Autoimmune Hepatitis Induced after Treatment of Syphilitic Hepatitis

Hasan Ali1*, Taqi Rizvi2, Muntaz Niazi3, Mark Galan4 and Nikolaos Pyrsopoulos3

1Department of Internal Medicine, Rutgers University New Jersey Medical School, Newark, NJ, USA; 2Edward Via College of Osteopathic Medicine, Spartanburg, SC, USA; 3Division of Gastroenterology and Hepatology, Rutgers University New Jersey Medical School, Newark, NJ, USA; 4Department of Pathology, Immunology and Laboratory Medicine, Rutgers University New Jersey Medical School, Newark, NJ, USA

Abstract

We present a unique case of biopsy-proven syphilitic hepatitis that presented as severe acute liver injury with significant elevation in aminotransferases and bilirubin, and improved with antibiotic therapy. However, the patient returned weeks after initial presentation with new-onset acute liver injury and had developed hypergammaglobulinemia, positive autoantibody titers, and repeat liver biopsy demonstrating interface hepatitis, supporting a diagnosis of autoimmune hepatitis. He had an otherwise unrevealing etiologic workup, and responded to glucocorticoid therapy. We believe that syphilitic hepatitis and its treatment subsequently triggered an immunologic response, leading to autoimmune hepatitis. Autoimmune hepatitis is a chronic liver disease thought to manifest as a result of predisposing genetic factors in combination with environmental insults, especially hepatotropic pathogens. Syphilis is a sexually transmitted disease caused by Treponema pallidum that has been associated with autoimmunity and the development of autoantibodies. We propose that in the setting of syphilitic hepatitis, a molecular mimicry event resulting from structural similarities between T. pallidum and liver antigens, as well as impaired regulatory T-cell function, led to the breakdown of immune tolerance and the onset of autoimmune hepatitis. To support this hypothesis, further molecular analyses and case series are necessary to determine if syphilitic hepatitis and its treatment are risk factors for the onset of autoimmune hepatitis. Autoimmune hepatitis should be considered early as the cause of acute liver injury in susceptible patients with risk factors for the disease, as prompt recognition and appropriate treatment may prevent progression of liver injury and result in improved outcomes.

Keywords: Autoimmune hepatitis; Syphilis; Molecular mimicry.

Introduction

Liver involvement is reported in approximately 10% of syphilis cases caused by the spirochete Treponema pallidum. Autoimmune hepatitis (AIH) is a chronic disease of the liver, thought to result from a combination of genetic and environmental risk factors. We report a case of AIH presenting after treatment of syphilitic hepatitis (SH), and propose that SH and its treatment are potential risk factors for AIH.

Case report

A 49-year-old male with a history of hypertension presented to the hospital complaining of right upper quadrant abdominal pain with associated chills, jaundice, and darkening urine. He denied taking any new medications or supplements, recent illnesses, travel, illicit drug use, body piercing, or family history of liver disease. Vital signs were normal on admission. Blood work revealed total bilirubin (Tbili) of 19.9 mg/dL, direct bilirubin of 15.5 mg/dL, alkaline phosphatase (ALP) of 147 U/L, aspartate aminotransferase (AST) of 1,280 U/L, alanine aminotransferase (ALT) of 1,652 U/L, and international normalized ratio (commonly referred to as INR) of 1.6. Abdominal imaging was unremarkable. Extensive work-up for common infectious, drug-related, and inherited causes of hepatitis was unrevealing. Serology was positive for antinuclear antibodies (ANA) with titer of 1:160. Anti-smooth muscle antibodies (commonly known as ASMA), antibodies against liver-kidney microsome type 1 (i.e. anti-LKM-1), antibodies against soluble liver antigen/liver-pancreas protein (i.e. anti-SLA/LP) were not detected. Immunoglobulin G (IgG) was normal at 1,301 mg/dL (reference range: 700–1,600 mg/dL). A liver core needle biopsy revealed acute hepatitis with inflammatory infiltrate, severe lobular inflammation, ballooning and degeneration of hepatocytes (Fig. 1). Given the severity of the patient’s liver injury and lack of clinical improvement, he was evaluated for liver transplant. Incidentally, rapid plasma reagin (RPR)
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was reactive, with a 1:2 titer and confirmed with positive fluorescent treponemal antibody absorption test (FTA-ABS). Subsequently, immunostaining of the liver biopsy revealed spirochetes (Fig. 1), confirming the diagnosis of SH. The patient was treated for late latent syphilis and SH with intramuscular penicillin G benzathine (benzylpenicillin). He experienced substantial clinical and biochemical improvement (AST of 350 U/L, ALT of 675 U/L, Tbill of 4.6 mg/dL) within days of the first dose, was discharged, and completed the antibiotic course as an outpatient.

