IgG4-related cholangitis : Case report and literature review

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Abstract

Case Presentation : **We describe a case of a patient who presents with jaundice, elevated cholestatic liver enzymes, an extreme weight loss and a midcholedochal stricture very suspect for a cholangiocarcinoma. In the conviction of malignancy, although the absence of anatomopathological prove, the patient underwent a choledochal resection. The anatomopathological specimen revealed no malignancy. In the year following resection, the patient keeps presenting with bile duct strictures and further weight loss. Ultimately the diagnosis of Ig G4-related cholangitis is withheld. Therapy with corticosteroids is initiated with a spectacular clinical, biochemical and radiographical result.**

Discussion : **IgG4-related cholangitis is the biliary presentation of IgG4-related disease, a recently discovered entity of fibroinflammatory masses which can affect virtually every organ in the body. It is characterized by a dense lymphoplasmacytic infiltrate, storiform fibrosis, obliterative phlebitis and a presence of > 30 IgG4-positive plasma cells per high power field. Main differential diagnosis contains cholangiocarcinoma and primary sclerosing cholangitis. Corticoids are cornerstone of therapy, with azathioprine frequently used as a maintenance in case of relapse.**

Conclusion : **With this case we want to draw the attention to a rather uncommon cause of biliary obstruction, easily mistaken for a cholangiocarcinoma.** (Acta gastroenterol. belg., **2015**, 78, **62-64**).

Key words : IgG4-related disease, IgG4-related cholangitis, biliary obstruction.

Introduction

In most of cases, the cause of biliary obstruction is obvious. However, in the absence of bile stones or evident malignancy, diagnosis can be more challenging. Our case describes IgG4-related cholangitis as a mimicker of a malignant stricture.

Case presentation

One year prior to the actual clinical history, a 55-year old male was admitted in a regional hospital with fever, jaundice and a weight loss of 5 kilograms. He had a history of ulcerative colitis, in clinical and endoscopic remission at the time of presentation. Blood analysis showed ALT of 96 U/l, AST of 204 U/l, GGT of 285 U/l, AF of 320 U/l and a bilirubin level of 4 mg/dl. Abdominal CT-scan showed dilatation of the intra- en extrahepatic bile ducts and enlarged perihilar lymph nodes. Antibiotics were initiated and the patient was referred to our hospital for an MRCP, which confirmed the dilatation of intra- and extrahepatic bile ducts and the presence of perihilar enlarged lymphnodes and also showed a midcholedochal stricture causing the obstruction. In the further diagnostic work up, an endoscopic ultrasound was performed, which showed a midcholedochal wall mass of 20 to 8 mm, very suspect for a cholangiocarcinoma. Fine needle aspiration (FNA) of the enlarged lymph nodes was performed. In the assumption of a malignant stricture, a fully covered metal stent was placed through ERCP to relieve biliary obstruction. Cytology, obtained through brushing of the common bile duct by ERCP and endoscopic ultrasound guided FNA of the perihilar lymph nodes revealed no malignancy. CA 19-9 level was normal. Because of the iconographic aspect of the stricture, not typical for PSC and very suspect for malignancy, the intramural mass seen on endoscopic ultrasound and the important weight loss of our patient, a tentative diagnosis of resectabel cholangiocarcinoma was retained and after thorough multidisciplinary discussion, the patient was referred for surgery. A resection of the stricture with hepaticojejunostomy was performed, since there was no evidence of malignancy in the perioperative specimen. Anatomopathologic analysis of the choledochus showed no malignancy. After a fast recovery, the patient was discharged and did not return to our centre.

One year later, this patient was referred to the hepatology department by his general practitioner due to an obstructive jaundice, fatigue and a further weight loss to a total of 17 kg. He had suffered several episodes of cholangitis in the past year. MRCP showed a dilatation of the intrahepatic biliary tract and a stricture of the remaining main hepatic duct. The anatomopathological results of the initial resection species were revised in detail and interestingly showed extensive fibrosis of the choledochal wall with presence of multiple plasma cells and IgG4, morphological and immunohistochemical typical for IgG4-related fibrosing cholangitis. Unfortunately, this message had not reached the attending physician after the initial surgery.

