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Case Report

IgG4 Cholangitis Simulating Cholangiocarcinoma: A Diagnostic Trap

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Abstract

IgG4-related sclerosing cholangitis (IgG4-SC) is the biliary manifestation of IgG4-related disease, systemic fibroinflammatory condition that is characterized by lesions with classical histopathological findings in involved organs. We presented a case of isolated IgG4-SC with the normal serum IgG4 which was hard to differentiate with cholangiocarcinoma.

Keywords: IgG4 cholangitis, cholangiocarcinoma, igG4 serum, jaunice, CT.

INTRODUCTION

IgG4 cholangitis is a rare manifestation of igG4 disease, whose clinic and imaging pose a serious problem of differential diagnosis with PSC and especially with cholangiocarcinoma. The aim of this work is to highlight the particularities of IgG4 cholangitis that can mimic a cholangiocarcinoma of the gallbladder and can lead to an inappropriate surgical treatment.

OBSERVATIONS

This is a 68-year-old patient who is followed for type II diabetes on metformin for 4 years, admitted for liver colic associated with weight loss. The clinical examination found an obese patient with a BMI: 30 KG/m2, apyretic with normocolored conjunctiva. The patient had enlarged parotid glands and tenderness in the right hypochondrium. In the biology, an inflammatory syndrome was found with a CRP of 236 mg/l, a hyperleukocytosis of 16980 elements/mm3 with a predominance of neutrophilic polynuclear (14650 elements/mm3). The liver function test showed cytolysis with ASAT at 4.8 upper limit normal and ALAT at 2.9 upper limit normal, anicteric cholestasis with GGT at 3 upper limit normal, PAL at 2 upper limit normal, total bilirubin at 30 mg/l without hepato-cellular insufficiency. Abdominal ultrasound found lithiasis cholecystitis and abdomen CT scan showed a tumor process of the gallbladder infiltrating segments IV and V classified as T3N0M0.

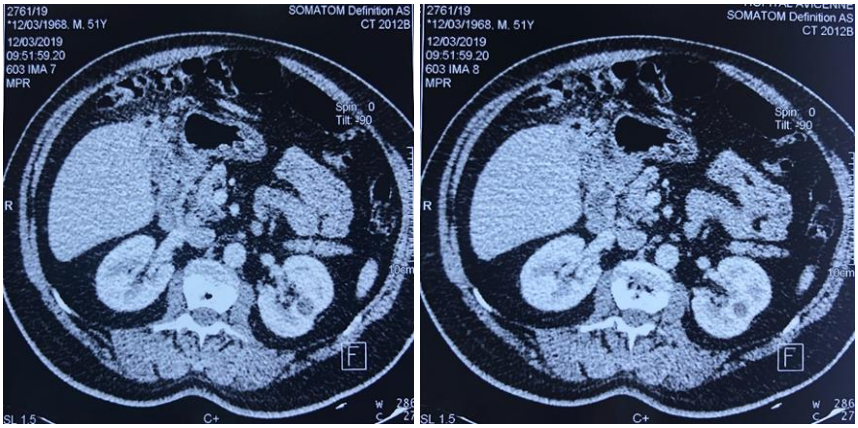

Figure 1: Injected abdominal CT scan showing a tumor process of the gallbladder infiltrating the liver

Tumor markers were negative (CA 19.9 and CEA). The diagnosis of a gallbladder carcinoma was retained and the patient underwent cholecystectomy. The postoperative course was simple with spontaneous normalization of liver function test. The anatomopathological study of the surgical specimen showed an inflammation made of lymphoplasmocyte and neutrophil polynuclear with the presence of a storiform fibrosis and an obliterating phlebitis evoking at first an IgG4 disease.

Immunohistochemistry showed the presence of IgG4 but unfortunately the calculation of the IgG4/ IgG ratio was not done. Postoperative serum IgG4 assay was negative on two occasions. A second intention blood test including autoimmune tests: AAN, anti M2, anti SLA, anti LKM1, and viral serologies: HBV, HCV, was negative. The CP-MRI showed a chronic liver disease with signs of autoimmune cholangitis.

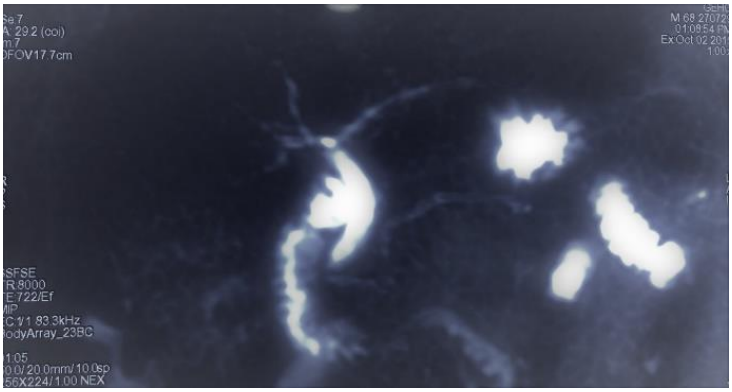

Figure 2: CP-MRI showing multiple segmental short stenoses in the right and left bile ducts

The endoscopic workup was normal. Additional examinations in search of other localizations were performed with the following results:

- Salivary gland biopsy showed lymphoplasmacytic sialadenitis.
- Thyroid ultrasound showed a pseudonodular thyroid on a background of thyroiditis. TSH, anti TG, and anti TPO blood tests were normal.
- Phosphocalcic and renal tests were also normal.