The patient’s follow-up blood work showed continued improvement; however, on an office visit at 10 weeks following discharge, he presented with worsening jaundice and generalized pruritus. Liver markers were significantly elevated, with Tbill of 10.3 mg/dL, direct bilirubin of 7.02 mg/dL, AST of 1,007 U/L, ALT of 1,000 U/L, ALP of 223 U/L and INR of 1.6. He was admitted to the hospital for further evaluation of worsening liver disease. Serology revealed elevated IgG of 2,275 mg/dL and atypical perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) with titer of 1:320, along with ANA titer of 1:160 (consistent with prior serology). ASMA, anti-SLA/LP, anti-LKM-1, cytoplasmic-ANCA (c-ANCA) and p-ANCA were undetected. Acute viral hepatitis panel was negative. RPR was still positive, with a titer of 1:2, along with positive FTA-ABS. Liver biopsy revealed severe acute hepatitis with bridging fibrosis and interface activity; this time, immunostaining for spirochetes was negative (Fig. 2). The presence of autoantibodies, hypergam-
maglobulinemia, absence of viral markers, and interface activity on biopsy translated to high scores on the revised and simplified AIH scoring system, indicating a diagnosis of AIH. The patient was treated with systemic glucocorticoids, producing marked improvement in liver function abnormalities and further supporting the diagnosis of AIH. He was discharged on oral prednisone, and outpatient follow-up lab work revealed AST of 90 U/L, ALT of 139 U/L, Tbilii of 2.5 mg/dL and INR of 1.1. The prednisone dose was tapered and the patient continued to have sustained improvement.

Discussion

We report a unique case of biopsy-proven SH, which improved with antibiotic therapy but subsequently triggered an immunogenic response suggestive of AIH, with recovery after glucocorticoid therapy.

AIH is an inflammatory disease caused by autoimmune-mediated disease of the liver parenchyma, with resultant chronic inflammation and fibrosis.1 It is characterized by elevated aminotransferases, interface hepatitis histologically and hypergammaglobulinemia, in particular IgG, along with the presence of autoantibodies against liver autoantigens, including ANA, ASMA, anti-LKM-1, anti-SLA/LP and seldom atypical p-ANCA.2,3

Clinical presentation of AIH ranges from asymptomatic elevation in aminotransferases to fulminant hepatitis, or as indolent inflammation progressing to cirrhosis, hepatocellular carcinoma and death.4 A numerical scoring system established by the International Autoimmune Hepatitis Group (commonly known as IAIGH) devised diagnostic criteria for AIH based on biochemical (hypergammaglobulinemia with elevated IgG), serologic (serum autoantibodies) and histologic (interface hepatitis) findings, with exclusion of alternative etiology of liver disease.4

Though the pathogenesis of AIH is not completely understood, evidence suggests that it involves an interplay of genetic predisposition, molecular mimicry and regulatory T cell processes.3 Various autoimmune diseases, including AIH, are known to manifest following the administration of a hepatic toxicant or infection. Molecular mimicry describes a phenomenon where a pathogen evades immune surveillance due to the structural similarities that its proteins share with the host’s self-antigens. However, once the pathogen is detected and eliminated by the host immune system, the sensitized immune system may go on to attack the host’s self-antigens that shared similarities with the pathogenic epitopes, resulting in autoimmunity.14 This phenomenon is commonly described in relation to viral pathogens with regards to AIH; however, bacteria, specifically Rickettsia species, have been shown to trigger AIH via molecular mimicry. Using molecular homology modeling and docking methods, researchers identified a statistically significant structural similarity between a region of the SLA/LP protein recognized by CD4+ T lymphocytes, and a region of a Rickettsia species protein called ‘surface antigen PS-L20’. This constitutes supporting evidence that CD4+ T lymphocytes that recognize the self-antigen SLA/LP can cross-react with foreign Rickettsia species’ antigens, inciting a molecular mimicry event that may result in the onset of AIH.15

