Society of Nephrology<sup>[9]</sup>, the diagnosis of IgG4-RKD was labeled as "possible". Because of the presence of xerostomia and xerophthalmia, a salivary glands biopsy was performed, showing a non-specific chronic inflammation. In the absence of specific histology, it was not possible to confirm the diagnosis of IgG4-related glandular disease because all diagnostic criteria were not satisfied<sup>[10]</sup>. Nevertheless, the probability of a false negative due to the previous long-term steroid therapy should be considered. The diagnosis of rheumatoid arthritis was finally ruled out and the persistent arthralgias may be related to IgG4-RD.

Despite the absence of histological confirmation, IgG4-related involvement of kidneys, salivary and lacrimal glands was strengthened by the full clinical and biochemical remission of respective manifestations after steroidal therapy.

Treatment with immunosuppressive agents is effective in IgG4-RD. Due to the rarity of the condition, there are currently no RCTs to point to the optimal therapeutic approach. Following a consensus statement from 17 referrals centers in Japan<sup>[11]</sup>, we treated the patient with prednisone as first line therapy, with subsequent introduction of azathioprine, obtaining a complete clinical, biochemical and radiological response with good tolerability.

Our experience underlines the complexity of IgG4-RD and its variable and sometimes progressive presentation, while pointing out the need for a careful and complete assessment for possible multi-organ involvement.

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