

## Autoimmune hepatitis – primary biliary cirrhosis and overlap syndrome: A case report

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### ABSTRACT

Important immune-mediated liver illnesses include autoimmunity hepatitis (AIH) and primary biliary cirrhosis. Typically, they are distinguished based on histological, biochemical, serological, and clinical parameters. Diagnostic criteria for many conditions are typically met by patients with autoimmune liver disease. The diagnosis of AIH/primary sclerosing cholangitis overlap is based on a mix of biochemistry, autoantibody profile, cholangiogram, and liver histology; there are no universally accepted criteria for this. The patient can remain asymptomatic or present with pruritis and jaundice. Diagnosis is through liver biopsy showing bile duct destruction and proliferation. The treatment is by high-dose ursodeoxycholic acid.

**Key words:** Autoimmune hepatitis, Liver biopsy, Liver function test, Primary biliary cirrhosis, Primary sclerosing cholangitis

The three major immune disorders of the liver are autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC) [1]. Variant forms of these diseases are generally called overlap syndromes, although there has been no standardized definition. Patients with overlap syndromes present with both hepatitis and cholestatic serum liver tests and have histological features of AIH and PBC or PSC [2]. An essential differential diagnostic in the difficult-to-treat patient with AIH is the presence of incompletely characterized syndromes.

### CASE REPORT

A 70-year-old male was admitted to the medicine ward with complaints of swelling of both feet, yellowish discoloration of eyes, along with a history of passing highly colored urine. The swelling was until the ankles which progressed to the knees. His personal medical history revealed that the patient had hypertension for the past 7 years and is on regular medications (calcium channel blocker). There was no history of alcohol consumption, drug abuse, or relevant family history of liver disease.

On physical examination, vitals were within normal limits. His skin and sclera were icteric. There was grade 1 pedal edema with minimal ascites; however, the abdomen was soft and non-tender. Other systemic examinations such as the central nervous

system, cardiovascular system, and respiratory system were found to be normal.

Laboratory tests showed that the total serum bilirubin was 35 mg/dl, direct–15 mg/dl, indirect – 20 mg/dl, alkaline phosphatase (ALP) was 970 IU/L (normal <130 IU/L), alanine aminotransferase was 937 IU/L (normal <40 IU/L), aspartate aminotransferase was 477 IU/L (normal <40 IU/L), erythrocyte sedimentation rate was 18 mm/h, serum albumin was 3.3 g%, immunoglobulin G (IgG) level was 4.8 g/dl, hemoglobin was 12 g/dl, total white blood cell was 7000/mm<sup>3</sup>, the differential count was P 68.3/L, 23.3/E, 1.1/M, 6.6%, platelet count was 210000/mm<sup>3</sup>, and serological tests for viral hepatitis A, B, C, and E were negative. Antinuclear antibody (ANA) immunofluorescence on HEP-2 and rat liver cells showed mixed pattern ANA and anti-cytoplasmic antibodies. It was strongly positive with a titer of >1:3200 showing positive for nuclear membrane with nucleus dotted (+++) and anti-mitochondrial antibodies (AMA) (+++). The ANA profile and liver profile also showed AMA-M2 (+++); anti-neutrophil cytoplasmic antibody was negative. Serum AFP and CEA were also normal. An autoimmune workup was done which included anti mitochondrial antibody, anti-LKM, and anti-SMA all of which were negative.

Ultrasound of the abdomen revealed enlarged liver, homogenous echotexture with dilatation of the proximal common bile duct (CBD) with smooth tapering of distal CBD, while the spleen was normal in size with normal portal vein size and flow. Ascites was present which was minimal. Contrast-enhanced

