Case Report

Overlap Syndrome of Autoimmune Hepatitis and Primary Biliary Cirrhosis: A Clinical Enigma

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Abstract

"Overlap syndrome" is a term used to describe variant forms of autoimmune hepatitis (AIH) which present with characteristics of AIH and primary biliary cirrhosis (PBC) or primary sclerosing cholangitis (PSC). Patients with overlap syndrome present with both hepatitic and cholestatic serum liver test and the clinical, biochemical, and histological features of these autoimmune diseases are overlapped. Thus, it is difficult to appreciate overlap syndrome as an actual diagnostic entity. AIH-PBC is the most common form of overlap syndrome, affecting almost 10% of adults with AIH or PBC. Transitions from PBC to AIH-PBC overlap syndrome have also been reported. Ursodeoxycholic acid is usually combined with immunosuppressive therapy but end-stage disease requires liver transplantation. We present a case of Overlap Syndrome (AIH-PBC) in a 16 year old girl who presented to us with features of obstructive jaundice. She had six months history of generalised itching, yellow discoloration of skin and urine, decreased appetite and intermittent abdominal pain. Liver function test revealed conjugated hyperbilirubinemia, with moderate elevation of liver enzymes. Antinuclear, anti-muscle M2 and anti-glycoprotein 210 antibodies were positive. Liver biopsy showed features of primary biliary cirrhosis. The patient responded to ursodeoxycholic acid and immunosuppression.

Keywords: Autoimmune hepatitis, Primary biliary cirrhosis, Primary sclerosing cholangitis, Overlap syndrome

Introduction

Overlap Syndromes (OS) are conditions in which patients have demonstrated autoimmune hepatitis (AIH) and also meet the clinical and histological criteria for primary biliary cirrhosis (PBC) or primary sclerosing cholangitis (PSC).[1,2,3] Overlaps among the three major autoimmune liver diseases, AIH, PBC, and PSC have been described various times since 1970. The AIH-PBC combination is more common in adults, whereas the AIH-PSC overlap usually occurs in children, adolescents, and young adults.[4,5] The prevalence of the AIH-PBC overlap varies. Approximately 4.8 to 19% of all patients with PBC have features of AIH, whereas 5% to 8.3% of all patients with AIH present with features characteristics of PBC.[6,7] These variations can be explained by the fact that criteria for OS have not been defined, so all studies do not share the same diagnostic criteria.

Case Presentation

A 16 year old female presented to our hospital with history of itching all over the body, yellowish discoloration of skin and urine, decreased appetite and intermittent abdominal pain since last 6 months. The itching was generalised with

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no localized infection or eczema, and not associated with dryness of skin. No history of passage of worms in stool. It also didn't start after intake of any drugs. She also had decreased appetite and weight loss of more than 10% of body weight in the last 6 months. There was no history of hematemesis, or melena. She did not give history of high risk behaviour, blood transfusion, needle prick injury or any hepatotoxic drug intake. She also had recurrent, right hypochondrial pain which was dull aching not associated with vomiting, skin rashes, oral ulcers, joint pain, or bloody diarrhoea. No history suggesting of connective disease disorder or autoimmune disease. Before presenting to our hospital she had consulted many private and government hospitals. There was no history of previous hospitalization or any surgical interventions.

Clinically the patient was thin built, poorly nourished, and deeply jaundiced with scratch marks present on abdomen and back. On general physical examination she had icterus but no spider nevi, palmar erythema, or duptyrens contracture. There was no pallor, cyanosis, clubbing, lymphadenopathy or pedal edema. On systemic examination liver was palpable 4 cm below right costal margin with a span of 16 cm, non-tender, smooth surface and rounded border. Free fluid was not present in abdomen.

