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Case Report

Autoimmune hepatitis presenting with concomitant chronic pancreatitis ☆,☆☆

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ABSTRACT

Autoimmune Hepatitis (AIH) is a progressive form of chronic hepatitis, with periods of remissions and exacerbations. Diagnosis includes abnormally high levels of immunoglobulins and multiple autoantibodies. Clinical presentation is variable, with a spectrum extending from asymptomatic cases to fulminant liver failure. Symptoms include abdominal pain, malaise, fatigue, and small joint arthralgia. We present a case of a 36-year-old male with a past medical history of alcohol dependence and acute pancreatitis who was diagnosed with AIH. There is limited data regarding patients with concomitant AIH and pancreatitis. Our patient presented with AIH with secondary acute on chronic pancreatitis, in the absence of additional autoimmune manifestations. The mechanism of AIH remains poorly understood; however, there is an association between the HLA gene and AIH. Genetic studies have shown HLA-DRB1*0301 and HLA-DRB1*0401 as primary and secondary genotypes susceptible to AIH, as well as genetic variants with CARD10 and SH2B3. Products secondary to metabolism of ETOH such as alcohol dehydrogenase, malondialdehyde, and acetaldehyde, can lead to development of autoantibodies. Additional research is indicated to evaluate the relationship between AIH and acute pancreatitis.

Introduction

Autoimmune Hepatitis is a progressive form of chronic hepatitis, characterized by periods of remissions and exacerbations. Diagnosis is made based on a combination of clinical and lab findings; abnormally high levels of immunoglobulins and multiple autoantibodies. The incidence of autoimmune hepatitis varies per geographic region, and has been com monly found in Scandinavian populations. In a Danish study

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evaluating 1721 patients with autoimmune hepatitis (AIH), the incidence was 1.68 per 100,000 population per year [1]. Of these patients who pursued biopsies (1318/1721), approximately 28% of them were found to have concomitant cirrhosis [1]. In this study, both history of cirrhosis and male gender were poor prognostic factors in terms of development of hepatocellular carcinoma and mortality [1]. In another Northern European study, the annual incidence of AIH was 1.9 per 100,000 [2]. In general with AIH, women have been found to have a greater predisposition for this disease when compared to men, with an approximate ratio of 3.6:1 [3]. In comparison, when we investigate incidence in the United States, the highest prevalence of 42.9 per 100,000, has been found in Alaska [4]. Here, we present a case of a 36-year-old male who was diagnosed with autoimmune hepatitis.

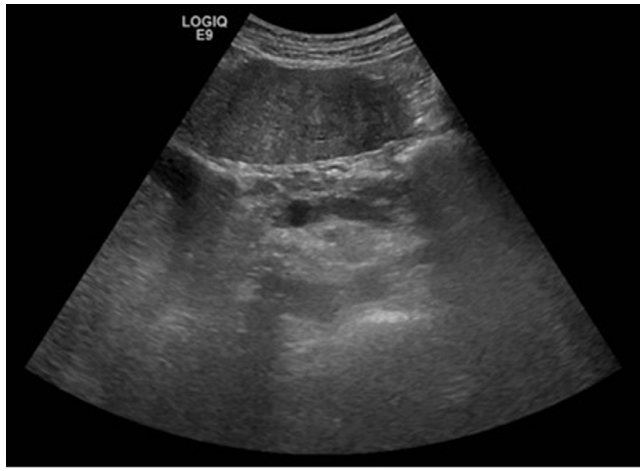
Case report

This is a 36-year-old African American male with a past medical history of alcohol use dependence (in remission for 2 years), tobacco use disorder, and acute pancreatitis, who presented to the Emergency Department (ED) with a chief complaint of abdominal pain for 2 days. The pain was reported to be nonradiating over the mid epigastric region and was described as dull in nature and 10/10 in intensity, with associated appetite loss, nausea, and approximately 8 episodes of NBNB vomiting. The patient endorsed his pain was exacerbated with movement and was mildly alleviated with rest. The patient denied relief of symptoms following a trial of over-the-counter Tylenol. He denied subjective fevers, chills, chest pain, dyspnea, diarrhea, constipation, unintentional weight loss, recent abdominal trauma or sick contacts. Of note, the patient endorsed similar complaints approximately 2 years prior when he was admitted for acute pancreatitis. The patient denied surgical history or family history of gastrointestinal disorders. In terms of his social history, he previously consumed 1 pint of hard liquor daily for a 10-year period, in which he discontinued 2 years prior to presentation. The patient endorsed tobacco use, smoking 10 cigarettes daily for 10 years.