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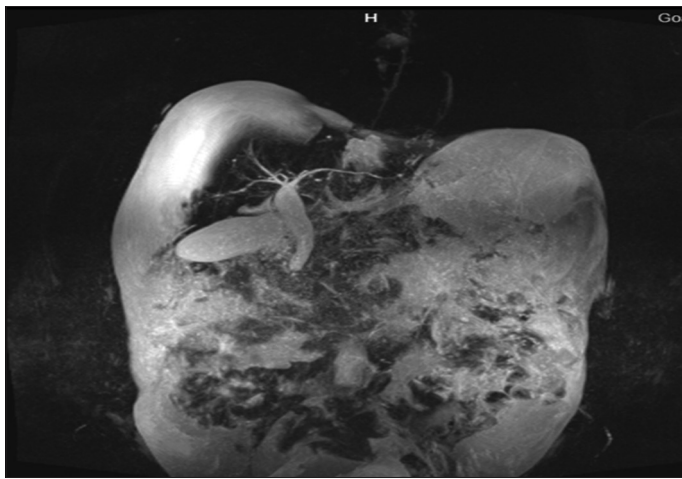
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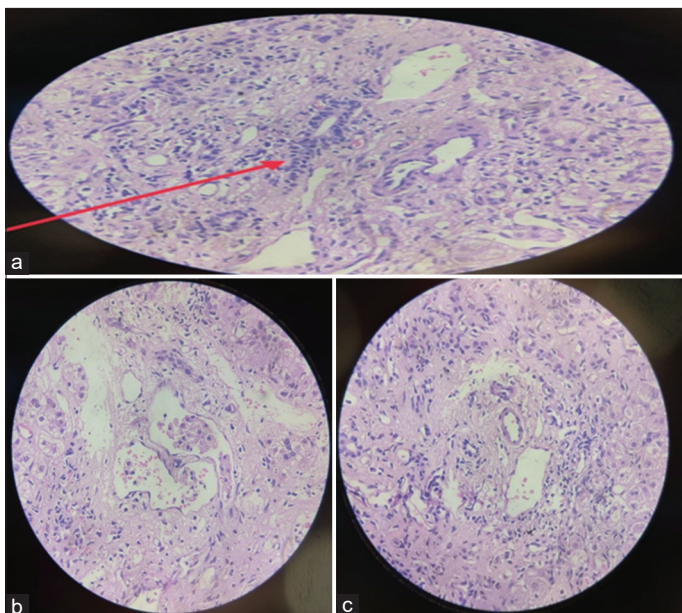
computed tomography abdomen revealed similar findings with extra-hepatic duct mildly dilated with no features of cholangitis. Magnetic resonance cholangiopancreatography (MRCP) revealed dilated common and hepatic duct dilatation with the distal end of CBD showing smooth tapering without any evidence of intrahepatic biliary radical dilatation, as shown in Fig. 1.

A liver biopsy revealed chronic hepatitis with cirrhosis with bile duct destruction with moderate cholestasis. Destruction of bile ductular epithelium with inflammatory cells was seen. Proliferating bile ductules were also seen. Features of interface hepatitis characteristic of AIH were seen. Based on clinical, biochemical, radiological, and histological findings (Fig. 2), a diagnosis of seronegative overlap hepatitis with early cirrhosis without portal hypertension is made which is not found in hepatic encephalopathy.

The patient was treated with ursodeoxycholic acid (UDCA) – 150 mg BD and methylprednisolone his condition



**Figure 1:** Magnetic resonance cholangiopancreatography image showing dilatation of common bile duct with smooth tapering of intrahepatic bile ductules



**Figure 2:** (a) Red arrow showing proliferative bile ductile; (b) Complete destruction of bile ductile; (c) Portal triad with inflammatory infiltrate

improved gradually. There was normalization of liver enzyme and excellent response to steroids (table before and after).

## DISCUSSION

The overlap syndromes occur in 3–7% of patients with autoimmune liver disease and the frequency of each overlap combination (outside PBC and PSC) is similar, regardless of the predominant disease component [3].

A label of AIH/PSC overlap may be present in up to 12.5% of cohorts with AIH and PSC. The two disorders can have a long time between diagnoses, and it is unknown what order they will be given. When used for patients with AIH/PSC overlap, diagnostic criteria that have been validated for AIH are problematic. A positive diagnosis of AIH/PSC overlap impacts therapeutic options and prognosis. There is a beneficial role for immunosuppression, although with a higher relapse rate and evidence of progressive liver disease despite immunosuppression in some cases. Liver-related outcomes sit somewhere between the constituent diseases, with better outcomes than PSC but poorer outcomes than AIH. There is an increasing body of data for patients with AIH/PSC overlap undergoing liver transplantation for end-stage disease. Nearly, half of patients with autoantibody-positive liver disease in childhood have autoimmune sclerosing cholangitis (ASC). ASC patients are differentiated from those with AIH by having abnormal cholangiograms. Histological analysis shows chronic hepatitis in <50% of ASC cases. The biochemical response to immunosuppression in ASC patients is less than that seen in AIH patients and cholangiograms commonly show progressive disease. Transplant-free survival of the ASC population is poorer than in AIH overlap syndrome with AIH and PSC [1]. Most patients show antibodies against mitochondrial antigens. Female predominance exists up to 90%.

