Acute Exacerbation to Autoimmune Hepatitis Mimicking Acute Viral Hepatitis—A Case Series and Review of Literature

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Background: Acute exacerbation of Autoimmune Hepatitis (AIH) poses a significant challenge for diagnosis as it can mimic acute viral hepatitis especially in absence of autoantibodies and hypergammaglobulinemia. **Aim:** To determine the clinical, laboratory, histopathological characteristics and response to treatment in AIH patients with acute exacerbation. **Methods:** A retrospective analysis of 16 patients with acute exacerbation of AIH diagnosed over a period of eight years (2008–2016). **Results:** Out of the 111 patients diagnosed with AIH, acute exacerbation of AIH was diagnosed in 16 (14.4%) patients. All patients were females with median age of 35 years. Nine patients (56%) had Type 1 AIH and seven (44%) patients were diagnosed with seronegative AIH. All 16 (100%) patients had acute viral hepatitis like illness at presentation. The median bilirubin was 4.2 mg/dl (range, 2.2–20), aspartate transaminase was 568 IU/L (range, 390–908), alanine transaminase was 430 IU/L (range, 257–1026) and serum alkaline phosphatase was 395 IU/L (range, 112–890) during symptomatic period. The histopathological examination showed underlying chronic hepatitis in 10 (71.4%) patients, only fibrosis in 2 (14.2) patients and cirrhosis with activity in 2 (14.2%). All 16 (100%) patients were treated with a combination of steroids and azathioprine. Thirteen (81%) patients achieved complete biochemical remission and three (19%) patients achieved partial remission out of which one (6%) patient succumbed to illness because of the complications of cirrhosis. **Conclusion:** A suspicion of acute exacerbation of AIH should be considered in patients with unexplained acute hepatitis mimicking acute viral hepatitis in the absence of positive viral markers. Through evaluation with immunoserological markers and liver biopsy can clinch the diagnosis of acute exacerbation of AIH in such cases. (J CLIN EXP HEPATOL 2018;8:98–103)

Autoimmune Hepatitis (AIH) is a chronic inflammatory liver disease of unknown etiology characterized by increased globulins and the presence of autoantibodies in the blood, with characteristic liver histology and a good response to immunosuppressive

therapy.^{1,2} The spectrum ranges from asymptomatic cases to acute hepatitis, chronic hepatitis, cirrhosis and fulminant hepatic failure. Acute AIH has been described in up to 25% cases and association with concomitant autoimmune diseases are reported in one-third patients.^{3,4} As recently proposed, acute presentation of AIH can now be classified into two subtypes, that is genuine acute AIH where there is no evidence of chronicity on liver biopsy and acute exacerbation of AIH where liver biopsy shows evidence of fibrosis and chronicity.⁵

Acute exacerbation of AIH poses a significant challenge for diagnosis as it can mimic acute viral hepatitis especially in absence of autoantibodies and hypergammaglobulinemia.⁵ Even though AIH is being recognized more frequently now, there is sparse literature on acute presentation of AIH from India. Hence this retrospective analysis was undertaken to determine the clinical, laboratory, histopathological characteristics, treatment and outcome of patients with acute exacerbation of AIH.

MATERIAL AND METHODS

This retrospective analysis was done to determine the clinical profile of all the 16 patients with acute

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Abbreviations: AASLD: American Association of Study of Liver; AIH: Autoimmune Hepatitis; ALKM-1: Liver/Kidney Microsomes; ALT: Alanine Transaminase; AMA: Antimitochondrial Antibody; ANA: Antinuclear Antibodies; ANCA: Anti-neutrophil Cytoplasmic Antibody; ASMA: Anti-smooth Muscle Antibodies; AST: Aspartate Transaminase; CBR: Complete Biochemical Response; CT: Computed Tomography; ELISA: Enzyme-linked Immunosorbent Assay; IAIHG: International Autoimmune Hepatitis Group; IIF: Indirect Immunofluorescence; INR: International Normalized Ratio; MRCP: Magnetic Response Cholangiopancreatography; PBC: Primary Biliary Cirrhosis; PBR: Partial Biochemical Response; PSC: Primary Sclerosing Cholangitis; SAP: Serum Alkaline Phosphatase
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exacerbation of AIH diagnosed and managed in the Department of Hepatology, Post Graduate Institute of Medical Education and Research, Chandigarh, India over a period of eight years from 2008 to 2016.