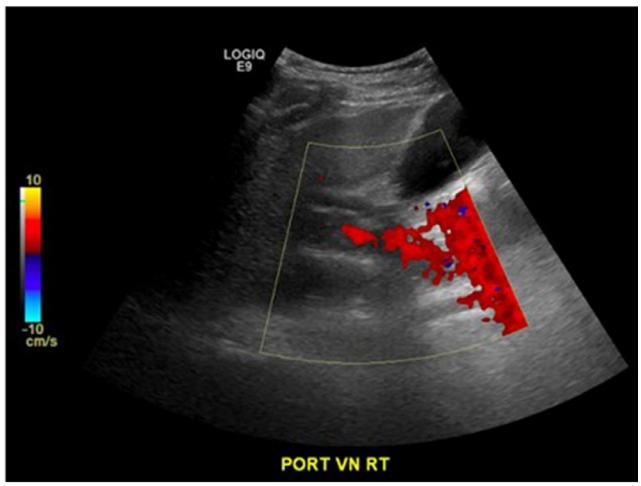
In the ED, the patient was hemodynamically stable, and he was afebrile. On his physical exam, there was no evidence of scleral icterus; however, the patient did exhibit icteric frenulum. In terms of his abdomen, on inspection, there was notable distension with absence of rash, ecchymoses, spider angiomas, or venous dilation. The patient had mid-epigastric tenderness to deep palpation, and was negative for splenomegaly, rebound tenderness, or voluntary guarding. The patient's liver span on percussion was 12 cm at the midclavicular line, without evidence of fluid wave or shifting dullness. Labs were significant for pancytopenia, lipase of 528, alkaline phosphatase of 129, AST of 114, ALT of 47, and hyperbilirubinemia with a total bilirubin of 4.9 (Table 1). Initial imaging with ultrasound (US) of the abdomen was notable for cirrhosis with possible cavernous transformation of the portal vein, heterogeneity of the pancreas, and gallstone sludge (Fig. 1A). The US portal vein was negative for portal venous thrombosis (Fig. 1B).

Table 1 – Initial laboratory studies.

Laboratory studies	Values	Reference ranges
WBC	3.9 × 10^3/mm^3	4.5-11.0
Hgb	12.6 g/dL	13.5-17.5
Hct	36.2%	41-53
Platelet Count	66 K/mm^3	140-440
Lipase	528 unit/L	11-82
Alkaline Phosphatase	129 unit/L	34-104
AST	114 unit/L	13-39
ALT	47 unit/L	7-52
Total Bilirubin	4.9 mg/dL	0.3-1.1



A



B

Fig. 1 – (A) [RUQ US] notable for cirrhosis. (B) [Portal Vein US] notable for cirrhosis with possible cavernous transformation of the portal vein.

The patient was admitted for further workup and management of acute pancreatitis. MRCP was performed, significant for cirrhotic liver with splenomegaly and varices, as well as with free fluid in the lesser sac along the pancreatic head, duodenum, and right retroperitoneum (compatible with acute pancreatitis). The CBD was dilated measuring 1cm greatest

