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Case Report

Internal Medicine Section

Autoimmune Hepatitis – Primary Biliary Cirrhosis Overlap Syndrome

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ABSTRACT

Autoimmune Hepatitis (AIH) and Primary Biliary Cirrhosis (PBC) are important immune mediated liver diseases. They are usually differentiated based on clinical, biochemical, serological and histological parameters. The presence of autoantibodies, clinical and serological findings can sometimes occur in different combinations leading to overlap syndromes, which is rare. Early recognition of such overlap syndromes is clinically significant from treatment point of view. Here, we report a case of AIH-PBC overlap syndrome with a brief review of literature on overlap syndromes.

Keywords: Antinuclear antibodies, Antimitochondrial antibodies, Immunofluorescence, Primary sclerosing cholangitis

CASE REPORT

A 50-year-old female was admitted to the medicine department with complaint of hematemesis for past 10 days. Her personal medical history revealed that she is a known case of hypertension since five years and diabetes mellitus since six months and on regular medications (β-blocker and insulin). There was no history of alcohol consumption, drug abuse or relevant family history of liver disease.

On physical examination, vitals were within normal limits. Her skin and sclera were icteric. On examination of abdomen, a nontender hepatomegaly was evident 6 cm below the right costal margin and splenomegaly, palpable 3 cm below the left costal margin. Other systemic examinations such as of the central nervous system, cardiovascular system and respiratory system were found to be normal.

Laboratory tests showed: Serum bilirubin: Total - 3.4 mg/dl, direct - 2.7 mg/dl, indirect - 0.7 mg/dl, alkaline phosphatase (ALP) - 541 IU/L (normal <130 IU/L), alanine aminotransferase - 49 IU/L (normal <40 IU/L), aspartate aminotransferase - 137 IU/L (normal <40 IU/L), international normalized ratio was 1.01, erythrocyte sedimentation rate - 60 mm/h, serum albumin - 4.8 g%, immunoglobulin G (IgG) level - 4.8 g/dl, hemoglobin - 9.3 g/dl, total white blood cell - 7400/mm^3, differential count - P 68.3/L 23.3/E 1.1/M 6.6%, platelet count - 210000/mm^3 and serological tests for viral hepatitis B and C were negative.

Antinuclear Antibody (ANA) immunofluorescence on HEP-2 and rat liver cells as shown in [Table/Fig-1,2] showed mixed pattern ANA and anticytoplasmic antibodies. It was strongly positive with a titer of >1:3200 showing positive for nuclear membrane with nucleus dotted (+++) and antimitochondrial antibodies (AMA) (+++). The ANA profile and liver profile also showed AMA-M2 (+++); Anti neutrophil cytoplasmic antibody (ANCA) was negative.

Ultrasonography was suggestive of hepatosplenomegaly and cirrhosis of the liver with portal hypertension. A liver biopsy showed moderate mixed portal and mild lobular inflammation with mild interface activity, mild reduction in interlobular bile ducts, periportal Mallory's hyaline with xanthomatous transformation, significant stainable copper-associated protein deposits and moderate portal and periportal focal bridging fibrosis. Histological features were suggestive of a chronic cholestatic process. Upper gastrointestinal endoscopy was suggestive of small and large esophageal varices, which was managed by endoscopic variceal ligation. Gastric biopsy specimen showed *Helicobacter pylori* induced gastritis, for which patient was receiving tablet pantoprazole 40 mg twice daily. The clinical, biochemical, serological and histopathological findings were suggestive of direct hyperbilirubinemia with raised levels of ALP with hyperglobulinemia, strongly AMA-M2 and ANA positive, histopathological examination was compatible with PBC. A diagnosis of PBC-AIH overlap syndrome was made depending on these findings.

The patient was treated by Ursodeoxycholic Acid (UDCA) – 150 mg BD and her condition improved gradually. Then, the patient reported after six months and her condition was still the same.