Following these different data, the case was discussed in multidisciplinary consultation and the alternative chosen was therapeutic abstention and quarterly monitoring of the liver blood test. Over a period of 36 months, the patient came regularly for consultation, and with no complaints of any symptoms, the liver assessment remained strictly normal.

DISCUSSION

IgG4 disease is a benign inflammatory systemic disease characterized by fibrosis and lymphoplasmacytic inflammatory infiltration, with predominance of IgG4+ plasma cells affecting multiple organs [1, 2]. IgG4 cholangitis is the hepato-biliary manifestation of this disease. IgG4 cholangitis rarely occurs in isolation, as in our patient, and is most often associated with autoimmune pancreatitis [3]. The age of onset of the disease is classically between 50 and 70 years, with an average age of about 60 years. The sex ratio is predominantly male, although there are variations depending on the organ involvement [2, 4].

The classic clinical presentation of IgG 4 cholangitis is characterized by the appearance of mucocutaneous jaundice (more than 75% of cases), pruritus and weight loss [2], which points to a neoplastic etiology. IgG 4 disease is often associated with diabetes [5]. This is the case in our patient. The biochemical features of igG4 cholangitis are elevation of serum markers of cholestasis, including alkaline phosphatase, gamma-glutamyl transferase and conjugated bilirubin. The tumor marker CA19-9 may also be elevated and responds rapidly to glucocorticoid treatment [6].

Serum IgG4 is elevated in about 75% of patients [7]. It is reliable for the diagnosis of IgG4-related disease when it is greater than 4 times the upper limit, however it is not specific [8]. In our patient the IgG4 blood test was negative. Doorenspleet et al [9] developed a quantitative PCR test measuring the IgG4/IgG RNA ratio in peripheral blood that can differentiate igG4 cholangitis from primary biliary cholangitis and biliary-pancreatic tumors with a sensitivity of 94% and specificity of 99%. Nevertheless, a large study of more than 200 patients invalidates these results [10]. Thus, prospective re-evaluation in well-defined cohorts is necessary for a better diagnostic approach.

Histopathologically, the diagnosis is based on the presence of a dense lymphoplasmacytic infiltrate, a storiform fibrosis and an obliterating phlebitis. These are considered major criteria [11], the presence of 2/3 of which is highly suggestive of the disease, which is the case of our patient. The increase in the number of tissue eosinophils and the presence of non-obliterative phlebitis are considered minor criteria whose presence

alone is neither sensitive nor specific. Immunohistochemical analysis contributes to the diagnosis with an IgG4+/IgG ratio greater than 40% and an increase in IgG4+ plasma cells, the threshold value of which depends on the tissue involved [12].

The cholangiographic characteristics are presented by the Japanese classification which distinguishes 4 types: Type I corresponds to a low choledochial stenosis, it represents the most frequent form. Type II corresponds to a diffuse intra- and extra-hepatic involvement. Types III and especially IV are characterized by a long and marked stenosis of the ducts of the perihepatic region associated (type III) or not (type IV) with lesions of the lower bile duct [13, 14]. Type IV is the form that leads to the discussion of a perihilar cholangiocarcinoma or a vesicular cancer extended to the hilum, and it is the form that was observed in our patient. The diagnosis of igG4 cholangitis is based on the HISORt criteria for igG4 cholangitis or the modified Japanese diagnostic criteria for IgG4 cholangitis of 2020 [15].

Table 1: HISORt criteria adapted for the diagnosis of IgG4 sclerosing cholangitis [16]

Histology bile ducts	Lymphoplasmacytic sclerosing cholangitis on resection: LP infiltrate > 10 IgG4+ cells/hpf, storiform fibrosis, phlebitis
Imaging bile ducts	One or more strictures involving intra- or extra-hepatic bile ducts Fleeting/migrating biliary strictures
Serology	IgG4 > 2 × ULN
Other sites	Pancreas: classic features of AIP on imaging or histology Retroperitoneal fibrosis Renal: parenchymal low-attenuation lesions Salivary/lacrimal gland enlargement
Rt response to treatment	Normalisation of LFTs or resolution of biliary stricture

IgG4-SC, immunoglobulin G4 sclerosing cholangitis; LP, lymphoplasmacytic; hpf, high powered field; ULN, upper limit normal; AIP, autoimmune pancreatitis; Rt, response to treatment; LFT, liver function test.

