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CASE REPORT

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Primary biliary cholangitis-autoimmune hepatitis overlap syndrome: Case report and literature review

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Abstract

Paris criteria remain practical for retaining the diagnosis of overlap syndrome. While liver histology is mandatory, its absence should not be an obstacle to the diagnosis and delay the initiation of treatment in countries where biopsy not available.

KEYWORDS

autoimmune hepatitis, immunosuppressive, overlap, primary biliary cirrhosis, ursodeoxycholic acid

1 | INTRODUCTION

Overlap syndrome associating primary biliary cholangitis and autoimmune hepatitis remain a rarely studied pathology. The diagnosis is based on diagnostic criteria. The criteria of Chazouillères et *al* (Paris criteria) were the most used. The combination of UDCA and immunosuppressants helped achieve remission in the majority of cases.

Primary biliary cholangitis (PBC) and autoimmune hepatitis (AIH) are two well-defined autoimmune liver diseases. PBC is an inflammatory cholestatic disease of the intrahepatic bile ducts characterized by an autoimmune reaction centered on the bile epithelium.[1,2] AIH is an inflammatory disorder of the hepatic parenchyma secondary to an autoimmune reaction targeting hepatocytes.[3] Their respective diagnosis is usually easy, based on well-defined clinical, biological, immunological, and histological criteria.[1-3] Their respective management is well-codified.[2,3] The characteristic elements of these two pathologies may be present in the same patient determining a PBC-AIH "overlap syndrome."[4] The prevalence of the latter in European countries varies according to the series ranging from 1.3% to 19%.[4,5] The prevalence of autoimmune liver disease in sub-Saharan Africa remains unknown.[6] This entity poses diagnostic and therapeutic difficulties.[1] No case of overlap syndrome combining PBC and AIH has been described in Madagascar. Our objective is to report an observation, discuss the diagnosis, and the current management of the overlap syndrome associating PBC and AIH.

2 | CASE REPORT

A 51-year-old woman of Malagasy origin was seen in consultation in January 2016 for chronic asthenia associated with jaundice. She is neither alcoholic nor smoking. She is type II diabetic treated with Metformin 1.5g/day and hypertensive treated regularly with Amlodipine® 10 mg/day and

Losartan® 50 mg/day. The history of the disease began in December 2015 with physical asthenia and in January 2016 a mucosal jaundice of progressive aggravation with dark urine and discolored stools. The patient complains of pruritus, especially, at night. She does not report any notion of fever. The physical examination was normal. The biological assessment reported disturbances of the hepatic balance cholestatic type associated with inflammatory syndromes with alanine aminotransferase (ALT) at 390 IU/l (N < 35 IU/L), aspartate aminotransferase (AST) at 220 IU/L (N < 45 IU/L), alkaline phosphatases (ALP) at 250 IU/L (N: 53 at 128 IU/L), γ-glutamyl transferases (γGT) at 990 IU/l (N < 55IU/l), total bilirubinemia (BT) at 50 µmol/l (N < 20 µmol/l) with conjugated bilirubin at 37 µmol / 1 (N < 9 µmol/l), 85% TP, albuminemia at 43 g/l, and hypergammaglobulinemia at 28 g/l and CRP 23 mg/l. Viral serologies A, B, and C were negative. Anti-nuclear, anti-smooth muscle, and anti-mitochondria type M2 antibodies were positive with significant levels at 1 / 80th, respectively. Anti-LKM1 and native anti-DNA antibodies were negative. Liver biopsy puncture was indicated but not available. The abdominal ultrasound showed normal liver parenchyma and undilated intrahepatic and extrahepatic bile ducts. There was no picture in favor of hepatic intraparenchymal lithiasis (Figure 1). Blood cultures and ECBU were negative. The chest X-ray was normal (Figure 2). The diagnosis of Overlap syndrome PBC-AIH was retained on the diagnostic Paris criteria (Chazouillères et *al*) with the presence of 2 criteria of primary biliary cholangitis (PBC) and 2 criteria of autoimmune hepatitis (AIH) (Table 1).[7] The presence of anti-smooth muscle antibodies at significant levels at 1 / 80th associated with a level of ALT 11 x ULN (upper limit than normal) are part of the criteria for autoimmune hepatitis (AIH) and the presence of alkaline phosphatase 3 x ULN associated with anti-mitochondria type M2 antibodies at a significant level at 1 / 80th are part of the criteria for primary biliary cholangitis (PBC) (Table 1). The patient was put on ursodeoxycholic acid (Delursan®) at a dose of 1000 mg/day (for a weight of 64 kg). Corticosteroid therapy (Prednisone®) at an initial dose of 1 mg/kg/day was started concomitantly with Delursan, for a period of 8 weeks followed by a degression. Azathioprine (Imurel®) at a dose of 2 mg/kg/day was started after 2 months of corticosteroid therapy. The Delursan/corticosteroid/azathioprine combination was well-tolerated. The patient had a partial response to 2 months of treatment with a reduction in more than 50% in the ALT (3 × ULN) level and normalization of γGT and alkaline phosphatases. The complete response was obtained after 2 years of treatment with normalization of transaminases, γGT and alkaline phosphatases.