Diagnosis of Autoimmune Hepatitis

The diagnosis of AIH was based on simplified IAIHG criteria⁶:

Definition of Acute AIH: A cut off of bilirubin >2 mg/dl and Alanine Transaminase (ALT) or Aspartate Transaminase (AST) levels >10 times the Upper Limit of Normal (ULN) with or without an abnormal International Normalized Ratio (INR).⁴

- Type 1 AIH was diagnosed by the presence of circulating Antinuclear Antibodies (ANA) and/or Anti-Smooth Muscle Antibodies (ASMA), elevated serum IgG and compatible histopathology.⁷
- Type 2 AIH was diagnosed by the presence of Antibodies to Liver/Kidney Microsomes (ALKM-1), elevated serum IgG and compatible histopathology.⁷
- Seronegative AIH was diagnosed by the absence of conventional autoimmune markers but elevated IgG and compatible histopathology.⁷
- Acute severe AIH was defined by the INR >1.5 in patients with elevated bilirubin.⁸
- The diagnosis of overlap syndrome was based on the Paris diagnostic criteria of the associated diseases.⁹ Patients with AIH-PBC overlap had associated positive Antimitochondrial Antibody (AMA) and compatible PBC histopathology whereas the diagnosis of AIH-PSC was based on associated radiological changes of PSC on MRCP with or without compatible histology.⁹

Clinical Assessment

A detailed clinical history using a precoded questionnaire and hematological and biochemical parameters were taken from the outdoor or indoor case record file of these patients. The history of onset of illness, acute or precipitating events, blood transfusion, surgery, menstrual abnormalities, history of alcohol and other hepatotoxic drugs, presence of concomitant autoimmune diseases and family history of autoimmune diseases were specifically noted.

Laboratory Investigations

The laboratory data included a Complete Blood Count (CBC), liver functions tests, renal function tests, coagulation profile and serological testing for chronic viral hepatitis B and C by ELISA (enzyme-linked immunosorbent assay). Since all patients had acute presentation, serologies for hepatitis A virus, hepatitis E virus, cytomegalovirus, Epstein-Barr virus and Herpes simplex virus were also obtained. The screening for Wilson's disease was done by serum ceruloplasmin assay.

Immunological Assessment

In all patients, immunological assessment was done by in-house Indirect Immunofluorescence (IIF) for Antinuclear

Antibody (ANA), Smooth Muscle Antibody (SMA), Liver Kidney Microsomal-1 antibody (ALKM-1), AMA and Anti-Neutrophil-Cytoplasmic Antibody (ANCA). These were considered positive in titers of at least 1:40. The nephelometry method was used to determine the serum Immuno-globulin-G (IgG) levels.

Radiological and Endoscopic Assessment

The results of the abdominal ultrasound, abdominal Computed Tomography (CT) scans or Magnetic Resonance Imaging (MRI) at the time of diagnosis were reviewed. The Magnetic Resonance Cholangiopancreatography (MRCP) was reviewed in patients with suspected overlap syndrome. The upper gastrointestinal endoscopic examination was performed to look for features of portal hypertension in patients with suspected cirrhosis.

Histopathological Assessment

A total of 14 patients underwent liver biopsy. Two patients refused for liver biopsy and were diagnosed by the clinical and laboratory criteria. Percutaneous liver biopsy was done in 11 patients. In three patients with deranged coagulogram and thrombocytopenia, an expert Hepatologist performed a transjugular liver biopsy. An experienced histopathologist examined all the 14 liver biopsies and specifically looked for features of acute AIH. The histopathological parameters that were assessed included: (1) components of necro-inflammatory score namely; portal inflammation, interface hepatitis, lobular inflammation and confluent hepatic necrosis (according to Ishak's modification of Knodell's scoring system); (2) fibrosis grading (according to Ishak's modification of Knodell's scoring system); the special histological parameters that were noted included: (a) type of portal inflammatory infiltrate; (b) the presence or absence of hepatocyte loss, lymphoid follicle, bile duct inflammation, steatosis, pericellular fibrosis, rosetting, emperipolesis, kupffer cell hyperplasia, feathery degeneration, intrahepatic and/or intracanalicular cholestasis, ductopenia and/or ductular proliferation (assessed by CK7 immunostain), cola colored granules in the periportal hepatocytes (evaluated by Orcein stain) and any dysplastic nodule. The necessary stains that were employed included Hematoxylin and Eosin, Reticulin, Masson Trichrome, Periodic Acid-Schiff (PAS) with and without diastase, Perls' and Orcein stains along with CK7 immunohistochemistry. The presence of portal based inflammatory infiltrate with or without the presence of plasma cells along with interface hepatitis, emperipolesis and hepatocyte rosette formation were considered consistent with the diagnosis of AIH.

