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Case Report

Navigating the Overlap: A Case of Autoimmune Hepatitis with Primary Biliary Cholangitis

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A B S T R A C T

The spectrum of immune mediated injury to the liver comprises of Autoimmune hepatitis, Primary Biliary sclerosis, Primary sclerosing Cholangitis, Immunoglobulin G-4 associated cholangitis and their poorly differentiated overlap syndromes. The diagnosis is based on histological, biochemical, serological and clinical parameters. Overlap syndromes can occur in 3 - 7 percent of the total cases. This is a case of a 51-year-old patient who presented in a tertiary hospital in Chennai, Tamil Nadu, with complaints of abdominal pain and vomiting for 1 week, who on progressive evaluation was diagnosed to be a case of overlap syndrome of Autoimmune hepatitis and Primary biliary cirrhosis.

Keywords: Autoimmune hepatitis; Primary biliary sclerosis; Primary sclerosing cholangitis; Immunoglobulin G-4 associated cholangitis

Introduction

Autoimmune hepatitis of the liver can present asymptomatically, acute or chronic liver disease and also as liver cirrhosis. It is characterized by unregulated T cell mediated immune damage to the hepatocyte and cholangiocyte. It can be triggered by a variety of other factors like environmental, viruses, bacteria, drugs, Eg: minocycline, toxins etc. They are characterized by predisposition from young to middle aged females, elevated transaminases, elevated gamma globulins organ specific and nonspecific auto antibodies.

Case Report

A 51-Year-old female had presented in a tertiary hospital in Chennai with complaints of abdominal pain for 1 week and vomiting for 1 week and upper gastrointestinal bleed **(Figures 1-3)**. She was taken for emergency endoscopic variceal ligation. On examination the patient had abdominal distension with massive splenomegaly:10cms below the left costal margin and pancytopenia, elevated total bilirubin, direct bilirubin, elevated transaminases and serum alkaline phosphatase **(Figures 4,5)**.

The following tables show the liver and renal function tests and hemogram of the patient **(Tables 1,2)**.

Table 1: Liver and renal function tests.

Total bilirubin	18
Direct bilirubin	14
SGOT	130
SGPT	99
Total protein	7.4
Serum Albumin	3.0
Alkaline phosphatase	353
Urea	20
Creatinine	0.6

Table 2: Hemogram of the patient.

Hemoglobin	8.9
Total count	7000
Platelets	48000
MCV	83
MCH	27
MCHC	32

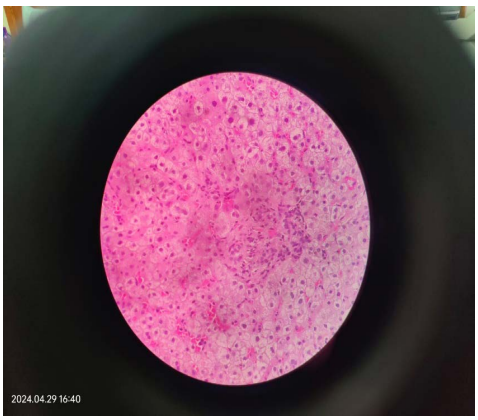

Figure 1: Interface Hepatitis.

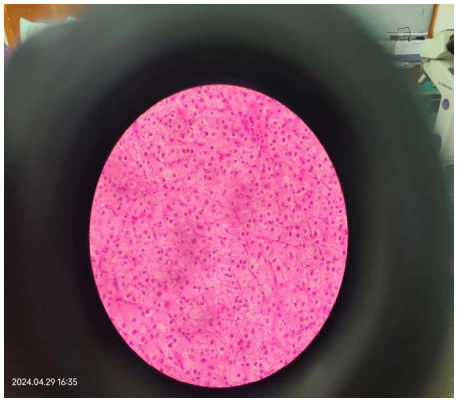

Figure 2: Ballooning of Hepatocytes.

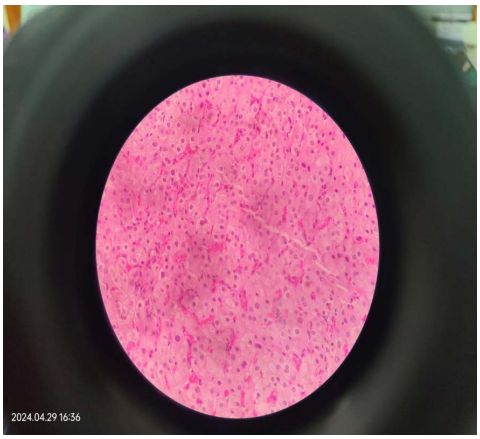

Figure 3: sinusoidal congestion with lymphocytic infiltration.

