

## CASE REPORT

# Syphilitic hepatitis: Case report of an overlooked condition

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## Abstract

Syphilis is an overlooked cause of hepatitis. Syphilitic hepatitis should be a differential diagnosis in all patients with abnormal liver biochemical marker levels. Syphilitic hepatitis has been defined as the combination of increased liver enzymes, positive serology for syphilis, the absence of alternative causes for hepatobiliary injury, and liver enzyme improvement with proper antibiotic therapy.

## KEYWORDS

Syphilis, Syphilitic hepatitis, *Treponema pallidum*

## 1 | INTRODUCTION

Syphilis is a sexually and vertically transmitted infection that is caused by the bacterium, *Treponema pallidum* (*T pallidum*), an obligate human pathogen well-known for its invasiveness and immune-evasive properties.<sup>1</sup> Syphilis was first described at the end of the fifteenth century, and it remains a major public health problem worldwide.<sup>2</sup> According to the most recent global estimation of the World Health Organization, approximately 19.9 million individuals had syphilis in 2016, and an estimated 6.3 million new cases occur every year.<sup>3</sup>

During its natural course, syphilis progresses from early (including primary, secondary, and early latent syphilis) to late stages (including late latent and tertiary syphilis) if left untreated. Primary syphilis classically presents with a single ulcer (chancre) or multiple lesions at the site of inoculation; these are typically painless, they resolve spontaneously, and they may go unnoticed by patients. Secondary syphilis, also known as the dissemination phase, is commonly characterized by a non-itchy skin rash that can mimic other infectious and non-infectious conditions, but the rash can spontaneously disappear even without treatment. When left untreated, the

infection enters a latent stage, which is asymptomatic and can last for years (early latent stage, infection with a duration of  $\leq 1$  year; late latent stage, infection with a duration of  $> 1$  year). Tertiary syphilis is characterized by the development of major complications during the latent phase, such as gumma, cardiosyphilis, or late neurosyphilis.<sup>1,4</sup>

Syphilis can involve multiple organs and produce diverse and often subtle clinical manifestations that can mimic other infectious and non-infectious conditions.<sup>1</sup> Liver involvement associated with syphilis is not observed in daily clinical practice. Here, we presented the uncommon case of a man with syphilitic hepatitis, which is an overlooked entity that warrants attention.

## 2 | CASE REPORT

A 48-year-old Caucasian man with a 2-week history of epigastric tenderness and asthenia was referred to our hospital owing to abnormal hepatic and biochemical test results (alanine aminotransferase [ALT] at 324 IU/L [normal, 3–45]; aspartate aminotransferase [AST] at 154 IU/L [normal, 15–50]; gamma-glutamyl transferase [GGT] at 1384 IU/L [normal  $< 55$ ]; and alkaline phosphatase at 390 IU/L [normal,

**Statements:** The authors obtained signed informed consent from the patient for the publication of his case.

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30–120]). The patient did not have a past medical history of liver disease or abnormal liver tests. Essential arterial hypertension under prolonged treatment with olmesartan was the only known medical condition and medication, respectively. He denied significant alcohol intake, as well as the use of acetaminophen, herbals, over-the-counter products, recreational drugs, or other potentially toxic substances. He also had no family history of gastrointestinal or hepatic diseases. He was single and frequently traveled for work. The patient mentioned a casual unprotected heterosexual intercourse 2 months prior to his present condition. He showed no signs and symptoms, and he had no history of sexually transmitted infections.

The admission physical examination was unremarkable. He was fully alert and oriented, with good reflexes and no flapping; his sclerae were anicteric; he had no skin lesions; his vital signs, heart, and lung sounds were normal; his abdomen was soft, without tenderness or appreciable hepatosplenomegaly.

The admission blood tests revealed normal complete blood counts and coagulation tests; a high C-reactive protein at 30.6 mg/L (<5.0 mg/L); levels of creatinine, albumin, amylase, lipase, and bilirubin within the normal ranges; and increased ALT (342 IU/L [3–45]), AST (93 IU/L [15–50]), GGT (1503 IU/L [<55]), and alkaline phosphatase (591 IU/L [30–120]). An abdominal ultrasound revealed normal liver parenchyma, biliary tract, gallbladder, pancreas, and spleen and the absence of lithiasis.

We admitted the patient for further investigation and surveillance. The consecutive blood tests showed a progressive increase in the liver enzymes (ALT, 844 IU/L; AST, 387 IU/L; GGT, 1763 IU/L; alkaline phosphatase, 763 IU/L) with normal liver function parameters. Two days after being hospitalized, the patient developed non-itchy, erythematous, maculopapular rashes on the palms of both hands (Figure 1). He showed no signs of liver failure. Serological test results were negative for hepatitis A, B, C, and E viruses, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, and human immunodeficiency virus (HIV). The usual liver autoantibodies were also negative. The levels of serum immunoglobulins were normal. Given the dermal findings, we tested him for syphilis and found a reactive venereal disease research laboratory (VDRL) titer of 1:64, a *T pallidum* hemagglutination assay of 1:640, and a positive IgM fluorescent *T pallidum* antibody absorbance (FTA-Abs IgM).

