

Syphilitic hepatitis mimicking autoimmune liver disease: a case report and review of the literature

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Case Report

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Abstract

Background

Syphilitic hepatitis is an uncommon manifestation of early syphilis and usually produces a cholestatic biochemical pattern. Its serological and histological overlap with autoimmune liver disease can create a clinically important diagnostic challenge.

Case presentation:

A 47-year-old Sri Lankan woman with well-controlled diabetes mellitus, hypertension and hypothyroidism presented with syncope followed by high-grade fever, transient circulatory compromise and progressive pruritic jaundice. A non-pruritic hyperpigmented macular rash involving the palms and soles had appeared approximately one month earlier, and a history of unprotected sexual exposure 2–3 months before presentation was elicited on repeat history-taking. Liver tests showed a predominantly cholestatic injury (R factor 0.4), with alkaline phosphatase up to 508 U/L, gamma-glutamyl transferase 315.6 U/L and total bilirubin up to 6 mg/dL. Antinuclear antibody was positive at 1:160, antimitochondrial antibody was positive, and serum IgG was 2150 mg/dL (1.34 times the upper limit of normal), prompting concern for autoimmune hepatitis-primary biliary cholangitis overlap. Imaging excluded biliary obstruction. Liver biopsy showed cholestatic hepatitis with bile-duct-centred mixed inflammation, ductular reaction, cholangitis and only mild interface activity. Venereal Disease Research Laboratory testing was reactive at 1:256 and *Treponema pallidum* particle agglutination was positive. Following antitreponemal treatment, symptoms and liver biochemistry resolved without corticosteroids. The VDRL titre fell to 1:8, and ANA, antimitochondrial antibody and IgG subsequently normalised.

Conclusions

Secondary syphilis may reproduce both the biochemical and immunopathological phenotype of autoimmune liver disease. In a patient with cholestatic hepatitis, compatible systemic or cutaneous features should prompt syphilis testing even when autoimmune serology is positive. Longitudinal resolution of liver injury and transient autoantibodies after antimicrobial therapy can be decisive and may prevent inappropriate immunosuppression.

Background

Syphilis, caused by *Treponema pallidum*, remains a prototypical multisystem infection and can involve the liver during early disseminated disease [1]. Syphilitic hepatitis is uncommon and is reported most often during secondary syphilis. The typical biochemical phenotype is cholestatic, with disproportionate elevation of alkaline phosphatase and gamma-glutamyl transferase relative to aminotransferases, although mixed and hepatocellular patterns are described [2, 3]. Histological appearances are variable

and non-specific, including portal and lobular inflammation, cholestasis, ductular reaction, bile-duct injury, interface activity, granulomas and plasma-cell-rich infiltrates [2, 4, 5].

The diagnostic challenge becomes greater when syphilitic hepatitis reproduces features of autoimmune liver disease. Positive antinuclear, smooth-muscle or antimitochondrial antibodies and hypergammaglobulinaemia have been reported, and several cases have mimicked autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), or a combination of these phenotypes [6–10]. Because immunosuppression may be harmful when an untreated infection is mistaken for autoimmune disease, clinicopathological correlation and longitudinal reassessment are essential.

We report a woman with secondary syphilis and cholestatic hepatitis whose ANA, antimitochondrial antibody (AMA), raised IgG and bile-duct-centred inflammatory histology initially suggested AIH-PBC overlap. The subsequent clinical, biochemical and serological course supported secondary syphilis-associated hepatitis with transient autoimmune features. Further the authors have presented a focused review of autoimmune-liver-disease mimics of syphilitic hepatitis.

Case presentation

Patient information and clinical course

A 47-year-old woman from Sri Lanka with well-controlled diabetes mellitus, hypertension and hypothyroidism was admitted after a transient loss of consciousness while getting out of bed. On admission she was alert, with a blood pressure of 100/70 mmHg and pulse rate of 96 beats/min. Later that day she developed symptomatic postural hypotension (sitting blood pressure 80/60 mmHg) and high-grade fever with chills and rigors. Over the next 48 hours she developed transient circulatory compromise that responded to intravenous crystalloid alone; vasopressors were not required.

Two days after admission she developed progressive jaundice, dark urine, pale stools, generalised pruritus, anorexia and vomiting. Around the eighth day of illness she developed inflammatory-type pain and tenderness involving the small joints of the hands, which resolved spontaneously within approximately one week.

