NEW-ONSET JAUNDICE IN A PATIENT WITH HISTORY OF RETROPERITONEAL FIBROSIS, A CASE REPORT

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ABSTRACT

***Introduction**: We describe a case of IgG4-related sclerosing cholangitis (IgG4-SC). IgG4-SC is the biliary manifestation of a recently defined clinicopathological entity, named IgG4-related disease (IgG4-RD).*

***Case presentation**: A 52-year-old woman with history of retroperitoneal fibrosis was admitted to our hospital for further evaluation of new-onset jaundice. Laboratory investigations revealed a rise of cholestasis indexes. Magnetic resonance (MR) examination revealed intra-hepatic bile duct dilatation and biliary stricture at the hepatic hilum, without pancreatic involvement. Corticosteroid treatment lead to an improvement of patient's clinical condition and decrease of cholestasis indexes.*

***Conclusion**: The differential diagnosis between IgG4-SC, primary sclerosing cholangitis (PSC) and cholangiocarcinoma (CCA) is very important because of the different therapeutic approach. The diagnosis of IgG4-related sclerosing disease should be considered in patients with sclerosing cholangitis, especially when it is associated with other fibroinflammatory disorder, to avoid unnecessary surgery.*

***Key words**: IgG4-related sclerosing cholangitis, retroperitoneal fibrosis, primary sclerosing cholangitis, cholangiocarcinoma, magnetic resonance imaging.*

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Introduction

IgG4-related disease (IgG4-RD) is a recently codified clinicopathological entity, characterized by systemic involvement with IgG4-positive plasma cell infiltration. The most common sites of involvement are pancreas (autoimmune pancreatitis), bile duct (sclerosing cholangitis) and retroperitoneum (retroperitoneal fibrosis). However, almost any organ can be affected: salivary gland (sclerosing disease), thyroid (Riedel's thyroiditis), kidney (tubulointerstitial nephritis), lung (interstitial pneumonia) and prostate (prostatitis)[(1)]. Several conditions, like Riedel's thyroiditis, retroperitoneal fibrosis or Ormond's disease, Küttner's tumor of the submandibular gland, Mikulicz's disease involving salivary and/or lacrimal gland, are now considered to be part of this systemic condition[(2, 3)].

In Boston, Massachusetts, on October 2011 there was an international symposium focused on the histopathology of IgG4-RD, described as "a newly recognized fibroinflammatory condition characterized by several features: a tendency to form tumefactive lesions at multiple sites; a dense lymphoplasmacytic infiltrate rich in IgG4 plasma cells; storiform fibrosis; and, often but not always, elevated serum IgG4 concentrations". Serum concentration of IgG4 was found normal in about 40% of patients[(4)].

Epidemiology has not been described definitively and no clear genetic predisposition has been identified. This disorder appears to affect more often middle aged/older men: the mean age at diagnosis for patients with IgG4-RD is approximatively 60 years with a male:female ratio of 8:3[5].

The exact etiology and pathogenesis remains unknown, although some abnormal immunological mechanisms are almost certainly involved. This condition was initially recognized in the pancreas as autoimmune pancreatitis (AIP), from which two different types had been described. Type 1 AIP is named as "Ig4-related pancreatitis", demonstrating the features of IgG4-RD, while type 2 AIP is thought to be a specific pancreatic disease[6].

IgG4-related sclerosing cholangitis (IgG4-SC) is the biliary manifestation, frequently associated with AIP (7). A few cases without pancreatic involvement, particularly difficult to diagnose, have also been reported[8].

Gallbladder can also be affected with acalculos cholecystitis as the most common manifestation[9]; sometimes gallbladder shows a sclerotic appearance[10].

Steroid treatment often produces noteworthy improvement reducing, and sometimes resolving, both clinical manifestations and imaging features; however, there is a risk of relapse[11].

The differential diagnosis is very difficult because of the cholangiographic features that can mimic other conditions, such as primary sclerosing cholangitis (PSC) and cholangiocarcinoma (CCA). Ruling out the above-mentioned progressive or malignant diseases is very important, because of the different therapeutic approach.

Case presentation

A 52-year-old woman was admitted to our hospital from emergency and first aid department for further evaluation of new-onset jaundice, fatigue and mild right upper quadrant pain. His medical history was notable for surgery 1 year earlier for hydronephrosis due to ureteral obstruction caused by retroperitoneal fibrosis. Physical examination showed jaundice, acholic stools, dark urine, abdominal pain and a positive Murphy's sign. Laboratory investigations (the day before therapy) revealed the following values: total bilirubin, 13.5 mg/dL; direct bilirubin, 8.6 mg/dL; γ glutamyl transferase, 299 IU/L; alkaline phosphatase 599 IU/L. Abdominal ultrasound demonstrated intra-hepatic bile duct dilatation and no signs of cholelithiasis. During the hospitalization she underwent a magnetic resonance cholangiopancreatography (MRCP).

