# A Case of a 65-year-old woman with Vitiligo and Diabetes presenting with Severe Autoimmune Hepatitis

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***ABSTRACT***
Autoimmune hepatitis (AIH) is a chronic liver disease with diverse clinical presentations and significant global variation in prevalence. AIH predominantly affects females and commonly manifests with nonspecific symptoms such as fatigue and malaise, often accompanied by extrahepatic autoimmune disorders. Here, we present the case of a 65-year-old Hispanic woman with vitiligo, type II diabetes mellitus, and severe AIH. Despite extensive diagnostic workup, including serological testing, the cause of this patient's hepatitis proved to be a challenge. Eventually, autoimmune testing revealed positive anti-smooth muscle antibodies and an elevated IgG, prompting percutaneous liver biopsy, which confirmed mild to moderate active hepatitis with mixed inflammatory infiltrate. Despite there not being a standardized diagnostic criterion for autoimmune hepatitis, the interdisciplinary hospital team agreed that the most likely diagnosis was autoimmune hepatitis, given her constellation of symptoms, serologic testing, and liver biopsy results. Treatment with prednisone was initiated, leading to clinical improvement. This case underscores the importance of a thorough diagnostic workup in suspected AIH cases, especially in patients with concomitant autoimmune conditions, to facilitate timely management and improve patient outcomes. It also highlights the need for a consensus among diagnostic criteria for autoimmune hepatitis.

***Keywords:*** *Autoimmune Hepatitis, Vitiligo, Jaundice*

## 1. Introduction

Autoimmune hepatitis is a chronic immune-mediated liver disease that presents with a variety of clinical presentations ranging from asymptomatic to fulminant hepatic disease.[1,2] It is a relatively rare disease with significant worldwide variation, with a global prevalence of 15.65 cases per 100,000 inhabitants.[2] While groups of patients have been reported in other countries, such as South America, these patients have not been sufficiently studied to determine the prevalence of the disease.[1,2] The disease predominantly affects females with a 3:1 female-to-male ratio, and the average age of diagnosis occurs around 40 years old1. If untreated, the 5-year survival rate is less than 25%; if appropriately treated, the 10-year survival rate is approximately 90%.[3]

Clinically, one-third of patients present with acute icteric hepatitis and cirrhosis, while the majority present with mild or subclinical disease.[1] Many patients report associated symptoms of fatigue, malaise, loss of appetite, and arthralgias1. Patients may present with extrahepatic autoimmune disorders such as Hashimoto thyroiditis, vitiligo, type 1 diabetes

mellitus, systemic lupus erythematosus, and rheumatoid arthritis–the strongest association being Hashimoto thyroiditis.[1]

In 2008, the International Autoimmune Hepatitis group developed a scoring system for clinical practice, which included four key features of the disease: hypergammaglobulinemia, autoantibodies, histology, and the absence of viral hepatitis. Characteristically, patients present with elevated IgG and normal IgM and IgA1. Patients may have positive antinuclear antibodies (ANA), smooth muscle antibodies (SMA), and antibodies to liver-kidney microsomes (LKM), all of which are not disease-specific.[1,4] On the other hand, antibodies to soluble liver antigen/liver-pancreas (SLA/LP) are disease-specific but are only present in a small portion of adult patients.[1]

On histology, typical autoimmune hepatitis includes interface hepatitis, portal, and periportal inflammation, presence of plasma cells, rosetting of hepatocytes, and emperipolesis (i.e., active penetration by one cell into and through a larger cell)[5,6] While vitiligo has been associated with autoimmune diseases, including type 1 diabetes mellitus, thyroiditis, and inflammatory bowel disease7,8, the association between type 2 diabetes mellitus and autoimmune hepatitis has not been adequately examined. Here, we present a case of a 65-year-old female with vitiligo, type 2 diabetes mellitus, and autoimmune hepatitis.