Drug-induced Liver Injury (DILI) secondary to penicillin G benzathine was investigated as a potential cause of liver injury in the second presentation. Many medications and herbal supplements have been implicated in DILI; however, first-generation penicillins are rarely implicated.16 Clinically significant penicillin-induced DILI is usually secondary to a severe hypersensitivity reaction, or presents as delayed cholestatic hepatitis, which is more commonly associated with broad spectrum penicillins.17 There is one reported case of DILI associated with benzylpenicillin, in which a patient treated with high dose, intravenous benzylpenicillin developed asymptomatic elevation in aminotransferases and peripheral eosinophilia 3 weeks after treatment initiation, which rapidly resolved upon changing the antibiotic to a cephalosporin.12 Our patient presented with acute hepatitis 9 weeks after completion of treatment of SH with intramuscular benzylpenicillin, which is later than would be expected in DILI, and, in contrast to the case presented above, did not exhibit any peripheral eosinophilia. Given the strong supporting evidence for AIH, differences from the reported case of benzylpenicillin-associated DILI, and rarity of DILI associated with first generation penicillins, it is unlikely that our patient’s acute liver injury was secondary to benzylpenicillin-induced DILI.11

After review of the literature, we believe this is the first reported case of AIH presenting after treatment of SH. This case was unique in that it demonstrated a paradigm shift in pathologic etiology of hepatitis from infection to autoimmunity. Exactly how this shift occurred and whether the two processes were interrelated is still in question.

Various autoimmune diseases, including AIH, are known to manifest following the administration of a hepatic toxicant or infection. Molecu
mune response that results in the production of autoantibodies against several targets. Syphilis has also been shown to affect cell-mediated immunity. One study demonstrated a depression in total T lymphocytes and subpopulations of T lymphocytes at specific stages of infection, resembling hematologic patterns observed in patients with systemic lupus erythematosus as well as other autoimmune diseases associated with increased autoantibody production. In another study, researchers observed ANA titers in patients with syphilis at 12 months after they had been appropriately treated for the infection. They observed ANA titer of 1:160 or above in all patients (10/10) who did not respond appropriately to treatment, compared to only 5.3% (2/38) of patients who were serologically cured. Researchers hypothesized that the destruction of host tissues in genetically susceptible individuals led to the breakdown of immune tolerance and production of autoantibodies.

A molecular database query investigating structural similarities between moieties on *T. pallidum* proteins and liver antigens has not yet been reported in the literature. Such a study would elucidate whether a molecular mimicry event could explain the association between SH and AIH. In our patient, the presence of syphilis antibodies was likely a result of previous infection, as serology for syphilis was negative at the time of presentation. Further study would elucidate whether a molecular mimicry event occurred in our patient.

The presence of ANA titers in patients with syphilis highlights the importance of considering autoimmune phenomena in the setting of infectious disease. This phenomenon, known as molecular mimicry, occurs when an infectious agent shares structural similarities with host proteins, leading to the generation of autoantibodies. In our patient, the presence of ANA titers in patients with syphilis suggests that molecular mimicry may have played a role in the development of AIH.

We present the first reported case of AIH presenting after treatment of SH. We hypothesize that SH and its treatment potentially triggered an immunogenic cascade, which ultimately resulted in AIH. Current literature suggests that there are several environmental triggers for AIH, among them viral and bacterial infections, and syphilis has been associated with autoimmunity via the generation of autoantibodies and alteration of T cell function. We propose that molecular mimicry played an important role in allowing *T. pallidum* to evade immune detection until clinical presentation of SH, and, after treatment eliminated the pathogen, continued immunogenic response against structurally similar liver antigens and altered regulatory T cell function resulted in the breakdown of immune tolerance and the onset of AIH. Further case studies and molecular analyses of *T. pallidum* antigens in comparison to liver antigens will help us understand the pathophysiologic relationship between SH and AIH.

**Conclusion**

We present the first reported case of AIH presenting after treatment of SH. We hypothesize that SH and its treatment potentially triggered an immunogenic cascade, which ultimately resulted in AIH. Current literature suggests that there are several environmental triggers for AIH, among them viral and bacterial infections, and syphilis has been associated with autoimmunity via the generation of autoantibodies and alteration of T cell function. We propose that molecular mimicry played an important role in allowing *T. pallidum* to evade immune detection until clinical presentation of SH, and, after treatment eliminated the pathogen, continued immunogenic response against structurally similar liver antigens and altered regulatory T cell function resulted in the breakdown of immune tolerance and the onset of AIH. Further case studies and molecular analyses of *T. pallidum* antigens in comparison to liver antigens will help us understand the pathophysiologic relationship between SH and AIH.