Taking the clinical and laboratory findings together, the patient was diagnosed with syphilitic hepatitis and initiated his intake of benzathine penicillin G 2.4 million units intramuscularly once weekly, for 3 weeks. Two days after the first dose, he was discharged. A month later, he was completely asymptomatic, the skin lesions had disappeared, the liver biochemical marker levels had completely normalized, and

the VDRL was already nonreactive (seroconversion), which confirmed the clinical cure (Table 1).

### 3 | DISCUSSION

Syphilitic hepatitis is a rare clinical presentation of syphilis, with an incidence ranging from 0.25% to 38%.<sup>5,6</sup> It occurs relatively more frequently among men who engaged in sexual intercourse with men or with patients with HIV infection, but the disease can emerge in any individual who gets infected.<sup>7</sup> Even though a local inflammatory response elicited by spirochetes is believed to be the cause of all clinical manifestations of syphilis, the precise mechanisms by which *T pallidum* causes liver damage and the reason behind certain patients with infection developing hepatitis while others do not remain unclear.<sup>1,6</sup>

Hepatic involvement in syphilis can be observed during any phase of the disease. A systematic review that includes 144 patients found that 89% of cases develop during early syphilis and 6% during late stages.<sup>7</sup> According to the same review, the most frequently occurring signs and symptoms in patients with syphilitic hepatitis are rashes involving the palms of both hands, soles, or any other body part (78%), followed by fatigue/poor appetite (57%), hepatomegaly (54%), jaundice (35%), lymphadenopathy (31%), fever (26%), weight loss (23%), abdominal pain (22%), and splenomegaly (14%).<sup>7</sup>

On the basis of other studies, syphilitic hepatitis can be diagnosed when all the following criteria are present: abnormal liver biochemical marker levels, serological evidence of syphilitic infection, exclusion of other etiologies of liver disease, and successful response to the antibiotic treatment with normalization of the liver enzymes.<sup>5,8,9</sup> The patient in the present case met all these criteria.

The pattern of abnormal liver test results in syphilitic hepatitis is typically cholestatic, but it can also be hepatocellular or mixed. Disproportionally high serum alkaline phosphatase and GGT levels with slight raised or normal serum transaminases and bilirubin are common.<sup>7-12</sup>

Serologic testing for the diagnosis of syphilis should include the use of both nontreponemal and treponemal tests. Either test can be used as the initial screening test. In our patient, we were still using the traditional approach (initial screening with nontreponemal test). This algorithm has shown a high positive predictive value when both tests are reactive, although very early primary and previously treated syphilis can be overlooked due to the lower sensitivity of nontreponemal tests. Nowadays, in numerous institutions including ours, the reverse algorithm is used (initial screening with treponemal tests). This approach is associated with higher costs, but it permits the detection and treatment of 99% of cases compared with the traditional algorithm in a low-prevalence setting.<sup>1</sup>

**FIGURE 1** Erythematous maculopapular rashes on the palms of both hands



**TABLE 1** Blood test changes before and after treatment

	Normal range	Hospital admission	Before treatment	One month after treatment
INR (ratio)	0.50–3.00	1.11	1.10	1.09
Albumin (g/L)	35–52	44	42	44
Bilirubin ( $\mu\text{mol/L}$ )	5.0–21.0	20.6	38.3	18.1
ALT (IU/L)	3–45	342	844	41
AST (IU/L)	15–50	93	387	35
GGT (IU/L)	<55	1503	1782	53
Alkaline phosphatase (IU/L)	30–120	591	763	118
VDRL (titer)	–	–	1:64	Nonreactive

*Note:* Abbreviations: INR, international normalized ratio; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyl transferase; VDRL, venereal disease research laboratory.

Liver biopsies performed in patients with syphilitic hepatitis often show portal and lobular inflammatory cell infiltrates, hepatocellular necrosis, cholestasis, and/or non-caseating granulomas. Since these findings are non-specific and spirochete recognition in liver specimens is difficult, even after immunohistochemical or Warthin-Starry staining, liver biopsy is not considered essential for the diagnosis of syphilitic hepatitis when there is a positive response to therapy.<sup>7–9</sup>

Penicillin remains the treatment of choice for patients in all stages of syphilis, with different regimens suggested based on the disease stage. In our case, as we could not be sure of the timing of the infection because the patient did not notice a chancre or any other primary lesion, we preferred to prescribe a 3-week course of intramuscular administration of benzathine penicillin G at 2.4 million units once weekly (as recommended for latent syphilis) rather than a single dose (used to treat early syphilis).<sup>2</sup>

Antibiotic treatment shows rapid improvement in the majority of cases of syphilitic hepatitis.<sup>6–8,13</sup> Very rarely,

syphilitic hepatitis can result in fulminant liver failure, as shown in the case of a patient who required a liver transplantation.<sup>14</sup>

In summary, this case report highlights syphilis as an overlooked etiology of hepatitis that should always be excluded during the evaluation of patients with abnormal liver biochemical marker levels of unknown etiology. Its diagnosis is usually straightforward, and a liver biopsy is not generally necessary for a positive response to antibiotic therapy. Timely diagnoses and prompt treatments are important for limiting clinical effects and preventing progression to tertiary syphilis.

#### CONFLICT OF INTEREST

None declared.

#### AUTHOR CONTRIBUTION

Pedro Marcos: revised the literature and drafted the manuscript. Liliana Eliseu: revised the manuscript. Martinha

Henrique and Helena Vasconcelos: revised the manuscript and approved the final version.

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