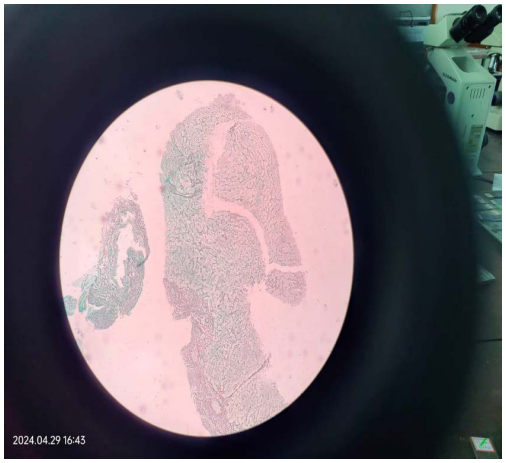

Figure 4: Slide in high power field stained using Reticulin.

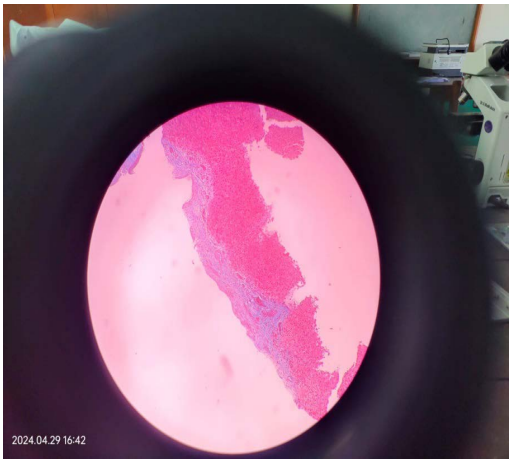

Figure 5: Slide in high power field stained with Trichome.

USG abdomen showed coarse liver echoes. Portal venous doppler showed Portal hypertension with collaterals. CT abdomen showed acute calculus cholelithiasis, minimal ascites and grade 3 esophageal varices, Fibro scan - 6.5kpa.

CECT abdomen showed atrophy of the posterior segment of the Right lobe of the liver, multiple hyperdense calculi noted in the fundus, body and neck of the gall bladder with largest measuring 1*0.7cmin fundus and pericholecystic fluid noted. Spleen appeared grossly enlarged with gamma gandy bodies main portal vein measuring 22 m and splenic vein measuring 9 mm. A diagnosis of chronic liver disease was made.

To find the etiology further work up was done. Drugs, toxins and alcohol history was ruled out. Viral markers such

as HbsAg and HCV were negative, which led to us suspecting an autoimmune etiology. Autoimmune panel of investigations were done and Antinuclear antibodies were +++ cytoplasmic filament pattern, Anti mitochondrial antibody -M2 was positive, IgG was elevated 3121. Since AMA-M2 was positive MRCP was done and it showed irregular liver surface, mild bilateral central intrahepatic biliary radicle dilatation, portal vein dilated to a maximum of 1.5cm, Acute calculus cholelithiasis with choledocholithiasis, splenic index of 2464, multiple hypointense punctate foci reflecting gamma gandy bodies.

Liver biopsy was done and it showed features of Autoimmune hepatitis like ballooning degeneration of hepatocytes and mild interface activity and overlapping features of Primary Biliary cirrhosis features like canalicular cholestasis, bile ductular proliferation and focal biliary injury hence overlap syndrome of autoimmune hepatitis and PBC was diagnosed **(Figure 6)**.

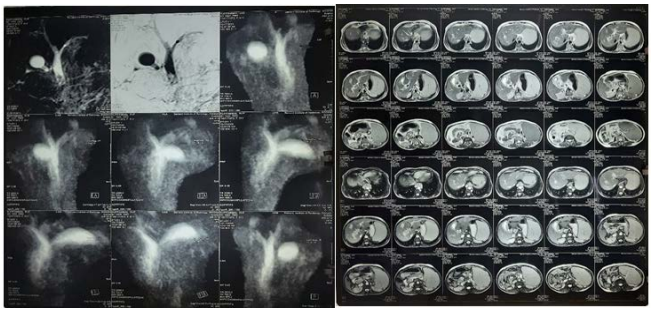

Figure 6: Magnetic resonance Pancreatocholangiogram of the patient showing abrupt narrowing of the smaller bile ducts.

