IgG4-related disease of the hepatobiliary tract : 2 case reports and review of the literature

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Abstract

IgG4-related disease is a rare inflammatory disorder that may mimic many infectious, malignant, and autoimmune conditions. The biliary tract is frequently involved, but hepatic lesions are rarely seen. Diagnosis is often delayed due to the absence of specific clinical and radiological signs, and the lack of an accurate diagnostic marker. Differential diagnosis includes cholangiocarcinoma, primary sclerosing cholangitis and intrinsic or metastatic liver disease. Corticosteroids are the cornerstone of therapy but treatment has not been standardized and relapse is common. Based on two cases of IgG4-related hepatobiliary disease, we review the current literature on this pathological entity. (Acta gastroenterol. belg., **2018**, 81, **83-87**).

Key words : IgG4-associated cholangitis, biliary obstruction, hepatic pseudotumor, pathophysiology, diagnosis, treatment

Case 1

A 63-year-old man was referred because of progressive jaundice with intense itching, weight loss and fatigue. The patient was a smoker and had untreated arterial hypertension. Several weeks earlier, an enlarged left axillary lymph node had been removed. Pathological examination ruled out malignancy. Blood analysis showed moderate inflammation, increased liver enzymes (both hepatocellular and cholestatic), and reduced kidney function. CA19.9 was increased (Table 1). A computed tomography (CT) scan of the abdomen revealed a biliary stricture in the hilar region with intrahepatic bile duct dilatation. Extrahepatic biliary tract, gallbladder and pancreas appeared normal. No tumoral mass or abnormal lymphadenopathy was detected. Mild hydronephrosis of the right kidney was present without obvious urolithiasis. The patient was hospitalized with presumed hilar cholangiocarcinoma and secondary cholangitis for which antibiotics were initiated. Magnetic resonance cholangiopancreaticography (MRCP) confirmed the CT findings (Fig. 1A) and also highlighted perivascular inflammation and fibrosis of the right common iliac vein with ipsilateral ureteral involvement. A plastic stent was inserted via endoscopic retrograde cholangiopancreaticography (ERCP) to relieve biliary obstruction (Fig. 1B). Hydronephrosis was resolved by stenting the ureter via ureterostomy. Liver enzymes and cholestatic markers subsequently improved, but renal dysfunction persisted (Table 1). In light of the patient's atypical disease presentation (obstructive

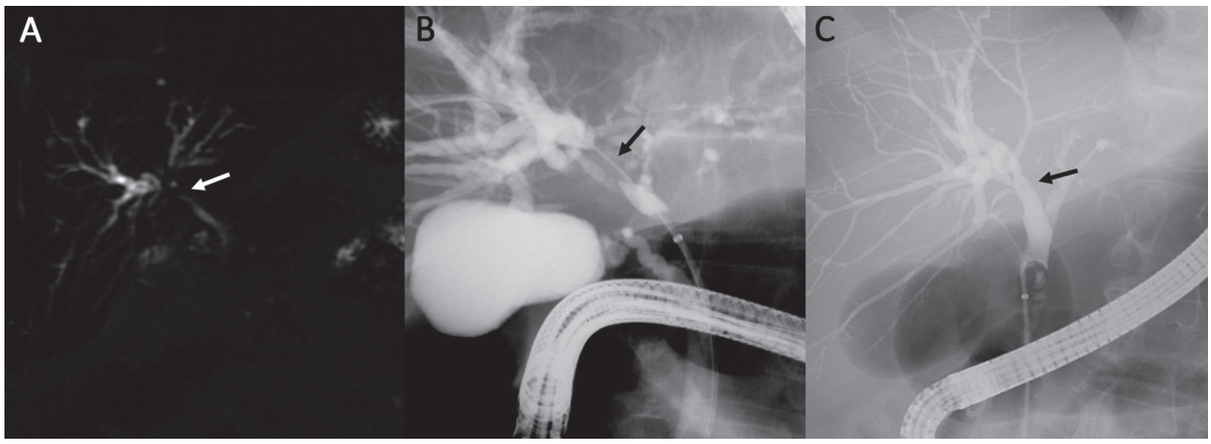

Figure 1. — (A) MRCP demonstrating a hilar stricture (white arrow) with dilatation of the intrahepatic bile ducts. (B) ERCP depicting a proximal biliary stenosis mimicking a hilar cholangiocarcinoma (black arrow). (C) ERCP after 4 weeks of corticosteroid treatment showing complete resolution of biliary stenosis (black arrow) and normal intrahepatic bile ducts.

