Seronegative Primary Biliary Cholangitis in a Middle Age Male- A Rare Entity

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INTRODUCTION

Primary Biliary Cholangitis (PBC) is rare, with a low prevalence of 19 to 402 cases per million persons.[1,2] Middle age women constitute about 90-95 percent of such rare disorders. Antimitochondrial antibodies (AMA) are the serological hallmark of PBC, present in approximately 95 percent of patients with PBC. There are very few case reports and case series of AMA-negative PBC in literature and this entity occurring in an Asian male patient makes it rarest. We report such a case of AMA and ANA negative PBC in middle age male subsequently diagnosed by histopathology.

PRESENTATION OF CASE

A 48 year old male from Chandigarh (India) presented to the OPD with complaints of right upper abdominal pain and yellowish discoloration of eyes and high colour urine for 8 months duration. He noticed generalised hyperpigmentation of skin, generalised itching for 2 months and had significant weight loss. The patient did not give previous history of Jaundice, pale stool, fever, altered bowel habit, abdominal distension, bleeding from the upper or lower gastrointestinal tract or any nodular swelling in any part of body or abdomen.

On physical examination, the patient had icterus, shiny white nails with no scratch mark. Per abdominal examination revealed only mild splenomegaly without any evidence of ascites or hepatomegaly. We admitted him for a thorough evaluation of his cause of obstructive jaundice.

His liver profile had a total serum bilirubin 29.6 mg/dL (normal, 0.2–1.0 mg/dL); conjugated 23.4 mg/dL; alkaline phosphatase 426 IU/L (normal in male, 40–130 IU/L); Gamma GT 65 IU/L (normal in male<50 IU/L), AST 39 IU/L, ALT 17 IU/L, prothrombin time was 14/14 seconds with INR 1.0 and serum albumin 4.0 gm/dL. His total serum cholesterol was 146 mg/dL, HDL 25 mg/dL, LDL 58 g/dL and TG 529 mg/dL. The viral markers HBsAg and Anti-HCV were negative. Antinuclear antibody (ANA) was Negative, serum immunoglobulin G (IgG) and IgM were normal. Serum thyroid stimulating hormone (TSH) was 9.10 µIU/ml. Serology for AMA, anti HAV, anti HEV, anti LKM-1 and anti-SM Ab, PCA, HIV were negative. Serum ceruloplasmin was 51.82 mg/dL (20-60 mg/dL, copper in 24-hour urine was 13.89 µg (normal adult 0-80 µg/24 hour). Serum Iron was 45 µg/dL (normal in male 59-138 µg/dL.

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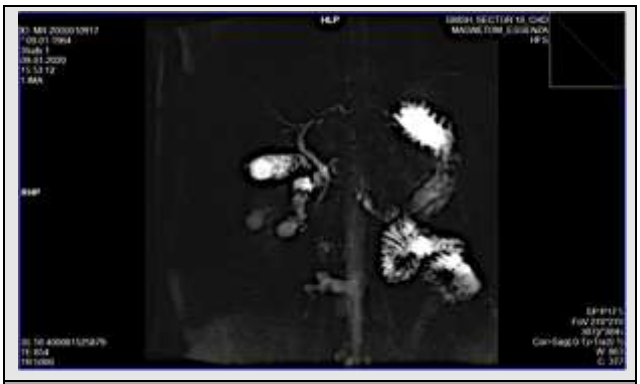

Figure 1a. MRCP Showing Normal Extrahepatic Biliary Tree

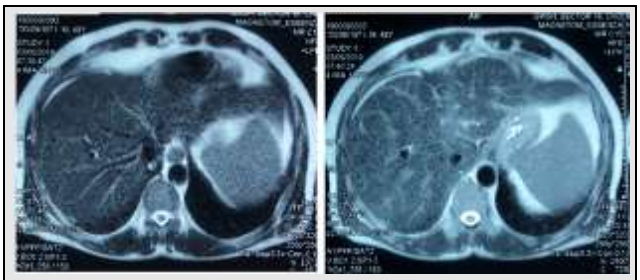

Figure 1b. MRCP Showing Normal Intrahepatic Biliary Tree

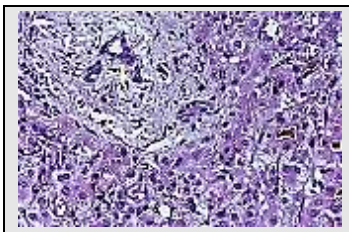

Figure 2. Histological Features Consistent with PBC

Abdominal ultrasonography showed mild splenomegaly with normal liver, normal portal vein diameter and no fluid in peritoneal cavity. Kayser Fleischer rings were absent on slit lamp examination. UGI endoscopy was normal. CECT Abdomen and triple phase CT reveal no added abnormality. MRCP showed normal biliary tree (figure 1a and 1b). Further ERCP revealed normal CBD.

