AUTOIMMUNE CHOLANGIOPATHY- A RARE CASE OF AN AUTOIMMUNE LIVER DISEASE

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Abstract : Autoimmune liver disease (AILD) is one of the rare cause of chronic liver disease in India with a prevalence of about 3.5 to 6.18 percentage among the chronic liver disease cases. Among the AILD the most commonly reported is autoimmune hepatitis, Primary biliary cirrhosis (PBC) is reported rarely. 90 percentage of PBC cases will have AMA (Antimitochondrial antibody) positivity. 10 percentage of the PBC cases present with negative serum AMA which is known as autoimmune cholangiopathy. We present one such case of an AMA negative PBC. An young female presented with cholestatic jaundice with negative virological markers and negative autoantibodies (AMA, ANA, ASMA) and normal imaging but liver biopsy showed features consistent with PBC histologically. She was diagnosed as autoimmune cholangiopathy and treated with ursodeoxycholic acid (UDCA) and steroids with improvement during follow up.

Keyword : Cholestatic jaundice, Primary biliary cirrhosis, Antimitochondrial Antibody, Autoimmune cholangiopathy.

INTRODUCTION: Autoimmune liver diseases are a group of chronic liver disease of unknown aetiology with aberrant auto-reactivity & a genetic predisposition with a variable prevalence among the patients with liver disease. Recently physicians have identified a number of patients with an atypical pattern of autoimmune liver diseases that defy a definitive diagnosis. We are reporting one such case of an atypical form of an AILD known as Autoimmune cholangiopathy.

CASE REPORT: 26 yrs old female, mother of 1 child, presented with history of progressive jaundice, clay coloured stools, itching, easy fatiguability & loss of appetite for 3 months duration. She gave history of fever of 10 days duration before the onset of jaundice. She took herbal treatment for jaundice for 1 month. She denied previous similar attacks, blood transfusion, jaundice during pregnancy or any chronic illness in the past. There was no history of alcohol consumption. There was no family history of liver disease or similar illness. EXAMINATION: The patient was moderately built with stable vitals. She had deep jaundice with just palpable liver, the rest of the examination was unremarkable. With the above history & clinical findings we considered the following differential diagnosis: 1. Viral hepatitis 2. Cholestatic jaundice? Cause