DISCUSSION

The major autoimmune disorders of the liver are AIH, PBC and Primary Sclerosing Cholangitis (PSC); variants are called overlap syndromes. The overlap syndromes occur in 3%-7% of patients with autoimmune liver disease and the frequency of each overlap combination (outside PBC and PSC) are similar, regardless of the predominant disease component [1]. AIH and PBC both are the most common hepatopathies. Although the mechanism of both is same, they can be differentiated based on clinical features, biochemical tests, serological markers, histopathology, course of the disease and treatment outcomes. AIH is a chronic inflammatory disease of the liver of unknown aetiology. It usually affects females of all age groups. Pathogenic mechanisms include environmental triggering factors (e.g., alcohol consumption and drug-induced hepatotoxic drugs), failure of immune tolerance mechanisms and genetic predisposition. All these factors collectively initiate a T-cell-mediated immune attack on liver antigens, leading to progressive inflammatory and fibrotic changes [2]. PBC is a chronic cholestatic disease of autoimmune aetiology that affects mainly females of middle age. AMA is a significant serologic marker of the disease, which is present in at least 90% of the patients [3]. In patients with a diagnosis of AIH, possibility of an overlap syndrome should be ruled out if cholestatic features are present.

Autoimmune Hepatitis

AIH is a chronic inflammatory disorder characterized by periportal inflammation, hypergammaglobulinemia, circulating autoantibodies and necrosis of the liver. It can affect any age group. It mainly affects young females. The majority of patients have autoantibodies such as ANA, soluble liver antigen and liver kidney microsomal antibody. In hypergammaglobulinemia, mainly IgG levels are raised. On histopathological examination, interface hepatitis is hallmark of the disease but the finding may differ depending upon course of the

disease. These cases have favorable response to steroid therapy resulting in better prognosis [3].

Primary Biliary Cirrhosis

PBC, also known as chronic nonsuppurative destructive cholangitis, is a disease mainly involving intrahepatic bile ducts. Its diagnosis is based on cholestatic serum enzyme pattern, serum AMA and PBC-specific AMA-M2 and a compatible histology (which includes bile duct lesions). 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 [3].

Primary Biliary Cirrhosis/Autoimmune Hepatitis Overlap

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 [4].

The AIH-PBC overlap syndrome is accepted when two or three criteria for PBC and AIH are fulfilled [Table/Fig-3] [5].

In the present case for AIH - the criteria met included serum IgG levels two times the upper limit of normal (ULN), strong positive for ANA and liver biopsy showing 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.

PBC in genetically predisposed patients of AIH can flare up autoimmune destruction of bile ducts which results in 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 [6].

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 [5]. Whereas, another study found that patients with overlap syndromes were more likely to develop esophageal varices, ascites, liver failure compared to patients with typical PBC [7]. In the present case study, we observed both the findings. Study of more cases is required to find whether these groups have different natural history and response to treatment.

Diagnosing an overlap syndrome has therapeutic implications. Immunosuppression is considered as standard effective therapy for AIH and UDCA is recommended to slow down the progression of PBC [4]. A complete clinical and biochemical response is achieved in patients after using combination therapy of UDCA and corticosteroids [5,8].

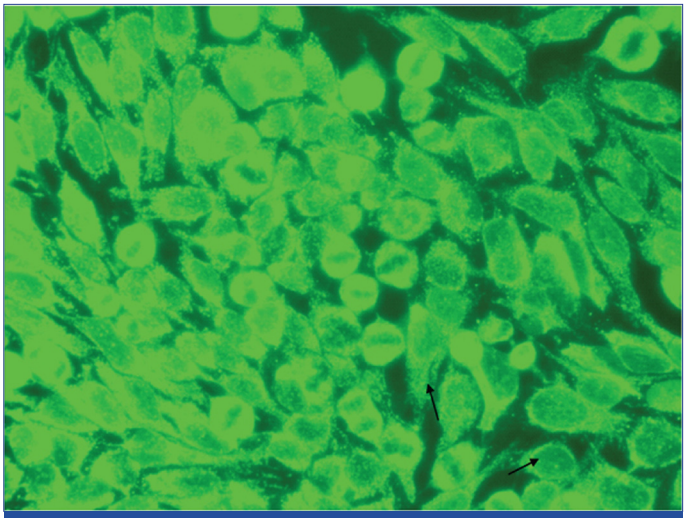
Study done by Angulo P et al. showed that administration of oral steroids in patients with PBC is associated with systemic side effects and significant worsening of osteoporosis; so, they should be used cautiously [9]. On the other hand, studies have shown that UDCA is helpful in patients diagnosed only with AIH and patients of PBC with associated features of AIH [10].