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Table 1. — **Case 1 – Laboratory data**

Blood test	***Reference range***	**On admission**	**After 3 weeks**	**After 6 weeks**	**After 8 weeks**	**After 11 weeks**	**After 19 weeks**
CRP (mg/L)	*< 5*	39.4	2.9	1.5	6.6	1.4	2.2
Creatinine (mg/dL)	*0.70 - 1.20*	2.01	1.87	1.74	1.78	1.78	1.67
AST (U/L)	*< 38*	328	73	42	32	38	33
ALT (U/L)	*< 50*	589	145	92	88	68	57
AF (U/L)	*40 - 129*	555	499	415	262	NM	282
GGT (U/L)	*8 - 61*	1387	970	876	738	972	823
Total bilirubin (mg/dL)	*< 1.1*	9.7	2.2	1.0	0.7	0.7	0.6
CA19.9 (kU/L)	*< 39*	103	NM	NM	101	107	81
IgG4 (g/L)	*0.03 - 2.01*	11.49	NM	NM	3.3	1.71	1.17

CRP = C-reactive protein, AST = aspartate aminotransferase, ALT = alanine aminotransferase, AF = alkaline phosphatase, GGT = gamma glutamyltransferase, IgG4 = immunoglobulin G4, NM = not measured

jaundice without evidence of a tumoral (peri)biliary lesion and the presence of retroperitoneal fibrosis with ureteral involvement), serum immunoglobulin (Ig) G4 levels were measured and found to be markedly elevated (11.49 g/L, normal value 0.03-2.01 g/L, Table 1). The diagnosis of IgG4-related cholangiopathy and perivasculitis was put forward. The diagnosis was supported by IgG4 immunostaining of the previously resected axillary lymph node which disclosed a high number of IgG4-positive plasma cells. Steroid treatment (methylprednisolone 0.5 mg/kg/day) was initiated resulting in improvement of the patient's clinical condition and further decrease of cholestasis. After 4 weeks of therapy, the biliary stent was removed. No residual strictures were visualized (Fig. 1C). Two months later, MRCP demonstrated sustained complete resolution of biliary stenosis and normalization of the intrahepatic bile ducts. Because signs of perivascular inflammation and fibrosis had vanished, the ureteral stent was removed shortly thereafter. After 6 months of progressive dose de-escalation, methylprednisolone was withdrawn and maintenance therapy with azathioprine 100 mg/day was initiated. The patient is currently in follow-up for 46 weeks without any signs of disease relapse.