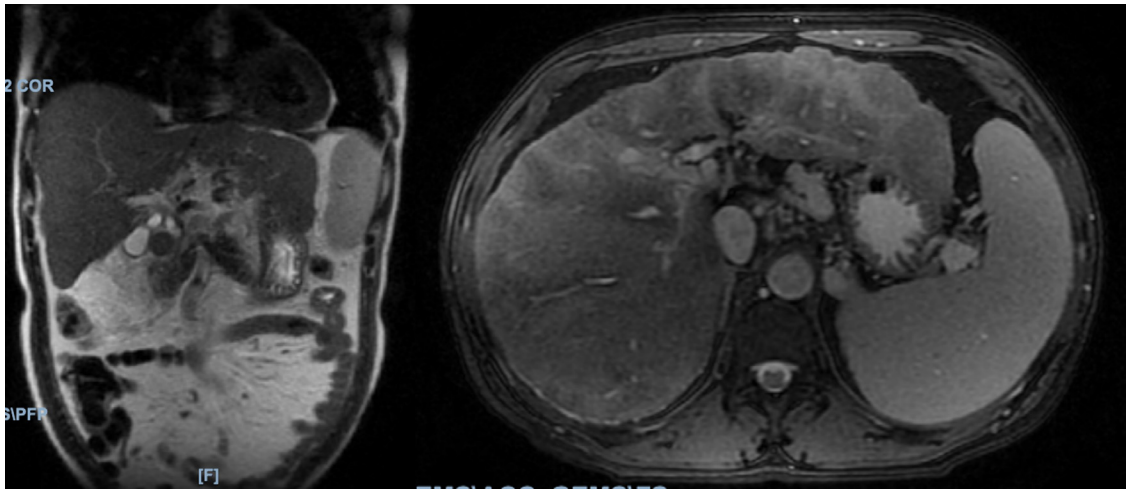


Fig. 2 – MRCP demonstrating cirrhotic liver with splenomegaly and varices, as well as with free fluid in the lesser sac along the pancreatic head, duodenum, and right retroperitoneum, with no evidence of choledocholithiasis (left coronal view, right axial view).

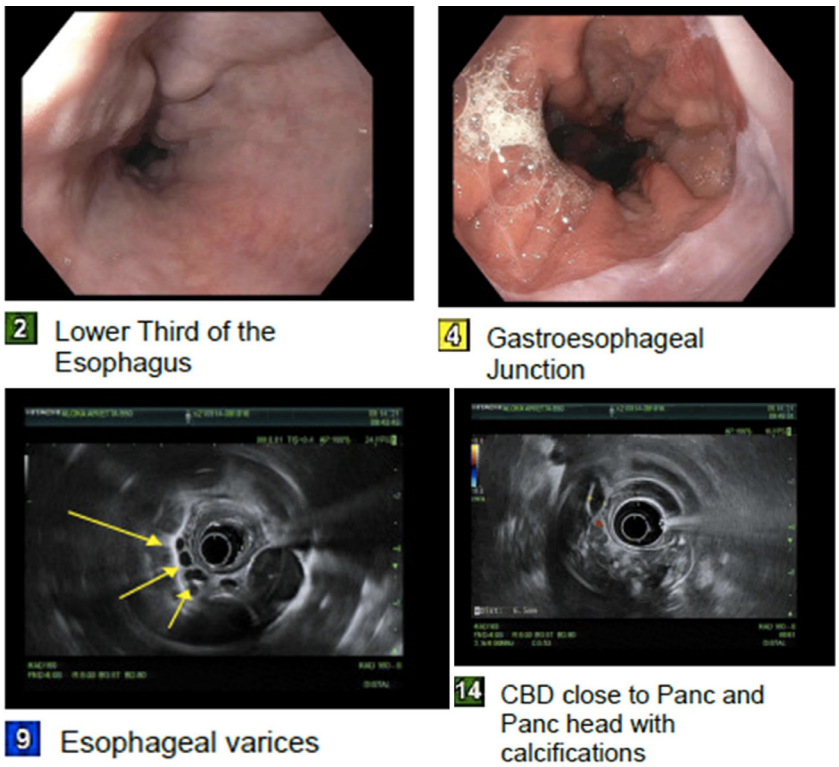


Fig. 3 – EGD with EUS significant for grade II and large (>5 mm) esophageal varices without evidence of bleeding or stigmata of recent hemorrhage (2, 4, 9), and pancreatic parenchymal abnormalities consisting of calcifications (14).

in diameter, with no evidence of choledocholithiasis (Fig. 2). EGD was performed, significant for grade II and large (>5 mm) esophageal varices without evidence of bleeding or stigmata of recent hemorrhage, with 2 cm hiatal hernia, portal hypertensive gastropathy, and pancreatic parenchymal abnormalities consisting of calcifications, diffuse echogenicity, hypoechoic foci and lobularity in the entire pancreas, consistent with chronic pancreatitis (Fig. 3).