Based on the risks and benefits of different treatment strategies, the majority think that trial of corticosteroids is a genuine approach in the treatment of patients with overlap syndrome.

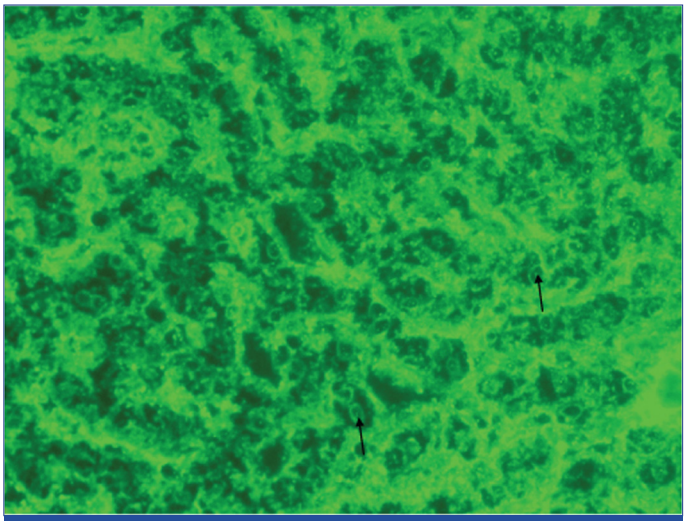
Only a small number of patients will be benefitted with improvement of biochemical and histopathological parameters. Steroids should be discontinued if serum level of liver enzymes does not improve and then treatment should be started with UDCA [11].

Treatment with UDCA may delay disease progression and prolong survival.

Recognition of overlap syndromes could have a significant impact in the treatment of patients who have inadequate response with therapy employed for any autoimmune liver disease, leading to overall improvement of survival and decrease the need of liver transplantation [7].



[Table/Fig-1]: Antinuclear antibody immunofluorescence on HEP-2 cell line showing nucleus dotted andcytoplasm coarse granular (↗).



[Table/Fig-2]: Antinuclear antibody immunofluorescence on rat liver cell showing nuclear membrane pattern (↗).

AIH (2 out of 3 criteria)
1. ALT levels>5× ULN value
2. Serum IgG levels>2× ULN or a positive test for ASMA
3. Liver biopsy showing moderate or severe periportal or periseptal lymphocytic piecemeal necrosis OR Liver biopsy showing interface hepatitis - a typical finding of AIH [4].
PBC (2 out of 3 criteria)
1. ALP levels>2 × or GGT levels>5 × ULN
2. Positive test for AMA
3. Liver biopsy specimen showing florid bile duct lesions

[Table/Fig-3]: Diagnostic criteria of AIH-PBC overlap syndrome proposed by Chazouilleres et al., in 1998 [5].

Abbreviations: ULN: Upper limit of normal, ASMA: Anti smooth muscle antibodies, GGT: γ-glutamyltranspeptidase, IgG: Immunoglobulin G, AIH: Autoimmune hepatitis, ALT: Alanine aminotransferase, PBC: Primary biliary cirrhosis, ALP: Alkaline phosphatase, AMA: Antimitochondrial antibodies

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 early diagnosis of overlap syndrome can lead to better prognosis of the patient. Till now treatment options

available are UDCA, corticosteroids and liver transplantation. Last but not the least, early diagnosis and intervention of this condition are required for the better outcome of the patient.

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