Case 2

A 56-year-old man was referred with diffuse arthralgia, fatigue and dyspnea. Except for a passed hepatitis B, his medical history was unremarkable. Fever, weight loss and nocturnal transpiration were absent. He denied recent travelling abroad, contact with animals and medication abuse. Blood analysis showed mild inflammation, striking eosinophilia (2520/mm^3, normal value 30-380/mm^3) and elevated calcium levels (2.57 mmol/L, normal value 2.15-2.50 mmol/L). Liver enzymes were normal. CT scan of the thorax revealed multiple enlarged axillar, mediastinal and hilar lymph nodes and bilateral ground-glass opacities in the upper lobes. Antinuclear and anti-neutrophilic cytoplasmic antibodies were absent. Complement levels were normal. Serum protein electrophoresis was compatible with a non-specific acute phase response without a monoclonal peak. Bronchoalveolar lavage revealed a high CD4$^+$/CD8$^+$ T-cell ratio. Viral, bacterial and parasitic cultures returned negative. Endobronchial ultrasound-guided transbronchial needle aspiration of a hilar lymph node was conducted but failed to obtain a relevant tissue sample. Echography of the hepatobiliary tract was unremarkable. A tentative diagnosis of sarcoidosis was made. A wait-and-see attitude was adopted, withholding immunosuppressive treatment. During follow-up, however, the patient developed progressive swelling of the axillary lymph nodes and tender enlargement of the right submandibulary salivary gland. A blood test showed an increased alkaline phosphatase (214 U/L, normal value 40-129 U/L) and gamma glutamyl transferase (193 U/L, normal value 8-61 U/L) levels. Additionally, magnetic resonance imaging (MRI) detected multiple T2-hyperintense liver masses, highly suggestive for metastatic disease (Fig. 2A and 2B). However, biopsy of liver lesions and resection of an axillar lymph node demonstrated an aspecific inflammatory reaction without evidence of malignancy. In view of the patient's atypical disease presentation with multi-organ involvement (salivary glands, lymph nodes, skin, lungs and liver), a thorough search for an underlying inflammatory systemic disease was performed. Hereby, very high serum IgG4 levels were detected (63.8 g/L, normal value 0.03-2.01 g/L). *Post hoc* IgG4 immunostaining of the liver and axillar lymph node specimens revealed high numbers of IgG4-positive plasma cells. This confirmed the diagnosis of IgG4-mediated systemic disease, in particularly affecting the liver. Methylprednisolone was started, initially at 0.5 mg/kg/day and subsequently tapered to 6 mg/day over a period of 4 months. The patient's clinical condition rapidly improved, IgG4 levels dropped, liver

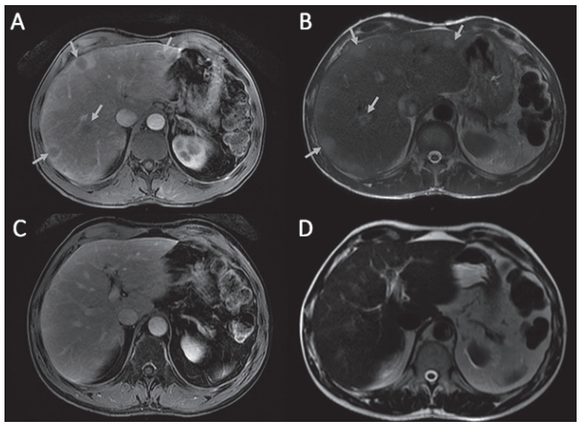

Figure 2. — MRI of the abdomen revealed the presence of multiple lesions in the liver parenchyma characterized by hypointense signals with peripheral rim enhancement after gadolinium administration on T1-weighted images (A) and hyperintense signals on T2-weighted images (B) highly suspected for metastatic liver disease (green arrows). After 6 months of therapy with corticosteroids, both T1-(C) and T2-(D) weighted images revealed a complete resolution of the hepatic masses.

enzymes normalized and the eosinophil count returned to normal. After 6 months of therapy, MRI demonstrated a remarkable involution of the hepatic masses (Fig. 2C and 2D). However, a recent blood test (32 weeks after diagnosis and initiation of therapy) showed a surge of IgG4 levels and symptoms of fatigue and arthralgia reoccurred. Although radiological signs of disease relapse were absent, therapy was intensified to methylprednisolone 12 mg/day and azathioprine 100 mg/day.

Discussion

IgG4-related disease (IgG4-RD) is an increasingly recognized multi-systemic inflammatory disorder that mimics many infectious, malignant and autoimmune conditions. It was first identified in 2003 in a patient with autoimmune pancreatitis (AIP) (1). Almost every organ can be involved either simultaneously or consecutively. Many diseases that were once regarded as isolated medical entities, such as retroperitoneal fibrosis (Ormond's disease), inflammatory swelling of the salivary and lacrimal glands (Mikulicz's disease), sclerosing sialadenitis (Kuttner's tumor) and Riedel's thyroiditis, are now recognized as part of the IgG4-RD spectrum (2).