The patient was managed with intravenous fluids for acute pancreatitis. Additional laboratory studies were remarkable for elevated actin smooth muscle antibody at 26 units (reference range: 0-19), ANA positivity, high alpha-1-antitrypsin levels and unremarkable ceruloplasmin levels. Ultimately, the patient decided to leave the hospital against medical advice; however, was provided with resources for hepatology follow up and referral to a university center for liver transplant.

Discussion

In general, patients who present with an autoimmune disorder have a higher susceptibility for developing additional autoimmune manifestations. However, per literature review, there is limited data surrounding incidence of patients who concomitantly present with AIH and pancreatitis. In a retrospective study analyzing AIH, 40% of patients were found to have an additional autoimmune process, with thyroiditis as the most common manifestation (10%) [5]. As for our patient, besides an episode of acute pancreatitis, thought to be directly related to his chronic alcohol use, there was no history of additional autoimmune disorders from the patient or from his family history. Our patient was an African American male, representing the minority of patients found to develop AIH. Our patient presented with a rare autoimmune disorder with secondary chronic pancreatitis, in the absence of additional autoimmune manifestations.

In terms of the pathophysiology of autoimmune hepatitis, the mechanism remains poorly understood. Evidence has demonstrated environmental and genetic factors, with association between the HLA gene and AIH [6]. Studies have demonstrated in the US that genetics may lead to differences in incidence of AIH, with alternate dispositions between Caucasian Americans and Black Americans [7]. There have been genetic studies regarding HLA-DRB1*0301 and HLA-DRB1*0401 as primary and secondary genotypes susceptible to AIH, as well as genetic variants with CARD10 and SH2B3 [8]. If our patient had been willing to undergo evaluation for hepatic transplant and additional testing, genetic studies may have been helpful in determining whether there was a genetic component to his development of AIH. In terms of the patient's past medical history, he did endorse chronic alcohol use for over 10 years, with a history of alcohol induced pancreatitis. It has been found that products secondary to metabolism of ETOH such as alcohol dehydrogenase, malondialdehyde, and acetaldehyde, can lead to development of autoantibodies [9,10]. Surprisingly, a case-control study based in New Zealand demonstrated that alcohol use decreased the risk of development of AIH with less than 50 g per week of consumption, with suspected moderate use of alcohol as a protective factor [11,12]. Additional studies have evaluated viral, bacterial, parasitic, microbiome, estrogen level, vaccination status, post-transplant outcomes, as well as vitamin D levels with regards to development of AIH. Ultimately, additional research is indicated to evaluate for clear, statistically significant etiologies of autoimmune hepatitis [13]. As our patient left the hospital against medical advice with limited workup completed, we are limited in our data when it comes to developing a suspicion for his etiology of AIH development.

There are several sequelae of concern that AIH patients are at risk of developing, some of which are related to specific treatment regimens, while others are simply due to disease progression. As with most other chronic liver diseases, AIH carries a substantial risk for progression to cirrhosis which studies have shown develops in nearly 33% of affected patients [14]. Further progression to a hepatobiliary cancer such as HCC is possible with AIH patients having a 15-fold greater incidence of developing such cancers compared to the general population, per a study done in New Zealand. This same study also found that patients with AIH had a 2-fold increased risk of developing extra-hepatic malignancies such as nonmelanoma skin cancers and hematological malignancies, but all the patients who developed these malignancies were on immunosuppressive therapy with either azathioprine, prednisone, or both for treatment of their AIH [11]. Such immunosuppressive therapies are known to put patients at increased risk for developing such extrahepatic malignancies and are commonly used first line agents for treatment of AIH. Other hepatic autoimmune diseases such as PSC and PBC may be present concomitantly with AIH and are called overlap syndromes when they present with it. A recent study found that the frequency of overlap with PBC is 7%-13% and overlap with PSC is 8%-17%, making this an important clinical presentation for clinicians to look out for as it can present as treatment resistant AIH and may require additional therapies such as ursodeoxycholic acid [15]. As previously stated, patients with 1 autoimmune condition such as AIH are at increased risk for developing nearly any other autoimmune condition.

