

CLINICAL VIGNETTE

A Case of Autoimmune Hepatitis

Mary C. Cambou and Adela M. Greeley, M.D.

Case Presentation

A 21-year-old previously healthy male with a two-month history of worsening jaundice was sent to the ER for aminotransferases elevated to the 2000s. He first noticed skin yellowing two months earlier. He subsequently developed fatigue, mild abdominal pain (worse on the right side), and intermittent nausea for one month. Initial evaluation by his primary doctor revealed mildly elevated aminotransferases, a negative hepatitis panel, and CT abdomen and abdominal US revealed only mild hepatic inflammation. He was referred to an outside gastroenterologist who performed an EGD with biopsy the day prior to admission. At that time, repeat liver function tests demonstrated markedly elevated transaminases, and he was advised to present to the ED immediately for further evaluation.

The patient reported a 15-pound weight loss secondary to anorexia and dark urine and loose stools of varying colors. He denied emesis, fevers, confusion, recent travel, seafood consumption, sick contacts, herbal supplement use, acetaminophen or NSAID use, and EtOH or illicit drug use, including mushrooms. He was taking bupropion intermittently prior to the onset of his symptoms and used marijuana occasionally. Vaccinations were up-to-date. Past medical and surgical histories were non-contributory. Per mother, there was no known family history of hemochromatosis, autoimmune disease, hepatocellular carcinoma, or liver disease.

Temperature was 36.7°C, HR 67, RR 18, BP 132/58, SpO2 96% on room air. Physical exam was significant for scleral icterus without Kayser-Fleischer rings, mild distention, and tenderness in the RUQ without rebound or guarding. His liver span measured greater than 10 cm, and he had mild splenomegaly. His skin was diffusely jaundiced, without bronzing or malar rash. Joints were free of erythema or effusions. The neurologic exam was unremarkable, without confusion or asterixis.

Laboratory findings were significant for AST/ALT 2103/2739 IU/L, Conjugated/Total Bilirubin 22.5/25.6 mg/dL, INR 1.7, and MELD Score 24. ANA was strongly positive (titer 1:320). Smooth muscle Ab was slightly positive (titer 1:40). Ferritin was markedly elevated (9539 ng/mL), Total Serum Iron was mildly elevated (194 ug/dL), TIBC was decreased (<216 ug/dL), and Ceruloplasmin was normal (26 mg/dL). Other

autoimmune (including Anti-Liver Kidney Microsomal-1 Antibody (Anti-LKM-1)), infectious, and drug-induced tests were negative. An abdominal US with Doppler was significant only for liver span 19.2 cm, without evidence of Budd-Chiari syndrome or cirrhosis.

He remained stable without encephalopathy or bleeding and was discharged after three days with hepatology follow-up. An outpatient transjugular liver biopsy was performed two weeks later. Pathology was significant for acute hepatitis with bridging and focal panlobular necrosis, suggestive of autoimmune hepatitis or drug-induced liver injury. The hepatology service started the patient on prednisone 40 mg PO daily for autoimmune hepatitis.

Discussion

Introduction: Autoimmune hepatitis (AIH) is a relatively rare, chronic inflammatory process of unknown etiology. AIH is marked by significantly elevated transaminases in a hepatocellular pattern, detection of serum antibodies, and characteristic histologic findings on liver biopsy.¹⁻³ The AIH diagnosis is further divided into two categories, Type 1 and Type 2, based on antibody profiles, which are typically reflective of the severity of the clinical presentations.^{1,2} Early diagnosis influences prognosis as untreated AIH can lead to cirrhosis, fulminant hepatic failure, and hepatocellular carcinoma.¹⁻³

Epidemiology and Genetics: The prevalence of AIH is estimated to be approximately 1 in 10,000 among Caucasian and Japanese populations.³ Women are at increased risk of AIH, comprising up to 75% of reported cases.^{1,3} While AIH has historically been associated with young women, recent epidemiological research suggests that AIH Type 1 affects all ages^{1,4} with evidence of increased presentation of AIH Type 1 later in life.⁵ Significant variations in the clinical presentations of AIH Type 1 and Type 2 exist among different populations on a global scale, likely secondary to genetic variations in the HLA genes.^{2,6}

Type 1 AIH is characterized by the presence of ANA, Anti-Smooth Muscle Antibody (ASMA), Anti-Soluble Liver Antigen and Liver-Pancreas Antigen (Anti-SLA/LP) or Anti-Actin, as well as associated with the HLA-DR3 allele.² Type 2

AIH is characterized by the presence of Anti-Liver Kidney Microsomal-1 Antibody (Anti-LKM-1) or Anti-Liver Cytosolic-1 Antibody (Anti-LC-1), as well as associated with HLA-DRB1 and HLA-DQB1 alleles.² Type 1 AIH is a milder form and more prevalent among Caucasians and Japanese populations. Type 2 is the more severe form, typically presenting in young women, often requiring long-term treatment or even transplant with high treatment failure rates reported in South American populations.^{1,6}

Pathogenesis: Although the exact details of the pathogenesis of AIH are unknown, growing evidence suggests that in individuals with certain HLA alleles, an unidentified exposure leads to molecular mimicry, resulting in a cytotoxic T-cell mediated response against hepatocytes.^{2,6} Drug exposures (including minocycline, nitrofurantoin, atorvastatin, methyl dopa, and infliximab), herbal supplements (including black cohosh and dai-saiko), and viral exposures (including the Hepatitis viruses, Epstein-Barr, and CMV) have been linked to autoimmune hepatitis.^{1,2} However, it remains unclear which environmental exposure is responsible for the molecular mimicry leading to AIH.