Anatomopathology

Lymphoplasmocytic organ infiltration, obliterative phlebitis and storiform fibrosis are the histopathological hallmarks of disease. Eosinophils are commonly present. Several caveats, however, must be borne in mind when interpreting microscopic findings. Although a high number of polyclonal IgG4-positive plasma cells in the affected tissue is a prerequisite for diagnosis, the cut-off value of a diagnostic IgG4-positive cell-count must be interpreted according to the specific organ site. Moreover, infiltration of IgG4-bearing plasmatocytes is not a pathognomonic feature, because affected organs in many inflammatory and neoplastic disorders may harbor similar cell types. Finally, fibrosis frequently predominates in longstanding disease and typical histological features may disappear making diagnosis cumbersome (1,3).

Pathophysiology

The pathophysiological mechanisms underlying IgG4-RD remain poorly understood. Both autoimmune and allergic processes might be involved. Linkage with a specific class 2 histocompatibility antigen genotype (DRB1-0405 DQB1-0401) has been described in Asian patients (4). T helper 2 (Th2) cells and secondarily induced regulatory T cells probably orchestrate chronic inflammation, tissue fibrosis and ultimately organ destruction. Intriguingly, Th2-cytokines (i.e. interleukin (IL)-4, IL-5, IL-10 and IL-13) may account for the activation of high serum IgE levels and eosinophilia, which is observed in up to 50% of affected patients. This finding may explain the significant co-existence with allergic disorders (e.g. rhinitis, atopic asthma), but needs further confirmation (5,6). Recent studies suggest that clonally expanded IgG4+ B cells play a pivotal role in the pathogenesis of IgG4-RD. Whether these B cells are driving the immune response or are secondarily induced in reaction to inflammatory (T cell mediated) processes remains unknown (7).

Antinuclear antibodies and antibodies against lactoferrin, carbonic anhydrase II, trypsinogens and amylase α-2A are frequently present. A possible role for molecular mimicry involving *Helicobacter pylori* has been postulated. Till now, no convincing proof has been delivered that autoimmunity contributes to the pathogenesis of IgG4-RD. Moreover, in contrast to "classic" autoimmune disorders which predominantly affect young female patients, IgG4-RD typically develops in middle-aged men (1,5).

The exact role of the IgG4-antibodies in the pathogenesis of IgG4-RD is topic of debate. Whether these antibodies contribute to tissue inflammation or are produced to "cool down" ongoing immune processes remains unknown. A unique feature of the antibody is its ability of so-called fragment antigen-binding (Fab)-arm exchange, a dynamic process by which half of the antibody is swapped with half of another IgG4 molecule. The resulting bi-specific functionally monovalent IgG4 antibody loses its capacity to cross-link antigens and consequently the ability to form immune complexes (1,8). Moreover, due to negligible binding to C1q and Fcγ receptors, IgG4 antibodies are poor activators of the complement cascade. However, observations in other

diseases (e.g. pemphigus vulgaris, myasthenia gravis and membranous glomerulonephritis) point to a pro-inflammatory role of IgG4 (9).

Hepatobiliary manifestations of IgG4-related disease

IgG4-associated cholangitis (IAC) is the biliary manifestation and one of the major localizations of IgG4-RD. Concomitant type 1 AIP is present in up to 92% of cases. The whole biliary tree can be affected, but the lower common bile duct is most frequently involved. Diagnosis can be challenging, particularly in the absence of AIP. Patients often present with painless jaundice, abdominal discomfort and weight loss (10). Radiological imaging with abdominal CT and cholangiography (ERCP or MRCP) may demonstrate biliary strictures with associated wall thickening and inflammation, and the presence of other organ involvement. In contrast, hepatic manifestations of IgG4-RD are poorly defined. Patients mostly develop fibrohistiocytic pseudotumors with dense infiltration of IgG4+ plasma cells. Overlap with autoimmune hepatitis has been reported but any pathophysiological link between these disease entities has not been recognized (5,6).

