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Persistent Jaundice in Autoimmune Hepatitis: A Case Report

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Abstract

A 24 years young male with no prior history of jaundice now presented with progressive jaundice and hepatomegaly. Autoimmune serology and liver biopsy revealed features of autoimmune hepatitis. He was started on oral prednisolone and azathioprine, following which he attained remission. However, he persisted in having hyperbilirubinemia with a predominant unconjugated fraction. Hemolytic causes of unconjugated hyperbilirubinemia were ruled out, and the diagnosis of Gilbert Syndrome was established.

Keywords: Autoimmune hepatitis • Hyperbilirubinemia • Gilbert syndrome

Background

Autoimmune Hepatitis (AIH) is a chronic inflammatory disease of the liver, causing immune-mediated hepatocellular injury. The disease is seen across all age groups with a higher predilection for the female sex [1,2]. Although the clinical presentation is highly inconstant, the usual presentation is hepatocellular jaundice, elevated transaminase, and constitutional symptoms. AIH can also present with specific overlap syndromes such as Primary Biliary Cholangitis (PBC), Primary Sclerosing Cholangitis (PSC), and cholestatic hepatitis with additional pruritus, a cholestatic pattern of deranged liver enzymes and positive specific autoimmune serology (positive antimitochondrial antibody (AMA)) [3]. Presence of unconjugated hyperbilirubinemia in such patients suggests either associated haemolysis or familial causes of hyperbilirubinemia. These article minutiae about patient who was diagnosed to be type 1 autoimmune hepatitis and attained a remission on steroids but persisted to have clinical jaundice, and on thorough workup for the cause, he was found out to be having Gilbert syndrome.

Case Presentation

A 24 years old male with no significant previous medical history presented with progressive jaundice and dull aching right upper quadrant pain for two months. The patient also had occasional nausea and vomiting. However, he denied any history of pruritus, alcohol abuse, prior blood transfusions, illicit drug or over the counter medication use, no recent travel or multiple sexual partners. He also denied any family history of the liver disease. The physical exam was completely normal.

Laboratory findings were noteworthy for deranged liver function tests in the form of raised AST (244 U/L), ALT (311 U/L) and total bilirubin of 28 mg/dl with a direct fraction of 18 mg/dl, the patient alkaline phosphatase was 245 IU/L, and International Normalized Ratio (INR) was 1.1. Ultrasound abdomen and Magnetic resonance cholangiopancreatography were unremarkable. An extensive workup was done to find the etiology of elevated liver enzymes. The patient serology for hepatotropic viruses (HBV, HCV, HEV, and HAV), Wilson disease, and hemochromatosis workup was negative. The patient serum autoantibodies for AIH, including Antinuclear Antibody (ANA), Smooth Muscle Antibody (SMA) were positive, anti-Liver Kidney Microsome (LKM) type 1, anti-liver cytosol antibody type 1 (anti-LC1), Anti-Mitochondrial Antibodies (AMA) was negative. The patient Total gamma globulin levels are also elevated (Table 1). Liver biopsy demonstrated lymphoplasmacytic infiltrate with marked interface activity and multiple areas of confluent necrosis consistent with autoimmune hepatitis. The patient was given a combination of prednisone (30 mg) and azathioprine (50 mg). The patient liver function tests showed improvement over 3 to 4 weeks in normalizing elevated transaminases. Total gamma globulin levels also normalized. However, the patient bilirubin was persistently elevated (bilirubin (total)-5 mg/dl), with an elevated indirect fraction.

He was further evaluated for evidence of any hemolytic cause of unconjugated hyperbilirubinemia, including hemoglobinopathies, which turned out to be negative. Given young male and unconjugated hyperbilirubinemia, a strong suspicion of gilbert syndrome was considered, and the genotyping showed polymorphisms in the UDP

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Glucuronosyltransferase Family 1 Member A Complex Locus (UGT1A) gene with significantly decreased enzyme activity.

Table 1: Gamma globulin levels.

