Primary Biliary Cirrhosis- Autoimmune Hepatitis Overlap Syndrome

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INTRODUCTION

Primary biliary cholangitis-autoimmune hepatitis overlap syndrome is a variant form of immunologically mediated hepatitis in which clinical and immunological features are suggestive of primary biliary cholangitis but histological evidence is in favour of autoimmune hepatitis. About 1% to 14% of patients with primary biliary cholangitis have evidence of autoimmune hepatitis. Primary biliary cholangitis-autoimmune hepatitis overlap syndrome has to be differentiated from classical primary biliary cholangitis as treatment is different and greater progression of disease to cirrhosis is seen in overlap syndrome, thus requiring frequent monitoring of liver biochemical functions.

PRESENTATION OF CASE

A 42-year-old female presented with complaints of fever for 5 days, with history of easy fatiguability for past 1-year worsening over the last 2 months associated with generalised pruritis all over her body which worsened during the night for same duration. She is a known case of diabetic mellitus, systemic hypertension with grade 2 retinopathy changes and chronic kidney disease. On examination she was febrile at presentation with tachycardia of 113 beats/min. systemic examination was unremarkable with no localising signs for fever. On initial evaluation for fever aetiology she was positive for scrub typhus and was treated with doxycycline 100 mg twice daily, after which she remained afebrile.

Investigation performed on admission revealed an isolated elevation of alkaline phosphatase (ALP) levels with other liver parameters with in normal limits. Liver function tests performed during the stay at the hospital, she had persistent isolation elevated ALP levels with other liver parameters being normal .Review of patient past medical records also revealed an isolated elevation in ALP levels. After review of her past medical records it was evident that she had isolated ALP levels for more than a year duration Gamma-glutamyl transpeptidase (GGT) levels was found to be elevated (134 IU/L), suggesting ALP source being hepatic in origin. Serial values of liver function tests are mentioned in table 1. Vitamin D was 48 ng/ml, with in normal limits.

	14/8/2018	14/9/2019	17/9/2019	21/9/2019	5/10/2019
Total bilirubin (mg/dl)	0.56	0.95	0.66	0.69	0.49
Direct bilirubin (mg/dl)	0.10	0.34	0.32	0.27	0.13
SGOT units/l	58	56	51	37	56
SGPT units/l	65	76	50	34	44
Alkaline Phosphatase (ALP) (IU/L)	296	376	306	285	265
Albumin (g/dl)	4.1	3.0	3.0	3.0	3.5
Globulin (g/dl)	4.5	4.5	4.0	4.2	4.4
Gamma Glutamyl Transferase (GGT) (U/L)				104	123

Table 1. Demonstrating Isolated Elevation in Alkaline Phosphatase Levels with Associated Elevation in Gamma Glutamyl Transferase (GGT), Suggesting ALP is of Hepatic Origin

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Ultrasound of abdomen liver was normal in size with 12.6 cm with normal echo texture of liver parenchyma, intrahepatic biliary radicals and common bile duct was normal. Patient also complained of symptoms suggestive of dry eyes, hence tear break up time (TBUT) was performed. TBUT was 5 seconds and 7 second in left and right eye respectively (normal more than 10 seconds), features consistent with bilateral dry eye disease. Antinuclear antibody (ANA BY IF) was positive with significant dilution (1:320) with nucleus dotted pattern which is associated with antibodies against sp100 (nuclear protein) and PML (promyelocytic leukemia factor) antigens, both of which are considered "PBC -specific" immunofluorescence patterns.[1] In view of suspected primary biliary cholangitis Antimitochondrial antibody (AMA) was performed. Antimitochondrial antibody (AMA) was positive (+++) with significant dilution.

CLINICAL DIAGNOSIS

With background symptoms of easy fatiguability and intense pruritus and an isolated elevation of ALP of hepatic origin with no evidence of extra biliary obstruction, bilateral dry eye (TBUT reduced)and ANA pattern specific for PBC which was nuclear protein sp100 with AMA positivity, primary biliary cholangitis (PBC) was diagnosed.[2] Liver biopsy was performed under ultrasound guidance. Biopsy showed moderate interphase hepatitis seen on portal circumference with no bile duct changes, with no evidence of fibrosis, hepatocyte degeneration or granulomas, above features suggestive of autoimmune hepatitis. Patient clinical and immunological characteristics was suggestive of PBC with biopsy showing features of autoimmune hepatitis, hence a diagnosis of primary biliary cholangitis -autoimmune hepatitis overlap syndrome was made.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of primary biliary cholangitis include other non-obstructive causes of cholestasis.