## 2. Case Presentation

The patient is a 65-year-old Hispanic female with a past medical history of diabetes mellitus II, vitiligo, hypertension, coronary artery disease, and dyslipidemia. She presented to the emergency department complaining of dizziness, nausea, non-bloody emesis for the past three days, and scleral icterus. On admission, the patient had a temperature of 36.7, pulse of 105, respiratory rate of 18, and blood pressure of 122/74. On physical exam, she had scleral icterus and diffusely jaundiced skin without bronzing or malar rash. The rest of the physical exam, including a neurological exam, was unremarkable. Initial labs showed anemia with a hemoglobin of 10.9, hematocrit of 32.5, WBCs of 6.7, and regular coagulation studies. Initial BMP showed hyponatremia at 130, creatinine at 1.09, and elevated glucose at 176. Hemoglobin A1C was 8.6%. Liver function studies were significant for ALT of 1504, AST of 1768, alkaline phosphatase of 837, total bilirubin of 8.5, direct bilirubin of 6.9, indirect bilirubin of 1.6, LDH of 497, and ammonia level of 57. TSH and ceruloplasmin were normal. Her brain CT was normal. An abdominal pelvic CT with IV contrast demonstrated right upper quadrant fat stranding adjacent to the gallbladder, possibly representative of cholecystitis, duodenitis, or peptic ulcer disease. There was a markedly enlarged porta hepatis with retroperitoneal lymph nodes, which were nonspecific. A right upper quadrant ultrasound revealed findings of possible cholecystitis. A HIDA scan demonstrated non-visualization of the small bowel, which raised suspicions about possible common bile duct obstruction.

MRCP showed acute hepatitis/acute hepatocellular disease with signs of periportal edema, gallbladder wall edema, and a trace amount of perihepatic fluid, negative for choledocholithiasis, and enlarged portocaval and porta hepatic lymph nodes, which were likely reactive. There was no evidence of obstructive cholangiopathy or choledocholithiasis. Portal hepatic Doppler showed slowed velocity in the main portal vein with mild splenomegaly, suggesting mild portal hypertension. The echocardiogram showed an ejection fraction of 55-60%. The hepatic synthetic function was well-preserved. Several days after admission, the patient's liver enzymes remained elevated, although they seemingly had plateaued. Antibody and antigen studies for CMV, EBV, Hepatitis C, B, and E were negative. HIV and QuantiFERON TB testing were also negative. Acetaminophen, salicylate, and alpha-1-antitrypsin were all negative. Copper levels were slightly elevated.

Since initial studies for the etiology of the elevation in LFTs and hyperbilirubinemia had been negative thus far, autoimmune testing was done. The patient had positive anti-smooth muscle antibodies, antimitochondrial antibodies,

and elevated IgG, so there was high suspicion of autoimmune hepatitis. She underwent percutaneous liver biopsy by interventional radiology. An emphasis was placed on testing for cell inclusions/heme deposits, specific immune testing for HSV, autoimmune hepatitis, and Prussian blue staining for hemochromatosis. Results of the biopsy showed mild to moderate active hepatitis with mixed inflammatory infiltrate (Figure I, II). There was no iron deposition or minimal fibrosis, but many inflammatory cells, including plasma cells, could indicate an autoimmune etiology (Figure III, IV). There were also eosinophils present. DNA testing for the most common HFE mutations for hemochromatosis was also negative. The differential diagnosis included autoimmune hepatitis versus drug-induced liver injury secondary to glipizide versus hemochromatosis. The patient was started on prednisone 40 mg daily following recommendations from the gastroenterology team and was discharged with the plan for her to have an outpatient follow-up with a gastroenterologist, ideally with a hepatologist.

Four months after the patient's discharge, she is feeling better. She was initially treated with prednisone 20 mg two tablets twice a day for a month. Then, one month and a half later, she was switched to azathioprine 500 mg oral daily. Her jaundice has resolved and her right upper quadrant abdominal pain has improved.