Initial history focused on common tropical and hepatobiliary causes. She had travelled within Sri Lanka two weeks before symptom onset, bathed in freshwater and undertaken jungle excursions. When the history and examination were revisited because fever and cholestasis persisted despite broad investigation, she reported a hyperpigmented, non-pruritic, non-scaly macular eruption involving the palms and soles approximately one month before admission and disclosed unprotected sexual exposure 2–3 months earlier. She denied alcohol use, intravenous drug use and exposure to recognised hepatotoxic medications. She did not report oral ulcers, photosensitivity, alopecia, Raynaud phenomenon or proximal muscle weakness.

Clinical findings

She was deeply icteric and had excoriations over the forearms. Hyperpigmented macules were visible on the palms and soles. Figure 1 contains the pictures of the said hyperpigmented macules. There were no stigmata of chronic liver disease, lymphadenopathy or hepatosplenomegaly. Cardiovascular, respiratory, abdominal and neurological examinations were otherwise unremarkable.

Diagnostic assessment

There was neutrophilic leucocytosis and a marked inflammatory response. The peak documented white-cell count was $22.31 \times 10^9/L$, with neutrophils $19.43 \times 10^9/L$, and C-reactive protein reached 358 mg/L. Liver biochemistry showed direct hyperbilirubinaemia and a cholestatic pattern: total bilirubin peaked at 6.0 mg/dL, alkaline phosphatase at 508 U/L, gamma-glutamyl transferase at 315.6 U/L, AST at 226 U/L and ALT at 264 U/L. The calculated R factor was 0.4. Serum albumin was initially 2.8 g/dL.

Ultrasonography and contrast-enhanced CT of the abdomen showed no intrahepatic or extrahepatic biliary dilatation, focal hepatic lesion, abscess or other obstructive explanation. Blood and urine cultures remained negative. Testing for hepatitis B and C, leptospirosis, malaria, tuberculosis and melioidosis was negative. An initial HIV-1/2 antigen-antibody screen was reactive, but repeat screening and HIV PCR were negative.

Autoimmune testing introduced a competing diagnosis. ANA was positive at a titre of 1:160 with a nuclear pattern, AMA was positive, and IgG was 2150 mg/dL (upper reference limit 1600 mg/dL). Anti-dsDNA, anti-Sm and anti-LKM antibodies were negative; complement C3 and C4 were normal. The combination of pruritic cholestasis, AMA positivity, raised IgG and interface activity raised concern for PBC, AIH or AIH-PBC overlap. However, the biochemical pattern was strongly cholestatic, IgG was only 1.34 times the upper limit of normal, and the eventual histology lacked the characteristic destructive duct lesion of PBC and showed only mild interface hepatitis.

VDRL became reactive on 16 March 2026 at a titre of 1:256, and *Treponema pallidum* particle agglutination testing subsequently confirmed treponemal infection. Liver biopsy showed preserved overall architecture with portal expansion by a mixed inflammatory infiltrate containing lymphocytes, neutrophils and plasma cells, ductular reaction, intrahepatic cholestasis and bile-duct-centred inflammation. There was mild interface hepatitis. Intraepithelial lymphocytes and granulocytes within bile-duct epithelium supported active cholangitis. No florid duct lesion, granulomatous cholangitis or ductopenia was identified. Overall, the pathology was best described as cholestatic hepatitis with bile-duct-centred inflammation and mild interface activity rather than diagnostic AIH or PBC. Figure 2 contains pictures of liver biopsy slides.

Therapeutic intervention

Empirical intravenous ceftriaxone and oral doxycycline were started early because of the initial concern for tropical infection. Ceftriaxone was later escalated to meropenem as fever and inflammatory markers persisted while doxycycline was continued. Ursodeoxycholic acid was added for symptomatic cholestasis. Fever settled before definitive penicillin therapy. Because doxycycline is an accepted alternative regimen for early syphilis when given as a complete course, partial antitreponemal activity may have contributed to the early clinical improvement [12].

After syphilis was confirmed, she received intramuscular benzathine penicillin G 2.4 million units as definitive therapy for early syphilis [12]. Pruritus resolved and the jaundice, appetite and liver biochemistry improved progressively. Importantly, no corticosteroid or other immunosuppressive treatment was administered.

