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A patient with primary biliary cholangitis, autoimmune hepatitis, and primary sclerosing cholangitis variant syndrome

Benedetta Terziroli Beretta-Piccoli [a,b,*], Luca Mazzucchelli [c], Chiara Taiana [d], Giuseppe Mossi [e], Corrado Usai [f], Diego Vergani [b], Giorgina Mieli-Vergani [g]

[a] Epatocentro Ticino, Lugano, Switzerland
[b] Institute of Liver Studies, MowatLabs, King's College Hospital, London, UK
[c] Cantonal Pathology Institute, Locarno, Switzerland
[d] Studio Medico, Canobbio, Switzerland
[e] Studio Medico, Maggia, Switzerland
[f] Radiology Department, Regional Hospital EOC, Locarno, Switzerland
[g] Paediatric Liver, GI and Nutrition Centre, MowatLabs, King's College Hospital, London, UK

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ABSTRACT

Overlap between autoimmune hepatitis (AIH) and either primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC) is not rare and has extensively been reported. We herein report the first well documented case of triple overlap. A 68-year-old male patient presented with asymptomatic PBC including normal alkaline phosphatase serum level, developed AIH five years later, associated with magnetic resonance cholangiopancreatography biliary changes typical for PSC. Despite treatment with ursodeoxycholic acid and mycophenolate mofetil, owing to prednisone and azathioprine intolerance, he continued to have interface hepatitis and developed increasing fibrosis at follow-up liver biopsy. Our case report raises awareness for this rare and difficult to diagnose and treat clinical phenotype.

1. Introduction

Autoimmune hepatitis (AIH), primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PCS) are distinct immune-mediated liver diseases, though some patients have clinical, biochemical, serological, radiological and histological features of both AIH and PBC or AIH and PSC (PBC/AIH and PSC/AIH variant syndromes). These disorders can present either simultaneously or sequentially, patients being usually classified according to the predominant disease [1,2]. We describe a male patient with classical PBC who during follow up developed histological and serological features of AIH in association with biliary tree changes typical of sclerosing cholangitis on magnetic resonance cholangiopancreatography (MRCP).

2. Case description

A 68-year-old male was diagnosed with PBC in 2008 during a routine health check. He was on ramipril for essential hypertension, did not drink alcohol or smoked, was obese (BMI 37) and had had a curative surgical resection of a right lung adenocarcinoma five years earlier. He had no family/personal history of liver/autoimmune diseases. Liver biochemistry showed elevated gamma-glutamyl transferase (GGT) and slightly elevated alanine aminotransferase (ALT) (Table 1). Therefore, a laboratory liver diagnostic work-up was performed, including testing for anti-mitochondrial antibody (AMA) and anti-nuclear antibody (ANA), which were both positive, ANA showing a rim-like staining pattern on HEp2 cells (Table 1). Owing to these laboratory results, the patient underwent a liver biopsy, which showed florid bile duct lesions (Ludwig stage II PBC) (Fig. 1A). Viral hepatitis A, B, C and E were excluded. Serum markers of iron and copper metabolism were normal. No treatment was initiated in view of his wellbeing. Five years later, a follow-up liver biopsy showed stage III PBC and appearance of interface hepatitis (Fig. 1B). He had elevated IgG and IgM levels, and positive ANA with a fine speckled immunofluorescence pattern on HEp2 cells (Table 1). He scored 8 at the simplified International AIH Group diagnostic score [3], fulfilling the criteria for definite AIH. Diagnostic criteria for AIH/PBC overlap

* Corresponding author. Via soldino 5, 6900, Lugano, Switzerland.
E-mail addresses: benedetta.terziroli@hin.ch (B. Terziroli Beretta-Piccoli), luca.mazzucchelli@ti.ch (L. Mazzucchelli), taiana.dott@tiscali.it (C. Taiana), g.mossi@bluewin.ch (G. Mossi), corrado.usai@eoc.ch (C. Usai), diego.vergani@kcl.ac.uk (D. Vergani), giorgina.vergani@kcl.ac.uk (G. Mieli-Vergani).

