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Primary biliary cirrhosis–autoimmune hepatitis overlap syndrome: Complete biochemical and histological response to therapy with ursodesoxycholic acid

To the Editor,

There are at least three reasons why there is no recognized definition for primary biliary cirrhosis–autoimmune hepatitis (PBC-AIH) overlap syndrome: (i) the syndrome only rarely occurs; (ii) no codified diagnostic criteria are available; and (iii) only retrospectively selected PBC-AIH patients from PBC cohorts have been studied.[1] Because no randomized controlled therapeutic trials have been carried out so far, recommendations for treating PBC–AIH overlap syndrome are usually based on the methods used to treat the two main autoimmune liver diseases separately.

A 48-year-old man with severe fatigue and abnormal liver biochemistry was referred to the hepatogastroenterology unit at Hyères Hospital, France, in May 2003. His serum alkaline phosphatase (ALP) and alanine transaminase (ALT) levels were more than twofold (288 IU/L, N < 136 IU/L) and fivefold (285 IU/L, N < 45 IU/L) higher than normal, respectively. His serum γ-glutamyl transpeptidase levels (GGT, 242 IU/L, N < 55 IU/L), IgG (37 g/L N < 16.4 g/L), and IgM (4.5 g/L, N < 3.1 g/L) were also above normal. Ultrasound examination showed moderate hepatomegaly and ruled out bile tree abnormalities. M2 subtype antimitochondrial antibodies (AMA) were detected by indirect fluorescence and confirmed by immunoblotting (1:640) but neither the antinuclear antibodies (ANA), nor the antismooth muscle antibodies (ASMA) were positive. Histological examination of a liver biopsy (1.3 cm long, six portal tracts, July 2003) showed the presence of a lymphoplasmacytic portal infiltrate, periportal hepatitis with a lymphoplasmacytic necroinflammatory infiltrate and Councilman body, as can be seen in Fig. 1, but ruled out the presence of bile duct damage. Ursodeoxycholic acid (UDCA) alone was prescribed in September 2003 at 15 mg/kg daily. The patient's ALP and ALT levels became normal after 3 months of treatment and stayed normal during the follow-up period. The histological findings on a second liver biopsy (1.2 cm long, six portal tracts) performed after 18 months of treatment (February 2005) showed complete regression of the liver features. A clinical and biochemical assessment performed in July 2005 showed the persistence of moderate fatigue and the liver tests were normal. Finally, a biochemical remission was obtained 3 months after the beginning of the treatment and remained effective during the following 22 months.

Since it was first identified, PBC–AIH overlap syndrome has always been controversial. However, the diagnostic criteria defined by Chazouillères *et al*. seem to be accurate and have been those most frequently used in clinical practice.[2] The diagnostic criteria defined by Chazouillères *et al*. are based on the presence of at least two of the following three types of features characteristic of each disease: biochemical (ALP levels at least twofold and ALT levels at least fivefold the upper normal PBC and AIH values, respectively); immunologic (presence of AMA in the case of BPC, and serum IgG levels at least twofold the upper normal values or the presence of ASMA in that of AIH); and histologic (florid bile duct lesions in the case of PBC and interface hepatitis in that of AIH). In the present case, the patient had all but one (bile duct damage) of the aforementioned diagnostic criteria.

Recommendations for the treatment of PBC–AIH overlap syndrome have not yet been standardized owing to the low prevalence of this autoimmune liver disease. Corticosteroid therapy alone can be effective on patients with both liver features,[1] but two studies have suggested that a combined therapeutic approach using both UDCA and corticosteroid could be more effective than either treatment alone.[2,3] The decision to treat this patient with UDCA alone was made for at least three reasons: (i) the patient refused to undergo corticosteroid therapy after being informed about the potential risk of side-effects; (ii) corticosteroids could still be added if there was no initial biochemical response to UDCA; and (iii) there is recent evidence that UCDA alone can have beneficial effects on patients with PBC–AIH overlap syndrome.[4] The aim of the latter study was to compare the response to UDCA versus placebo in PBC patients with and without features of AIH (12 patients with features of HAI were randomized to UDCA). Patients treated with UDCA had a similar improvement in the biochemical (bilirubin, ALP, aspartate transaminase [AST]) and immunologic markers (IgM) whether or not they had features of AIH. Histologic changes were also assessed in nine UDCA patients with AIH features after 24 months of treatment. Although either an improvement (three patients) in the degree of lobular

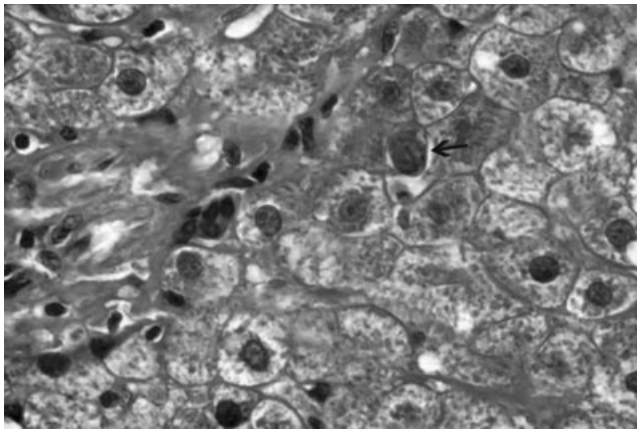

Figure 1 Initial biopsy with a periportal piecemeal necrosis containing a lymphoplasmacytic necroinflammatory infiltrate and Councilman body (arrow).

inflammation or no changes (four patients) were observed, complete normalization of histologic features did not occur in any of them.

