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Case Report

Three Case of Three Extremes of Autoimmune Hepatitis from Bangladesh and Review of Literature

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Abstract

Autoimmune hepatitis is a rare chronic liver disease of genetic predisposition, which is triggered by environmental factors. Although autoimmune hepatitis affects all ages and genders across the world, it is often encountered in white females in their twenties, sixties or seventies. Like diagnosis, treatment of autoimmune hepatitis remains challenging and often demands long-term, tailored specialist attention. In specialist Hepatology practice, one must remain vigilant to pick up autoimmune hepatitis early and manage appropriately, as without which the disease may be associated with frustrating prognosis.

Keywords: Autoimmune Hepatitis; Liver Cirrhosis; Bangladesh

Introduction

Autoimmune hepatitis (AIH) is a rare immune mediated inflammatory liver disease, defined by the European Association for the Study of the Liver (EASL) as a liver disease characterized by circulating autoantibodies, raised immunoglobulin G (IgG) and characteristic histological features [1]. The condition results from loss of immunologic tolerance to hepatocytes in genetically predisposed individuals triggered by environmental factors [2]. It affects people of all ages and genders across the globe irrespective of race and ethnicity [3]. Worldwide annual incidence and prevalence of AIH has been estimated at 1.37 and 17.44 per 100,000 population respectively [4]. It is rarer in Asians compared to US and Europeans

due to higher frequency of HLADR3 and DR4 in white population. Besides environmental factors like improved hygienic and living conditions and diet that alter gut microbiome effecting gut-liver axis and the immune system are also held responsible [5].

Here we present 3 cases representing 3 extremes of AIH from Bangladesh along with review of relevant literature.

Case Presentation

The first patient, a middle aged gentleman presented with easy fatigability and right sided upper abdominal pain. On investigation his serum bilirubin was 0.7 mg/dL, serum ALT 125 U/L, serum AST 134 U/L, serum albumin 4.4 gm/dL, international normalized ratio (INR) 1.11, haemoglobin 14.4 gm/dL, total white blood cell (WBC) count 8120/cumm, total platelet count 1,00,00/cumm, random plasma glucose 7.17 mmol/L, hemoglobin A1c (HbA1c) 5.9%, serum thyroid stimulating hormone (TSH) 1.69 mIU/L, free triiodothyronine (FT3) 5.22 pmol/L, free thyroxine (FT4) 1.44 ng/dL, serum creatinine 0.83 mg/dL, serum total cholesterol 185 mg/dL, serum HDL-cholesterol 38 mg/dL, serum LDL-cholesterol 135 mg/dL, serum triglycerides 113 mg/dL, serum iron 68 µgm/dL, serum ferritin 104.7 ngm/mL, serum ceruloplasmin 160 mg/L and urinary copper 24 µgm/L. His peripheral blood film showed non-specific morphology with thrombocytopenia. His anti-HCV, HBsAg, anti-HBc (total), anti-nuclear antibody (ANA), anti-smooth muscle antibody (ASMA), anti-liver kidney microsomal antibody-1 (anti-LKM-1) and anti-mitochondrial antibody (AMA) tested negative.

Ultrasonography of hepatobiliary system showed fatty liver (grade I), fibroscan revealed hepatic fat content (CAP) 272 dB/m and hepatic fibrosis 7.6 kPa, while his endoscopy of upper gastrointestinal tract was normal. There was no K-F ring on slit lamp ophthalmologic examination.

Per-cutaneous liver biopsy was done which showed, moderate distortion of lobular architecture. His total NAS score was 6/8 (steatosis 2 (approx. 35% hepatocytes), lobular inflammation 2 (3 foci/200x), hepatocyte ballooning 2 (many hepatocytes)) and fibrosis 2 (perisinusoidal and portal).

Diagnosis of fatty liver was thus made, and he was advised life style modification and tab. saroglitazar (4 mg) orally daily. At 6 months follow up, his fibroscan showed hepatic fat content i.e. continued attenuation parameter (CAP) 231 dB/m and liver stiffness measurement (LSM) was 9.3 kPa. Although he had no more significant hepatic fat, his hepatic fibrosis increased, and his serum ALT and AST were still high *i.e.* 83 U/L and 85 U/L respectively.