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Table 1
Biochemical and serological profile over time.

	Normal range	11.2008	6.2013	7.2013	7.2014	9.2015	9.2016	12.2017	7.2019
		No therapy	No therapy	Prednisone					
				Azathioprine					
				Mycophenolate mofetil					
				UDCA					
AST IU/l	<41	32	43	24	31	24	16	25	25
ALT IU/l	<41	49	35	21	30	23	15	9	15
ALP IU/l	<129	125	86	61	64	69	78	62	55
GGT IU/l	<61	214	189	94	119	77	25	22	24
Total bilirubin μmol/l	<19.0	6.3	17.2	11.6	15.2	17.1	11	15	11.5
IgG g/l	7–16	16.82	24.14		15.6	11.1	14.14		12.9
IgM g/l	0.4–2.3	4.53	5.81			3.74			1.5
ANA	<1:80	1:1280 *	1: 320 §		1:160 §	<1:80 §	1:2560*	1:2560*	<1:80
SMA	<1:40	1:40	<1:40		<1:40	<1:40	<1:40	<1:40	<1:40
Anti-LKM	<1.0	0.1	0.2		0.1	0.2		0	
AMA U/ml	<5	143	130		152	145		48	1:160 IIF
Anti-SLA U/ml	<20		neg		neg	neg		neg	neg
ANCA	<1:10	neg			<1:10	<1:10		<1:10	<1:10
Anti-gp210 U/ml	<25				126	118			
Anti-sp100 U/ml	<25				12	7			

UDCA, ursodeoxycholic acid; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; IgG, immunoglobulin G; IgM, immunoglobulin M; ANA, anti-nuclear antibody; SMA, smooth muscle antibody; anti-LKM, anti-liver kidney microsomal antibody; AMA, anti-mitochondrial antibody; SLA, soluble liver antigen; ANCA, anti-neutrophil cytoplasmic antibody; neg, negative; IIF, indirect immunofluorescence. * rim-like immunofluorescence pattern on HEp2 cells. § fine-speckled immunofluorescence pattern on HEp2 cells.

syndrome were also met [4]. Prednisone 30 mg/day and azathioprine 50 mg/day, as well as ursodeoxycholic acid (UDCA) 15mg/kg/day, were started. Azathioprine was withdrawn for gastrointestinal intolerance after 2 months. Prednisone was slowly tapered to 5 mg/day. Twelve months after starting treatment, a liver biopsy showed worsening of portal and interface hepatitis, markedly increased fibrosis, and bile duct proliferation (Fig. 1C). MRCP, performed to exclude bile duct obstruction in view of poor response to treatment, showed intrahepatic bile duct changes characteristic of sclerosing cholangitis (Fig. 1D). Inflammatory bowel disease was excluded macro/microscopically at colonoscopy and upper endoscopy. A diagnosis of PBC/AIH/PSC overlap was made. Treatment was escalated by adding mycophenolate mofetil (MMF) 2g/day, and increasing the prednisone dose, starting with 40mg/day, slowly tapered to 5 mg/day over 3 months. UDCA was continued. Prednisone had to be withdrawn after 6 months for severe osteoporosis. After five years of MMF/UDCA therapy, blood tests remain normal (including normalization of GGT and IgM levels), apart from AMA and transitory re-appearance of rim-like ANA positivity, without signs of portal hypertension, though a liver biopsy performed after one year of MMF/UDCA treatment, showed persistent interface hepatitis and advanced fibrosis (Fig. 1E).

