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Single Case

A Novel Presentation of Autoimmune Hepatitis with IgG1 Elevation

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Abstract
Autoimmune hepatitis (AIH) is a common and debilitating pathology that has acute, subacute, and chronic presentation, requiring prompt diagnosis and early intervention. Several serologic markers are found to be associated with the pathogenesis and progression of autoimmune hepatitis, most notably antinuclear antibodies and anti-smooth muscle antibodies [Front Immunol. 2018;9:609]. In addition, AIH is also characterized by the elevation of gamma globulin levels, mainly immunoglobulin G (IgG) [World J Gastroenterol. 2015;21(1):60–83]. Although the literature has well established the presence of increased IgG levels in AIH, few studies have evaluated the subtypes of IgG and their differential levels associated with AIH. Here, we present a rare case of AIH that lacks the common serologic markers but instead reveals an elevation in IgG1 level. Our patient was subsequently placed on corticosteroids, and her symptoms quickly resolved. We intend to introduce this case to the medical community in the hope of aiding in the proper diagnosis and timely intervention of subsequent cases with similar presentations.

Introduction

Autoimmune hepatitis is characterized by chronic and progressive immune-mediated destruction of liver parenchyma and functions. The worldwide prevalence of the disease ranges from 4 to 25 per 100,000 population per year, with female predominance [1–5]. The hallmarks of autoimmune hepatitis are the presence of a number of autoantibodies and/or the

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elevation of serum gamma globulin levels. The disease follows a diagnosis of exclusion: etiologies with similar presentations as acute AIH, such as viral hepatitis, alcoholic hepatitis, drug-induced liver injury, and Wilson's disease, must be ruled out. In chronic cases of AIH, consideration should also be given to rule out alpha-antitrypsin deficiency, hemochromatosis, and celiac disease. In addition, the diagnosis of AIH requires compatible histological findings, including interface hepatitis and/or lymphocyte-predominant inflammatory infiltrate [6]. It is further supported by the following features, including the elevation of one serum aminotransferase two times the upper limit of the reference range and the presence of at least one serologic marker or gamma globulin elevation. Serologic markers that have been reported to be present in autoimmune hepatitis are, but not limited to, antinuclear antibodies (ANA), anti-smooth muscle antibodies, anti-liver-kidney microsomal-1 antibodies (anti-LKM-1), anti-mitochondrial antibody, and less commonly, anti-liver cytosol antibody-1 (ALC-1), anti-soluble liver antigen/liver pancreas antibody (anti-SLA/LP), and atypical perinuclear anti-neutrophil cytoplasmic antibodies [7–9]. Twenty percent of cases of the AIH cases are seronegative and diagnosis is based on elevated liver enzymes, biopsy, and ruling out other etiologies [10]. Due to the varied clinical and laboratory presentations of AIH, a simplified score system was developed to diagnose AIH. This system calculates a score based on the following features: the level of ANA or SMA, LKM1 antibody, SLA, IgG, liver histology, and presence of viral hepatitis. A final score of 6 or above suggests probable AIH, while a score of 7 or above indicates definite AIH [11].

Despite a well-built association of gamma globulin elevation in AIH, there is scarce literature that characterizes the involvement of different subtypes of IgG in AIH. Herein, we report a case of AIH with a distinctly elevated IgG1 level. The patient was successfully treated with corticosteroids.

The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000530517).

Case Report

A 24-year-old Latino female was admitted to our department with right upper quadrant abdominal pain. She had a 2-week history of jaundice, nausea, vomiting, dark urine, and fatigue. Her past medical history was significant for polycystic ovarian syndrome. There was no history of hepatotoxic substances or drug intake. There was no family history of liver conditions or autoimmune diseases.