Serum IgG4-level was elevated (320 mg/dl). Corticoids were initiated and tapered over a period of three months, followed by the initiation of a maintenance

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therapy with azathioprine. The clinical, biochemical and radiological response was spectacular. A MRCP one month after start of therapy showed a complete resolution of the strictures and the normalization of the intrahepatic bile ducts. A complete normalization of the liver enzymes was seen after four months of therapy. The patient regained his initial weight after only two months and is currently in good health under a maintenance therapy with azathioprine.

Discussion

IgG4-related cholangitis is the biliary presentation of IgG4-related disease, a multi-system disease that was only recognized in the early 21th century. Fibroinflammatory tumoral masses were already described in the late 19th century and went on by the name of their discoverer : Mikulicz's disease (salivary glands), Kuttner's tumour (sclerosing sialadenitis) and Riedel's thyroiditis. (1-4) But it took as long as until 2003, before the link between these different disease entities was identified. In 2001 Hamano (5) described very high IgG4-levels in sclerosing auto-immune pancreatitis type 1 and infiltration of IgG4-bearing plasma cells in pancreatic tissue samples. In 2003 Kamisawa (6) found infiltration of IgG4-bearing plasma cells in extrapancreatic tissue samples in patients with autoimmune pancreatitis (AIP) type 1. IgG4-related disease can affect virtually every organ in the body : the biliary tree, pancreas, lymph nodes, salivary glands, periorbital tissues, kidneys, lungs, pericardium, skin, aorta, meninges, breast, prostate and thyroid. (1-3).The histopathological features of IgG4-related disease are characterized by a dense lymphoplasmacytic infiltrate, storiform fibrosis, obliterative phlebitis and a mild-to-moderate eosinophil infiltrate (1-2). The histological appearance of IgG4-related disease requires immunohistochemical confirmation with IgG4 immunostaining, with presence of >30 IgG4-positive plasma cells per high power field considered as reasonably specific. (1). The pathogenesis of IgG4-related disease is not clearly recognized. Multiple immune-mediated mechanisms contribute to the fibroinflammatory process. There is some genetic susceptibility with certain HLA-subtypes (DRB1-0405 DQB1-0401) in Japanese populations. (7). Molecular mimicry could play a role in the pathogenesis.

For example, there is some homology between the plasminogen-binding protein of Helicobacter pylori and the ubiquitin-protein ligase E3 component n-recognin 2, which is expressed in pancreatic acinar cells. In one study the majority of patients with autoimmune pancreatitis have antibodies against the pBp of H. pylori. Autoimmunity probably also plays an important role. IgG4 related disease is a Th2-cell and Treg-cell mediated inflammatory response, mediated by cytokines Il-4, Il-5, Il-10, Il-13. Elevated IgE levels, eosinophilia and allergic diseases are common in IgG4-related disease. The role of IgG4 antibodies is unclear. They may behave as tissue destructive antiglobulins or they may just be an overexpression of these antibodies in response to an unknown inflammatory stimulus (1).

IgG4-related cholangitis is the biliary manifestation of IgG4-related disease. In the majority of cases, it is seen in combination with auto-immune pancreatitis type 1 (92%), but it can exist as an entity on its own. It typically affects the large bile ducts, and the lower common bile duct in particular. (8) IgG4-related cholangitis is mostly seen in males in the 5th and 6th decade of life and typical symptoms consist of obstructive jaundice and weight loss. Because of its presentation and radiological features it is easily mistaken for a cholangiocarcinoma. Histopathological features are the same as elsewhere in the body (3,4).

Diagnosis is particulary challenging in the absence of autoimmune pancreatitis. Imaging with abdominal CT scan and cholangiography (MRCP and ERCP) is usefull in detecting stenosis, associated inflammation and wall thickening and associated lymphadenopathies. Serum IgG4- levels can be normal in up to 20% of cases. Diagnosis must be confirmed histopathologically. Brush cytology can be used to exclude malignancy, but does not allow the diagnosis. Immunostaining on ampullary biopsies can show IgG4-positive plasma cells with a sensitivity of 50-80% in AIP. Bile duct biopsies have the same sensitivity for IgG4, but can also show typical histopathological features (4,9).