Table 2: Japanese Clinical Diagnostic Criteria for IgG4-related cholangitis, 2020

Diagnostic criteria

A. Diagnostic items

I Narrowing of the intrahepatic and/or extrahepatic bile duct:
- a. ERC
- b. MRCP

II Thickening of the bile-duct wall:
- a. EUS/IDUS
- b. CT/MRI/US

III Serological findings
Elevated levels of serum IgG4 (≥ 135 mg/dL)

IV Pathological findings among i)-v) listed below:
- a. i), ii), and v) are observed
- b. v) is observed
- c. All of i), ii), and v) and either or both of iii) or iv) are observed
- (i) Marked lymphoplasmacytic infiltration and fibrosis
- (ii) More than 10 IgG4-positive plasma cells per high-power microscopic field
- (iii) Storiform fibrosis
- (iv) Obliterative phlebitis
- (v) No neoplastic cells identified

V Other organ involvement (OOI):
- a. Type 1 autoimmune pancreatitis
- b. IgG4-related dacryoadenitis/sialadenitis (Mikulicz disease), IgG4-related retroperitoneal fibrosis, IgG4-related kidney lesion

VI Effectiveness of steroid therapy
A steroid trial could be performed by pancreato-biliary specialists after eliminating possible misdiagnoses, such as pancreatic cancer and biliary tract cancer. It is mandatory to conduct cytological and histological examinations of the bile ducts, to differentiate from IgG4-SC and malignancy. A facile steroid trial without exclusion of definite malignancy should be avoided. Criterion VI includes IVb. Steroid effectiveness should be assessed based on ERC and/or MRCP imaging within 2 weeks after administering steroids. If steroids do not ameliorate the condition, repeat investigations, including histopathology, should be performed.

Diagnosis	
Definite and probable diagnoses are IgG4-SC	
I. Definite diagnosis	
① Va+	
Cholangiographic classification Types 1, 2	Ia/b + IIa/b + III/VI
Cholangiographic classification Types 3, 4	Ia + IIa + IVb + III/VI
② Va−	
Cholangiographic classification Types 1, 2, 3, 4	Ia + IIa + III + IVa/VI
③ Pathological definite diagnosis	
IVc	
II. Probable diagnosis	
① Va+	
Cholangiographic classification Types 1, 2	Ia/b + IIa/b
Cholangiographic classification Types 3, 4	Ia + IIa + IVb
	Ia/b + IIb + VI
② Va−	
Cholangiographic classification Types 1, 2, 3, 4	Ia + IIa + IVa
	Ia + IIa + III + IVb
	Ib + IIa + III + VI
III. Possible diagnosis	
① Va+	
Cholangiographic classification Types 3, 4	Ia/b + IIa
	Ib + IIb + III
② Va−	
Cholangiographic classification Types 1, 2, 3, 4	Ia + IIa + III/Vb/VI
	Ib + IIb + III + VI
*Refer to explanation Ic on the cholangiographic classification	
"+" refers to "and", and "/" refers to "or"	

All affected patients with active and symptomatic disease require treatment. However, the involvement of vital organs, in particular the liver and the biliopancreatic crossroads, is an indication for treatment even in the absence of symptoms because of the risk of irreversible evolution towards fibrosis [6]. Glucocorticoids are the first-line treatment and allow clinical, biological and radiological improvement. However, surgical resection or biliary drainage have their place in the therapeutic alternatives of igG4 cholangitis.

Indeed, a retrospective observational study by Jianchun Xiao *et al*., [17], which included 39 patients followed for igG4 cholangitis and compared the 3 therapeutic options, showed that 29 patients were treated with glucocorticoid and the rest with biliary drainage: 29 patients were treated with glucocorticoids, 2 of whom relapsed after the corticotherapy was stopped, 4 patients benefited from an immediate surgical treatment whose evolution after the intervention was marked by the resolution of the strictures and/or normalization of the liver function test without the need for recourse to corticotherapy, and lastly 8 patients, in therapeutic abstention, had a spontaneous resolution of the biliary strictures.

Another study by Ghazale *et al*., [16] comparing the evolution after corticosteroid therapy, surgical resection and conservative treatment, showed that 53% of the patients had relapsed after stopping corticosteroid therapy, whereas 56% did not relapse after surgical treatment. These authors noted that the proximal location of the stenosis is a predictive factor of relapse and recommend a long-term background treatment.

IgG 4 cholangitis can mimic a cholangiocarcinoma in every way, as in the case of our patient who presented with clinical and radiological signs that first suggested cholangiocarcinoma of the gallbladder. The patient benefited from a surgical treatment whose anatomopathological study of the operative part made it possible to rectify the diagnosis on the one hand, and in the other hand to not have recourse to a medical treatment.

CONCLUSION

IgG4 cholangitis is an emerging benign disease with an unknown pathogenic mechanism, which poses a problem of differential diagnosis with cholangiocarcinoma despite the progress made in the diagnosis of this pathology. It should be considered in the presence of atypical forms, in particular isolated cholangiocarcinoma, by performing a serum igG4 assay or even a trial treatment with corticosteroids, while weighing the benefits and risks involved. The knowledge of this pathology can avoid a heavy and especially useless surgical treatment.

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