Although the patient's hepatic fat content had reduced significantly on follow-up, he still had elevated liver enzymes and progressive hepatic fibrosis. This raised concern that whether the patient has a second underlying liver pathology which may have been overlooked. We therefore, decided to review the liver histopathology report, which revealed chronic hepatitis with dense portal lymphoplasmacytic infiltrate, moderate interface hepatitis, mild lobular necroinflammatory activity and moderate periportal fibrosis. Progressive fibrosis of the limiting plate leading to enlargement of portal tracts and stellate periportal extension was noted. Features related to autoimmune hepatitis like hepatocyte rosettes, perivenular necrosis, emperipolesis, interface hepatitis, cholestasis and bile duct injury were also seen (Figure 1).

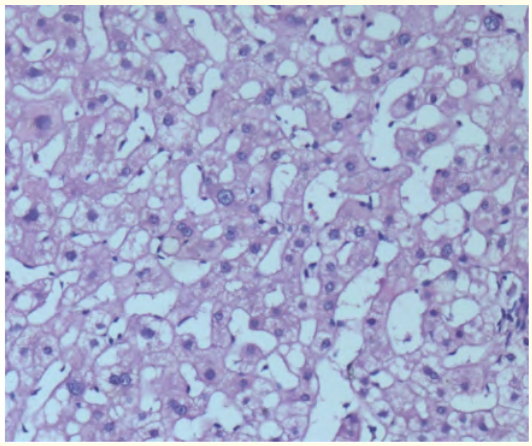

Figure 1: H&Ex200; Hepatic histopathology of the first patient showing hepatocyte rosettes, perivenular necrosis, emperipolesis, interface hepatitis and glycogenetic nuclear changes.

The diagnosis was revised as autoimmune hepatitis and periportal fibrosis and moderate steatosis. Since his liver enzymes were elevated, he was put on oral prednisolone 10 mg/day and then switched over to maintenance therapy with oral azathioprine 50 mg/day. The second patient was a middle-aged gentleman

aged 50 years who presented with right upper abdominal pain and malaise. On examination, he had vascular spiders, palmar erythema and caput Medusa. The diagnosis was liver cirrhosis and he was investigated for etiology and complications. The patient's hemoglobin was 12.2 gm/dL, total WBC count 3700/cumm, platelet count 96,000/cumm, serum bilirubin 0.6 mgm/dL, serum alanine aminotransferase (ALT) was 25 U/L, serum alanine aspartate aminotransferase (AST) 23 U/L, serum albumin 4.56 gm/dl, INR 1.10, serum alpha feto-protein (AFP) 2.1 ngm/mL, serum IgG 19.54 gm/L, serum sodium 135 mmol/L, serum potassium 3.6 mmol/L, serum chloride 102 mmol//l and serum creatinine 1.05 mgm/dL.

He tested positive for ANA, but negative for ASMA, and anti-LKM1 and AMA. He was also negative for HBsAg, anti-HBc (Total) and anti-HCV. His serum ceruloplasmin was 250 mg/L, urinary copper was 52.4 µgm/day and he tested negative for KF ring on ophthalmologic examination.

His upper gastrointestinal tract (UGIT) endoscopy revealed esophageal varix (grade II) and erosive antral gastritis. His computed tomography (CT) scan of hepato-biliary system revealed smaller size liver with hypertrophied caudate lobe with coarse and heterogenous parenchymal attenuation and splenomegaly and on fibroscan his CAP was 197 dB/m and LSM was 19.2 kPa.

The diagnosis of AIH was confirmed at hepatic histology which revealed mild distortion of lobular architecture and mild dysplasia in hepatocytes. He had chronic hepatitis with dense portal lymphoplasmacytic infiltrate, moderate interface hepatitis, mild lobular necroinflammatory activity and moderate periportal fibrosis. Progressive fibrosis of limiting plate led to enlargement of portal tracts and stellate periportal fibrosis extension. Hepatocyte rosettes, perivenular necrosis, interface hepatitis, cholestasis and bile duct injury were also present (Figure 1).