To our knowledge, this is the first time that a complete regression of the biochemical and histologic signs has been reported in a PBC–AIH overlap syndrome patient treated with UDCA alone. These findings confirm Heathcote's recommendation that the treatment should start with UDCA alone, and if the biochemical response is not satisfactory, corticosteroid therapy can then be added in tolerable doses.[5] Histological assessments should also be proposed even if there is a good biochemical response, in order to confirm the initial therapeutic decision, as occurred in the present case, or to help make the subsequent decision to add corticosteroids if the histologic features worsen.

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Compound heterozygosity for factor V and methylenetetrahydrofolate reductase mutations in a patient with Budd–Chiari syndrome

To the Editor,

Budd–Chiari syndrome (BCS) is a rare disorder caused by obstruction of hepatic venous outflow, leading to sinusoidal congestion, ischemic injury to liver cells, portal hypertension and progression to cirrhosis.[1] The etiology of BCS is complicated and in approximately 30% of cases the cause is undetermined.[2] Here we report a patient with BCS who was found to be heterozygous for both factor V Leiden and methylenetetrahydrofolate reductase (MTHFR) mutations.

A 36-year-old man was admitted to our institution with hematemesis of 1 day duration. He was a diagnosed case of BCS in an outside hospital in 2002 and was scheduled for liver transplantation. Upon physical examination the patient was jaundiced with icteric sclera. Laboratory findings were as follows: hemoglobin 8.3 g/dL, hematocrit 24.0%, leukocytes 7.5×10^9/L, platelet count 87×10^9/L, total protein 56 g/L, albumin 27 g/L, aspartate aminotransferase 42 U/L, alanine aminotransferase 24 U/L, total bilirubin 2.9 mg/dL, and direct bilirubin 1.5 mg/dL. His prothrombin time was 18.6 s (normal: 11–14 s) and activated thromboplastin time was 32.5 s (normal: 27–36 s). Gastroscopy showed grade III esophageal varices. The patient was transfused with packed red blood cells and fresh frozen plasma. Contrast-based computed tomography (CT) scan showed hepatosplenomegaly with evidence of cirrhosis and portal hypertension. The portal vein was slightly enlarged and the hepatic vein could not be visualized. The appearance was consistent with BCS and liver cirrhosis (Fig. 1).

Work-up for the underlying cause of the patient's disease was carried out. An exhaustive etiological investigation to detect a procoagulable state (fibrinogen level, factors VII and VIII activities, Lupus anticoagulant and anticardiolipin/antiphospholipid antibodies, antithrombin III, protein S, protein C, serology for hepatitis B and C, markers for autoimmune hepatitis, tests for Wilson's disease, hemochromatosis and α_1-antitrypsin) was negative. The patient had no family history of thrombosis. Polymerase chain reaction (PCR) analysis documented heterozygosity for both factor V Leiden and MTHFR mutations (Fig. 2). DNA was extracted from the sample according to the extraction protocol supplied by the manufacturer (Factor V StripAssay by ViennaLab, Vienna, Austria). Briefly, 100 µL of blood sample was lyzed twice in red blood cell lysis buffer. The reaction tubes were run at the following conditions: 94°C for 2 min followed by 30 cycles of 94°C for 15 s, 58°C for 30 s, and 72°C for 30 s. Hybridization of

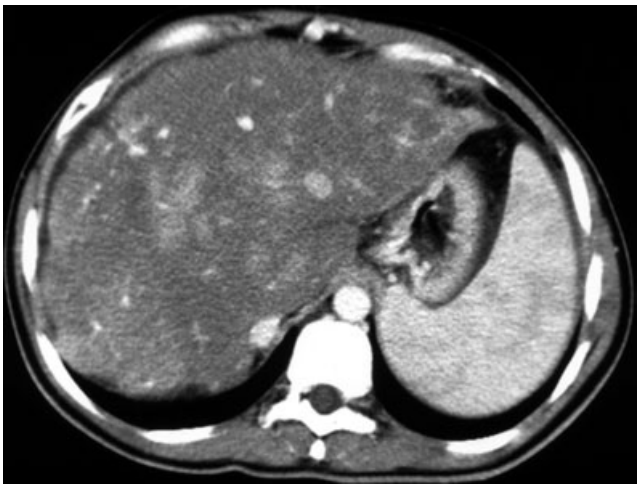

Figure 1 Computed tomography scan of the abdomen showing hepatosplenomegaly. The liver is heterogeneous with an irregular contour. The hepatic vein could not be visualized.