Treatment

The absolute indications for treatment were a serum AST >10 times the ULN or serum AST >5 times the ULN and

serum globulin level >2 times the ULN and presence of bridging necrosis or multiacinar necrosis on histopathological examination or presence of incapacitating symptoms. The relative indications for treatment were symptoms (fatigue, arthralgia, jaundice), serum AST and/or serum globulin less than absolute criteria and presence of interface hepatitis on biopsy.¹⁰ We defined the response to treatment as complete or partial biochemical remission according to liver enzyme levels and improvement in clinical symptoms. The Complete Biochemical Response (CBR) was defined as normalization of the liver enzymes, and Partial Biochemical Response (PBR) was defined as a reduction of liver enzymes to less than two times the ULN. All patients were started on a combination of prednisolone 30 mg and azathioprine 50 mg once a day as per the AASLD guidelines.¹⁰ All patients with overlap syndrome received ursodeoxycholic acid in the dose of 13–15 mg/kg/day.

Statistical Analysis

The continuous variables were expressed as mean, Standard Deviation (SD), median and ranges. The Student's *t*-test or Mann-Whitney test, was used to assess differences in the means of continuous data. Statistical analysis was performed using SPSS version 18.0 (SPSS, Chicago, IL, USA). *P*-value <0.05 was considered statistically significant.

RESULTS

Clinical and Demographic Characteristics

Out of the 111 patients diagnosed with AIH over a period of eight years, acute exacerbation of AIH was diagnosed in 16 (14.4%) patients. All 16 (100%) patients were females with the median age of 35 years (range, 16–52 years). Acute exacerbation was more commonly seen in older age group of 30–50 years in 12 (75%) patients rather than at younger age. Type 1 AIH was diagnosed in nine (56%) patients with median age of 45 years (range, 16–52 years) and seronegative AIH was diagnosed in seven (44%) patients with median age of 33 years (range, 21–47 years). Severe acute AIH was observed in eight (50%) patients. There was no history of drug intake in all the patients. The presence of overlap syndrome was seen in four (25%) patients. AIH-PBC overlap was diagnosed in three (19%) patients and AIH-PSC overlap was diagnosed in one (6%) patient. All the 16 (100%) patients were symptomatic and had jaundice at initial presentation. The clinical and demographic characteristics of patients are shown in Table 1.

Laboratory Investigations

Type 1 AIH was diagnosed in nine (56%) patients based on the positive ANA and/or ASMA. ANA alone was positive in four (25%) patients ASMA alone was positive in one (6%)

Table 1 The Demographic And Clinical Characteristics Of Patients With Acute Exacerbation Of AIH.

Demographic and clinical characteristics	Total patients (n = 16)
Age (years)	35 (16–52)
Sex (female:male)	16:0
Duration of symptoms (months) from onset to diagnosis	3.5 (1–36)
Duration of follow up (months)	46.5 (10–96)
Concurrent autoimmune disease, n (%)	4 (25)
1. Hypothyroidism	3 (19)
2. Celiac disease	1 (6)
Symptoms, n (%)	
• Jaundice	16 (100)
• Fatigue	11 (68.7)
• Anorexia	7 (43.7)
• Abdominal discomfort	6 (37.5)
• Pedal edema	5 (31.2)
• Fever	3 (18.7)
• Pruritus	3 (18.7)
• Menstrual abnormalities	3 (18.7)
• Arthralgia	1 (6.2)
• Weight loss	1 (6.2)
Signs, n (%)	
• Icterus	16 (100)
• Pedal edema	5 (31)
• Hepatomegaly	5 (31)
• Ascites	4 (25)
• Splenomegaly	2 (12.5)
• Acne	2 (12.5)

Values are presented as median (range) unless otherwise stated.

patient, and four (25%) had both ANA and ASMA positivity. Seven (44%) patients were classified as seronegative AIH being negative for ANA, ASMA, and anti-LKM antibodies. AMA-M2 was positive in all three patients with AIH-PBC overlap. The baseline laboratory parameters of the patients are shown in Table 2.

Radiological and Endoscopic Characteristics

The ultrasound imaging showed evidence of portal hypertension in four patients (25%). The MRCP of AIH-PSC overlap patient showed multiple strictures in both intrahepatic and extra hepatic bile ducts with beaded appearance. Gastroscopy demonstrated features of portal hypertension in seven (44%) patients with the presence of small esophageal varices in six (38%) and large esophageal varices in one (6%) patient. Portal hypertensive gastropathy (PHG) was present in five (31%) patients, and the combination of varices with PHG was observed in four (25%) patients.

Table 2 The Baseline Laboratory Investigations Of The Patients With Acute Exacerbation Of AIH.