**Figure 1: Liver biopsy showing portal plasma cell-rich inflammation, interface hepatitis, and lobular chronic inflammation typical of autoimmune hepatitis.**

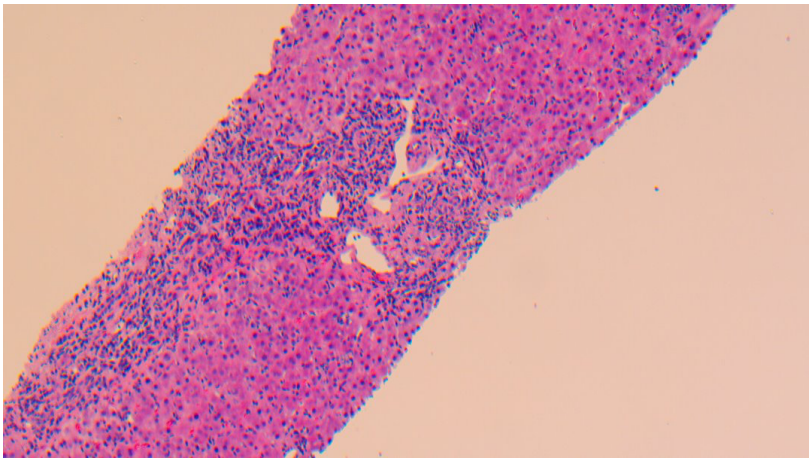


**Figure 2: Closer magnification portal plasma cell-rich inflammation, interface hepatitis, and lobular chronic inflammation typical of autoimmune hepatitis.**

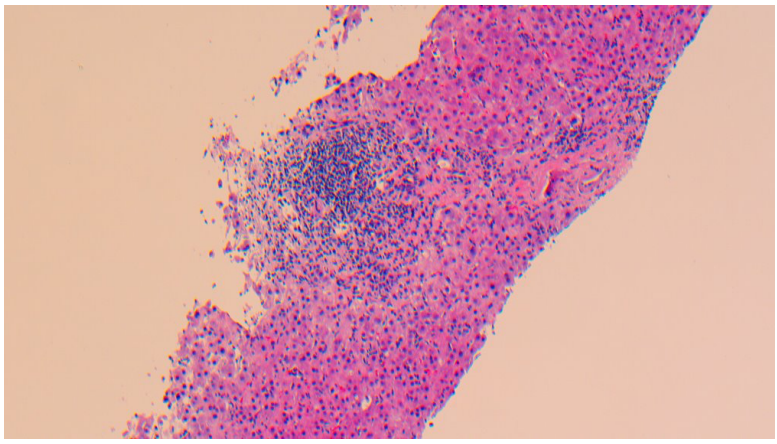


**Figure 3. Closer magnification of portal area with lymphocytic infiltrate and interface hepatitis with multinucleated giant cell (arrow).**