In terms of treatment and prognosis guidelines have been set aside for various approaches to treatment options and length of medical regimen. One may also question what the consequences are if proper treatment is not started. Due to the continuous circulating autoantibodies, severe forms of untreated AIH often may lead to fibrosis of the liver which may result in cirrhosis needing liver transplant [16]. However milder forms of the disease where the synthetic function of the liver remains to be practically unaffected may continue without any form of treatment and close monitoring. Prior to starting treatment, it is recommended that a liver biopsy is obtained to have a clear visualization of the histological appearance of the liver and histological remission being the goal. It is recommended that patients with lab findings of AST >10 times the upper limit or normal, AST >5 times the upper limit and total IgG >2 of the upper limit should be started on immunosuppression therapy in a timely manner [17]. The current recommended regimen remains to be induction with prednisolone which has also been shown to prolong survival.

Alternatively, a lower dose of prednisolone 30-60 mg in combination with azathioprine 1-2 mg/kg/d has been shown to provide maintenance of remission [18]. The added benefit of combination treatment allows the use of a lower dose of steroids to avoid unnecessary side effects. Maintenance treatment for severe forms is preferred with Azathioprine which is often started 2-4 weeks after Prednisolone therapy and often starts at a 50 mg/d and increases the dose by 1-2 mg/kg/d with the goal being to discontinue the prednisolone. However medical management should be based on histological findings as transaminases and IGG may not always correlate with the pathological disease burden on the liver [18].

Currently the most promising alternative regiment has been mycophenolate mofetil at a dose of 2 g daily which has shown improvements in about 39%-84% of the patients [19]. Alternatively, multiple immunosuppressive therapy is being studied for the use of AIH. Of those the most studied Cyclosporine, which is a calcineurin inhibitor ultimately works on the calcium dependent signaling and inhibits T cells function. Two promising case studies have shown a positive response rate of roughly 80% however not currently studied in

randomized controlled trials [20]. Although a variety of immunosuppressive agents are available to use, many are limited with the number of clinical trials and others being hepatotoxins. Currently mainstream agents are to induction with prednisolone and ultimately switch to azathioprine or mycophenolate.

In our patient given that he signed out AMA multiple times from the hospital he was not able to be started on proper treatment. Efforts were made for proper outpatient follow-up however given poor compliance the patient was not started on prednisolone and was not able follow up with ultimate course of treatment.

Conclusion

Typically, patients with pre-existing autoimmune conditions have a higher chance of developing autoimmune hepatitis; however, limited literature is available with regards to patients with chronic pancreatitis and AIH. Here we describe a patient diagnosed with AIH who had no underlying autoimmune comorbidities. As our patient routinely consumed alcohol, his substance use was considered a possible contributing factor, as byproducts of alcohol metabolism can lead to autoantibody development. Steroids can be utilized for treatment, with alternative treatment of mycophenolate. This case introduces a patient with no known autoimmune comorbidities who presented with concomitant chronic pancreatitis and autoimmune hepatitis. Ultimately, additional research is warranted to fully understand the relationship between alcohol use, chronic pancreatitis, and autoimmune hepatitis.

Ethical review

Ethical review is not necessary, because this is a case report.

Author contribution

Dhruv Patel and Ahmed Salem are the article guarantors. Dhruv Patel, Ahmed Salem, and Brooke Kania performed the literature review and wrote the manuscript. All authors assisted in the collection of the patient's clinical data. All authors took part in the medical management of the patient and edited the final manuscript for submission. All work was performed at St. Joseph's University Medical Center at the corresponding author address.

Patient consent

Informed consent for publication of their case was obtained from the patient.

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