The patient's vitals were stable upon admission: the body temperature was 97.5°F, heart rate was 67 beats per minute, blood pressure was 110/50 mm Hg, and respiration rate was 16 breaths per minute. The patient presented with mild scleral icterus. There was no abdominal distension, shifting dullness, palpable abdominal masses, spider angioma, or any manifestation of cirrhosis. Subsequent laboratory results revealed serum aspartate aminotransferase (AST) of 1,085 U/L (normal range: 13–39 U/L), alanine aminotransferase (ALT) of 1,529 U/L (normal range: 7–52 IU/L), alkaline phosphatase (ALP) of 105 IU/L (normal range: 34–104 U/L), total bilirubin of 8.0 mg/dL (normal range: 0.3–1.0 mg/dL), prothrombin time of 16.6, international normalized ratio of 1.46, and albumin of 3.0 (normal range: 3.5–5.7 g/dL).

There was no presence of any of the autoantibodies associated with AIH, including ANA, anti-mitochondrial antibodies, anti-smooth muscle antibodies, or anti-chromatin antibodies. However, serum IgG was elevated: 2,279 mg/dL (normal range: 600–1,640 mg/dL). Of the four subtypes of IgG, IgG1 was elevated compared to the subtypes (2, 3, and 4): 966 mg/dL (normal range: 382–929 mg/dL).

Serum virology workup for viral hepatitis A, B, C, and E was negative. Meanwhile, there was also the absence of serological markers for other viral infections, including infectious mononucleosis, cytomegalovirus, herpes simplex virus, adenovirus, or human immunodeficiency virus. Laboratory workup for alpha-1-antitrypsin deficiency and Wilson's disease revealed normal alpha-1-antitrypsin level (159 mg/dL, normal: 83–199 mg/dL) and ceruloplasmin level (26 mg/dL, normal: 18–53 mg/dL).

HFE genetic testing was performed, which revealed that this patient was negative for the C282Y and H63d pathogenic variants. This negative result significantly reduces the likelihood of hereditary hemochromatosis.

Right upper quadrant ultrasound reveals normal liver size and echogenicity. The gallbladder was contracted with cholelithiasis without evidence of acute cholecystitis. The portal venous system, splenic vein, and hepatic veins are patent and have normal flow directionality. There was no intrahepatic or extrahepatic duct dilation or segmental bile duct strictures. MRI reveals normal hepatic parenchyma.

Liver biopsy revealed extensive portal and lobular mixed inflammatory infiltrate shown in Figure 1a, including lymphocytes, neutrophils, and eosinophils. Significant interface activity associated with hepatocyte ballooning, scattered acidophil bodies, focal confluent hepatocyte necrosis, and pigment-laden macrophages was also observed, evidenced by Figure 1b and c. No viral inclusion was detected, and immunostaining for cytomegalovirus was negative.

Our patient was ultimately diagnosed with autoimmune hepatitis associated with elevated IgG1 levels. Initial dose of Solu-Medrol 125 mg was given on hospital day 5 followed by Solu-Medrol 40 mg every 8 h until discharge. From the initiation of steroids, liver enzymes trended down drastically, shown in Table 1 and Figure 1d. The patient was subsequently discharged with a tapering oral prednisone regimen. Repeat laboratory workup 3 days following discharge shows AST of 165 U/L, ALT of 506 U/L, ALP of 106 IU/L, and total bilirubin of 3.4 mg/dL. The patient reported feeling well during her follow-up appointment a month following discharge. She reported continued resolution of her abdominal pain, nausea, and vomiting. The patient was taking 25 mg of prednisone daily at the time of the encounter. A phone interview with the patient 2 months following the discharge revealed good medication compliance and tolerability. Laboratory workup 2 months following discharge revealed total bilirubin of 0.6 mg/dL, AST of 51 U/L, ALT of 42 U/L, and ALP of 53 IU/L.