- **Primary Sclerosing Cholangitis (PSC)**
  PSC is a progressive disorder is characterised by inflammation, fibrosis, and stricturing of medium and large ducts in the intrahepatic tree with or without extra hepatic biliary tree. Patients may be asymptomatic and diagnosed on workup for cause for isolated elevation in alkaline phosphatase. Inflammatory bowel disease is commonly associated with PSC. The diagnosis of PSC is made by demonstration of characteristic multifocal stricturing and dilation of intrahepatic and extra hepatic bile ducts on cholangiography usually obtained by magnetic resonance cholangiopancreatography (MRCP). PBC is differentiated from PSC from fact that there is normal intrahepatic biliary radicals on imaging.
- **Autoimmune Hepatitis (AIH)**
  AIH is characterised by chronic inflammatory disease of liver associated with circulating autoantibodies and elevated serum globulin. AIH may be seen in any age group and in all ethnic groups predominantly in women. It is usually associated with other autoimmune diseases such as rheumatoid arthritis, ulcerative colitis, type 1 diabetes mellitus and systemic lupus erythematosus. One characteristic finding in AIH is an elevation of gamma globulins, particularly IgG. ANA is the most common associated antibody. Anti-smooth muscle antibodies (AMSA) are more specific for AIH. Other antibodies found include Anti-liver-kidney microsomal -1 antibodies (ALKM-1), Anti-soluble liver antigen/liver pancreas antibodies (anti-SLA/LP).

PATHOLOGICAL DISCUSSION

In patients with clinical diagnosis of primary biliary cholangitis there is around 1 to 14%[3,4] who have immunological or histological evidence of autoimmune hepatitis .clinical profile of a classical primary biliary cholangitis is a middle aged female in the age group of 30 to 65 years, who is usually asymptomatic or has history of suffering from easy fatigue or pruritus, with biochemical evidence of cholestasis on a background of no biliary tract obstruction and a positive AMA. Criteria of diagnosis of PBC are discussed below[2] AMA is serological hallmark of primary biliary cholangitis which is found in around 95% of patients with PBC[5] and specificity of 98% for the disease.[6] Characteristic histological features in a liver biopsy in PBC is presence of degenerating bile duct epithelium with focal bile duct obliteration and formulation of granuloma known as florid duct lesion.[7]

A diagnosis of PBC is established if there is no extrahepatic biliary obstruction, no comorbidity affecting the liver, and at least two of the following are present-

1. An alkaline phosphatase at least 1.5 times the upper limit of normal.
2. Presence of antimitochondrial antibodies (AMA) at a title of 1: 40 or higher (or other PBC specific autoantibodies (sp100 or gp210), if AMA is negative)
3. Histologic evidence of PBC on suppurative destructive cholangitis).

PBC-AIH (primary Biliary Cholangitis- Autoimmune Hepatitis) Overlap Syndrome: This clinical entity has been described in patient who has clinical and immunological features in favour of PBC as mentioned above but histological features are in favour of autoimmune hepatitis[8] The histological hallmark of autoimmune hepatitis is interface hepatitis[9] Our case has features of PBC with histological evidence of interface hepatitis with no bile duct changes, hence this patient was diagnosed to have overlap syndrome. complications of both PBC and overlap syndrome include cirrhosis, portal hypertension, hepatocellular carcinoma,[10] metabolic bone disease including osteopenia and osteoporosis. Other complications include clinical

manifestations secondary to malabsorption of fat soluble vitamins.[11] Need for differentiating overlap syndrome from classical PBC is emphasized on the fact that rate of disease progression to cirrhosis and other complications are faster in overlap syndrome compared with classical PBC and hence the need for frequent follow up with liver function tests and screening for complications.

DISCUSSION OF MANAGEMENT

The patient was started on tablet prednisolone 5 mg along with ursodeoxycholic acid (UDCA), on follow up patient alkaline phosphatase reduced to 189 IU/L and GGT to 36 IU/L. Patient is on regular follow up with periodic biochemical liver function tests which showed decreasing ALP and GGT level.

For management of patients with overlapping features with PBC and AIH, several studies have demonstrated a positive response to immunosuppressive therapy and UDCA[12,13] Patient with overlap features with histological features suggestive of AIH rapidly progress to cirrhosis of liver when treated with UDCA alone when compared to those treated with corticosteroids and UDCA.[14] Follow up of this patient is of foremost importance as there is faster rate of progression of disease when compared with classical PBC with periodic liver function assessment and repeat liver biopsy.

FINAL DIAGNOSIS

Primary Biliary Cholangitis-Autoimmune Hepatitis (PBC-AIH) Overlap Syndrome.

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