Discussion

Autoimmune hepatitis (AIH) is a chronic inflammatory disease of unknown etiology characterized by the presence of circulating autoantibodies, hypergammaglobulinemia, cytotoxic T cells and plasma cells mediated necro inflammatory changes on hepatic histology, associated histocompatibility haplotypes and a dramatic response to immunosuppressive therapy. Humoral antibodies contribute to the extrahepatic manifestations of autoimmune hepatitis **(Table 2)**.

Table 2: Type 1 Autoimmune hepatitis is characterized by marked gamma globulin elevation, HLA B8, DR3, DR4 association. Type 2 Autoimmune hepatitis has increased chances to progress to cirrhosis.

	TYPE 1 AUTOIMMUNE HEPATITIS	**TYPE 2 AUTOIMMUNE HEPATITIS**
ANTIBODIES	Anti-nuclear anti smooth muscle antibody, anti-actin antibody and pANCA Hypergammaglobulinm-ia	Anti-liver kidney microsomal (LKM) 1 and/or anti-LKM3 and/ or anti-liver cytosol 1 (LC1)[1,2] antibodies. IgA levels reduced.
HAPLOTYPES	HLA DR3/ HLA DR4	HLA DRB1/DQB1
PREDILECTION	Prevalent among young women	pediatric age group
Overlap with PBC	Seen in adults	Not reported.
Remission after drug withdrawal	Possible	Rare, usually need long term immunosuppression.

Clinical Features

The patient may present with fatigue, anorexia, malaise, ascites, variceal bleeding. In some patient's portal hypertension, coagulopathy, encephalopathy and hypersplenism can be seen. Extrahepatic manifestations like arthralgia, arthritis, pleuritis, pericarditis, sicca symptoms.

Diagnosis

The diagnostic scoring system of the International Autoimmune Hepatitis Group (IAIHG) was created by an international panel in 1993, revised in 1999 and it was simplified in 2008. The original revised scoring system has greater sensitivity for AIH compared to the simplified scoring system, whereas the simplified scoring system has superior, specificity and accuracy, using clinical judgment as the gold standard.

(1) Elevated serum aminotransaminase levels; (2) Elevated serum IgG level and/or positive serological marker(s); (3) Exclusion of viral, hereditary, metabolic, cholestatic and drug-induced diseases that may resemble AIH.

Laboratory studies typically show elevation of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, but levels are generally <500U/L. Some patients may have high conjugated bilirubin and alkaline phosphatase. The alkaline phosphatase rarely exceeds 4 times the baseline and generally remains <2 times normal. Another characteristic laboratory feature of AIH is hypergammaglobulinemia, with a selective increase in IgG, which is 1.2–3.0 times higher than the upper level of normal, Cases of hyper viscosity due to elevated IgG levels have been noted[3].

The histologic hallmark of AIH is a lymphoplasmacytic periportal infiltrate invading the limiting plate, also called piecemeal necrosis or "Interface hepatitis". Emperipolesis is present in 65% of patients with AIH and hepatocyte rosettes are present in 33%.

Treatment

The backbone of AIH treatment involves corticosteroid treatment. Corticosteroids doesn't improve the condition in asymptomatic individuals with inactive disease. Patients without cirrhosis who undergo treatment have a 10-20-year survival probability more than 80%, similar to the general population, rarely sometimes untreated Population may recover[4]. The absolute indications for treatment are incapacitating symptoms, multiacinar or bridging necrosis in histology or AST >/=10 times the upper limit of normal or AST>/=5 times the upper limit of normal and hypergammaglobulinemia >/=2 times the upper limit of normal. Prednisone (20 – 60mg/day) can be used as monotherapy in adults, in combination therapy (15 – 30 mg/day) with azathioprine (50 – 100 mg/day) or 6-mercaptopurine (25-100 mg/day). Combination therapy can be used in cases where treatment for more than 6 months is advocated[6]. However, patients with a homozygous mutation of thiopurine methyltransferase are at increased risk for serious side effects and death from azathioprine or mercaptopurine. Genetic testing should be considered. Patients with severe pathology, including cirrhosis on initial presentation or Type 2 AIH, typically require life-long treatment. AIH patients who are refractory to prednisone treatment or who present with end-stage liver disease may require liver transplant.