Laboratory investigation (normal)	Median (range)
Bilirubin (0.1–1.2 mg/dl)	4.2 (2.2–20)
AST (2–40 IU/L)	568 (390–908)
ALT (2–41 IU/L)	430 (257–1026)
SAP (40–129 IU/L)	395 (112–890)
Albumin (3.5–5.3 g/dl)	3.5 (2–4.5)
Globulin (2–3.5 g/dl)	3.6 (2.7–9)
Total IgG (650–1850 mg/dl)	2276 (1264–6700)
INR	1.45 (1.07–2.6)
Sodium (mEq/L)	139.5 (136–148)
Creatinine (mg/dl)	0.7 (0.4–0.9)
Hemoglobin (g/dl)	12.1 (8.3–13.2)
TLC ($\times 10^3 \mu\text{l}$)	8.1 (4.2–22.3)
Platelet count ($\times 10^5 \mu\text{l}$)	1.7 (0.59–4.53)
Immunological markers	n (%)
1. ANA	4 (25)
2. ASMA	1 (6)
3. AMA	3 (19)
4. ANA + ASMA	4 (25)

Values are presented as median (range) unless otherwise stated, n – number of patients.

Histopathological Characteristics

On histopathological examination, three cases showed predominantly fibrosis and one of them showed an occasional pre-cirrhotic nodule. These biopsies were transjugular liver biopsies and were tiny, thereby precluding an adequate assessment of all the histopathological parameters in two out of these three biopsies. All the cases showed at least stage 2 fibrosis, the mean fibrosis score being 3. None of the cases showed any perivenular hepatocyte dropout or necrosis. The clinical, biochemical and serological evaluation of all these patients along with the histopathology findings were consistent with the diagnosis of AIH. It is noteworthy to mention that all the features of classical AIH were not present in all the cases and a clinical correlation was warranted. The histopathological characteristics of the patients are described in Table 3.

Treatment and Response of Acute AIH

Since all 16 patients had acute exacerbation of AIH they were treated with a combination of steroids and azathioprine with a median duration two months (range, 1–5 months) for starting treatment after the presentation to the liver clinic. Fifteen (94%) patients received prednisolone with starting dose of 30 mg/day and budesonide was given in one non-cirrhotic young patient at a dose of 9 mg/day in view of severe acne vulgaris. All patients

received a starting dose of 50 mg/day of azathioprine. Steroids were tapered as per response, and azathioprine dose was escalated to a maximum tolerated dose (1.5–2 mg/kg). In three (19%) patients thrombocytopenia worsened requiring dose reduction of azathioprine and one (6%) patient developed acute pancreatitis necessitating azathioprine withdrawal. Minor side effects like acne were observed in two (13%) patients and recurrent infections such as UTI, and soft tissue infections were observed in three (19%) patients with steroids. None of the patients required hospitalization for these complications except one patient with acute pancreatitis that improved with conservative treatment. Thirteen (81%) patients out of 16 who received immunosuppression achieved normalization of biochemical parameters along with complete resolution of symptoms. The mean duration to achieve biochemical remission was 11.6 ± 11.8 months (range, 1–38 months) with 10 (62.5%) patients achieving within 12 months. Three (19%) patients achieved complete resolution of clinical symptoms along with partial biochemical remission out of which one (6%) patient succumbed to illness because of the complications of cirrhosis after 48 months of follow-up. No patient required second-line drug treatment for achieving biochemical remission. Successful withdrawal of steroids could be possible in two patients with Type I AIH based on persistent biochemical remission. Four (25%) patients developed flares during therapy, two (12.5%) developed flare during reduction of the dose of steroids and two (12.5%) patients were non-compliant to treatment. These flares were managed with increasing the dose of steroids or restarting of immunosuppression.

DISCUSSION

AIH is more diverse than other liver diseases and usually runs a slowly progressive smoldering course. AIH is relatively rare in India with a prevalence of around 5–8.5% of all patients with chronic liver disease.¹¹ The studies from Europe have reported a prevalence of around 16–18 cases per 1 million people.^{12,13} The acute presentation of AIH has been reported in up to 25% of patients worldwide.^{1,3,4} In our study, the acute presentation was seen in 14.4%, this is similar to previous studies from West as well as India.^{11,14,15} The prevalence of AIH-PBC overlap is low ranging from 7% to 9.2%.^{21,22} These patients have more severe disease, younger age of presentation and worse outcome regarding response to therapy and liver-related mortality.^{23–25} Similarly in our study three (18.7%) patients that presented with AIH-PBC overlap syndrome had younger age and more severe disease.