Magnetic resonance (MR) examination was performed with a closed-configuration superconducting unit with a 1.5-T field strength, using an 8-channelo torso coil. The MR imaging protocol included SSFP (steady state free precesson) in the axial plane, T2-weighted SSFSE images in the axial and coronal planes, T1-weighted GRE in-phase and opposed-phase in the axial plane, 12 radial coronal T2-weighted SSFSE cholangiographyc acquisitions centered on the bile duct at an angle of 8 degrees and obtained during breath-hold (slab of 5.0 cm), both breath-hold and respiratory-triggered 3D heavily T2-weighted FSE sequences in the axial and coronal oblique plane, axial diffusion weighted imaging (b value=500 and 800) and 3D fat suppressed T1-weighted GRE in the axial plane.

Intravenous contrast administration was not performed because of a history of previous allergic reaction. MR revealed intra-hepatic bile duct dilatation, more evident in the left lobe, with biliary stricture at the hepatic hilum, involving the confluence of right and left hepatic bile ducts and the proximal part of the common hepatic duct (Figure 1).

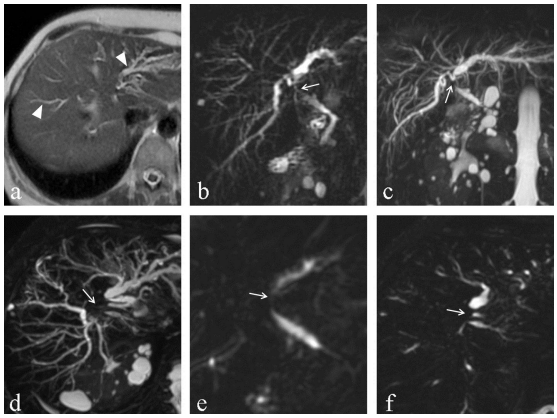

Figure 1: MRI findings.
(a) Axial 2D single-shot fast spin-echo (SSFSE) T2-weighted image shows intra-hepatic bile ducts dilatation (white arrowheads), more evident in the left lobe. (b) Coronal thick-slab (thickness 50 mm) 2D SSFSE image and (c) coronal and (d) axial Maximum intensity projection (MIP) images obtained from 3D FRFSE heavily T2-weighted sequences (thickness 3 mm) show intra-hepatic bile ducts dilatation and biliary stricture at the hepatic hilum (white arrows), involving the confluence of right and left hepatic bile ducts and the proximal part of the common hepatic duct. (e) Coronal and (f) axial 3D FRFSE heavily T2-weighted single partitions images confirm the above mentioned findings without superimpositions (white arrows).

The downstream bile duct showed no dilatation. We also found normal appearance of the pancreas and of the main pancreatic duct, exhibiting no irregularity or narrowing. A lesion responsible for the imaging findings was not identified. Even so, CCA needed to be ruled out. According to patient's anamnesis of retroperitoneal fibrosis, we suggested evaluation of serum IgG4 concentration; laboratory test showed elevation of serum IgG4 concentration (189 mg/dl). Endoscopic retrograde cholangiopancreatography (ERCP) was also performed, which revealed hilar stricture and dilatation of the intrahepatic bile ducts mostly in the left lobe. After mild sphincterotomy, endoscopic brush cytology at the level of hilar stricture was performed and resulted negative for malignant cells. After a few days of corticosteroid treatment, patient's condition improved significantly and cholestasis indexes normalized (Table 1).

ACUTE PERIOD					
	DATE	TOT BIL (mg/dl)	DIRECT BIL (mg/dl)	γ GT (U/L)	ALKALINE PHOSPHATASE (U/L)
PRE - THERAPY	11-gen	4.79	3.63	…	…
	12-gen	4.8	…	…	…
	15-gen	6.9	4.4	259	532
	17-gen	10.4	6.3	…	…
	19-gen	13.5	8.6	299	599
DURING THERAPY	20-gen	11.9	7.9	277	523
	23-gen	6.8	3.7	…	519
	26-gen	5.1	2.5	451	515

Table 1: Main laboratory examinations performed in the acute period. Note as after a few days of corticosteroid treatment biliribin levels normalizes, though alkaline phosphatase and γ glutamyl transferase still remain high. *TOT BIL: total bilirubin, DIRECT BIL: direct bilirubin, γ GT: γ glutamyl transferase.*

In the follow-up period a rise of cholestasis indexes occurred in relation to a temporary suspension of the corticosteroid therapy, cholestasis indexes normalized again when patient underwent a new cycle of corticosteroid therapy (Table 2). The therapeutic regimen was as follows: in the acute period, prednisone 25 mg/bis in die for seven days; in the follow-up period, prednisone 25 mg/die and Ursodeoxycholic acid (UDCA) 450 mg/die. All drugs were administered per os.

