Digestive and Liver Disease 47 (2015) 432–435

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Short Report

The overlap syndrome between primary biliary cirrhosis and primary sclerosing cholangitis

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ARTICLE INFO

Article history:
Received 28 October 2014
Accepted 4 February 2015
Available online 11 February 2015

Keywords:
Overlap syndrome
Primary biliary cirrhosis
Primary sclerosing cholangitis

ABSTRACT

Background: The overlap syndrome between primary biliary cirrhosis and primary sclerosing cholangitis is an extremely rare condition that has been reported in only six published cases so far.
Methods: Here we report two cases showing the clinical manifestations of both primary biliary cirrhosis and primary sclerosing cholangitis.
Results: In one case the overlap condition was associated with psoriatric arthritis, and the patient successfully underwent dual treatment with ursodeoxycholic acid and the anti-tumour necrosis factor-alpha agent adalimumab. In the second case, the predominant condition was, initially, an antimitochondrial antibody-negative primary biliary cirrhosis with progressive course towards end-stage liver disease; the patient then developed either antimitochondrial antibody positivity or changes in the biliary tree compatible with primary sclerosing cholangitis.
Conclusions: These two cases add information on a controversial issue in the literature, and indicate the importance of recognizing a possible overlap syndrome to optimize treatment.

1. Introduction

Some patients presenting with an autoimmune liver disease have a phenotype with evidence of two overlapping conditions [1]. In the majority of the cases, the so-called overlap syndromes are between autoimmune hepatitis (AIH) and primary biliary cirrhosis (PBC) or AIH and primary sclerosing cholangitis (PSC) [2]. Overlap between PBC and PSC has been described in only 6 cases so far [3–7; Supplementary Table S1]. The first reported case was described in a 52-year-old man with AMA positivity, whose cholestatic history started at the age of 44 years. An oral cholecystography was performed when the patient was 51 years old, revealing multiple strictures and dilatations of the intrahepatic biliary tree. A liver biopsy showed findings that were non-specific for either PBC or PSC, and the authors thus hypothesized a coexisting PBC and PSC, without excluding biliary carcinoma or drug-induced cholestasis.

The second reported case [4] was described in a 40-year-old female with past cholecystectomy and with recurrent bouts of ascending cholangitis. The patient underwent two liver biopsies, of which the first showed results consistent with PBC, and the second revealed the classical onion-skinning fibrosis around medium-sized ducts. Intrahepatic and extrahepatic PSC was well documented by endoscopic retrograde cholangiopancreatography.

Kingham and Abbasi [5] reported two cases of overlapping PBC/PSC from a cohort of 261 consecutive patients with autoimmune liver disease followed prospectively over a 20-year period.

Jevaagan [6] reported a case of PBC/PSC overlap syndrome in a 64-year-old woman who was diagnosed as having AMA-negative PBC and then had a cholangiography consistent with PSC. The

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http://dx.doi.org/10.1016/j.dld.2015.02.002
1590-8658/

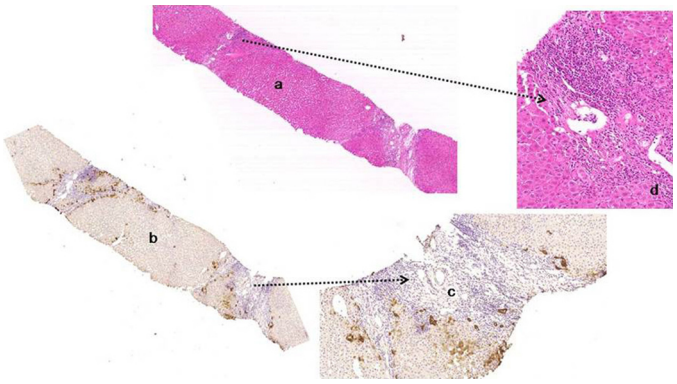

Fig. 1. Consecutive sections of core needle biopsy stained by (a) Haematoxylin &Eosin and (b) Cytokeratin 7 showing two expanded portal tracts with porto-septal fibrosis and bile duct loss. Native bile ducts are absent or very lacking as shown by Cytokeratin 7 immunostaining; notice the ductular metaplasia of periportal hepatocytes and ductular reaction (c, a higher magnification from b, arrow); interface hepatitis can also be seen (d, a higher magnification from a, arrow). a, b: ×4, c: ×20, d: ×40.

more recent report in the literature describes a patient with PBC, with normal cholangiography, showing "onion-skin" type periductal fibrosis at liver histology [7].

None of the cases reported in the literature was associated with inflammatory bowel disease (IBD). Moreover, the diagnosis of overlapping was controversial in some cases, mainly due to the insufficient definition of the biliary tree with the new generation imaging techniques, the poor description of extrahepatic manifestations, and the incomplete information on the autoimmune serologic profile. Here we report two cases showing the clinical manifestations of both PBC and PSC.