Differential diagnosis includes cholangiocarcinoma, primary sclerosing cholangitis (PSC), and – in case of hepatic involvement – primary or metastatic liver disease. An accurate diagnostic marker is lacking. High serum IgG4 titers are often detected in IAC, yet normal values have been reported in up to 30% of patients. Moreover, other diseases – including PSC and malignancies of the pancreatico-biliary system – are also associated with elevated IgG4 levels. The search for cut-off serum IgG4 levels to discriminate IAC from cancer has produced conflicting data. A rise of CA19.9 is frequently observed in IAC and therefore not a reliable marker for differentiation with malignancy (8,9). Recently, dominant IgG4+ B-cell receptor clones in serum of patients with active IgG4-RD have been identified and may become a specific marker for IgG4-RD (7). These findings, although promising, need confirmation in prospective studies. Tissue biopsy remains the gold standard for diagnosis. However, acquisition of high-quality histological samples can be difficult. ERCP with brush cytology can rule out malignancy but does not allow diagnosis of IAC. In patients with IAC and concomitant AIP, endoscopic biopsy of the ampulla of Vater has a sensitivity of 52% and a specificity of 89% when a diagnostic threshold of >10 IgG4+ plasma cells per high-power field is applied (11). Intrabiliary biopsies have similar sensitivity and specificity, but may also reveal typical histopathological features of IgG4-RD (12).

Other organ involvement - a valuable diagnostic clue

Involvement of other organs is an important clue to the diagnosis of IgG4-RD (1,8). In both described cases, the presence of unexplained extra-hepatobiliary disease raised suspicion for IgG4-RD. Admittedly, intrinsic renal disease might have (partially) caused kidney failure in the first patient since creatinine levels did not normalize completely after resolution of ureteral obstruction. Although IgG4-related tubulointerstitial nephritis has been reported, it was unlikely to be the causal mechanism, as complement levels were normal and no substantial improvement under immunosuppressive therapy was observed (13). Positron emission tomography/computed tomography (PET/CT) is useful to evaluate the extent of organ involvement and to monitor disease activity during treatment. False-negative results, however, were reported in patients with brain or kidney involvement. Moreover, PET/CT does not permit reliable distinction between IgG4-RD and cancer (1,8).

Treatment options

Corticosteroids are the cornerstone of therapy for IgG4-RD. Yet, many issues remain unsolved (e.g. mechanism(s) of action) or topic of debate (e.g. optimal dose and duration of therapy). Treatment with prednisolone 0.6-1 mg/kg/day is recommended. After 4 weeks the dose must be tapered by 5 mg every 1 or 2 weeks according to clinical, biochemical and radiological evolution (14). Although the response rate on corticosteroids is high, more than 50% of the patients may relapse after discontinuation of treatment (8,10). No consensus exists regarding maintenance therapy. Other immunomodulatory drugs such as azathioprine (1-2 mg/kg/day) and mycophenolate mofetil (750-1000 mg twice daily) have been proposed as steroid-sparing agents. More recently, small studies suggest a potential role of rituximab or bortezomib as "escape" therapy in steroid-refractory cases. However, none of these agents has been tested in randomized controlled trials and evidence for their efficacy and safety in the treatment of IgG4-RD is scarce (5,8,9).

Monitoring of serum IgG4 levels can be useful to assess disease activity and may identify early (subclinical) relapse. In >10% of patients with disease recurrence, however, IgG4 concentrations remain normal. Moreover, significant clinical and radiological remission has been reported despite persistent or new elevations of IgG4. Therefore, IgG4 should never be used as the sole determinant in treatment decisions. Repeated measurement of serum IgG4+ plasmatocytes is probably superior to IgG4 concentrations for follow-up (1).

Evolution

Long-term survival is good in adequately treated IgG4-related hepatobiliary disease. Surgery for biliary structures is generally not necessary. However, significant morbidity has been demonstrated in chronic active disease (e.g. liver cirrhosis and failure, portal

vein thrombosis, diabetes mellitus and chronic kidney failure). Whether these patients are also at higher risk to develop malignancies, as occasionally reported, is unclear and needs further study (15).

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