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**Conflict of interest**

NP has been an associate editor of *Journal of Clinical and Translational Hepatology* since 2021. The other authors have no conflict of interests related to this publication.

**Author contributions**

Study design (HA, TR, MN, NP), drafting of the manuscript (HA, TR, MN, MG), critical revision of the manuscript for important intellectual content (MN, NP), and study supervision (NP).

**Informed consent**

Signed informed consent was obtained from the patient for publication of his protected health information.

**References**

[1] Christen U, Hintermann E. Pathogens and autoimmune hepatitis. Clin Exp Immunol 2018;195(1):35–51. doi:10.1111/cei.12303.

[2] Gossard AA, Lindor KD. Autoimmune hepatitis: a review. J Gastroenterol 2012;47(5):498–503. doi:10.1007/s00353-012-0586-z.

[3] Floreani A, Restrepo-Jiménez P, Secchi MF, De Martin S, Leung PSC, Kra-witt E, et al. Etiopathogenesis of autoimmune hepatitis. J Autoimmun 2018;95:133–143. doi:10.1016/j.jaut.2018.10.020.

[4] Hennes EM, Zeniya M, Czaja AJ, Paredes A, Dalekos GN, Kra-witt EL, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology 2008;48(1):169–176. doi:10.1002/hep.22322.

[5] Liberali R, Longhi MS, Mieli-Vergani G, Vergani D. Pathogenesis of au-toimmune hepatitis. Best Pract Res Clin Gastroenterol 2011;25(6):653–664. doi:10.1016/j.bpgs.2011.09.009.

[6] Huang J, Lin S, Wang M, Wang B, Zhu Y. Syphilis hepatitis: a case report and review of the literature. BMC Gastroenterol 2019;19(1):191. doi:10.1186/ s12877-019-1112-z.

[7] Narang N, Al-Jashaami L, Patel N. Spirochetes in the liver: an unusual presen-tation of a common STI. Case Rep Med 2019;2019:1012405. doi:10.1155/ 2019/1012405.

[8] Bleich LM, Taubin HL. Syphilitic hepatitis. Pract Gastroenterol 2019;35(11): 76–78.

[9] Keidanian M, Friedman LS, Brandt LJ. Siesengger and Fordtran’s Gastroin-testinal and Liver Disease: Pathophysiology/Diagnosis/Management. 10th Ed. Philadelphia, PA: Elsevier/Saunders; 2016.

[10] Davern TJ. Drug-induced liver disease. Clin Liver Dis 2012;16(2):231–245. doi:10.1016/j.cld.2012.03.002.

[11] LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Penicillin G and V. [Updated 2014 Jan 16]. Available from: https://liver.tox.niddk.nih.gov/books/NBK547993/.

[12] Bauer TM, Bircher AJ. Drug-induced hepatocellular liver injury due to ben-zylpenicillin with evidence of lymphocyte sensitization. J Hepatol 1997; 26(2):429–432. doi:10.1016/s0168-8278(97)80062-1.

[13] Hara A, Iwasa Y. Autoimmune diseases initiated by pathogen infection: mathematical modeling. J Theor Biol 2020;498:110296. doi:10.1016/j.jtbi. 2020.110296.

[14] Paladini A, Pascarella S. Structural mimicry between SLA/CP and Ricketts- sia surface antigens as a driver of autoimmune hepatitis: insights from an in silico study. Theor Biol Med Model 2013;10:25. doi:10.1186/1742-4682- 10-25.

[15] Wicher K, Wicher V. Autoimmunity in syphilis. Immunol Ser 1990;52:101- 124.

[16] Jensen JR, From E. Alterations in T lymphocytes and T-lymphocyte sub-populations in patients with syphilis. Br J Vener Dis 1982;58(1):18–22. doi:10.1136/sti.58.1.18.

[17] Pastuszczak M, Kotnis-Gąska A, Jakubowicz B, Wojas-Pelc A. Treponema pallidum-specific immune responses and autoimmunity in patients who re-main serofast after treatment of syphilis. Postepy Dermatol Alergor 2019; 36(5):620–625. doi:10.5114/ada.2018.77497.