FOLLOW-UP PERIOD					
	DATE	TOT BIL (mg/dl)	DIRECT BIL (mg/dl)	γ GT (U/L)	ALKALINE PHOSPHATASE (U/L)
PRE - STEROID SUSPENSION	2-Feb	4.3	2.94	508	556
	9-Feb	2.2	1.86	306	317
	27-Feb	1.7	0.95	300	295
DURING STEROID SUSPENSION	3-Mar	3.8	3.95	756	579
	4-Mar	5.9	4.11	874	591
	6-Mar	6.2	4.29	792	523
	9-Mar	6.2	4.81	745	425
AFTER STEROID REINTRODUCTION	26-Mar	1.5	0.62	197	176
	1-Apr	1.3	0.46	122	141
	31-lug	0.9	0.32	240	233
	06-ago	0.7	0.2	255	209

Table 2: Main laboratory examinations performed in the follow-up period. The table shows the variations of cholestasis indexes during the follow-up period. The increment of bilirubin during the follow-up is due to the temporary suspension of the corticosteroid therapy. Alkaline phosphatase and γ glutamyl transferase still remain high. *TOT BIL: total bilirubin, DIRECT BIL: direct bilirubin, γ GT: γ glutamyl transferase.*

Discussion

In 2012, Ohara et al. proposed 4 criteria to diagnose IgG4-SC:

- characteristic biliary imaging findings: narrowing and thickening of the bile duct;
- elevation of serum IgG4 concentrations, with a cutoff value of 135 mg/dl;
- coexistence of IgG4-related diseases except those of the biliary tract;
- characteristic histopathological features: fibroinflammatory involvement mainly in the submucosa of the bile duct.

They also considered the effectiveness of steroid therapy as an extra criteria to confirm diagnosis[12].

In 2013, Nakazawa et al. suggested a cholangiographic classification into 4 types based on the stricture regions; each type with his own differential diagnosis (Table 3)[13].

In 2014, Joshi et al. specified the three major histopathological features of IgG4-RD:

- IgG4-positive lymphoplasmacytic tissue infiltrate;
- storiform fibrosis;
- obliterative phelibitis.

Type		Stricture Localization	Differential Diagnosis
1		stenosis only in the lower part of the common bile duct	Chronic pancreatitis Pancreatic cancer Bile duct cancer
2a		stenosis diffusely distributed throughout the intrahepatic and extrahepatic bile ducts with (2a) or without (2b) prestenotic dilatation	Primary sclerosing cholangitis
2b			
3		stenosis in the hilar hepatic region and in the lower part of the common bile duct	Bile duct cancer
4		stenosis only in the hilar hepatic region	

Table 3: . Classification of IgG4-related sclerosing cholangitis into 4 types based on the stricture location. Differential diagnosis is provided for each type. Adapted from Nakazawa et al. (Nakazawa).

Serum IgG4 higher than 135 mg/dl are not always detectable, so they should be considered only a support to the diagnosis. Serum IgG4 levels have been reported to be normal in about one third of cases[11, 14].

Diagnostic imaging, particularly MRCP, has an important role in the evaluation of IgG4-SC. Any part of the biliary tree can be involved, however it has to be remembered that a stricture of the distal common bile duct is often present when IgG4-SC is associated with pancreatic involvement[11].

Imaging findings alone are not nearly enough to distinguish IgG4-SC from PSC, pancreatic cancer, and CCA[12].

Unfortunately tumor markers are not of great help: elevated serum levels of Ca 19-9 can be found in IgG4-SC as well as in cholangiocarcinoma[15]. Transpapillary bile duct biopsy or cytological examination could be necessary.

PSC is a rare chronic liver disease, characterized by inflammation and scarring of bile ducts with a "beads-on-a-string appearance", leading to progressive cholestasis and culminating in cirrhosis[9].

Differential diagnosis between PSC and IgG4-SC is very difficult basing on cholangiographic features alone, even considering that the beaded appearance typical of PSC is not observed in IgG4-SC[12].

To distinguish these two conditions is very important also from a therapeutic point of view: PSC often requires liver transplantation, while IgG4-SC is usually treated with steroids[16].

PSC, as well as other chronic inflammatory diseases of the bile ducts, is also a risk factor to develop CCA, while a relation between the latter and IgG-SC has not been proved. However, a few cases of CCA in patients with IgG4-SC have been described in literature[17].

In our case the diagnosis of IgG4-SC was postulated according to patient's anamnesis, MRCP findings, elevation of serum IgG4 concentrations, response to corticosteroid treatment and correlation of clinical symptoms and cholestasis indexes with corticosteroid therapy.

Concerning MR imaging criteria our case can be classified as type 4 (according to the classification of Nakazawa), with an isolated stenosis of the bile duct in the hilar hepatic region, mimicking a CCA. No pancreatic involvement was found.

In conclusion, the diagnosis of IgG4-related sclerosing disease should be considered in patients with sclerosing cholangitis, especially when it is associated with any fibroinflammatory disorder, to avoid unnecessary surgery. A multidisciplinary approach involving clinical history, imaging findings, laboratory studies and histopathological features is the only key to the diagnosis.

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