3. Discussion

We describe the first well documented patient with an overlap between the three autoimmune liver diseases, primary biliary cholangitis, autoimmune hepatitis and primary sclerosing cholangitis. The rare overlap between PBC and PSC has been reported in only 11 patients in the literature to date [5–13]. One case report suggests the occurrence of the three autoimmune conditions in one patient, but the diagnosis of AIH is in doubt since histological confirmation is lacking and the pattern of the ANA detected is not specified [5]. Thus, while homogeneous or speckled patterns are present in AIH, the rim-like and the multiple nuclear dots patterns are exclusive to PBC. In addition, one case report describes a young man with PSC who later developed AIH with transient AMA positivity, but without histological features of PBC [14]. Our patient initially fulfilled diagnostic criteria for PBC, with serology positive for AMA and the PBC-specific rim-like ANA in addition to elevated IgM and, most importantly, classical histological PBC ductular lesions. Of note, he had normal serum alkaline phosphatase (ALP) levels, and the diagnosis of PBC would have been missed without a liver biopsy, the only biochemical cholestasis marker being elevated GGT level. Interestingly, it has recently been reported that the majority of AMA-positive patients with normal ALP levels have PBC histological changes, similarly to what we observed in our patient [15]. Five years after the PBC diagnosis, he fulfilled diagnostic criteria of AIH, having developed florid interface hepatitis, increased IgG levels and fine speckled ANA, present in some 30% of AIH type 1 patients [16]. Six years later he was found at MRCP to have bile duct changes typical of PSC, though it is impossible to exclude that PSC was present from onset, as cholangiographic studies had not been performed at presentation. Of note, serum transaminase levels were only minimally altered and the patient was clinically asymptomatic throughout the observation period, liver biopsies being essential for diagnosis and management. Though initially treatment was deemed unnecessary, in view of his wellbeing, the severity of his inflammatory histological lesions prompted us to initiate the standard therapy schedule for AIH, in addition to UDCA for his underlying PBC. Because of side effects of azathioprine first and prednisone later, the latter probably in part ascribable to his age, AIH could not be treated adequately and the disease was still histologically active after one year of maintenance treatment with full-dose MMF and UDCA. His GGT became normal after starting immunosuppressive treatment and UDCA and liver function tests remain normal to date, his quality of life is excellent and he has no signs of portal hypertension or progression to decompensated cirrhosis.

This case prompts three types of considerations. First, classical diagnostic elements of the three autoimmune liver diseases can co-exist, possibly reflecting common pathogenic pathways. Second, it underscores a physician's dilemma as it shows that the presence of an