Discussion

Our young female patient presented with acute onset of jaundice, nausea, and elevated transaminases, consistent with acute hepatitis. Hepatitis is a syndrome of liver parenchymal inflammation and impaired functions caused by a constellation of differentials, the most common being alcohol or drug-induced etiologies and viral hepatitis. Through extensive laboratory and imaging investigations, we have ruled out other etiologies with similar presentation to AIH, including viral hepatitis, alcohol or drug-induced liver injury, alpha-1-antitrypsin deficiency, Wilson's disease, primary sclerosing cholangitis, and hereditary hemochromatosis. This diagnosis was further supported by compatible liver histology. This patient received the final diagnosis of seronegative AIH with a score of 6 of the simplified AIH diagnostic system (absence of viral hepatitis, serum IgG 2,279 mg/dL, >1.1 times the upper limit of normal). This patient subsequently received treatment with IV Solu-Medrol daily and transitioned to oral prednisone daily. Her liver enzymes gradually trended down. Her abdominal pain and jaundice subsequently resolved, along with normalization of liver function tests 2 months following her discharge.

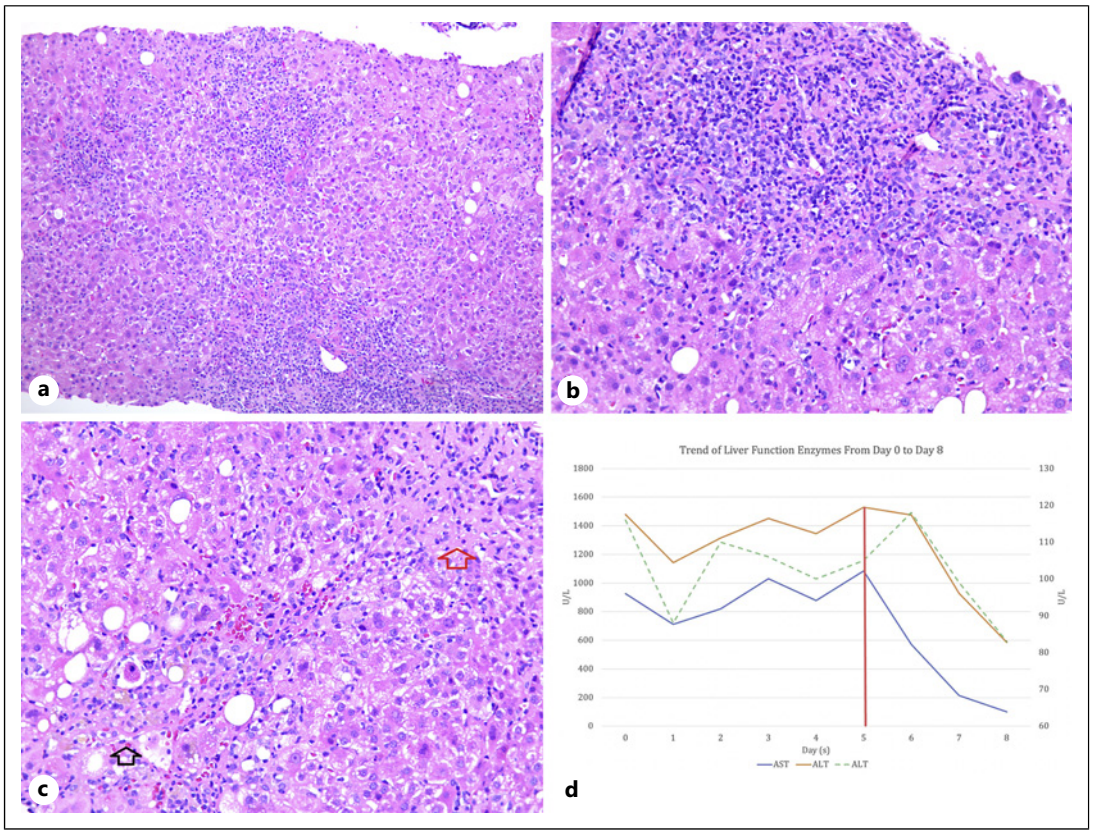

Fig. 1. a Histological evaluation of hepatic parenchyma. Low power image of the liver showing diffuse portal and lobular mixed inflammatory infiltrate including lymphocytes, plasma cells and eosinophils. **b** Close view of histological evaluation of hepatic parenchyma. Here we can observe a close view of prominent interface activity. **c** Histological evaluation of hepatic parenchyma. Red arrow points to the area of confluent hepatocyte necrosis and the black arrow points to an area of pigment-laden macrophages and one acidophil body (apoptosis). **d** Liver function test value trends from hospital day 0 to day 8. Red line marks hospital day 5 when steroid was introduced.

Table 1. Liver function tests values from hospital day 0 to day 8. Steroid was introduced on hospital day 5, after which liver function test values down trended

	Hospital day 0	Hospital day 1	Hospital day 2	Hospital day 3	Hospital day 4	Hospital day 5	Hospital day 6	Hospital day 7	Hospital day 8
AST	926	712	820	1,031	877	1,085	571	214	100
ALT	1,480	1,143	1,315	1,452	1,346	1,529	1,472	928	585
ALP	116	88	110	106	100	105	118	99	83
Total bilirubin	5.7	5	5.9	7	5.6	8	6.7	5.2	4.2

Our patient illustrates a unique case of AIH with IgG1 elevation. IgG1 has been reported to be associated with several autoimmune etiologies, including primary biliary cirrhosis, rheumatoid arthritis, systemic lupus erythematosus, Sjogren syndrome, and systemic sclerosis [12, 13]. The exact role of IgG1 in inducing autoimmunity remains unclear. However, one study has demonstrated that a common IgG1 single-nucleotide polymorphism (SNP) in East