Investigation	Day 1	Day 7	Day 14	Day 21	Day 45	Day 60	Day 90
Hb (13-15gm/dl)	12.5	13.5			14.2		13.9
TLC (4000-7000/mm^3)	11200	9400			7900		8200
Platelet count (1.5-4lakh/mm^3)	349000	421000			389000		375000
Bilirubin (T) 0.3-1.2 mg/dL	28	24	9.5	6.5	4.54	4.1	5.65
Bilirubin (D)	18	12	4.3	0.89	0.33	0.48	0.45
AST/ ALT (0-40 IU/dl)	244/311	151/182	114/160	49/72	38/42	18/20	11/20
ALP (30-240U/L)	245	468	187	165		141	156
GGT (0-55U/L)	38	24				23	22
Protein (6.4-8.3mg/dl)	9.9	7.8	6.9			8	7.6
Albumin (3.5-5gm/dl)	4.2	4.4	3.8			4.6	5
Total IgG levels (<1600mg/dl)	4500						899

Results and Discussion

Autoimmune Hepatitis (AIH) was first described in 1951 [4] as a chronic inflammatory liver disease of unknown etiology, causing immune-mediated hepatocyte injury [5]. It is characterized by the presence of interface hepatitis with plasma cell infiltration on histology, hypergammaglobulinemia, and autoantibodies [6]. Both the categorization and diagnosis of AIH depend primarily on serum autoantibodies. Based on different serum autoantibodies, AIH is categorized into three types (types I, II, and III) [7]: ANA, SMA, LKM type 1, and anti-SLA. Other autoantibodies, including Anti–F-actin b, Anti–LKM 3, Anti–Asialoglycoprotein Receptor (ASGPR), and anti–LC1, are less often tested but have both diagnostic and prognostic significance [8]. Simplified Diagnostic Criteria (SDC) were validated by the International Autoimmune Hepatitis Group (IAIHG) in 2008 [9], which require specific autoantibody titres (ANA, SMA, or anti-LKM1), hypergammaglobulinemia, and characteristic histological features in patients with suspected AIH after ruling out other conditions that resemble AIH. A score of 6 is considered likely, while a 7 is deemed diagnostic of AIH, with a sensitivity of 97 to 100 % and a specificity of 66 to 92 % [9]. Overlap syndromes are defined by the presence of AIH and characteristics of cholestatic liver disorders, implying that AIH coexists with either PBC or PSC [8]. The primary goal of therapy is to achieve remission. Glucocorticoids (both prednisolone, budesonide) with or without azathioprine remains the mainstay of treatment in the setting of disease flares in AIH [5]. Both prednisolone monotherapy and prednisolone with azathioprine combination therapy are equivalent in efficacy for induction with azathioprine monotherapy as maintenance [10]. The presence of unconjugated hyperbilirubinemia raises pathophysiologic suspicion of various conditions involving increased bilirubin production or altered bilirubin metabolism (uptake and conjugation) or both. Haemolysis is common in autoimmune hepatitis; both coombs positive autoimmune hemolytic anemia due to polyautoimmunity and coombs negative hemolytic anemia due to splenomegaly are possible. Unconjugated hyperbilirubinemias can also be caused by inherited bilirubin conjugation abnormalities such Gilbert and Crigler-Najjar syndromes. This inherited syndrome occurs due to mutations in the UGT1A1 gene and impairs bilirubin conjugation. The complete or near-complete absence of UGT1A1 enzyme activity occurs in Crigler-Najjar syndrome, wherein decreased UGT1A1 enzyme activity (10 to 30% of normal) results in mild unconjugated hyperbilirubinemia in Gilbert syndrome [11]. The decreased activity of UGT1A1 results from the addition of extra Thymine-Adenine (TA) repeats in the TATAA box region of the UGT1A1 gene promoter Individuals with an increased number of TA repeats in the gene promoter for UGT1A1 (usually >7 in both alleles) are often diagnosed with Gilbert [12]. Gilbert syndrome occurs in up to 10% of the general population and Gilbert syndrome being a benign disorder require no treatment. Although incidence of AIH less in male population, when presented with AIH with persistent Unconjugated hyperbilirubinemias a clinical possibility of Gilbert syndrome to be kept after ruling out haemolytic causes.

Conclusion

Autoimmune Hepatitis (AIH) is characterized by a chronic immune-mediated liver injury, which is often complicated and needs the evaluation of several parameters. Jaundice in AIH is predominantly hepatocellular type. The presence of cholestatic type liver injury predicts the coexistence with either Primary Biliary Cholangitis (PBC) or Primary Sclerosing Cholangitis (PSC). Pre hepatic jaundice/unconjugated hyperbilirubinemia is uncommon, but when present, one has to think of additional hemolytic causes or inherited syndrome such as gilbert syndrome.

Author Contributions

Conceptualization and initial draft preparation: Budumuri Gautam V Kumar. Manuscript editing: Rohit Gupta. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors have no personal, financial, or other conflicts to disclose.

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