



## Case Report

# Autoimmune Hepatitis Induced after Treatment of Syphilitic Hepatitis

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### Abstract

We present a unique case of biopsy-proven syphilitic hepatitis which 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 immunogenic 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.

**Abbreviations:** AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, anti-neutrophil antibody; ASMA, anti-smooth muscle antibody; AST, aspartate aminotransferase; DILI, drug induced liver injury; FTA-Abs, fluorescent treponemal antibody absorption test; IgG, immunoglobulin G; INR, international normalized ratio; anti-LKM-1, antibodies against liver-kidney microsome type 1; p-ANCA, perinuclear anti-neutrophil cytoplasmic antibody; RPR, rapid plasma reagin; anti-SLA/LP, antibodies against soluble liver antigen/liver-pancreas protein; SH, syphilitic hepatitis; Tbili, total bilirubin.

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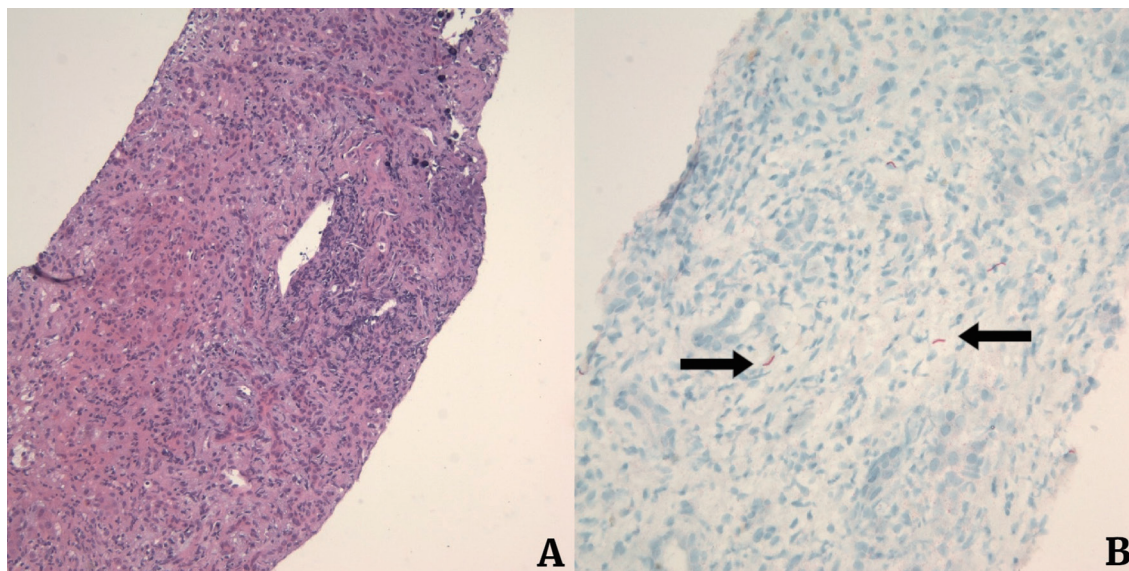
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### Introduction

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)