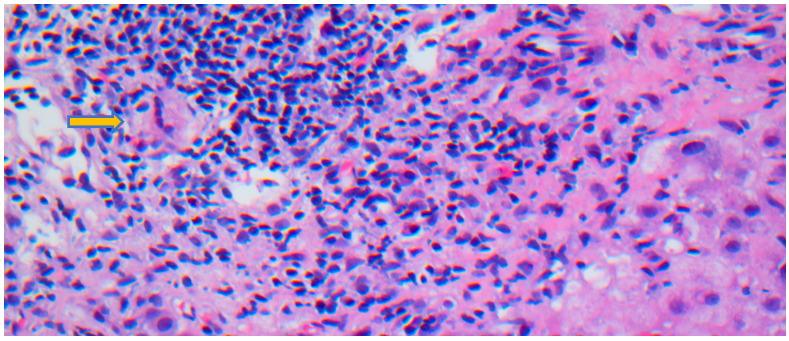
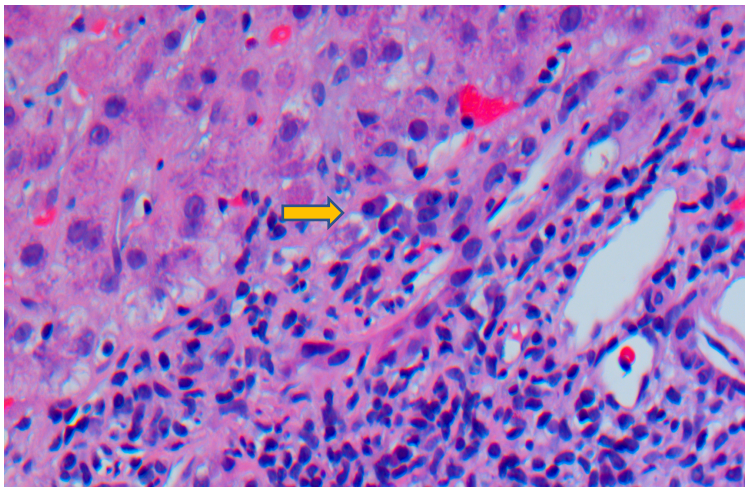


**Figure IV. Plasma cells (arrow)**



## 3. Discussion

Autoimmune hepatitis is a rare autoantibody-mediated inflammatory disease of the liver.9. While practical therapeutic guidelines have been clinically demonstrated for 60 years, AIH remains a diagnostic challenge. AIH can be divided into types 1 and 2.[10] Type 1 is associated with ANA, ASMA, and IgG antibodies and is typically diagnosed in the fifth or sixth decade of life11. Type 2 is associated with anti-liver-kidney microsomal antibody type 1 (anti-LKM1) and anti-liver-cytosol type 1 (anti-LC1) and is commonly diagnosed in children.[11-13] Histology and liver enzymes are frequently required to exclude other causes of liver disease. While AIH is associated with a variety of histologic findings, there are no pathognomonic features6. Instead, clinicians must rely on clinical, serological, and pathologic features to diagnose AIH. Histologic findings of AIH include portal lymphoplasmacytic inflammation, lobular hepatitis, emperipolesis, and rosettes[5-14]. Liver enzymes are significantly elevated, with aminotransferases being disproportionately elevated[15,16]. AIH has been associated with other autoimmune conditions, including psoriasis, rheumatoid arthritis, Sjogren's, IBD, hypothyroidism, and SLE[7,8,15,17]. The pathogenesis of AIH has been hypothesized as a result of several mechanisms, including autoantigen exposure, genetic predisposition, and defective immunoregulatory mechanisms[18]. Czaja specifies that class II major histocompatibility complex (MHC) with lysine at position Drbeta71 is the culprit of autoantigen presentation in AIH. Lohse1 demonstrated different HLA subtypes associated with AIH based on geographic and ethnic groups. First-line treatment is a glucocorticoid with or without

azathioprine until the patient improves clinically and liver enzymes return to baseline[1,11] The clinician should decide on the length of treatment based on remission and complete resolution of symptoms.

Vitiligo, a skin condition caused by selective loss of epidermal melanocytes, is the most common depigmentation disorder worldwide, with a prevalence of 0.5-2%[19,20]. Vitiligo is a multifactorial disorder associated with a variety of etiologies, including stress, family history, and autoimmune disorders[19-22]. Cumali et al. reported two patients with vitiligo and AIH and primary biliary cirrhosis overlap syndrome (AIH/PBC)23. Seiglie et al.,[24] also examined the relationship of AIH/PBC to vitiligo, emphasizing the need to investigate this variant form and underlying pathogenesis further. The incidence of AIH/PBC23-25 overlap and its distant association with extrahepatic conditions may warrant further workup to determine the etiology and possible association with vitiligo and other conditions. Kern et al. reported on a T2DM patient with vitiligo who developed autoimmune hepatitis secondary to initiation of liraglutide therapy[25.]