Since the patient also had no biochemical anomaly, he was put on azathioprine 50 mg/day, orally maintenance therapy.

The third patient was a middle-aged lady aged 60 years present with right upper right quadrant abdominal pain, loss of appetite and recent weight loss.

Her hemoglobin was 12.8 gm/dl, total WBC count 10,000/cumm, total platelet count 220,000/cumm, serum bilirubin 0.49 mg/dl, serum ALT 99 U/L, serum AST 102 U/L, serum albumin 4.47 g/dl, INR 1.00 and alpha feto-protein 2.97 ng/ml.

Her ANA was positive, but HBsAg, anti-HBc (total), anti-HCV, ASMA, anti-LKM-1 and AMA tested negative. Contrast enhanced triphasic computed tomography (CT) scan of hepatobiliary system showed coarse hepatic parenchyma with multiple hypodense areas in both lobes of liver, which showed homogeneous enhancement. Endoscopy of UGIT was normal.

Liver biopsy was done. Histopathology showed, mild distortion of lobular architecture with moderate dysplasia of hepatocytes. Chronic hepatitis with dense portal lymphoplasmacytic infiltrate, moderate interface hepatitis, mild lobular necro-inflammatory activity and moderate periportal fibrosis, progressive fibrosis of the limiting plate leading to enlargement of portal tracts and stellate periportal fibrous extension was noted. Features related to autoimmune hepatitis like hepatocyte rosettes, perivenular necrosis, emperipolesis, interface hepatitis, cholestasis and bile duct injury were also seen. A few syncytial multinucleated giant cells were present (Figure 3). Diagnosis of autoimmune hepatitis and periportal fibrosis was thus made.

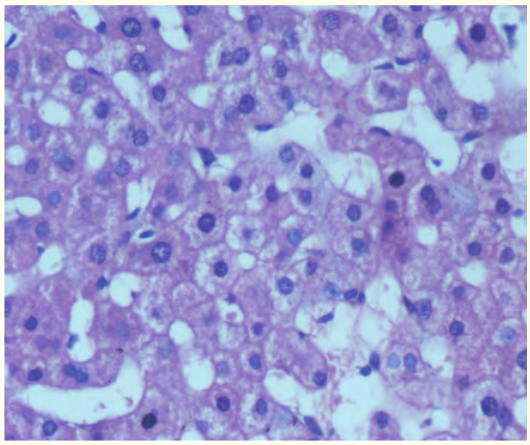

Figure 2: H&Ex200; Hepatic histopathology of the patient showing hepatocyte rosettes, moderate interface hepatitis, moderate periportal fibrosis, enlargement of portal tracts and stellate periportal fibrosis extension.

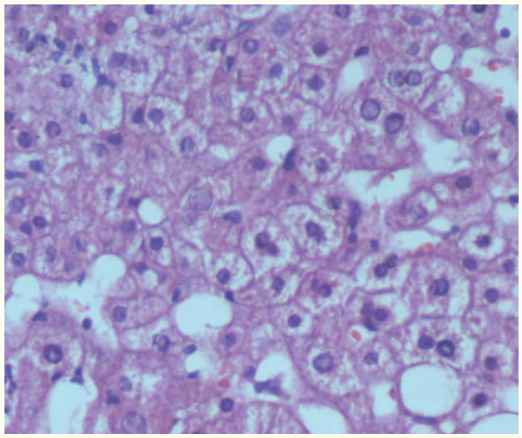

Figure 3: H&Ex200; Hepatic histopathology of the patient showing hepatocyte rosettes, perivenular necrosis, emperipolesis, interface hepatitis and glycogenotic nuclear changes of hepatocytes.

Fine needle aspiration cytology of hepatic space occupying lesion revealed moderate cellular smears showing atypical epithelial cells mostly in trabecular pattern in small aggregates and singly. These cells had hyperchromatic nuclei and eosinophilic nucleoli and moderate amount of cytoplasm. These cells were mildly pleomorphic. Some of the cells contained bile within cytoplasm with blood and few inflammatory cells on the background (Figure 4).