Liver biopsy was performed subsequently to resolve diagnostic dilemma. Histological feature showed destruction of bile and proliferation at places. Bile ducts surrounded by lymphoplasmacytic and neutrophils cell infiltrate and formation of occasional granulomas. Portal tract shows increase in fibrocollagenous tissue and hepatocytes showing hydropic changes with marked cholestasis. Histology staging: stage-3 (figure 2). Biopsy was reported as Primary biliary cholangitis (pre- cirrhotic stage).

CLINICAL DIAGNOSIS

Considering the typical history of progressive jaundice, pruritis, weight loss and clinical examination, various causes of obstructive jaundice were considered like Bile duct obstruction from gallstones or malignancy, Primary sclerosing cholangitis (PSC), IgG4-related disease and viral infections. Thus patient was admitted for further evaluation.

DIFFERENTIAL DIAGNOSIS

Includes the common causes of cholestasis like Bile duct obstruction from gallstones or malignancy, Primary sclerosing cholangitis (PSC), IgG4-related disease, Drug-induced cholestasis, Hepatic Infiltrative diseases, Sarcoidosis, Bacterial, fungal, and viral infections, Hepatic amyloidosis, Lymphoma and solid organ malignancies, Endocrine dysfunction, Cardiac diseases, Intrahepatic cholestasis of pregnancy and Viral hepatitis

Present and past use of medication history was sought in detail, Bile duct obstruction is suggested if the patient has the acute onset of jaundice or right upper quadrant pain or if the aminotransferases are moderately elevated. It should also be considered in patients with painless jaundice. It is ruled out by biliary imaging with a right upper quadrant ultrasound, magnetic resonance cholangiopancreatography (MRCP), or if suspicion for a common bile duct obstruction is high, endoscopic retrograde cholangiopancreatography (ERCP). PSC should be considered if the patient does not have extrahepatic biliary obstruction and is AMA-negative. PSC is typically diagnosed with cholangiography (MRCP or ERCP). Patients with viral hepatitis occasionally present with cholestasis, though they typically also have aminotransferase elevations. Testing for hepatitis A, B, C, and E should be performed if there is no evidence of extrahepatic biliary obstruction and if the AMA is negative.

Findings that suggest a diagnosis of PBC include skin hyperpigmentation, pruritus, a positive antimitochondrial antibody (AMA), and hypercholesterolemia. Other diagnoses are more likely in patients who are male and in patients who are <30 years old or >65 years old. However, the diagnosis of AMA-negative PBC requires a liver biopsy that demonstrates the typical features of bile duct destruction seen in PBC. Liver biopsy also helps in the diagnosis of infiltrative disorders.

PATHOLOGICAL DISCUSSION

Primary biliary cirrhosis (PBC) is a chronic, progressive autoimmune liver disease. It is characterized by non-suppurative T lymphocyte mediated attack on small intralobular bile ducts. A continuous assault on the bile duct epithelial cells leads to their gradual destruction and eventual disappearance causes the signs and symptoms of cholestasis and eventually may result in cirrhosis and liver failure.[3,4,5,6] Fatigue and pruritus are by far the most common symptoms reported by the patient with PBC. Jaundice is a late sign signalling a poor prognosis. Right upper quadrant abdominal pain is reported in 10% of patients.[7] given the infrequency of the disease in Asian population, manifestation of PBC is less understood. The female to male ratio is 9:1. Ten percent are male, in whom the disease runs a similar course.[8] the incidence is much lower in developing countries like India. 90 to 95% cases of PBC shows AMA positivity. It is directed against E2 component of the pyruvate dehydrogenase complex (PDC-

E2), the E2 unit of the branched-chain 2-oxo-acid dehydrogenase complex (BCOADC- E2) and the E2 subunit of the 2-oxo-glutarate dehydrogenase complex (OGDC-E2).[9] the disease severity is not related to antibody titres whose levels are seen to persist even after liver transplant without disease recurrence.