Follow-up and outcomes

The liver test panel normalised within approximately one month. The VDRL titre fell from 1:256 on 16 March to 1:8 on 23 April and remained 1:8 on 29 May, representing a greater than fourfold serological decline. On later follow-up, ANA and AMA were negative and IgG had fallen to 1206 mg/dL. Relevant details are summarized in Table 1. The disappearance of autoimmune serological abnormalities in parallel with clinical and biochemical recovery, without immunosuppression, argued strongly against primary AIH, PBC or AIH-PBC overlap. The final diagnosis was secondary syphilis with syphilitic hepatitis, presenting as a transient autoimmune liver disease phenotype.

Table 1
Key laboratory findings and longitudinal response

Parameter	Peak/initial relevant value	Follow-up
Total bilirubin	6.0 mg/dL	0.97 mg/dL
ALP	508 U/L	Normalised clinically
GGT	315.6 U/L	113.8 U/L on 22 Apr
ALT	264 U/L	24.4 U/L on 22 Apr
AST	226 U/L	20.9 U/L on 22 Apr
CRP	358 mg/L	10 mg/L on 22 Apr
ANA	1:160, nuclear pattern	Negative
AMA	Positive	Negative
IgG	2150 mg/dL (ULN 1600)	1206 mg/dL
VDRL	1:256 (16 Mar 2026)	1:8 (23 Apr and 29 May 2026)
TPPA	Reactive	—

ALP alkaline phosphatase; GGT gamma-glutamyl transferase; CRP C-reactive protein; ANA antinuclear antibody; AMA antimitochondrial antibody; IgG immunoglobulin G; VDRL Venereal Disease Research Laboratory; TPPA Treponema pallidum particle agglutination.

Discussion

This case illustrates a diagnostically important form of the ‘great imitator’: secondary syphilis producing not only cholestatic hepatitis but also an autoimmune-like serological and histological phenotype. The initial autoimmune signal was substantial. The patient was a middle-aged woman with pruritus, marked cholestasis and positive AMA, while ANA positivity, elevated IgG and interface activity suggested an AIH component. Taken cross-sectionally, these findings could reasonably raise the possibility of AIH–PBC overlap. The longitudinal course, however, was discordant with primary autoimmune liver disease: interface activity was only mild, characteristic PBC duct lesions were absent, and the entire syndrome resolved without immunosuppression, accompanied by loss of ANA and AMA and normalisation of IgG.

The diagnosis of syphilitic hepatitis remains clinical because there is no single pathognomonic biochemical or histological feature. Commonly used criteria, derived from the clinical series by Mullick and colleagues, include abnormal liver enzymes, serological evidence of syphilis, exclusion of other causes of liver injury and improvement after appropriate antimicrobial therapy [4]. Our patient met all four elements. The palmoplantar eruption, arthralgia and compatible sexual exposure provided additional evidence for secondary syphilis, while the high VDRL titre and positive treponemal test established the infection. The cholestatic pattern and bile-duct-centred inflammation were within the recognised spectrum of syphilitic hepatitis [2–5].

A focused review of the literature shows that autoimmune-liver-disease mimicry is uncommon but repeatedly documented. Kern et al. described syphilitic hepatitis with cholestasis and positive AMA mimicking PBC, with improvement in both liver injury and antibody levels after treatment [6]. Haddadin et al. reported concurrent PBC and secondary syphilis, emphasising that infection and genuine autoimmune liver disease can coexist [8]. Kaufman et al. described presumed autoimmune hepatitis preceding fulminant syphilitic retinitis, illustrating the potential consequences of diagnostic misclassification and immunosuppression [9]. More recently, Stanavage et al. reported syphilitic hepatitis with positive smooth-muscle antibody and resolution of both liver abnormalities and autoimmune titres after benzathine penicillin [10]. Our case adds a phenotype that simultaneously reproduced major PBC and AIH signals—AMA-positive cholestasis with bile-duct injury together with ANA positivity, raised IgG and interface hepatitis—yet all autoimmune abnormalities subsequently regressed.

Importantly, the autoimmune phenotype after syphilitic hepatitis may not always be transient. Ali et al. reported a patient with biopsy-proven syphilitic hepatitis who initially improved after penicillin therapy but returned weeks later with recurrent acute liver injury, new hypergammaglobulinaemia and positive autoimmune serology; repeat liver biopsy demonstrated interface hepatitis, and the patient responded to

glucocorticoid treatment for true autoimmune hepatitis [7]. Although this does not establish that syphilitic hepatitis predictably causes later AIH, it demonstrates that genuine autoimmune hepatitis can emerge after apparent microbiological and biochemical improvement. Therefore, patients with prominent autoimmune features at presentation warrant longitudinal liver-biochemistry follow-up, with repeat IgG and autoimmune serology when initially abnormal; persistent or recurrent hepatitis should prompt reassessment for true AIH rather than being attributed indefinitely to transient infection-associated immune activation [7, 11].