3 | DISCUSSION

We report a case of simultaneous association of primary biliary cholangitis and autoimmune hepatitis. This rarely described entity is a diagnostic and therapeutic problem in the low-income country. Epidemiologically, the frequency of PBC-AIH overlap syndrome (OS) varies from study to study. Thus, it accounts for 4.3 to 9.2% of PBC and approximately 8 to 10% of AIH with variations ranging from 1.9% to 19%.[4,5] This should encourage clinicians to remain vigilant in their diagnosis, due to the therapeutic implications. However, our case was the first reported in Madagascar.

According to the literature, 83 to 100% of patients with PBC-AIH overlap syndrome are woman. The average age was 45 years (38-56 years) in the reported cases and between 44 and 54 years depending on the series.[7,8] Ethnically, the disease appears to be ubiquitous where all races are affected.[8]

The diagnosis of PBC-AIH OS sometimes remains difficult because the clinical manifestations of are not specific. It is mentioned before all cytolytic and cholestatic liver diseases.[7,8] Our patient presented a symptomatic form associating asthenia, jaundice with pruritus. Symptomatic forms are the most frequent.[7,8] In a French study, 82% of cases (9 out of 11) were symptomatic.[7] This percentage was similar to that found in another study by the Mayo Clinic team in Rochester, Minnesota, in which asthenia (76%) and pruritus (57%) frequently occurred.[8] In the absence of validated diagnostic criteria for the diagnosis of PBC-AIH OS, the Paris criteria developed by Chazouillères et al are the most commonly used.[7] The diagnosis would be established in the presence of at least two of three diagnostic criteria recognized for each of the two pathologies (PBC and AIH). Thus, the PBC criteria included: (a) alkaline phosphatases ≥ 2xULN and/or γGT ≥ 5xULN, (b) presence of anti-mitochondria antibodies at a significant level ≥ 1/80th,

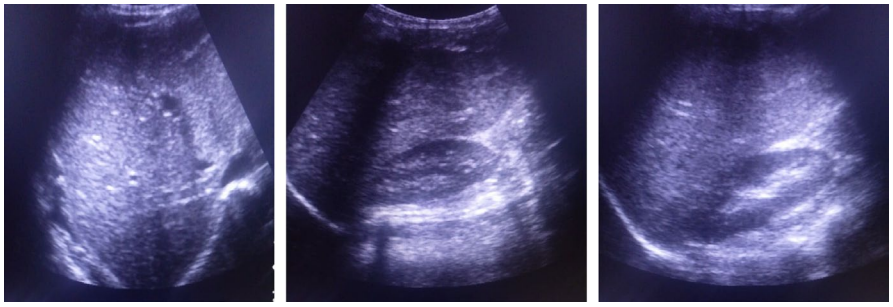

FIGURE 1 Liver ultrasound image of the patient

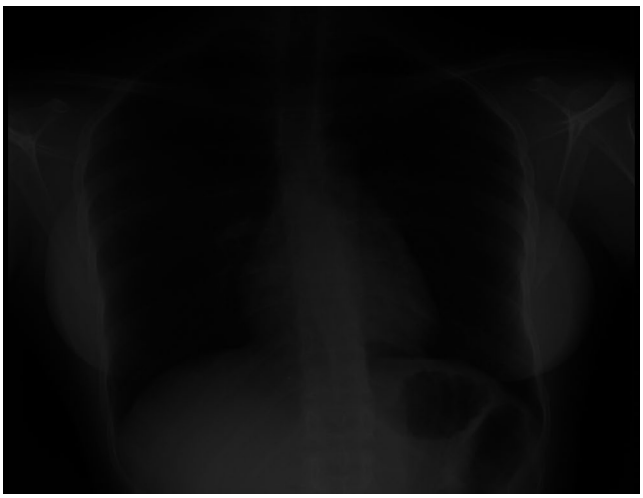

FIGURE 2 Image of the patient's chest X-ray

The absence of a liver biopsy in this observation constitutes a limit for the diagnosis. It is not yet available in Madagascar. EASL recommends performing the liver biopsy puncture because it specifies the presence of interface hepatitis. It is an essential element in the diagnosis of autoimmune hepatitis.[10,11]