ANA is present in nearly half of the cases of PBC and in up to 85% of AMA-negative PBC. Antibodies against gp210 (anti-gp210) are found in 25% of patients of AMA-positive PBC and in up to 50% of AMA negative cases. ANA with MND (multi-nuclear dots) and rim-like patterns are specific for PBC and can be considered a surrogate marker of PBC in AMA-negative cases.[9, 10] PBC can be diagnosed based on biochemical and histological features as well as AMA positivity. In AMA-negative cases, other possible differentials are to be ruled out by MRCP and viral and autoimmune marker testing. The newly described antibodies to gp210 can be used to diagnose the disease in AMA-negative cases.

American Association for the Study of Liver Diseases (AASLD) guidelines suggest that PBC should be considered in patients with elevated serum ALP levels and the diagnosis is established if two of the following three criteria are met: AMA is detected; elevated ALP levels are indicative of cholestasis; and a liver histology confirms the nonsuppurative destruction of intrahepatic ducts.[11] With the sensitivity and specificity of AMAs approaching 95%, detection of AMA becomes extremely important in the diagnosis of PBC.

However, the diagnosis of AMA-negative PBC requires a liver biopsy that demonstrates the typical features of bile duct destruction seen in PBC. The diagnosis is more certain if granulomas are present. Immunoglobulin M levels are lower in AMA-negative than AMA-positive patients with PBC. A recent meta-analysis of 52 patients compared AMA positive and negative cases and biochemical response to UDCA.The authors observed and concluded no difference.[12] a higher titer of ANA, anti-smooth muscle antibody, gamma globulin, and lower IgM have been demonstrated in patients with AMA-negative PBC compared with those with AMA-positive PBC.[12]

Improvement in sensitivity of techniques for detecting AMAs will further bridge the gap between AMA-negative and AMA-positive PBC.[13] Diagnosis of PBC should still be considered in seronegative case when other common cause of intrahepatic cholestasis has been ruled out. Liver histology becomes key to diagnosis. Such cases should be managed like other PBC patients.[12]

DISCUSSION OF MANAGEMENT

Includes Treatment of the symptoms and complications that result from chronic cholestasis and Suppression of the underlying pathogenic process.

Patients with PBC who are clinically jaundiced may develop diarrhoea and weight loss due to the malabsorption of dietary fat (steatorrhea).[14] Symptomatic steatorrhea due to bile acid insufficiency can be partially corrected by restricting dietary fat. If pancreatic insufficiency is suspected, it is easier to empirically treat with pancreatic enzyme replacement. Patients with PBC may have malabsorption of the fat-soluble vitamins A, D, E, and K requiring supplementation. Approximately 20 percent of patients with PBC have or will develop hypothyroidism[15] may require treatment with thyroxin. Because planar xanthomas greatly diminish quality of life, they are usually treated. Treatment consists of large-volume plasmapheresis performed at one- to two-week intervals.[16] Patients with advanced PBC, similar to patients with other types of end-stage cirrhosis, develop signs and symptoms of liver failure such as ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, muscle wasting, and massive bleeding from oesophageal varices. Management is similar to that in other causes of liver failure. Fatigue is common in patients with PBC and can be severely debilitating. However, there is no recommended therapy for treating fatigue.

The most widely accepted treatment is UDCA. It is the only drug approved by the US Food and Drug Administration (FDA) as a treatment for PBC and the only agent endorsed by the AASLD for this purpose.[11] UDCA (13 to 15 mg/kg per day) delays the progression to end-stage liver disease, enhances survival, and is well tolerated. UDCA is thus advocated as first-line therapy in PBC. The extent of the biochemical response to UDCA during the first year of therapy is a simple and useful marker of long-term prognosis. Patients taking UDCA are monitored with liver biochemical tests.[17] Improvement typically occurs within six months.

Once UDCA ceases to control the disease and the patient progresses to end-stage liver disease, liver transplantation should be considered, regardless of the patient's AMA status.[18]

Based on normal Imaging of biliary tree and after ruling out common causes of cholestasis with typical histopathology a final diagnosis of AMA and ANA negative PBC was considered and patient was started on ursodeoxycholic acid (UDCA) and other conservative/supportive treatment. The patient improved symptomatically and is under regular follow up.

FINAL DIAGNOSIS

Seronegative Primary Biliary Cholangitis

CONCLUSIONS

Primary Biliary Cholangitis is a rare disease in Asian countries especially in male population. In appropriate clinical settings consistent with PBC, AMA and ANA negative patient should be considered for liver biopsy to making diagnosis and management early.

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