CASE REPORT

Hepatitis in patients with syphilis: an overlooked association

Ana Carina Pizzarossa, Martín Rebella

Clínica Médica C, Hospital de Clínicas, Montevideo, Uruguay

Correspondence to

Dr Ana Carina Pizzarossa, carina491986@gmail.com

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SUMMARY

We present the case of a patient who sought treatment for fever and a maculopapular rash involving the trunk, limbs, palms and soles. The patient also presented with hepatomegaly and elevated levels of liver enzymes (with a higher increase of alkaline phosphatase). With the proposal of early syphilitic hepatitis, during the stage of secondary syphilis, a venereal disease research laboratory and *Treponema pallidum* haemagglutination tests were requested, which confirmed the diagnosis. All altered parameters improved with antibiotic treatment for secondary syphilis. Syphilitic hepatitis is an often overlooked presentation of syphilis and should be considered as a differential diagnosis in patients with elevated levels of liver enzymes and risk factors for syphilis.

BACKGROUND

This case was chosen because it represents an overlooked presentation of a common disease and thus it serves as a reminder of an important clinical lesson. Syphilis continues to be a public health problem, even in the 21st century. The median incidence rate of syphilis was 25.1 cases per 100 000 adults among the 55 countries that participated in the 2015 WHO report of sexually transmitted diseases. The rate in Uruguay is above the median, with 78 cases per 100 000 inhabitants.¹

Liver damage associated with syphilis should be ruled out among patients with hepatitis of an unknown aetiology, especially in the presence of risk factors for contracting syphilis.

CASE PRESENTATION

We present the case of a female patient with a history of partially controlled asthma with irregular treatment and impaired fasting glycaemia.

The patient reported high-risk behaviours for sexually transmitted diseases (multiple casual contacts with no condom). No alcohol consumption or contact with/consumption of toxins was reported.

The patient consulted for 4–5 days of fever accompanied by myalgia, headache and generalised non-pruritic rash. Initial physical examination revealed macular erythematous lesions on the trunk, limbs, palms (figures 1 and 2) and soles. Hepatomegaly was also detected. Of note, jaundice was not observed.

INVESTIGATIONS

Alkaline phosphatase 721 IU/L (35–105 IU/L), alanine aminotransaminase 247 IU/L (<33 IU/L),

aspartate aminotransaminase 321 IU/L (<32 IU/L), gamma glutamyl transpeptidase 550 IU/L (5–36 IU/L), total bilirubin 1.07 mg/dL (0.20–1.20 mg/dL), direct bilirubin 1.01 mg/dL (0–0.30 mg/dL) and indirect bilirubin 0.06 mg/dL (0–0.90 mg/dL). The prothrombin time was unaltered.

Test results for HIV and pregnancy were negative.

Imaging studies revealed hepatomegaly.

Given the characteristics of the skin lesions and the presence of fever and risk factors, a diagnosis of secondary syphilis was considered. Secondary syphilis also explained the alterations in transaminases.

A venereal disease research laboratory (VDRL) test was requested. The result of the VDRL test was 32 IU (positive) and *Treponema pallidum* haemagglutination (TPHA) test was positive; therefore, syphilis was confirmed.

Viral causes of hepatitis were excluded (hepatitis A virus, hepatitis B virus, hepatitis C virus, cytomegalovirus, and Epstein-Barr virus serologies came back negative). In our hospital, we cannot order testing for hepatitis E virus.

DIFFERENTIAL DIAGNOSIS

The syphilitic aetiology of the liver injury in this clinical setting is clear. However, when confronted with a patient with liver injury, infectious, drug-induced, alcoholic, autoimmune and vascular aetiologies should be considered. In this particular case, only infectious aetiology was ruled out (and it could be argued that it was not mandatory to do so, due to the clinical characteristics of this case).