According to the literature, the therapeutic choice in the presence of an PBC-AIH OS remains controversial and less well-codified. Randomized controlled trials could not be performed due to the low prevalence of OS.[12] Although UDCA may induce a response in some patients with OS, most require the combination of UDCA and immunosuppressants.[12,13] In the French series, hepatic biology was generally completely normalized only when treatment was combined.[7] A recent meta-analysis confirms the superiority of the combined treatment with UDCA and corticosteroid therapy to treatment with UDCA alone for biochemical improvement, but does not show any improvement in survival without transplantation.[14] Treatments allowing cortisonic sparing are useful in case of prolonged corticosteroid therapy. By extrapolation from studies on AIH, azathioprine is most commonly used. Remission rates fluctuate between 85% and 100% when combined with corticosteroid therapy and UDCA. The definition of remission varies, however, from study to study.[4,7,15,16] The predictors of remission are not well-established. Only Czaja and his collaborators were able to show that the therapeutic response was only complete whether the alkaline phosphatases were initially less than 2xULN.[4] The duration of remission is variable depending on the series or the cases reported. Remission was obtained after 24 months in most of the series or cases

TABLE 1 Paris criteria and the criteria that our case meets

Paris criteria (Chazouillères et al)		Our case
Autoimmune hepatitis	1. Alanine aminotransferase (ALT) ≥ 5 x upper normal limit	Yes
	2. Immunoglobulin G (IgG) ≥ 2 x ULN or presence of anti-smooth muscle antibodies	Yes
	3. Liver biopsy with moderate or severe periportal or periseptal lymphocytic piecemeal necrosis	not available
Primary biliary cholangitis	1. Alkaline phosphatase (ALP) ≥ 2 x upper normal limit or gamma-glutamyl transferase ≥ 5 x upper normal limit	Yes
	2. Presence of AMA	Yes
	3. Liver biopsy with florid bile duct lesions	not available
At least 2 of 3 accepted criteria for PBC and AIH, respectively, should be present.		2 criteria of AIH and 2 criteria of PBC

and (c) hepatic histology showing destructive lymphocytic cholangitis. For HAI, the criteria are (a) ALT ≥ 5xULN, (b) IgG ≥ 2xULN and/or presence of anti-smooth muscle antibodies at a significant rate ≥ 1/80th, and (c) liver histology showing marked periportal and lobular inflammatory lesions. These criteria were used in several cohorts.[7-9] However, it is difficult to determine their performance in the absence of gold standard.[10] In practice, the Paris diagnostic criteria are the easiest to implement because they are both simple and precise. The European Association for the Study of Liver (EASL) approves these criteria.[10,11] Therefore, the diagnosis of an PBC-AIH Overlap syndrome of our patient was retained by the Paris criteria before the association of 2 criteria of primary biliary cholangitis (PBC) and 2 criteria of autoimmune hepatitis (AIH).

reported.[4,7,16,17] Our patient was put on UDCA/Corticoid/azathioprine with a complete remission after 24 months of treatment, confirming the effectiveness of combined treatment.

4 | CONCLUSION

The primary biliary cholangitis-autoimmune hepatitis overlap syndrome of our patient would be the first case reported in our practice. Despite the fact that the treatment of this pathology remains poorly codified, the UDCA/Corticosteroid/azathioprine combination enabled complete remission after 2 years in our case. A large-scale study would be desirable to verify the effectiveness of this treatment in the Malagasy population.

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CONFLICT OF INTEREST

None declared.

AUTHORS CONTRIBUTIONS

Chantelli I. Razafindrazoto: collected data and wrote the manuscript. Andry LR Rakotozafindrabe: conceived the original idea, followed the patient, and revised the manuscript. Nitah H. Randriamifidy: made the bibliographic review. Anjaramalala S. Rasolonjatovo: revised the manuscript. Tovo H. Rabenjanahary: revised the manuscript. Soloniaina H. Razafimahefa: revised the manuscript. Rado M. Ramanampamonjy: revised the manuscript. All authors provided critical feedback and helped shape the manuscript.

ETHICAL STATEMENT

This was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Published with the written consent of the patient.

DATA AVAILABILITY STATEMENT

Data are available on request from the corresponding author.

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