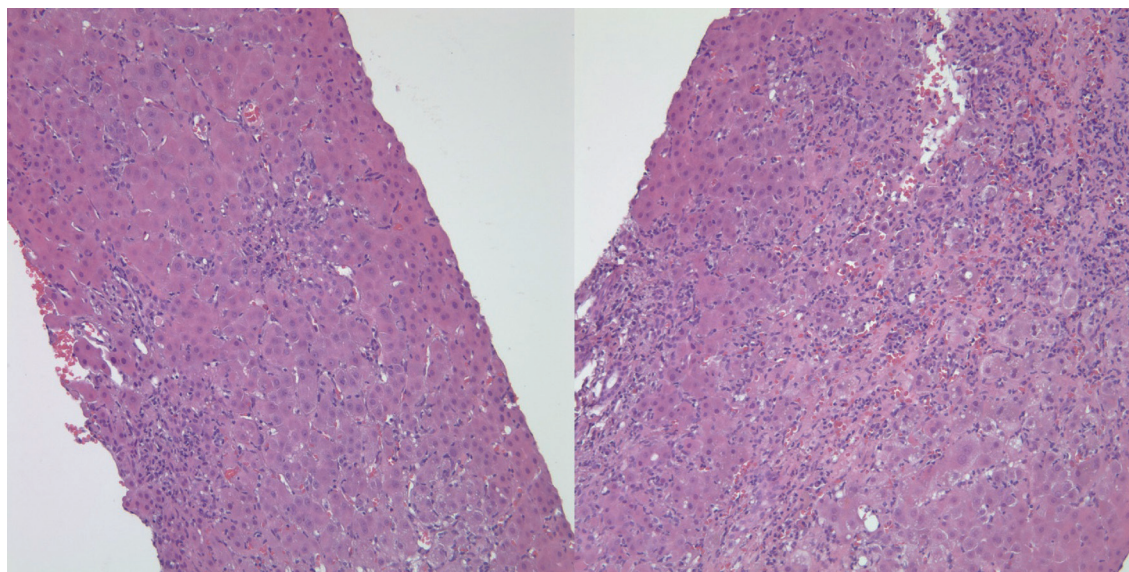


**Fig. 1. Liver needle biopsy.** (A) Active acute hepatitis with inflammatory infiltrate, severe lobular inflammation, ballooning and degeneration of hepatocytes. Hematoxylin-eosin staining. Magnification: 100 $\times$ . (B) Immunohistochemical staining of the liver biopsy revealed spirochetes, confirming the diagnosis of SH. Magnification: 100 $\times$ .

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, Tbili 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 Tbili 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 anti-neutrophil 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-



**Fig. 2. Liver needle biopsy.** Severe acute hepatitis with interface activity, portal and lobular infiltrate, zone 3 hemorrhage, collapse and necrosis, bridging fibrosis, and mild cholestasis. Hematoxylin-eosin staining. Magnification: 100 $\times$ .

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, Tbili 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 destruction of the liver parenchyma, with resultant chronic inflammation and fibrosis.<sup>1</sup> 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.<sup>2,3</sup>

Clinical presentation of AIH ranges from asymptomatic elevation in aminotransferases to fulminant hepatitis, or as indolent inflammation progressing to cirrhosis, hepatocellular carcinoma and death.<sup>3</sup> A numerical scoring system established by the International Autoimmune Hepatitis Group (commonly known as IAHG) devised diagnostic criteria for AIH based on biochemical (hypergammaglobulinemia with elevated IgG), serologic (serum autoantibodies) and histologic (interface hepatitis) findings, with exclusion of alternate etiology of liver disease.<sup>4</sup>

Though the pathogenesis of AIH is not completely understood, evidence suggests that it involves an interplay of genetic predisposition, molecular mimicry and regulatory T lymphocytes. Immune reactions against liver antigens not adequately contained by impaired regulatory T cells are believed to be the main contributors to AIH.<sup>5</sup>

Environmental factors associated with AIH include hepatitis A, B and C viruses, measles virus, varicella zoster virus, cytomegalovirus and Epstein-Barr virus. Viruses with hepatic tropism have the potential to cause AIH secondary to inflammation and subsequent cytotoxic immune response targeting the pathogen, leading to an abnormal T cell response.<sup>1</sup> The only known bacterial genus associated with AIH is *Rickettsia*, as one of its proteins drives an autoimmune response mediated by CD4+ T cells.<sup>3</sup>

Syphilis is a sexually transmitted infection caused by *Treponema pallidum*, a spirochete. Its presentation is characterized by stages, including primary, secondary, latent, and tertiary syphilis.<sup>6</sup> *T. pallidum* is a non-hepatotropic pathogen that causes hepatitis.<sup>7</sup> Interestingly, liver damage in syphilis often occurs early in the disease course and is often misdiagnosed.<sup>6</sup>

Clinical presentations of SH are nonspecific and variegated. Patients may present with low-grade fever, abdominal pain, sore throat, weight loss, arthralgia, myalgia, jaundice or maculopapular rash on the trunk, palms and soles.<sup>7</sup> Histologically, SH manifests as inflammatory bile duct infiltration, hepatocellular periportal necrosis, hepatic granulomas, and visualization of spirochetes by immunogenic or Warthin-Starry staining.<sup>7,8</sup> Serologically, SH presents with elevated ALP, gamma-glutamyl transferase and abnormal aminotransferases, with disproportionate elevation of ALP due to pericholangiolar inflammation.<sup>6,8</sup> Initial screening is accomplished by RPR and venereal disease research labo-

ratory tests.<sup>9</sup> Positive FTA-ABS and visualization of spirochetes on liver biopsy confirms the diagnosis of SH; however, spirochetes are only visible by staining in up to half of patients with SH.<sup>10</sup>