TREATMENT

With secondary syphilis diagnosed, the patient was treated with 2.4 million IU of penicillin G benzathine according to national guidelines.²

OUTCOME AND FOLLOW-UP

The patient progressed well; the skin lesions disappeared. Liver enzymes values returned to normal a week after treatment and the VDRL decreased to 8 units 2 weeks after treatment. We were not able to find the sexual partners of the patient so we could test them and eventually treat them.

DISCUSSION

Syphilis, known as ‘the great simulator’, has a proteiform clinical presentation and is an unrecognised cause of hepatitis. Liver involvement occurs as a consequence of the invasion of the liver via spirochaetes during the dissemination phase.³

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Figure 1 Lesions on left palm. The photographs were taken 24 hours after receiving the only dose of penicillin treatment.

The reported incidence among patients with syphilis ranges from 0.25% to 38%.⁴⁻⁶

Liver involvement in syphilis can be observed during any stage of the disease. In a 2018 systematic review of syphilitic hepatitis that included 144 cases, it was shown that 128 (88.9%) patients had early syphilis (including primary and secondary syphilis), 7 (4.9%) latent syphilis and 9 (6.3%) tertiary syphilis.⁷

Recently, the association between syphilitic hepatitis and HIV infection has gained importance.⁸ The Crum-Cianflone series of 2009⁶ only included patients coinfecting with HIV and showed the highest incidence, with 12 of 32 cases studied (38%). In the previously mentioned systematic review, 78 out of 127 with information available (61.4%) were coinfecting with HIV.⁷

In the aforementioned review, rashes were the most common clinical manifestations of syphilitic hepatitis (74/97, 77.9%), followed by fatigue or poor appetite (55/97, 56.7%), icterus (34/97, 35.1%), fever (25/97, 25.8%), weight loss (22/97, 22.7%) and abdominal pain (21/97, 21.6%). Hepatomegaly was present in 52/97 (53.6%) cases, whereas lymphadenopathy was seen in 30 (30.9%) patients and splenomegaly in 14 (14.4%).⁷

Based on previous reports,^{9,10} syphilitic hepatitis can be defined by the following criteria: (1) increased levels of liver enzymes that indicate hepatic involvement; (2) serological evidence of syphilis with a positive treponemal test; (3) the exclusion of alternative causes of liver injury and diseases of the biliary tract and (4) improvement in liver enzyme levels with appropriate

Figure 2 Lesions on right palm.

treatment. The patient in our case met all of these criteria and is a good example of the most frequent clinical features of syphilitic hepatitis. In the case reported, the increase in liver enzymes was accompanied by a rash that suggested secondary syphilis (and that was confirmed with VDRL and TPHA tests). Other possible causes of liver injury were excluded, and liver enzyme values returned to normal after appropriate treatment.

Importantly, a predominance of altered alkaline phosphatase was one of the liver enzyme alterations, and bilirubin and transaminase levels were either slightly altered or normal. Although this cholestatic alteration pattern is more common, cases of predominantly hepatocellular alteration have been observed.¹¹

As the definition presented in the previous paragraphs demonstrates, a biopsy is not mandatory for diagnosis but helps in cases of atypical presentations. Biopsies typically reveal non-specific changes, such as lymphocytic periportal infiltration with focal necrosis of liver cells around the central veins, portal areas and lobules. *Treponema* or granulomatous changes are observed in half of all cases.^{6,12,13}

Most cases have improved with antibiotic treatment^{14,15}; spontaneous improvement has also been reported.¹⁶ Fulminant hepatic failure can occur and should be considered when no response to initial treatment occurs.¹⁷

The identification of syphilis cases and their treatment prevents progression to tertiary syphilis in affected individuals and the spread to other individuals. Therefore, it is important to rule out syphilis in patients with risk factors and elevated liver enzymes.

Learning points

- Syphilitic hepatitis is an overlooked form of syphilis.
- Syphilitic hepatitis should be a differential diagnosis in patients with liver dysfunction and risk factors for syphilis.
- Alkaline phosphatase levels are the most elevated in these cases.
- Liver enzyme levels have been reported to improve after antibiotic treatment with penicillin G benzathine.

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