PBC, also known as chronic non-suppurative destructive cholangitis, is a disease mainly involving intrahepatic bile ducts. The treatment of the patient with UDCA can slow down the course of the disease, but till today, no drug is available which can stop the progression of PBC. Overlap syndrome is the term used for patients presenting with features of disorders within the spectrum of autoimmune liver diseases (i.e., AIH, PBC, and PSC). Overlap syndrome lacks specific definitions [3]. In the present case for AIH, the criteria met included serum IgG levels 2 times the upper limit of normal, strongly positive for ANA, and liver biopsy showed interface hepatitis. For PBC, the criteria met included serum tests strongly positive for AMA-M2 and nuclear membrane and liver biopsy showing bile duct lesions. For these reasons, overlap syndrome was diagnosed [4].

PBC, in genetically predisposed patients of AIH, can flare up autoimmune destruction of bile ducts which result in the mixed clinical presentation of AIH and PBC in such patients. PBC enhances the autoimmune mechanism and genetic predisposition, along with resulting inflammatory hepatitis with most of the features of AIH. However, it is not sure whether this categorization is clinically significant or not. One study has suggested that PBC

patients with superimposed features of AIH progress rapidly to cirrhosis and liver failure, whereas another study found that patients with overlap syndromes were more likely to develop esophageal varices, ascites, and liver failure compared to patients with typical PBC. In the present case study, we observed both findings. A study of more cases is required to find whether these groups have different natural histories and responses to treatment [2].

Immunosuppression is considered as a standard effective therapy for AIH and UDCA is recommended to slow down the progression of PBC. A complete clinical and biochemical response is achieved in patients after using a combination therapy of UDCA and corticosteroids. A study done by Aguilar-Nájera *et al.* [5] showed that administration of oral steroids in patients with PBC is associated with systemic side effects and significant worsening of osteoporosis; so, they should be used cautiously. On the other hand, studies have shown that UDCA is helpful in patients diagnosed only with AIH and patients of PBC with associated features of AIH. Based on the risks and benefits of different treatment strategies, the majority think that the trial of corticosteroids is a genuine approach in the treatment of patients with overlap syndrome. Only a small number of patients will be benefitted from the improvement of biochemical and histopathological parameters. Steroids should be discontinued if the serum level of liver enzymes does not improve and then treatment should be started with UDCA [6]. Liver biopsy is not necessary to confirm the diagnosis in most patients with PBC and should be performed in only the minority of AMA-positive patients with a serum ALP level <1.5 times normal or a serum AST level >5 times normal. The preliminary lesion on a liver biopsy specimen in PBC is damage to epithelial cells of the small bile ducts. The most essential and solely diagnostic clue in many instances is ductopenia, described as the absence of interlobular bile ducts in increased than 50% of portal tracts. The florid duct lesion, in which the epithelium of the interlobular and segmental bile ducts degenerates segmentally, with the formation of poorly defined, non-caseating epithelioid granulomas, is nearly diagnostic of PBC but is determined in an exceedingly small number of cases, basically in the early tiers.

An advantageous dose of UDCA (13–15 mg/kg/day) has been used in patients with interface hepatitis and inflammation. UDCA has been shown genuinely to enhance survival free of a liver transplant. The treatment with UDCA leads to fast enhancement in liver biochemical take a look at tiers and a decrease in the histologic severity of interface hepatitis, inflammation, cholestasis, bile duct paucity, and bile duct proliferation [7]. AMA-negative PBC is the designation for these patients who clinically, biochemically, and histologically show up to have the basic facets of PBC, however, are located now not to have AMA in serum by way of indirect immunofluorescence or immunoblotting techniques. Of sufferers

who have PBC through all other criteria, 5% are confirmed AMA negative [8]. The absence of AMA makes liver biopsy obligatory to appear for points of PBC and rule out different liver diseases. Furthermore, imaging through MRCP is necessary to discover different cholangiopathies such as fundamental sclerosing cholangitis. Liver biopsy and MRCP, alongside selected laboratory tests, will enable the exclusion of conditions that have to be regarded in the differential diagnosis, such as celiac disease, hepatitis C, sarcoidosis, small-duct PSC, and IgG4-associated autoimmune cholangitis. Patients with AMA-negative PBC must be handled with UDCA in a dose of 13 to 15 mg/kg/day. When histologic features of superimposed AIH are detected, the mixture of glucocorticoids and UDCA should be regarded.

## CONCLUSION

AIH-PBC is one of the most common overlap syndromes and should always be kept in mind by clinicians while diagnosing AIH. Neither the diagnostic criteria nor the treatment strategy for this variant of PBC is standardized, but the early diagnosis of overlap syndrome can lead to a better prognosis for the patient. The treatment options available till now are UDCA, corticosteroids, and liver transplantation. Last but not the least, the early diagnosis and intervention of this condition are required for the better outcome of the patient.

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