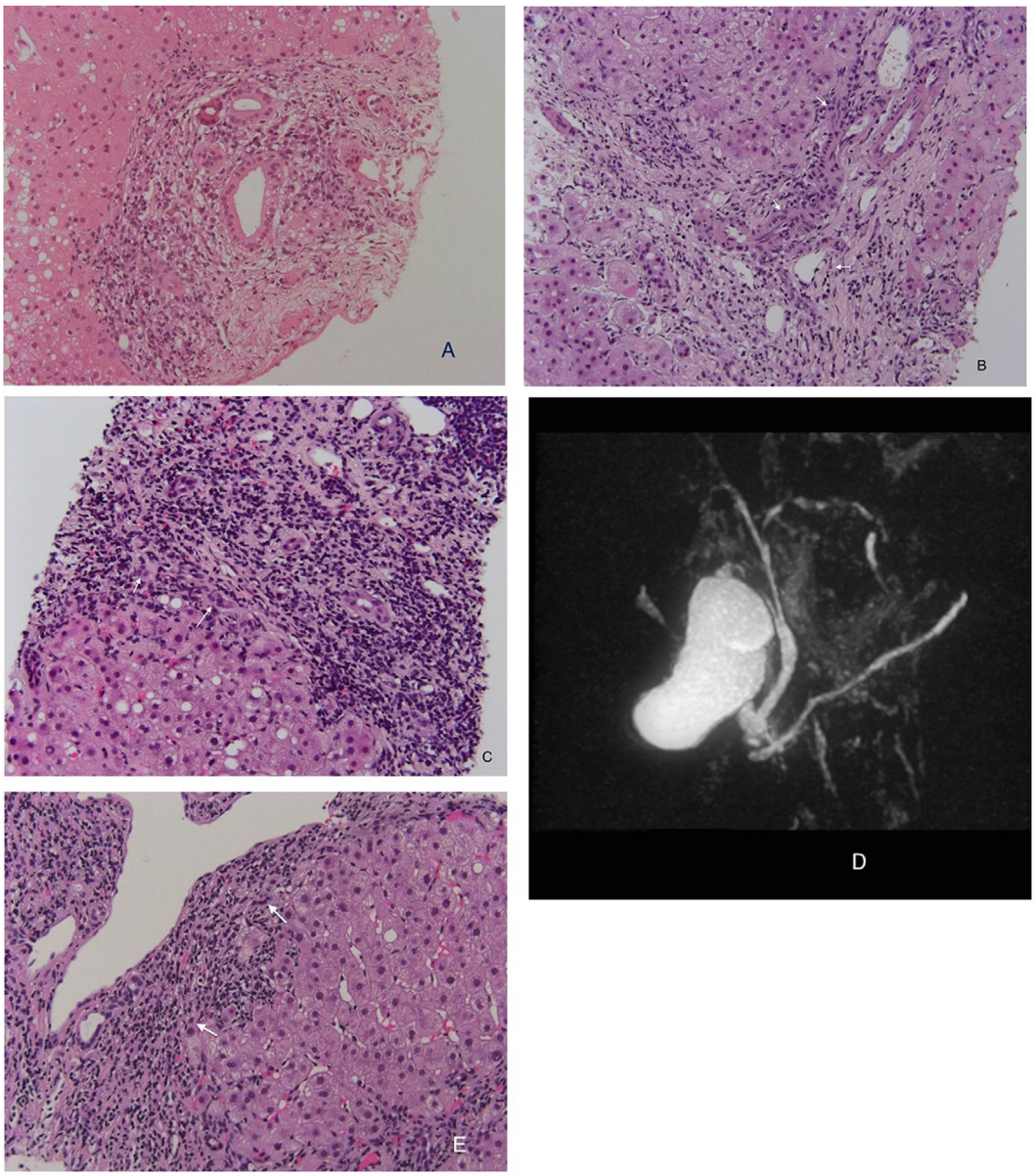

Fig. 1. (A) Moderate chronic inflammation of the portal tract associated with epithelioid cells adjacent to the bile ducts and ductal proliferation. (B) Severe inflammation of the portal tract, with diffuse interface hepatitis and plasma cells (arrows). Ductal inflammation and ductal damage. (C) Severe chronic portal and interface hepatitis, with presence of plasma cells near the limiting plate (arrows). Ductal epithelium shows mild atypia, associated with inflammation. Severe architectural distortion compatible with cirrhosis. (D) Multifocal stenosis and dilatation of the intrahepatic bile ducts involving the second and third liver segments (E) Persistence of lympho-histiocytic infiltrate in the portal area, associated with interface hepatitis. A few plasma-cells (arrows) are present near the limiting plate.

overlap between PBC, AIH and PSC can be almost completely asymptomatic despite severe histological changes. Third, it highlights the central role of liver histology in PBC and AIH: histological PBC changes may be present despite normal ALP level, suggesting that GGT may be the only biochemical marker of cholestasis in PBC; and serum transaminase levels may be normal despite a diagnosis of AIH. Of note, transaminase levels are not included in the International AIH Group diagnostic score [3].

According to published recommendations [1], our patient was treated for his prevalent disease, AIH. His progression to decompensated cirrhosis was probably prevented, but he developed significant side effects that required careful tailoring of his treatment.

In conclusion, this case of coexisting PBC, AIH and PSC, raises awareness of this rare variant autoimmune liver disease syndrome, of its challenging diagnosis and of the difficulty in personalising its management.

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Potential competing interests

None.

Specific author contributions

BTBP: caring for the patient, writing up and approving the final report submitted. LM: reading the liver biopsies, providing the histological images with legends, approving the final report submitted. GM, CT: caring for the patient, approving the final report submitted. CU: reading the radiological images, providing the radiological image with legend, approving the final report submitted. DV and GMV: advice on patient's

management, critical revision and final approval of the report.

Patient's written informed consent for publication was obtained.

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