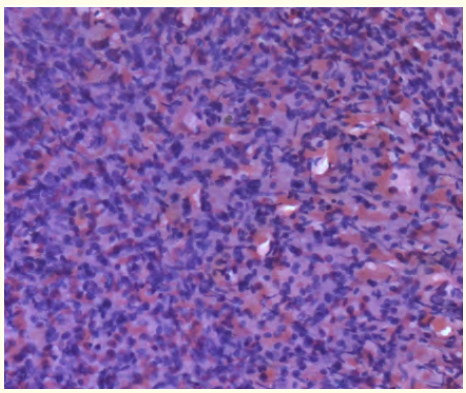

Figure 4: Papanicolaoux400; Hepatic fine needle aspiration cytology of the patient showing atypical epithelial cells mostly in trabecular pattern in small aggregates and singly. These cells have hyperchromatic nuclei and eosinophilic nucleoli and moderate amount of cytoplasm. Some of the cells contains bile within cytoplasm.

The final diagnosis was therefore autoimmune hepatitis related cirrhosis of liver with hepatocellular carcinoma. She underwent transarterial chemoembolization (TACE) and was prescribed oral prednisolone 10 mg/day till normalization of liver enzymes and then azathioprine 50 mg/day orally maintenance therapy. She also received lenvatinib 8 mg/day orally. Both the second and the third patients tolerated azathioprine well without any adverse event.

Table 2 summarizes the finding of the three patients for easy comparision.

Literature Review

AIH is seen in genetically predisposed individuals. The two HLA alleles that have been predominantly associated with AIH are HLA-DR3 and HLA-DR4 [6]. However, these may vary in different ethnic groups and geographic locations [7]. Imbalance between pro-inflammatory and regulatory immune mechanisms are important in the development of AIH [8,9]. AIH results when the fine balance between regulatory cells (Th1, Th17 and Th22), activated macrophages, complement and natural killer cells is disrupted [10].

However, environmental factors are crucial for triggering the expression of AIH. Viral infections (e.g. hepatitis viruses, measles virus, cytomegalovirus, Epstein-Barr virus and varicella zoster virus), drugs (e.g. nitrofurantoin, minocycline, oxyphenistatin, ornidazole, diclofenac, atorvastatin, methyldopa, interferon, infliximab, natalizumab and adalimumab and herbal medicines) and vaccines (e.g. SARS-CoV-2) have all been implicated as potential environmental triggers for AIH [2,11-20]. Recently the aberrant activation of the immune system by commensal microbiomes of the gut has also been implicated as environmental trigger. Increase in *Veillonella*, *Klebsiella*, *Streptococcus*, *Lactobacillus*, *Lachnospiraceae*, *Bacteroids*, *Roseburia*, *Faecalibacterium*, *Blautia*, *Hemiphilus*, *Eubacterium*, *Butyricicoccus* and *Ruminicoccaceae* and decrease in *Prevotella*, *Dilaster*, *Bifidobacterium* and *Parabacteroids* in the gut flora may trigger AIH expression acting through the gut-liver axis [21-24]. Besides, there is also alteration in oral microbiome in AIH with rise in *Streptococcus*, *Veillonella* and *Leptotrichia* [25].

Most patients present with AIH in their second, fifth or sixth decades, of whom 75% are females [26]. Clinical presentation of AIH is extremely varied. The commonest presentation is acute hepatitis with serum transaminases at least 5-10 times the upper

normal limit, jaundice and prolonged INR [27-32]. A fraction of these patients progress to develop fulminant hepatic failure [33-35]. Patients may also present with insidious onset with non-specific symptoms, e.g. fatigue, malaise, arthralgia and amenorrhea [36-39]. Sometimes liver cirrhosis may be the initial presentation [40,41]. AIH patients may also be asymptomatic, often associated with extra-hepatic autoimmune diseases, e.g. thyroid disease, coeliac disease and rheumatologic conditions and is often diagnosed incidentally [36-41].

