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Syphilis mimicking primary biliary cholangitis

Sífilis mimetizando colangite biliar primária

Sífilis que simula una colangitis biliar primaria

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Abstract
Introduction: Syphilitic hepatitis can be defined as a cholestatic pattern of elevated enzymes with treponemic serological evidence, when there is an absence of alternative causes of hepatic aggression. Infections are considered important environmental factors that contribute to decreased tolerance to autoantigens, which can trigger autoimmune diseases. The aim of this article is to report a case in which syphilis mimicked the clinical picture and laboratory findings of primary biliary cholangitis, an autoimmune cholestatic disease. Case report: a 20-year-old man, immunocompetent, admitted with nausea, pruritus, jaundice, choluria, fecal acolia, inappetence, vomiting, fever, chills, epigastric pain and weight loss for about 20 days. Laboratory exams showed hyperbilirubinemia at the expense of direct bilirubin and elevated liver enzymes with a canalicular pattern, VDRL reagent 1/256, antimitochondria 1/80. After eradication of Treponema with benzathine penicillin, the patient developed complete recovery of the clinical picture, an important decrease in VDRL (1/4), disappearance of autoantibody and complete biochemical normalization. Conclusion: The present case highlights the importance of properly performed anamnesis, physical examination and adequate follow-up until the response or not to treatment, to confirm the diagnosis. It is important to include secondary syphilis among the possible causes of liver disease.
Keywords: Syphilis; Syphilis, Latent; Primary Biliary Cholangitis; Hepatitis, Autoimmune.

Resumo
Introdução: A hepatite sifilítica pode ser definida como um padrão colestático de elevação das enzimas com evidência sorológica treponêmica, na ausência de causas alternativas de agressão hepática. As infecções são consideradas fatores ambientais importantes que contribuem para a quebra da tolerância aos autoantígenos, podendo desencadear doenças autoimunes. O objetivo desse artigo é relatar um caso em que a sífilis mimetizou o quadro clínico e os achados laboratoriais de uma colangite biliar primária, doença colestática autoimune. Relato de caso: Homem de 20 anos, imunocompetente, admitido com náuseas, prurido, icterícia, colúria, acolia fecal, inapetência, vômitos, febre, calafrios, dor epigástrica e perda de peso há cerca de 20 dias. Exames mostravam hiperbilirrubinemia às custas de bilirrubina direta e elevação de enzimas hepáticas com padrão canalicular, VDRL reagente 1/256, antimitocôndria 1/80. Após a erradicação do Treponema com penicilina benzatina, o paciente evoluiu recuperação completa do quadro clínico, queda acentuada do VDRL (1/4), desaparecimento do auto anticorpo e normalização bioquímica completa. Conclusão: O presente caso ressalta a importância da anamnese e exame físico adequadamente realizados e do

seguimento adequado até a resposta ou não ao tratamento, para confirmação do diagnóstico. É importante incluir a sífilis secundária entre as possíveis causas de doença hepática.
Palavras-chave: Sífilis; Sífilis Latente; Colangite Biliar Primária; Hepatite Autoimune.

Resumen
Introducción: La hepatitis sifilítica puede definirse como un patrón colestásico de enzimas elevadas con evidencia serológica treponémica, en ausencia de causas alternativas de agresión hepática. Las infecciones se consideran factores ambientales importantes que contribuyen a la ruptura de la tolerancia a los autoantígenos, lo que puede desencadenar enfermedades autoinmunes. El objetivo de este artículo es informar de un caso en el que la sífilis imitó el cuadro clínico y los hallazgos de laboratorio de la colangitis biliar primaria, una enfermedad colestásica autoinmune. Informe de caso: Un hombre inmunocompetente de 20 años fue ingresado con náuseas, prurito, ictericia, coluria, acolia fecal, pérdida de apetito, vómitos, fiebre, escalofríos, dolor epigástrico y pérdida de peso durante aproximadamente 20 días. Los exámenes mostraron hiperbilirrubinemia por bilirrubina directa y elevación de enzimas hepáticas con patrón canalicular, reactivo VDRL 1/256, antimitocondria 1/80. Después de la erradicación del Treponema con penicilina benzatínica, el paciente experimentó una recuperación completa del estado clínico, una fuerte caída del VDRL (1/4), la desaparición del autoanticuerpo y una normalización bioquímica completa. Conclusión: Este caso resalta la importancia de una adecuada anamnesis y examen físico y un adecuado seguimiento hasta la respuesta o no al tratamiento, para confirmar el diagnóstico. Es importante incluir la sífilis secundaria entre las posibles causas de enfermedad hepática.
Palabras clave: Sífilis; Sífilis Latente; Colangitis Biliar Primaria; Hepatitis Autoinmune.