While some studies have shown an association between AIH and both types of diabetes mellitus26,27, the relationship between vitiligo and autoimmune hepatitis with type 2 diabetes mellitus has not been adequately studied. This triad of conditions could be causally linked based on the autoimmune hypothesis of the conditions.

The prevalence of AIH is 38.7 per 100,000 cases in Caucasian patients and 41.5 per 100,000 cases in Hispanic patients28. The odds of AIH diagnosis are higher in Latinx patients compared to the White patients reference group (OR 25, $P < 0.05$)29,30. Additionally, upon initial presentation, Latinx patients have more severe disease and a higher prevalence of cirrhosis30. Furthermore, a systematic review and meta-analysis conducted by Chang et al. demonstrates that vitiligo is significantly associated with both type 1 and 2 diabetes mellitus (OR 2.899, $P = 0.001$ and OR 2.371, $P <0.001$, respectively)31. The association between vitiligo and type 1 DM is likely due to autoreactive cytotoxic T-cell-mediated destruction31. The pathogenesis for the association between vitiligo and type 2 DM is not very clear, but one hypothesis is that the oxidative stress from type 2 DM may cause apoptosis of melanocytes and lead to the development of vitiligo31,32. Vitiligo is also associated with autoimmune hepatitis3. In a systematic review of cutaneous diseases related to AIH, Beretta-Piccoli et al. concluded that the most common skin conditions in AIH patients are vitiligo, psoriasis, and alopecia areata3. Kern et al. reported on a T2DM patient with vitiligo who developed autoimmune hepatitis secondary to initiation of liraglutide therapy[25]. While some studies have shown an association between AIH and diabetes mellitus,[26,27] the relationship between vitiligo and autoimmune hepatitis with type 2 diabetes mellitus has not been adequately studied.

In this patient's case, there was a question of whether this was truly AIH versus drug-induced hepatitis due to the findings of eosinophils in the biopsy. For autoimmune hepatitis, the diagnostic criteria include autoantibodies, hypergammaglobulinemia, and interface hepatitis on histology[27,28]. The patient had autoantibodies, elevated IgG, and mild interface hepatitis on the pathology report. The report also noted a high presence of inflammatory cells, including significantly elevated plasma cells, indicating autoimmune hepatitis. Although eosinophils were present, which could indicate drug-induced hepatitis, other etiologies, including autoimmune hepatitis, need to be ruled out before diagnosing drug-induced hepatitis[27,29]. This patient's medications were also discontinued during her hospitalization, and her LFTs never reached normal or near normal levels, which also decreases the likelihood of this being a drug-induced hepatitis.

## 4. Conclusion

Identifying autoimmune hepatitis presents a challenge to clinicians due to the diversity of hepatic etiologies that need to be excluded and the constellation of symptoms that can initially present. This case demonstrated the complexity of the workup required to diagnose someone with autoimmune hepatitis. This patient had significantly elevated LFTs,

LDH, alkaline phosphatase, and bilirubin, which prompted the workup for a hepatic versus cholecystic origin. The patient underwent extensive testing to rule out infectious, genetic, and autoimmune etiologies for hepatitis. All other etiologies must be excluded before diagnosing autoimmune hepatitis, including drug-induced hepatitis. Clinicians need to do a thorough workup to exclude underlying causes such as tuberculosis, HIV, and viral hepatitis and to do a rigorous medication review also to rule out drug-induced hepatitis. When trying to make the final diagnosis of autoimmune hepatitis, it was noted that there is no set diagnostic criteria or consensus on how to make a diagnosis. Several diagnostic recommendations are in place; however, many of them conflict with one another. Future recommendations would be to create a consensus using a combination of expert opinions and existing evidence to formulate a standardized diagnostic criterion for autoimmune hepatitis. This could make the diagnostic process more accessible and streamlined for clinicians and patients and decrease the chances that patients with this condition will be missed.

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