Treatment is often maintained for at least 2 years before withdrawal of drug therapy. The side effects of long-term steroid therapy can be seen like hyperlipidemia, adrenal insufficiency, osteoporosis can occur. The end points for treatment are remission,

treatment failure, incomplete response or development of drug toxicity. Patients should be vaccinated against Hepatitis B and C. Patients should be screened for HCC at 6-month interval and for variceal bleeding at 1-3 years interval by upper esophageal endoscopy.

Primary biliary cirrhosis (PBC) is a progressive inflammatory liver disease characterized by autoimmune-mediated destruction of intrahepatic bile ducts. In small and medium sized blood vessels inflammation and necrosis of cholangiocytes is seen. It primarily occurs among women aged 40-60 years. A probable diagnosis of primary biliary cirrhosis is based on meeting 2 of the following 3 criteria[5-8]. When PBC is strongly suspected in AMA-negative patients, PBC-specific antinuclear antibodies (ANA), should be determined, including sp100 and gp210[9].

- Positive serum antimitochondrial antibody (AMA) result (titers >1:40) most common is M2 type. Anti AMA antibodies are positive in 95 percent of the cases. These are antibodies against the lipoic acid in inner mitochondrial membrane proteins that are enzymes of pyruvate dehydrogenase complex. They are nonpathogenic. 5 percent are AMA negative. The time from detection of AMA to development of PBC is about 6 years (range 1-19 years)[10]. AMA negativity necessitates the need for liver biopsy.
- Cholestatic pattern of liver enzymes for more than 6 months.
- Histopathologic evidence of asymmetric destruction of intrahepatic bile ducts. With progression the number of small ducts decrease and proliferation of small ductules is seen leading to periportal fibrosis and bridging fibrosis.

Clinical Features

Most prominent symptom is fatigue out of proportion. 50 percent of the individuals have pruritis. Osteopenia or osteoporosis can be present.

Jaundice, splenomegaly, ascites, edema, hepatomegaly can be seen. Other features are hyperpigmentation, xanthelasma because of altered cholesterol metabolism.

Elevated gamma glutamyl transpeptidase, alkaline phosphatase, mild elevation in SGOT and SGPT and hyperbilirubinemia can be seen. Thrombocytopenia, Anemia and leukopenia can be seen due to hypersplenism.

Treatment

Abdominal ultrasonography, CT scanning or MRI are important to exclude biliary obstruction.

Ursodeoxycholic acid (UDCA) is the major medication used to slow the progression of the disease. It does not reverse or cure the disease.

UDCA is given in doses of 13-15 mg/kg per day dosage. Some patients may have worsening of pruritis with initiation of therapy.

In May 2016, the FDA approved Obeticholic acid a synthetic derivative of endogenous chenodeoxycholic acid to be used in combination with UDCA for primary biliary cholangitis (PBC) in adult patients with an inadequate response to UDCA monotherapy for 1 year or as a single therapy in adults unable to tolerate UDCA[11].

The incidence of recurrent PBC after liver transplantation is about 30% at 10 years and about 40% at 15 years[12] Median time to recurrence is 3-5.5 years. Diagnosis of recurrent PBC after liver transplantation is often challenging because AMA is persistently positive in most patient after transplantation[13].

Conclusion

Autoimmune hepatitis and primary biliary cirrhosis overlap syndrome is the most common of all the overlap syndromes. The Paris criteria is used to identify patients with overlapping features of autoimmune hepatitis and PBC. Corticosteroids are used to treat Autoimmune hepatitis and UDCA is used to delay progression of PBC, definitive treatment in unresponsive cases progressing to liver cirrhosis would be liver Transplantation. Patients with autoimmune hepatitis and cirrhosis should be screened for HCC with ultrasound at 6-month intervals and for gastroesophageal varices with upper gastrointestinal endoscopy at intervals of 1–3 years, based on severity of liver disease. UDCA, Corticosteroids and liver transplant are the treatment modalities available. Early diagnosis and intervention would definitely help in delaying the progression as well as preserving the lifestyle of the patient. The patient in the above case discussion is started on steroids and UDCA and is planned for liver transplantation.

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