INVESTIGATIONS: Complete hemogram: was normal except for anaemia; Hb 7.9 g/dl, WBC 4.3×10⁹/cumm; RBC 3.17×10⁹/cumm; Platelet 2.45,000/cumm; ESR 1 hour - 80 mm (normal 20 mm/h). Peripheral smear study was normal. Liver function test: showed conjugated hyperbilirubinemia with Serum aspartate transaminase (SGOT) & S.Alanine transaminase (SGPT) elevated > 2 times the normal & S. Alkaline Phosphatase (ALP) elevated > 4 times the normal with elevated Gamma-glutamyl transpeptidase (GGT) and normal S.Proteins. - Sr. Bilirubin: 22 mg/dl (normal-0.3-1.3 mg/dl), direct bilirubin 7.6 mg/dl (normal -0.1-0.4 mg/dl), SGOT 103 IU/L (normal 5-40 IU/L), SGPT 119 IU/L (normal 5-35 IU/L), ALP 832 IU/L (normal 35-130 IU/L), GGT 129 IU/L (normal 10-48 IU/L), total protein 6.2 g/dl (normal 6.7-8.6 g/dl), serum albumin 3.5 g/dl (normal 4.0-5.0 g/dl), globulin 2.7 g/dl. Prothrombin time 21 seconds (normal 12.7-15.4 seconds). Urine examination: showed the presence of bile salts & bile pigments. Viral markers: HBs Ag, Anti HCV, Anti HAV antibody- all negative. Since the patient had a cholestatic jaundice picture with negative viral markers, viral hepatitis was ruled out Ultrasound abdomen (USG): showed liver size 17.3 cm, with diffuse gallbladder wall thickening & no intrahepatic biliary radical dilatation, with features suggestive of cirrhosis. Since there was no dilatation of bile ducts, we did Autoantibodies to rule out AILD. Autoantibodies: AMA (anti mitochondrial antibody), ANA (anti nuclear antibody), ASMA (anti smooth muscle antibody) were done which were all negative. Because of the negative immunological profile, we did MRCP to rule out primary sclerosing cholangitis which will demonstrate the typical biliary duct irregularities. Magnetic Resonance Pancreatography (MRCP) showed thickening of gall bladder wall, common bile duct (CBD) was not dilated, no filling defect seen. There was mild wall oedema of CBD, features suggestive of cholangitis. Since MRCP was also normal, we finally proceeded with liver biopsy which showed: 1. Cholestasis, canicular bile plug and feathery degeneration. 2. The portal tract showing mild fibrosis and bile ductular proliferation surrounded by scattered lymphocytes and polymorphs. 3. There was no granuloma / inflamatory bodies or evidence of cirrhotic changes. The above histopathological findings were diagnostic of Primary biliary cirrhosis. The patient is confirmed to have PBC by liver biopsy though AMA is Negative. This atypical form of PBC is known as AMA negative Primary biliary cirrhosis or Autoimmune cholangiopathy.
It is the second most common AILD which affects middle aged women (40-60 years) in 90% of the cases. The cause is unknown, probably autoimmune process directed against the self-epitopes expressed on the small duct biliary epithelial cells. All races are affected with a variable frequency worldwide. The annual incidence of PBC has been found to be 0.7-4.9 cases per million population. Familial clustering has been reported. Symptomatic patients will present with the following diagnostic features: 1. Middle aged women with pruritus followed by slowly progressive jaundice. 2. Liver palpable. 3. Serum bilirubin about twice normal; serum alkaline phosphatase about 4 times normal; serum aspartate transaminase about twice normal; serum albumin normal 4. Anti-mitochondria antibodies (AMA) POSITIVE in 1:40 titre 5. Liver biopsy appearances compatible. 6. MRCP (if in doubt like negative AMA) — normal intra hepatic bile ducts. **AMA is the hallmark for PBC** which is present in 90-95% of the cases. The antigen to which the antibodies are directed are located in the inner mitochondrial membrane. They will have high serum IgM & elevated serum cholesterol & bile acids. Liver biopsy will show: 1. Stage 1: florid bile duct lesion with lymphocyte aggregates, stage 2: ductular proliferation, stage 3: septal fibrosis & bridging, stage 4: cirrhosis. PBC can be associated with other autoimmune diseases like Sjogrens syndrome, Rheumatoid arthritis, thyroiditis. Diarrhoea, skin xanthomas, bone changes, bleeding oesophageal varices are the complication. Hepatocellular carcinoma is rare. Natural history of the histological changes of PBC have demonstrated that majority will progress to advanced stage within 2 years. Asymptomatic patient will survive for 10 years. In those with symptoms & jaundice the survival is about 7 years. The treatment of choice is Ursodeoxycholic acid (UDCA) which is a non-hepatotoxic hydrophilic bile acid which protect the cell membranes against the detergent effect of hydrophobic bile acids. It was found to improve the liver function & slow the disease progression. It also improves the survival & reduce the need for liver transplantation. It is given in a dose of 13-15mg/kg/day. However it is not useful for pruritus. Pruritus is treated with cholestanine 4g/day. For UDCA non-responders combination of budesonide with UDCA was found to improve the liver histology. Prognosis: Patients with PBC have 3 fold increased mortality compared to the general population. Patients not responding to UDCA is a poor prognostic indicator. The Mayo clinic prognostic model predicts survival and the optimal time for liver transplantation is Mayo risk score of 8. MELD (Model for end stage score) predicts short term survival. If MELD is >16, it is an indication for liver transplantation. The patient should be considered for transplant if the serum bilirubin approaches 6mg/100ml. Liver transplantation is indicated if the patient has poor quality of life secondary to intractable pruritus or fatigue, end stage liver disease or bleeding varices, hepatic encephalopathy. Survival after transplant is >90% at 1 year & >80% at 5 years. Disease recurs in transplanted liver in 17% of the cases at a mean of 3.7 years. **AUTOIMMUNE CHOLANGIOPATHY**: or **AMA-negative PBC** is an autoimmune cholestatic disease first described in 1987 and the name immune cholangitis was first introduced by Brunner et al. It is a rare condition. The patient is usually a female presenting with a slow onset of cholestasis. It will resemble PBC clinically, biochemically & histologically but immunologically they will be **AMA negative**. Serum antinuclear antibody (ANA) & anti-citrullinated antibody (ACA) are present in high titres. Autoimmune cholangiopathy lack a uniform diagnostic criteria.
The criteria for diagnosis of autoimmune cholangiopathy were laboratory features of immunoreactivity including ANA and/or SMA seropositivity and/or hypergammaglobulinemia. Absence of AMA by indirect immunofluorescence. Seronegativity for HBsAg and anti-HCV. Absence of other etiological basis for liver injury. It may represent a transitional stage of PBC. It is also said that patients with autoimmune cholangiopathy present an overlap between PBC & autoimmune hepatitis. Prognosis is probably the same as PBC. Prednisolone therapy results in decrease in serum transaminases and evidence of less inflammatory activity in liver biopsy specimens; however it has little impact on the bile duct lesions. It should be administered in low dose of 5-15mg/day. Treatment of choice is UDCA. It may represent a variant expression of diverse established autoimmune liver diseases. A transitional state between one autoimmune disease and another or a single disorder with varying manifestation. The above patient has clinical, biochemical, histological resemblance to Primary biliary cirrhosis. Immunologically AMA is negative. Thus it is considered as AMA-negative PBC or autoimmune cholangiopathy. However AMA which usually will be positive in high titres in autoimmune cholangiopathy is lacking. In a study by CZAJA ET AL.4 out of 20 patients with autoimmune cholangiopathy tested negative for ANA & thereby say ANA has low disease specificity & the likelihood that ANA positivity characterize a histologically distinct subgroup of autoimmune cholangiopathy is low. Thus this case represent an atypical form of autoimmune liver disease. CONCLUSION: In many instances AILDs have been thought to represent spectra or variable presentation of similar disease entity as represented by the above case. Knowing the expected course of a particular disease lends insight into the treatment intervention & lifestyle changes that might best used to halt the disease progression. Early definitive diagnosis can help in planning liver transplantation in those cases where liver transplant may be needed. AILD should be suspected in all cases of chronic liver diseases especially in middle aged women with no alcohol or viral aetiology as well as in all patients with known autoimmune diseases.

REFERENCES: