Seronegative autoimmune hepatitis – A case report

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ABSTRACT

Autoimmune hepatitis (AIH) is a complex liver disease. It is reported in children and adults of all age groups. An 11-year-old male child was admitted in our hospital for anorexia and yellowish discoloration of eyes, skin, and urine for 2 months. He had fever, itching was passing pale-colored stools. The child had hepatosplenomegaly and viral hepatitis markers as well as autoimmune markers were negative. Liver biopsy was suggestive of AIH. The child was started on prednisolone and showed drastic improvement clinically as well as biochemically. This was a case of seronegative AIH, which responded very well to corticosteroids. Hence, high index of suspicion is required to diagnose the case of seronegative AIH.

Key words: *Autoimmune hepatitis, Liver biopsy, Prednisolone, Seronegative*

Autoimmune hepatitis (AIH) is a complex liver disease of unknown cause which results in immune-mediated liver injury with varied clinical presentations. Seronegative AIH follows a similar course to autoantibody-positive disease and diagnosis might be challenging. Delay in appropriate treatment might lead to the progression of liver disease and liver failure. AIH occurs more commonly in females between the ages of 40 and 50 years, though it has been reported in children and adults of all ages. Diagnostic criteria used for conventional AIH might not be applicable to cases with seronegative AIH [1]. There is no diagnostic scoring system specially designed for children.

CASE REPORT

An 11-year-old boy was admitted in our hospital with a history of yellowish discoloration of eyes, skin, and high-colored urine for 2 months. Anorexia was also reported for 2 months. He had fever for 1½ months and itching for 15 days. He was passing clay-colored stools for 2 days. Yellowish discoloration of eyes and skin was acute in onset and progressive in nature, which was associated with high-grade intermittent fever, which was relieved on taking antipyretics. There were no history of pain or distension in abdomen, vomiting, or altered bowel and bladder movements. There was no history of bleeding, edema, altered sensorium, convulsions, skin rashes, or joint pain.

The child was admitted once in private hospital for 4 days where he was put on IV fluids and medications. The child was given ursodeoxycholic acid, L-ornithine-L-aspartate, and laxatives, but his condition did not improve. One week after discharge, the child was brought to our hospital for further management.

The patient is born of the second-degree consanguineous marriage and there was a history of cousin sister with hyperbilirubinemia. There was no significant birth or neonatal history of any major illness. On admission, the child was conscious, cooperative, well oriented to time place and person. The child was icteric and febrile (101°F), but other vital parameters were normal. There were no signs of liver cell failure. Kayser–Fleischer ring was absent. Systemic examination showed hepatomegaly with liver span 13.5 cm. Liver was non-tender, smooth surface, firm consistency with rounded margins. Spleen showed mild splenomegaly, non-tender, soft consistency, well-defined margins and notch felt 3 cm below costal margins.

Investigations showed elevated liver parameters (Table 1) with hepatitis A, hepatitis E, immunoglobulin M antibodies, hepatitis b virus surface antigen, anti-hepatitis C virus negative, and Widal test negative. Urine bile salts and bile pigments were present. Renal functional tests were normal. Ultrasonography abdomen showed hepatomegaly with altered echotexture suggestive of parenchymal disease, splenomegaly, and mild ascites. The child was further investigated for etiology. Serum ceruloplasmin levels were within normal limits.

Autoimmune markers were negative for serum anti-nuclear antibodies (ANAs), anti-smooth muscle antibodies (anti-SMAs), anti-mitochondrial antibodies, and liver-kidney microsomal antigen 1 (anti-LKM-1). Liver biopsy was done which showed diffuse parenchymal mononuclear, as well as portal infiltration (Fig. 1), lymphocytic or lymphoplasmacytic interface hepatitis (Fig. 2) and portal tract with dense lymphoid infiltrate, and only rare plasma cells (Fig. 3). Chronic hepatitis was seen with mild activity and portal-portal bridging (Ishak Stage 5). Histopathological findings were clearly suggestive of AIH.

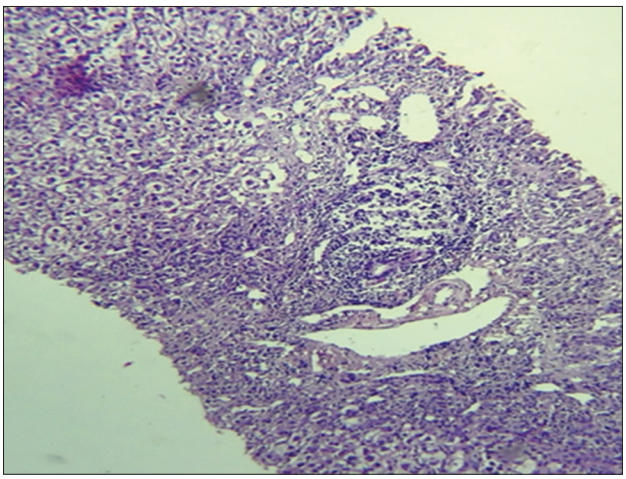

Figure 1: Low-power view with brisk diffuse parenchymal mononuclear infiltrate

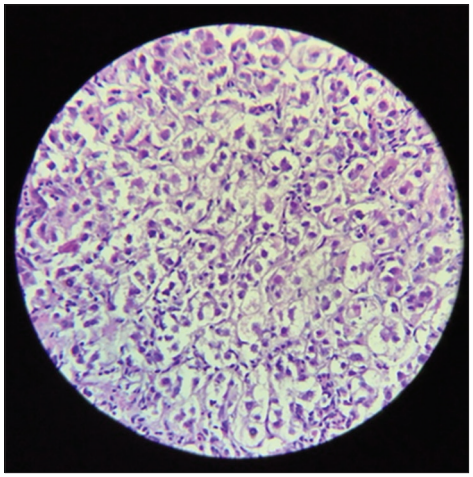

Figure 2: Typical features with lymphoplasmacytic infiltrate with interface activity

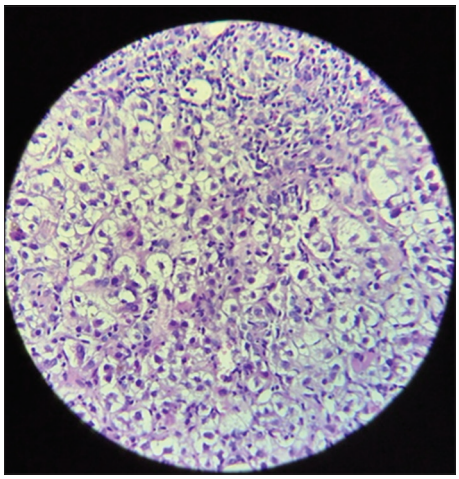

Figure 3: Portal tract with dense lymphoid infiltrate with occasional plasma cells

The child was put on prednisolone only regimen. Dose of prednisolone is shown in Table 2. The child was started at a dose of 2 mg/kg/day oral prednisolone, then was tapered weekly depending on response clinically and biochemically to prednisolone. After 3 days of tablet prednisolone, the child showed drastic improvement clinically with improved appetite, reduced icterus, and became afebrile. Liver function test (LFT) at day 3 and day 5 also showed drastic improvement (Table 1). The child was called for follow-up weekly and LFT was repeated during follow-up.

Table 1: LFTs

LFT	Day 1 (before prednisolone)	Day 3	Day 5	Day 15	Day 21	Day 28
AST	1125	159	90	85	77	78
ALT	1900	262.9	173.3	166.4	135	111
ALP	556	277	205.8	198	189	180
TBR	26.8	11.1	5.7	5.0	2.4	1.9
DBR	14.2	6.0	3	2.8	1.4	0.8

AST: Aspartate aminotransferase, ALT: Alanine transaminase, ALP: Alkaline phosphatase, TBR: Total bilirubin, DBR: Direct bilirubin, LFT: Liver function test

Table 2: Prednisolone dosage

Dosing intervals	Prednisolone (mg)
Week 1	60
Week 2	40
Week 3	20
Week 4	10

DISCUSSION

AIH is a rare autoimmune disorder causing chronic liver inflammation. It is a chronic progressive disease, characterized by immune-mediated destruction of the liver parenchyma and the presence of autoantibodies in the periphery. Wide range of clinical manifestations ranging from asymptomatic to fulminant hepatic failure is seen. Common initial symptoms include fatigue, muscle aches, and signs of acute liver inflammation including fever, jaundice, and right upper quadrant abdominal pain. Some individuals with AIH often have no initial symptoms and the disease is detected by abnormal LFTs. It is associated with other autoimmune diseases in one-third of the cases. The prevalence of AIH was 1.3% and 8.74% among all liver disease and chronic liver disease patients [2-4]. Although it presents at all ages, it is more common in adult females [5]. Majority of the cases are Type 1 [3-6] and are ANA or anti-SMA positive. Type 2 cases are anti-LKM-1 positive. Type 3 is rare and is positive for antibodies to soluble liver antigen (anti-SLA).

Seronegative AIH still occurs in <5% of cases [5]. Amarapurkar *et al.* in their study found that 18% were autoimmune marker negative [3]. Diagnosis of AIH is reached after careful exclusion of other more common viral, metabolic, and drug-induced liver diseases. Patients classically have elevated transaminases, raised immunoglobulin G, and positive autoantibodies [6]. It is a poorly defined inflammatory liver disease, without a specific diagnostic marker. Clinically, serologically, and histologically, it represents chronic relapsing hepatitis associated with plasma cell hepatic infiltrate, hypergammaglobulinemia, and positive autoantibodies. Exclusion of viral causes, drug-induced hepatitis, and metabolic liver disease is required to confirm the diagnosis. Histological features include lymphoplasmacytic interface hepatitis, lobular

hepatitis, and centrilobular necrosis [5,7,8]. Although AIH is uncommon, its diagnosis is important as early treatment is associated with significant good long-term prognosis. It is essential to reduce liver inflammation and improve prognosis [2,3,7]. AIH responds satisfactorily to immunosuppression [7].

Patients who have the features of AIH but not the autoantibodies are currently classified as cryptogenic chronic hepatitis [9]. These patients are indistinguishable from patients with type 1 AIH by age (mean age 42 years vs. 45 years), female predominance (67% vs. 79%), serum AST levels at presentation (mean serum level 491 U/L vs. 504 U/L), serum gamma globulin concentrations at accession (mean serum level 2.8 g/dL vs. 3.4 g/dL), human leukocyte antigen (HLA) status, and histologic findings [10,11]. Furthermore, they respond well to corticosteroid therapy as type 1 counterparts, entering remission (83% vs. 78%) and deteriorating during treatment (9% vs. 11%) [10,11].

In contrast, these patients differ from those with chronic viral hepatitis by having greater laboratory derangements at presentation, a higher frequency of multilobular necrosis on histologic examination, and different HLA haplotypes [10]. Their similarities to type 1 AIH and distinctions from chronic viral hepatitis justify their designation as autoantibody-negative AIH [11]. The previous studies have shown that 14% of patients with autoantibody-negative AIH have anti-SLA [12] and 33% have other immunoreactivities such as antibodies to liver/pancreas [13]. These findings suggest that autoantibody-negative patients have AIH that has escaped detection by conventional immunoassays.

Alternatively, these patients might be seropositive for SMA or ANA (or both) but seronegative at the time of testing. Autoantibodies can fluctuate in titer, and such spontaneous fluctuations might render some patients transiently seronegative [14]. Novel immunoassays and serial assessments for conventional autoantibodies promise to secure the diagnosis of AIH in many of these patients [9]. Importantly, they must be distinguished from individuals with cryptogenic chronic liver disease. In the former instance, patients have an active, potentially aggressive, inflammatory process [10,11], whereas in the latter instance, patients have an inactive, frequently end-stage, non-descript cirrhosis [15,16].

CONCLUSION

Seronegative AIH is a rare cause of chronic liver disease in India, especially in children. Typical serological picture might not be seen in seronegative AIH. Hence, high index of suspicion is required to diagnose this variant of AIH as early as possible and start the treatment at the earliest to achieve the best outcome.

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