The mechanisms underlying transient autoantibody production in syphilis are incompletely defined. Polyclonal B-cell activation, immune cross-reactivity and broader infection-associated immune dysregulation are biologically plausible explanations, but these mechanisms should not be inferred from serology alone. The key clinical principle is therefore not that positive autoantibodies are 'false', but that they are not disease-specific and must be interpreted in relation to biochemical phenotype, histology, competing infections and longitudinal behaviour. Current AIH guidance continues to place diagnosis on an integrated clinicopathological assessment rather than any single antibody result [11].

The biopsy in this patient was particularly informative because it argued against treating the serology in isolation. Syphilitic hepatitis can contain plasma cells and show interface activity, while ductular reaction and bile-duct inflammation can resemble cholangiopathic autoimmune disease [2, 5]. Conversely, the absence of florid duct lesions or ductopenia and the mild rather than dominant interface hepatitis reduced support for established PBC or AIH–PBC overlap. Direct demonstration of treponemes in liver tissue can support the diagnosis but is neither consistently present nor required when the clinical criteria are fulfilled [2, 4].

The early fall in fever before benzathine penicillin deserves cautious interpretation. The patient had received a short course of doxycycline, which has antitreponemal activity but was not completed for the guideline-recommended duration [12]. Clinical improvement may therefore have reflected partial treatment. Definitive treatment and subsequent serological response followed benzathine penicillin.

For clinicians evaluating unexplained cholestatic hepatitis, the practical lesson is to revisit exposure history and the skin examination before committing to an autoimmune diagnosis. Syphilis should be included among infectious mimics when systemic or dermatological clues are present, even when ANA, AMA or IgG appear to point toward autoimmune liver disease. In such cases, treatment response and longitudinal serological reassessment can prevent unnecessary or potentially harmful immunosuppression; conversely, recurrent hepatitis after successful antitreponemal treatment should trigger reconsideration of true autoimmune liver disease [7].

Conclusions

Secondary syphilis can produce cholestatic hepatitis with bile-duct-centred inflammation and transient autoimmune serology that closely resembles PBC, AIH or an overlap phenotype. Positive autoantibodies and autoimmune-like histology should therefore be interpreted in the full clinical context. In patients with

unexplained cholestasis, particularly when palmoplantar rash, constitutional symptoms or relevant sexual exposure is present, syphilis testing should be considered before immunosuppressive treatment. Resolution of liver injury and disappearance of autoimmune markers after antitreponemal therapy strongly support infection-associated mimicry rather than primary autoimmune liver disease.

Abbreviations

AIH	autoimmune hepatitis
ALP	alkaline phosphatase
AMA	antimitochondrial antibody
ANA	antinuclear antibody
CRP	C-reactive protein
GGT	gamma-glutamyl transferase
IgG	immunoglobulin G
PBC	primary biliary cholangitis
TPPA	Treponema pallidum particle agglutination
VDRL	Venereal Disease Research Laboratory.

Declarations

Ethics approval and consent to participate

Ethics approval was not required

Consent for publication

Informed written consent was obtained from the patient for the publication of her clinical and personal details along with the accompanying images.

All data relevant to the case are included in the manuscript.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

PA (Dr Pesala Adikaranayake): Contributed in Conceptualization, gathering clinical data relevant to the case, for data curation, searching the literature regarding syphilitic hepatitis, creating a draft and presenting for further modification

CW (Dr Chiranthi Welhenge): Contributed in Conceptualization, Interpreting the gathered clinical data to provide a meaningful diagnosis, reviewing the literature and modifying the initial draft of the case report.

PW (Dr Praveen Weeratunga): Contributed for disease diagnosis and management.

UW (Dr Ushani Wariyapperuma): Contributed in interpretation of clinical data and achieving a final diagnosis, patient management, reviewing the literature, case report writing, editing and supervising the process.

All authors critically reviewed the manuscript, approved the final version, and agreed to be accountable for all aspects of the work.

Open AI was used solely for language editing.

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Figures



Figure 1

Palmoplantar hyperpigmented non-pruritic macular eruption. (A) Soles. (B) Palms.