There is no specific symptom, sign, biochemical or histological feature characteristic of AIH and therefore diagnosing AIH remains a challenge [26]. Several autoantibodies, namely ANA, ASMA, anti-LKM1, anti-liver cytosol antibody type-1 (anti-LC1) and anti-soluble liver antigen/liver pancreas antibodies (anti-SLA/LP) have been associated with AIH and are hallmarks of the disease. IgG may be raised in serum. Role of imaging in AIH is limited and is restricted to assessment of liver cirrhosis and its complications [42].

Histology of liver is mandatory for diagnosing AIH. Liver histology typically reveals interface hepatitis, which is the histologic hallmark of the disease and is characterized by portal inflammation with dense plasma-rich infiltrates extending beyond limiting plates Liver histology typically reveals interface hepatitis [43]. However, as there is no specific histologic feature pathognomonic of AIH, presence of at least two of three histologic features, namely interface hepatitis, emperipolesis and hepatocellular rosettes is mandatory for confirmatory diagnosis of AIH [44].

The diagnosis of AIH is based on simplified scoring system, which allows distinction between AIH from other conditions with concurrent immune features (Table 1) [45,46]. ANA and ASMA are markers of type-1 AIH, while anti-LKM1 and anti-LC1 are present

Variable	Cut-off	Points[a]
ANA or SMA/F-actin	Positive[b]	1
ANA or SMA/F-actin	Strongly positive[c]	
Or anti-liver/kidney/microsomal antibody type 1	≥1:40	2
Or anti-soluble liver antigen antibody	Positive	
IgG	>Upper limit of normal	1
	>1.1× upper limit of normal	2
Liver histology (with evidence of hepatitis)	Compatible with AIH	1
	Typical AIH	2
Absence of viral hepatitis	Yes	2

Table 1: Simplified criteria for autoimmune hepatitis (AIH): update of serologic criteria [26].

ANA = Antinuclear Antibodies; F-actin = Filamentous Actin; IFT = Indirect Immunofluorescence; SMA = Smooth Muscle Antibodies.

[a]Addition of points achieved (maximum 2 points for autoantibodies). ≥6 points = probable AIH; ≥7 points = definite AIH.

[b]IFT ≥1:40 when assessed on tissue sections; ≥1:80 or 1:160 for ANA when assessed on HEp-2 cells, depending on local standards; enzyme linked immunosorbent assay with locally established cut-offs.

[c]IFT ≥1:80.

Variable	First Patient	Second Patient	Third Patient
Serum bilirubin	0.7 mg/dL	0.6 mg/dL	0.49 mg/dL
Serum ALT	125 U/L	25 U/L	99 U/L
Serum AST	134 U/L	23 U/L	102 U/L
Serum albumin	4.4 gm/dL	4.56 gm/dL	4.47 gm/dL

INR	1.1	1.1	1.0
α-feto protein	-	2.1 ng/ml	2.97 ng/ml
Haemoglobin	14.4 gm/dL	12.2 gm/dL	12.8 gm/dL
Total WBC	8120/cumm	3700/cumm	10,00/cumm
Platelet count	100,000/cumm	96,00/cumm	220,000/cumm
Serum ceruloplasmin	160 mg/L	250 mg/day	-
Urinary copper	24 αgm/L	52.4 **αgm/day**	-
Anti-HCV	Negative	Negative	Negative
HBsAg	Negative	Negative	Negative
Anti-HBc Total	Negative	Negative	Negative
ANA	Negative	Positive	Positive
ASMA	Negative	Negative	Negative
Anti LKM1	Negative	-	Negative
AMA	Negative	-	Negative
Abdominal ultrasonography/CT	Fatty liver (grade I)	Coarse liver, hypertrophied caudate lobe, splenomegaly	Coarse liver, multiple hypodense areas
CAP (baseline)	272 dB/m	197 dB/m	-
LSM (baseline)	7.6 kPa	19.2 kPa	-
Endoscopy of UGIT	Normal	Oesophageal varix (grade II)	Normal
K-F Ring	Absent	Absent	-
NAS score	6/8	-	-
Serum ALT (at 6 months)	83 U/L	-	-
Serum AST (at 6 months)	85 U/L	-	-
CAP (at 6 months)	231 dB/m	-	-
LAM (at 6 months)	9.3 kPa	-	-
Histopathology	Consistent with AIH	Consistent with AIH	Consistent with AIH
Fine needle aspiration cytology	-	-	Consistent with HCC

Table 2: Findings of the patients.

in type-2 AIH [1]. However, this sub-classification of AIH is of no clinical significance, as it does not affect treatment [47,48].