Investigation

Patient had a few laboratory reports with her before coming to us. Haemoglobin was 11.2 g/dl, total leukocyte count 8000/dl, total bilirubin of 16.80 mg/dl (direct 9.60, indirect 7.20), SGPT 192 U/L, SGOT 177 U/L, alkaline phosphatase 340 U/L. HBsAg and serology for HIV, HAV, HCV and HEV were non-reactive. At admission to our hospital her bilirubin was 28.9 mg/dl with a direct fraction of 26.2 mg/dl, SGOT 171 U/L (reference 15-35 U/L), SGPT 186 U/L (reference 15-35 U/L) and alkaline phosphatase of 360 U/L (reference 50-120 U/L) and Gamma Glutamyl Transferase (GGT) was 47 U/L (reference value 5-36 U/L). Lipid profile showed moderately increased triglyceride level of 345 mg/dl (reference value 50-200 mg/dl). Both direct and indirect Coomb's tests were negative. Lactate dehydrogenase (LDH) was 611 U/L (reference 220-600 U/L). Pan-malarial antigen and RK-39 antigen tests were negative. Thyroid profile was normal. Iron profile including ferritin and urinary copper excretion were normal. Rheumatoid factor and C-reactive protein were negative. Immunoglobulin G was increased (1811 mg/dl) with a normal IgM level. ANA was positive in dilution of 1:40 but cANCA, pANCA, Anti-LKM, and anti-smooth muscle antibody were negative. Nuclear antigen line assay showed an anti-muscle antibody M2 (4+) and anti-glycoprotein 210 (4+) highly positive. Coagulation profile was normal. USG abdomen showed an enlarged non-coarsened liver with normal pancreatico-biliary system. Contrast-enhanced CT abdomen showed an enlarged liver with subcentimetric lymph nodes. Upper gastrointestinal endoscopy was normal. MRCP showed evidence of primary biliary cirrhosis. Liver biopsy showed interface hepatitis, fibrous expansion of portal tracts with inflammatory infiltrates (figure 1), canalicular cholestasis (figure 2), bile duct injury with pseudorosseting (figure 3) and Mallory hyaline bodies. Ductal proliferation and fibrous expansion of portal tracts was better seen in Masson's trichrome stain (figure 4). No granuloma was seen and staining for acid fast bacilli was negative. A diagnosis of "Overlap Syndrome" was made with features of both primary biliary cirrhosis and auto immune hepatitis, using the diagnostic criteria.[8]

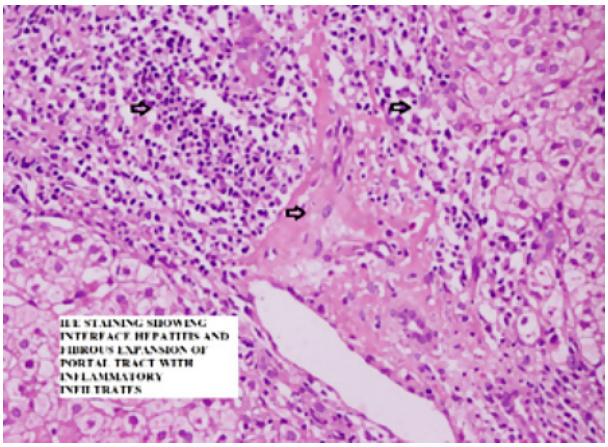

Figure 1.HE staining showing interface hepatitis and fibrous expansion of portal tracts with inflammatory infiltrates (arrows)

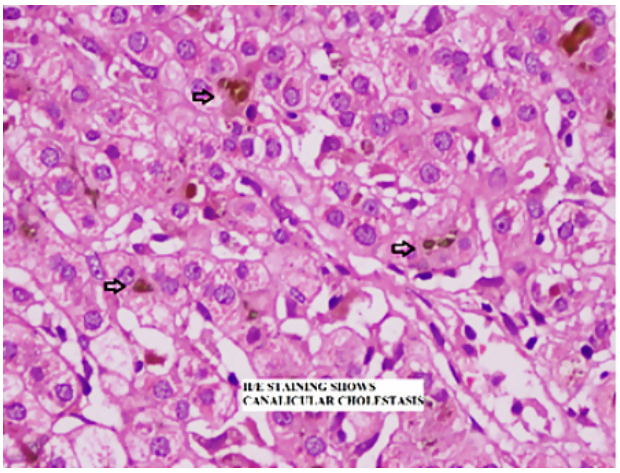

Figure 2.HE staining showing canalicular cholestasis (arrows)

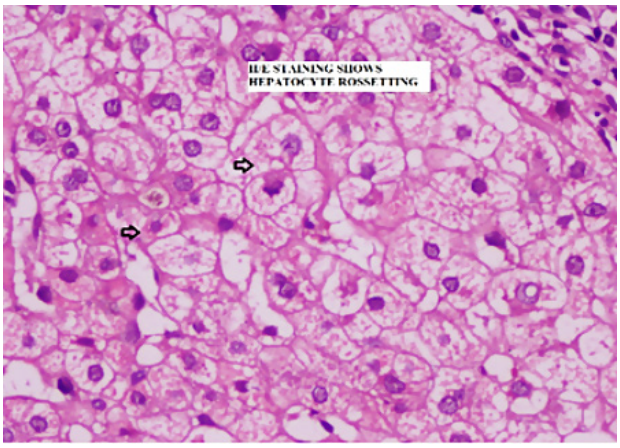

Figure 3.HE staining showing hepatocyte pseudorossetting (arrows)