In our study all patients were females with median age of 35 years. An earlier series from Japan also reported older age of presentation in patients with acute exacerbation of AIH as compared to chronic AIH (56.0 ± 20.0 years vs.

Table 3 Histopathological Findings And Diagnosis In Patients With Acute AIH.

Pathological characteristic	Score		
Mean portal tract inflammation score	2.9		
Mean interface hepatitis score	2.8		
Mean lobular inflammation score	2.1		
Mean confluent hepatic necrosis score	0		
Presence of lymphocytes, <i>n</i> (%)	12 (100)		
Presence of plasma cells, <i>n</i> (%)	9 (75)		
Presence of eosinophils, <i>n</i> (%)	6 (50)		
Presence of polymorphs, <i>n</i> (%)	3 (25)		
Kupffer cell hyperplasia, <i>n</i> (%)	10 (83)		
Rosetting, <i>n</i> (%)	9 (75)		
Hepatocyte loss, <i>n</i> (%)	6 (50)		
Emperipolesis, <i>n</i> (%)	3 (25)		
Ductopenia, <i>n</i> (%)	2 (17)		
Bile duct inflammation, <i>n</i> (%)	2 (17)		
Intrahepatocytic cholestasis, <i>n</i> (%)	8 (67)		
Intracanalicular cholestasis, <i>n</i> (%)	3 (25)		
Orcein positive granules in periportal hepatocytes, <i>n</i> (%)	3 (25)		
Histopathological diagnosis	Total (<i>n</i> = 14)	Type 1 AIH (<i>n</i> = 7) ^a	Seronegative AIH (<i>n</i> = 7)
Chronic hepatitis	10 (71.4)	5 (71.4)	5 (71.4)
Inadequate biopsy (only fibrosis)	2 (14.2)	1 (14.2)	1 (14.2)
Cirrhosis with activity	2 (14.2)	1 (14.2)	1 (14.2)

Values are presented as number (percentage) unless otherwise stated.

^aBiopsy was not available in 2 patients.

45.5 ± 15.0 years, $P < 0.05$).¹⁶ All our patients had initially presented like acute viral hepatitis and were later diagnosed as AIH on work up for persistently deranged liver functions. In our study the autoantibodies were undetectable in 44%, this is similar to other studies from Italy, The United States and Japan where 27%, 31% and 29% patients were negative for ANA, 18%, 15% and 68% patients were negative for ASMA respectively.^{17–20}

Liver biopsy and histopathological examination are warranted in all patients with AIH because of frequent deviations from the classical phenotype. Approximately 18–55% have shown evidence of acute exacerbation of AIH in previous studies.^{26–29} The studies have also shown that around 30% of AIH patients have cirrhosis at presentation.^{30–34} In our study, all the 16 (100%) patients had evidence of acute exacerbation and in four (25%) patients who presented with ascites; only two (50%) patients had evidence of cirrhosis on histopathology. None of our cases showed pure acute hepatitis in the form of perivenular hepatocyte necrosis or multiacinar or panacinar confluent hepatic necrosis on histopathology. Instead all the patients in this study showed evidence of activity in the form of portal inflammation, interface hepatitis and lobular inflammation in the background of

portal fibrosis of at least stage 2. The presence of background portal fibrosis often is an important clue to the patients with acute exacerbation. In a previous study by Fujiwara K et al. which included 18 patients with acute AIH only seven (39%) showed severe acute hepatitis and 10 (56%) showed severe activity with fibrosis stage 2–3 suggesting acute exacerbation similar to our study.³³ In a recent study by Abe et al. which comprised of 41 patients with biopsy proven acute AIH most patients showed (87.8%) acute exacerbation and only five patients were in (12%) acute hepatitis phase,³⁴ suggesting that most patients have underlying chronicity on biopsy even if they present acutely similar to our study.

Only a few case studies are available regarding the treatment regimens and prognosis in patients with acute exacerbation of AIH. In the earliest report by Nikias et al. patients with acute exacerbation of AIH have shown a good response to corticosteroids.²⁹ Similarly in our study also 81% patients achieved biochemical remission, i.e., normalization of LFT along with complete resolution of symptoms and 19% achieved partial biochemical remission. More than 50% patients achieved remission within 12 months, however we could stop steroids in only two patients on subsequent follow-up.

In conclusion a suspicion of acute exacerbation of AIH should be considered in patients with unexplained acute hepatitis mimicking acute viral hepatitis in the absence of positive viral markers. Through evaluation with immunoserological markers and liver biopsy can clinch the diagnosis of acute exacerbation of AIH in such cases.

CONFLICTS OF INTEREST

The authors have none to declare.

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