Treatment of AIH is challenging, but at the same time rewarding too as untreated patients may develop liver failure. If untreated, the average survival in AIH is 5 years, while with treatment patients achieve long term survival with good quality of life [26]. The mainstay of treatment is to induce remission evidenced by normalization of serum transaminases and IgG levels [49], which may take up to 6 months to achieve. However, complete remission is achieved in 75% patients. Persistently mildly elevated serum transaminases may lead to progression of hepatic fibrosis [50,51]. Steroids remain the preferred first-line drug for AIH management, with 0.5 to 1 mg/kg body weight prednisolone administered orally. However, in case of fulminant AIH, high dose intravenous prednisolone up to 100 mg daily is administered. In case of the later group of patients, lack of improvement of liver function with first 7-14 days is an indication of emergency liver transplantation as these patients are at risk of developing fulminant hepatic failure [34,35]. In most cases however, response to steroid is rapid and liver function improves within 7 days.

Budesonide at a starting dose of 9 mg/day is an alternative first-line treatment of AIH, which is not associated with steroid-related

adverse events. Having said so, budesonide takes longer time to induce remission and may be associated with the development of diabetes mellitus [52,53].

Azathioprine is the drug of choice for maintenance therapy, usually started at a lower dose of 50 mg/day orally after steroid-induced remission is achieved [54,55]. The dose of azathioprine is increased to 1-2 mg/kg body weight either as monotherapy or in combination with low dose steroid. Once full biochemical response is achieved, steroid is tapered off and minimum dose of azathioprine is continued, just enough to sustain the response.

Intolerance to azathioprine is not uncommon. In such cases 6-mercaptopurine is used, which is the first metabolite of azathioprine and is well tolerated by up to 50% patients who are intolerant to azathioprine [56,57]. For patients who are intolerant to both azathioprine and 6-marcaptopurine, the second-line drug of choice is mycophenolate mofetil at a dose of 2 gm/day. Allopurinol is added if the response is insufficient and when this approach also fails third-line options are limited due to lack of controlled clinical trials [56,58].

Treatment of AIH is long-term and usually life-long. Immunosuppression can be eventually withdrawn in 10-20% AIH patients. Liver transplantation is indicated in fulminant hepatic failure, decompensated liver cirrhosis and hepatocellular carcinoma as a consequence of AIH. The later develops in 1-9% patents with AIH with an annual incidence of 1.1-1.9% [59-61]. AIH recurs in 8-12% AIH patients within first 5 years and in 36-68% after 5 years following liver transplantation [26].

We reviewed the literature for case reports of AIH from Bangladesh. In 2008, our group reported the first two cases of AIH from Bangladesh [62]. The cases represented two extremes of the disease spectrum. One of the patients was a young female in her twenties, who was asymptomatic and was diagnosed with AIH based on positive ANA and hepatic histopathology, while exploring for her unexplained raised serum transaminases levels. The second patient, on the other hand, was an elderly gentleman in his early seventies. He had decompensated liver cirrhosis. In this case also the diagnosis was reached as ANA tested positive and hepatic histopathology supported the diagnosis. More recently, two cases of pediatric AIH have been reported [63]. Both patients were females, aged 8.5 and 10.5 years respectively. The first patient had decompensated liver cirrhosis. The second patient also had liver cirrhosis which was compensated and initially diagnosed and treated as systemic lupus erythematosus (SLE). Both patients were anti-LKM1 positive, while the second patient also tested positive for ASMA. In both cases, the diagnosis was confirmed by hepatic histopathology. All these four cases of AIH, so far reported from Bangladesh were managed with initial prednisolone, followed by azathioprine-maintenance therapy.

Conclusion

Diagnosis and management of AIH remains challenging and

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