Differential diagnosis includes primary sclerosing cholangitis and cholangiocarcinoma. IgG4- levels can be misleading, as they can also be elevated in malignancy (10). Several studies have tried to use serum IgG4-levels for differentiating between IgG4-related cholangitis and malignancy (9-12). One study was able to find a level for IgG4 to discriminate between malignancy and IgG4 cholangitis (9). However, IgG4-levels alone are not a sensitive and specific tool for diagnosis, and should only be used in addition to other diagnostic tools.

Corticosteroids are the cornerstone of therapy. There are no randomized controlled trials available. Following current recommendations corticoids are started in a dose of 30-40 mg prednisolone for four weeks, followed by slow tapering by 5 mg per 2 weeks. Typically a clinical and cholangiographic improvement is expected within 4 to 6 weeks. Relapse is frequent (57%) after tapering or discontinuation of corticoids and can be treated by immunomodulatory drugs like azathioprine (1-2 mg/kg/day) or mycophenalate mofetil (750-1000 mg twice daily). In some patients, intolerant for immunomodulatory therapy and dependant of high-doses corticosteroids, rituximab can also play a role in therapy (4).

Conclusion

With this case we want to draw the attention to a rather uncommon cause of biliary obstruction. Because of the spectacular presentation with pseudotumoral masses, enlarged lymph nodes and strictures, IgG4-related fibrosing cholangitis is easily mistaken for a cholangiocarcinoma.

When diagnostic work out for malignancy is negative, it is important to take this uncommon cause of biliary strictures and cholangitis in the differential diagnosis.

References

1. STONE J.H., ZEN Y., DESHPANDE V. Mechanisms of disease : IgG4-Related Disease. *N. Engl. J. Med*., 2012, **366** : 539-550.
2. CHEUK W., CHAN J.K.C. IgG4-related Sclerosing Disease. A Clinical Appraisal of an Evolving Clinicopathologic Entity. *Adv. Anat. Pathol*., 2010, **17** (5) : 303-332.
3. PIERINGER H. *et al*. IgG4-related disease : an orphan disease with many faces. *Orphanet Journal of Rare Diseases*, 2014, **9** : 110.
4. JOSHI D., WEBSTER G.J. Biliary and Hepatic involvement in IgG4-related disease. *Aliment. Pharmacol. Ther*., 2014, **40** : 1251-1261.
5. HAMANO H. *et al*. High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N. Engl. J. Med*., 2001 Mar 8, **344** (10) : 732-8.
6. KAMISAWA T. *et al*. A new clinicopathological entitiy of IgG4-related autoimmune disease. *J. Gastroenterol*., 2003, **38** (10) : 982-4.
7. KAWA S. *et al*. HLA DRB10405-DQB10401 haplotype is associated with autoimmune pancreatitis in the Japanese population. *Gastroenterology*, 2002 May, **122** (5) : 1264-9.
8. GHAZALE A. *et al*. Immunoglobulin G4-associated cholangitis : clinical profile and response to therapy. *Gastroenterology*, 2008 Mar, **134** (3) : 706-15.
9. ZEN Y. *et al*. Immunoglobulin G4-related sclerosing cholangitis : pathologic features and histologic mimics. *Semin. Diagn. Pathol*., 2012, **29** : 205-211.
10. OSEINI A.M. *et al*. Utility of Serum Immunoglobulin G4 in Distinguishing Immunoglobulin G4- associated Cholangitis from Cholangiocarcinoma. *Hepatology*, 2011, **54** : 940-948
11. TABATA T. *et al*. Differentiating Immunoglobulin G4-Related Sclerosing Cholangitis from Hilar Cholangiocarcinoma. *Gut Liver*, 2013 Mar, **7** (2) : 234-8.
12. OHARA H. *et al*. Establishment of a serum IgG4 cut off value for the differential diagnosis of IgG4-related sclerosing cholangitis : a Japanese cohort. *J. Gastroenterol. Hepatol*., 2013, **28** (7) : 1247-51.