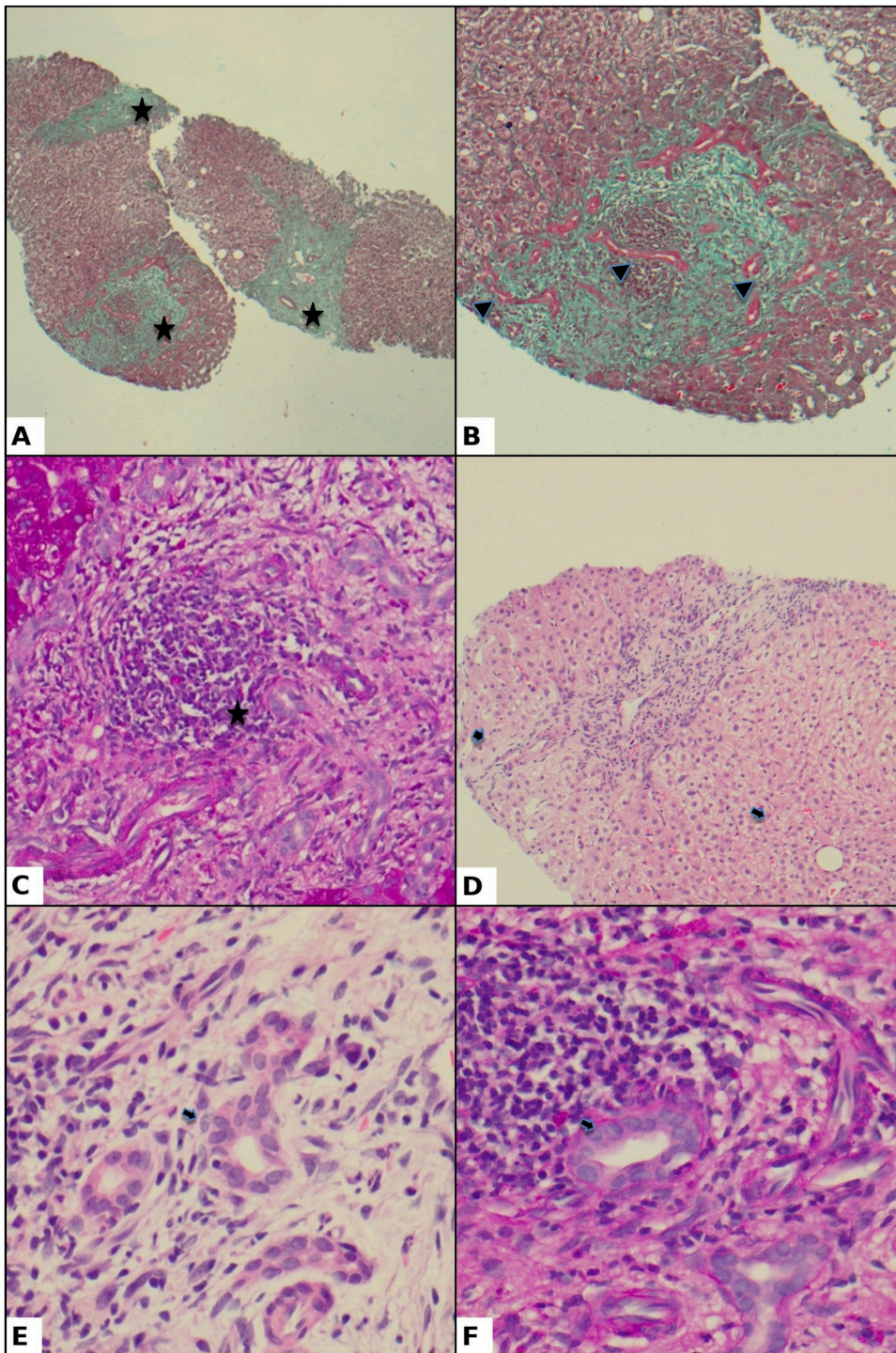


Figure 2

Liver biopsy. (A) Portal tract expansion by fibrosis indicated by black stars (Masson trichrome, x40) (B) Ductular proliferation of a portal tract indicated by arrow heads (Masson trichrome, x100). (C) Presence of lymphoid aggregate in portal tract marked by a star (H&E, x200). (D) Moderately mixed inflammatory infiltrate of a portal tract with mild interface hepatitis shown by arrows (H&E, x100). (E) Intraepithelial

lymphocytes and granulocytes within bile-duct epithelium, consistent with cholangitis indicated by arrows (H&E, x200). (F) Periductal inflammation and cholangitis indicated by arrows (PAS, x400).