Presentation: The clinical presentation of AIH is broad, ranging from non-specific, flu-like symptoms of fatigue, malaise, and nausea to fulminant hepatic failure with altered mental status.^{1,2} Patients may report emesis, abdominal pain, dark urine, pale stools, or pruritus. On physical exam, AIH patients will commonly present with jaundice, RUQ tenderness, abdominal distention, and hepatosplenomegaly, occasionally with stigmata of chronic hepatic disease.^{1,2} Rare signs include markers of an autoimmune process, such as a malar rash or joint effusions.¹

Histology: Although biopsy-confirmed autoimmune hepatitis is not pathognomonic for the disease, greater than 90% of cases demonstrate periportal infiltrate (inflammation at the border of the portal tract and parenchyma) on histologic evaluation.^{1,2} Additionally, plasma-cell infiltrates is one of the distinguishing features of autoimmune hepatitis from other forms of hepatitis. In AIH patients with fulminant hepatic failure, histologic findings are often significant for submassive necrosis in addition to the characteristic periportal infiltrate.²

Diagnosis: Given the heterogeneous presentation of AIH, proper diagnosis can be challenging. However, the differential diagnosis for AST/ALT elevations to the thousands is fairly limited, including autoimmune hepatitis, viral-induced hepatitis, drug or toxin-induced hepatitis, Wilson disease, Hemochromatosis, Budd-Chiari syndrome, and hepatic shock. The diagnosis of AIH is based on the combination of clinical suspicion, markedly elevated aminotransferases (typically >25 times the upper limit of normal), antibody titers $\geq 1:80$, histologic confirmation, and absence of another cause. The International Autoimmune Hepatitis Group devised two sets of criteria for AIH diagnosis, an extensive and simplified scoring

system, which includes clinical, laboratory, histologic findings, and corticosteroid response.⁷ The simplified scoring system was recently validated, demonstrating high sensitivity and specificity.⁷

Treatment: The backbone of AIH treatment involves corticosteroid treatment.^{1,3} Prednisone (20 – 60mg/day) can be used as monotherapy in adults, in combination therapy (15 – 30 mg/day) with azathioprine (50 – 100 mg/day), or 6-mercaptopurine (25-100 mg/day). Corticosteroid treatment has been shown to confer greater than 90% ten-year-survival rate among AIH patients without cirrhosis.² However, patients with a homozygous mutation of thiopurine methyltransferase are at increased risk for serious side effects and death from azathioprine or mercaptopurine. Genetic testing should be considered before starting patients on either medication.² Patients with severe pathology, including cirrhosis on initial presentation or Type 2 AIH, typically require life-long treatment. AIH patients who are refractory to prednisone treatment (as measured by routine aminotransferase and yearly liver biopsies) or who present with end-stage liver disease may require liver transplant.² However, for the majority of AIH patients, prompt diagnosis, routine monitoring, and appropriate immunosuppression therapy are highly effective in the treatment of uncomplicated AIH.

REFERENCES

1. **Gleeson D, Heneghan MA; British Society of Gastroenterology.** British Society of Gastroenterology (BSG) guidelines for management of autoimmune hepatitis. *Gut.* 2011 Dec;60(12):1611-29. doi: 10.1136/gut.2010.235259. Epub 2011 Jul 13. PubMed PMID: 21757447.
2. **Krawitt EL.** Autoimmune hepatitis. *N Engl J Med.* 2006 Jan 5;354(1):54-66. Review. PubMed PMID: 16394302.
3. **Lohse AW, Mieli-Vergani G.** Autoimmune hepatitis. *J Hepatol.* 2011 Jul;55(1):171-82. doi: 10.1016/j.jhep.2010.12.012. Epub 2010 Dec 15. Review. PubMed PMID: 21167232.
4. **Manns MP, Czaja AJ, Gorham JD, Krawitt EL, Mieli-Vergani G, Vergani D, Vierling JM; American Association for the Study of Liver Diseases.** Diagnosis and management of autoimmune hepatitis. *Hepatology.* 2010 Jun;51(6):2193-213. doi: 10.1002/hep.23584. PubMed PMID: 20513004.
5. **Parker DR, Kingham JG.** Type I autoimmune hepatitis is primarily a disease of later life. *QJM.* 1997 Apr;90(4):289-96. PubMed PMID: 9307764.
6. **Czaja AJ, Manns MP.** Advances in the diagnosis, pathogenesis, and management of autoimmune hepatitis. *Gastroenterology.* 2010 Jul;139(1):58-72.e4. doi: 10.1053/j.gastro.2010.04.053. Epub 2010 May 5. Review. PubMed PMID: 20451521.
7. **Abdollahi MR, Somi MH, Faraji E.** Role of international criteria in the diagnosis of autoimmune

hepatitis. *World J Gastroenterol.* 2013 Jun
21;19(23):3629-33. doi: 10.3748/wjg.v19.i23.3629.
PubMed PMID: 23801865; PubMed Central PMCID:
PMC3691026.

Submitted January 8, 2015