Our patient initially presented with acute hepatitis of unknown etiology, and blood work incidentally revealed positive RPR and confirmatory FTA-ABS. Visualization of *T. pallidum* on liver biopsy confirmed the diagnosis of SH, and the patient responded well to a course of benzylpenicillin. On the patient's subsequent admission weeks later, evidence pointed towards AIH as the cause of acute liver injury, with elevated IgG, positive ANA and atypical p-ANCA titers, and interface hepatitis on liver biopsy, a hallmark finding of AIH. Immunostaining was negative for *T. pallidum*, which excluded the diagnosis of recurrent or incompletely treated SH.

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.<sup>11</sup> 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.<sup>12</sup> 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.<sup>13</sup> 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.<sup>11</sup>

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 resolution of an 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.<sup>14</sup> 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-120'. 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.<sup>15</sup>

Several studies have investigated the immunopathologic mechanisms that link *T. pallidum* and autoimmunity. It has been established that syphilis triggers a humoral autoim-

mune response that results in the production of autoantibodies against several targets.<sup>16</sup> Syphilis has also been shown to effect 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.<sup>17</sup>

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.<sup>18</sup>

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 as it presented in this case, and help determine if SH and its treatment are risk factors for 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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None to declare.

## 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.13203.
- [2] Gossard AA, Lindor KD. Autoimmune hepatitis: a review. *J Gastroenterol* 2012;47(5):498–503. doi:10.1007/s00535-012-0586-z.
- [3] Floreani A, Restrepo-Jiménez P, Secchi MF, De Martin S, Leung PSC, Krawitt 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, Parés A, Dalekos GN, Krawitt EL, *et al*. Simplified criteria for the diagnosis of autoimmune hepatitis. *Hepatology* 2008;48(1):169–176. doi:10.1002/hep.22322.
- [5] Liberal R, Longhi MS, Mieli-Vergani G, Vergani D. Pathogenesis of autoimmune hepatitis. *Best Pract Res Clin Gastroenterol* 2011;25(6):653–664. doi:10.1016/j.bpg.2011.09.009.
- [6] Huang J, Lin S, Wan B, Zhu Y. A systematic literature review of syphilitic hepatitis in adults. *J Clin Transl Hepatol* 2018;6(3):1–4. doi:10.14218/jct.2018.00003.
- [7] Huang J, Lin S, Wang M, Wan B, Zhu Y. Syphilitic hepatitis: a case report and review of the literature. *BMC Gastroenterol* 2019;19(1):191. doi:10.1186/s12876-019-1112-z.
- [8] Narang N, Al-Jashaami L, Patel N. Spirochetes in the liver: an unusual presentation of a common STI. *Case Rep Med* 2019;2019:1012405. doi:10.1155/2019/1012405.
- [9] Bleich LM, Taubin HL. Syphilitic hepatitis. *Pract Gastroenterol* 2015;39(11):76–78.
- [10] Feldman M, Friedman LS, Brandt LJ. Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management. 10th Ed. Philadelphia, PA: Elsevier/Saunders; 2016.
- [11] Davern TJ. Drug-induced liver disease. *Clin Liver Dis* 2012;16(2):231–245. doi:10.1016/j.cld.2012.03.002.
- [12] 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://www.ncbi.nlm.nih.gov/books/NBK547993/>.
- [13] Bauer TM, Bircher AJ. Drug-induced hepatocellular liver injury due to benzylpenicillin with evidence of lymphocyte sensitization. *J Hepatol* 1997;26(2):429–432. doi:10.1016/s0168-8278(97)80062-1.
- [14] 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.
- [15] Paiardini A, Pascarella S. Structural mimicry between SLA/LP and Rickettsia 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.
- [16] Wicher K, Wicher V. Autoimmunity in syphilis. *Immunol Ser* 1990;52:101–124.
- [17] Jensen JR, From E. Alterations in T lymphocytes and T-lymphocyte subpopulations in patients with syphilis. *Br J Vener Dis* 1982;58(1):18–22. doi:10.1136/sti.58.1.18.
- [18] Pastuszczak M, Kotnis-Gąska A, Jakubowicz B, Wojas-Pelc A. Treponema pallidum-specific immune responses and autoimmunity in patients who remain serofast after treatment of syphilis. *Postepy Dermatol Alergol* 2019;36(5):620–625. doi:10.5114/ada.2018.77497.