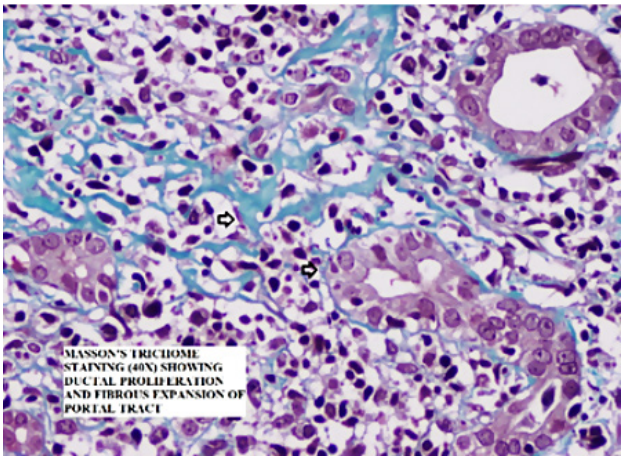

Figure 4.Masson's trichrome staining (40x) showing ductal proliferation and fibrous expansion of portal tracts (arrows)

Treatment, outcome and Follow-Up

Once the diagnosis was confirmed she was given ursodeoxycholic acid, prednisolone and azathioprine in standard doses. There was a remarkable improvement seen after a repeat LFT with a decrease in bilirubin level from 28.9 to 14.7 mg/dl and improved SGOT, SGPT and ALP levels. Patient is in regular follow up.

Discussion

PBC and AIH are the most frequent autoimmune liver disease with a female preponderance. Clinical presentation depends on predominant component of disease. Patients with overlap syndromes usually present with nonspecific symptoms, including fatigue, arthralgia, myalgia, jaundice and pale stools. Serum liver tests typically show a hepatitic pattern in AIH and a cholestatic pattern with marked

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elevation of ALP and GGT, but mild elevation of serum transaminases in PBC. While serum IgG is the predominant immunoglobulin elevated in AIH, serum IgM is elevated in most patients with PBC. Patients presenting with clinical, biochemical, serological and histological features of both these diseases have been reported and described as "overlap syndrome". The predominant disease component determines the nature and behaviour of the overlap syndrome.[9] An overlap syndrome should be suspected in all patients with predominant manifestations of AIH, PBC, who have atypical findings. The Paris criteria provide an objective basis for making the diagnosis of the overlap syndrome of AIH and PBC. It has a sensitivity of 92% and a specificity of 97% with clinical judgment as the gold standard.[10,11]

These criteria have been endorsed by the European Association for the Study of the Liver (EASL) with the stipulation that all patients have interface hepatitis on histological examination.[12] Patients outside the Paris criteria may have less severe forms of the AIH-PBC overlap syndrome, and they should not be excluded from the diagnosis. Patients may also have features of AIH and a cholestatic phenotype in the absence of classic features of PBC. These patients lack AMAs, and they have a normal cholangiogram. The histological findings of bile duct injury or loss suggest an overlap syndrome, and they may have AMA-negative PBC. The various scoring systems for AIH should not be used to diagnose the overlap syndromes. These systems were not designed for this application, and their ability to demonstrate AIH in patients with cholestatic liver disease is poor (sensitivity55%-62%). The liver biopsy examination is the strongest independent predictor of an overlap syndrome, and clinical judgment is the gold standard for the diagnosis.[13]

Recommendations for the treatment of PBC–AIH overlap syndrome have not yet been standardized owing to the low prevalence of this autoimmune liver disease. 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. Ursodeoxycholic acid (13-15 mg/kg daily) is usually given primarily. However, if this therapy does not induce an adequate biochemical response in a 3 months period or in patients with predominantly hepatitic serum liver tests, a corticosteroid should be added.[14] Prednisone has been used at an initial dose of 0.5 mg/kg daily and should be progressively tapered once ALT levels show a decrease response. The role of other immuno-suppressants, like azathioprine in the long-term management of patients with AIH-PBC overlap syndrome is unclear, but it is an alternative to corticosteroids for long-term immunosuppressive therapy. Budesonide and cyclosporine A has also been used in patients with AIH-PBC overlap syndrome with success.[15] Liver transplantation is regarded as the treatment of choice for end-stage disease.

Conclusion

Occurrence of autoimmune hepatitis and primary biliary cirrhosis in a same patient is rare. Occurrence of both AIH-PBC in young patient is even more rarer. We should suspect overlap syndrome in female patients with clinical and laboratory features of both hepatitis and obstructive jaundice so that timely intervention may slow down/stop the progression to end-stage liver disease.

Conflict of Interest: None

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