Asian populations is associated with evading checkpoint mechanism that normally inhibits autoreactive IgG-positive B cells. These autoreactive IgG1s then in turn cause immune complex formation, tissue destruction, and multi-organ pathology. This SNP polymorphism was selectively elevated in SLE patients and associated with increased disease severity [14] Therefore, we postulate that similar mechanism might play a role in the pathogenesis of AIH in our patient, where a polymorphic variant of IgG1 bypasses regulatory checkpoint and induces self-reactivity, which in turn activates hepatic lymphocytic response and parenchymal inflammation.

Although AIH can ultimately lead to liver failure without treatment, it is a highly treatable disease that responds well to corticosteroids [15]. Therefore, early intervention before the genesis and exacerbation of fibrosis is the key to improving disease prognosis. Subtypes of IgG were rarely studied in autoimmune disorders, particularly AIH. We are yet to understand the role of IgG1 in the pathogenesis and disease progression of AIH. We hereby hope this case with unique IgG1 elevation raises the question and piques interest in investigating IgG1, a common biomarker for autoimmunity, and its association with AIH, which will further enhance the awareness and understanding of AIH and aid in the timely diagnosis and early treatment of this disease. In addition, we hope this newly discovered association contributes to developing a new potential biomarker for AIH, thus making the diagnosis of AIH, a condition with highly variable laboratory associations, a more comprehensive and sensitive system.

Statement of Ethics

Ethical approval is not required for this study in accordance with national guidelines. Identifying information about the patient was not included in the manuscript or its supplementary files. Written informed consent was obtained from the patient for publication of the details of their medical case and accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to report.

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Author Contributions

Yujiao Zhang wrote the introduction, case presentation, discussion/conclusion, and literature review. Bilal Niazi provided review and edit of the manuscript, review of the current literature, and interpretation of laboratory, imaging, and pathology evaluation. Hongfa Zhu provided histology with interpretation. Auda Auda, Amer Jarri, Angel Chacko, Abdifatah Mohamed, Saad Ali, and Syed Sirajuddin assisted in reviewing the entire manuscript.

Data Availability Statement

All data analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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