2. Case 1

A 51-year-old woman presented in April 2012 with persistent abnormal cholestasis enzymes since 2009. Clinical history included a laparoscopic cholecystectomy in 1987 for symptomatic gallstones. In September 2010, a magnetic resonance imaging (MRI) of the upper abdomen revealed a slightly irregular profile of the right hepatic ducts proximal to the insertion with the common bile duct; no intrahepatic bile stones were observed. The patient was started on ursodeoxycholic acid (UDCA) at a dose of 10 mg/kg/day. In September 2011, she also developed a mild psoriasis with 4th right finger dactylitis and arthritis of the 4th right metacarpo-phalangeal joint. Treatment with tapered steroids and oral methotrexate gave poor results.

In April 2012, her biochemical tests showed: alkaline phosphatase 201 IU/ml (ULN, 141), gamma-glutamyltransferase (GGT) 229 IU/ml (ULN, 45), AMA positivity (1:160 titre), and an immunoblotting positivity for M2, 3E, and anti-pg210, as well as antinuclear antibody positivity (1:40 titre with speckled pattern), negative ANCA antibodies, normal IgG4 serum levels, total serum cholesterol 240 mg/dL, increased serum IgM (7.31 mg/dL), normal aminotransferases, and negative serum markers for hepatitis B and C. On physical examination, dactylitis of the 4th right finger, as well as swelling, redness, and pain of the distal interphalangeal (DIP) joint of the 2nd right finger were observed. The patient's body mass index (BMI) was 24.9.

In May 2012, a liver biopsy showed marked fibrosis in the portal tracts extending to the parenchyma, interface hepatitis, and a vanishing bile duct picture with the remaining ducts showing regressive alterations of cholangiocytes together with biliary metaplasia (Fig. 1). As histology was compatible with stage III PBC, UDCA dosage was increased to 15 mg/kg/day; a partial reduction in GGT and alkaline phosphatase followed.

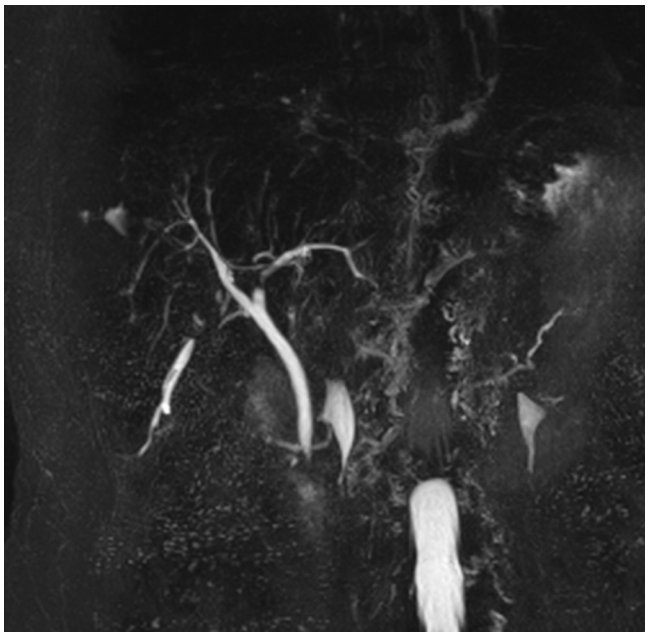

Fig. 2. Magnetic resonance cholangiopancreatography, maximum intensity projection rendering image, showing an ectopic drainage of the common bile duct in the distal part of descending duodenum; marked stenosis of the right antero-inferior segmental duct and the left hepatic duct with upstream dilatation, and multiple segmental irregularity, narrowing and dilatation of intrahepatic bile ducts.

In July 2012, the patient underwent an upper abdomen MRI that revealed a marked reduction of the right segmental duct extended for 2.5 cm, with upstream dilatation, and a marked stenosis of the biliary tree in the 5th and 6th hepatic segment with the characteristics of PSC. Colonoscopy was negative for IBD.

In October 2012, the patient developed a distal interphalangeal arthritis in the 4th right finger with severe onychodystrophy. After a collegial discussion of the case, treatment with human anti-tumour necrosis factor-alpha (TNFα) adalimubab (40 mg every other week) was started. The patient reported marked relief in pain and stiffness. After 3 months, the rheumatologic assessment with 4 questionnaires (the Health Assessment Questionnaire, the Disease Activity score, the Clinical Disease Activity Index, and the Simplified Disease Activity Index) indicated disease remission. Liver function tests improved together with a normalization of alkaline phosphatase levels and a decrease in GGT (to 124 IU/L) and IgM (to 5.35 mg/L). In December 2014, a new MRI confirmed the previous changes of the biliary tree (Fig. 2).

3. Case 2

A 60-year-old woman presented in January 2013 for a re-evaluation of hepatic cholangitis (possible overlap PBC/PSC). Her relevant medical history included: excision of malignant melanoma in her right arm in 1978, left ovariectomy in 1994, and excision of a frontal meningioma in 2003. In 2000 the patient was diagnosed with arterial hypertension, and in 2010 with type-1 diabetes and subclinical hypothyroidism. Her BMI was 24.

Since 1989 the patient was aware of her abnormal cholestasis enzymes; in 1996, she underwent a laparoscopic cholecystectomy for symptomatic gallstones. In 2001, a liver biopsy showed oedematous portal tracts with granulomatous destructive infiltrate compatible with PBC (Fig. 3). The immunologic profile revealed ANA positivity (1:80) and AMA negativity. Since October 2010, the