1. Introduction

Syphilis is a chronic infection caused by Treponema pallidum that, despite having its natural history well studied, still lacks a better understanding of its pathogenic mechanism (Cunha Neves et al., 2022). The disease has a latency period, when the patient is asymptomatic, despite the replication of Treponema. The infection is transmitted between people mainly sexually during oral, anal or vaginal sex, but also through direct contact of the genitals. The natural course of the disease varies, ranging from early to chronic syphilis in the absence of treatment (Supronowicz & Rogalska, 2024). Secondary syphilis, or the spreading phase, can present with a variety of nonspecific symptoms, including fatigue, fever, weight loss, and abdominal pain (Romeiro et al., 2018; Solomon et al., 2024). It is in this stage that the liver enzymes are most commonly elevated. Syphilitic hepatitis can be defined as a cholestatic pattern of elevated enzymes with treponemic serological evidence, in the absence of alternative causes of hepatic aggression. It is estimated that 3% of cases of secondary syphilis may be present as syphilitic hepatitis, but among all patients with syphilis, hepatitis occurs in 0.2% to 3% of patients (Alemam et al., 2021).

Primary biliary cholangitis (PBC) is a chronic, slowly progressive, immune-mediated cholestatic liver disease characterized histologically by portal inflammation and destructive, lymphocytic cholangitis of the small bile ducts. In most cases carriers of the disease have anti-mitochondrial antibodies (AMA) (Bauer et al., 2021; Trivella et al., 2023; Bauer & Habior, 2025). Lack of early diagnosis and treatment results in progressive cholestasis, fibrosis, cirrhosis and liver failure. The global prevalence of PBC is estimated to be between 40 and 400 cases per million inhabitants, with a female predominance (Xu et al., 2023). The disease is multifactorial, individuals with predisposed genetic factors may develop PBC as a consequence of environmental triggers. Bacterial infection is considered one of the most important environmental factors that contribute to decreased tolerance to mitochondrial autoantigens (Tanaka et al., 2019; Bauer et al., 2021).

This article aims to report a case in which syphilis mimicked the clinical picture and laboratory findings of primary biliary cholangitis. If the infection was not diagnosed, the patient could present a very serious outcome considering the natural evolution of the disease.

2. Methodology

A descriptive (qualitative nature) and quantitative (values of laboratory tests) study was conducted in the form of a case report (Pereira et al., 2018; Toassi & Petry, 2021). This case report was conducted following the current bioethical

standards and was submitted and approved by the Research Ethics Committee (CAAE 86712325.2.0000.8667; opinion Nº 7.475.980).

The research was carried out in 3 stages and was based on the description of retrospective data regarding a case considered rare, through the study of the patient's electronic medical record and review of the literature on digital platforms to subsequently correlate the bibliographic findings with the patient's condition.

The first stage consisted of analysis and documentation of the clinical and laboratory findings of the patient; then scientific publications on the hepatic manifestations of syphilis, with emphasis on autoimmune liver diseases, preferably primary biliary cholangitis, on the digital platforms PubMed, ScienceDirect and Google Scholar was carried out; in the last stage the case described with the findings of the literature were discussed.

3. Case Report

20-year-old man, immunocompetent, admitted to the hospital with complaints of nausea and prurience about 20 days ago. Five days after the onset of the condition, jaundice, choluria, fecal acolia, inappetence, vomiting, fever, chills and epigastric pain unrelated to food began to present. He said he lost more than 20kg due to severe anorexia. During the complementary interview, he reported the appearance of penile lesions, prior to the onset of the systemic symptoms. He had been diagnosed with syphilis, but did not receive specific treatment. He denied alcohol consumption, smoking, or illicit drug use. Physical examination showed jaundice (4+/4+), with pain on deep palpation of the right hypochondrium (HD), as well as whitish ulcerated lesions on the foreskin, friable, without lymph node enlargement or secretion.

It carried VDRL reagent 1/256. The first laboratory exams during hospitalization showed hyperbilirubinemia at the expense of direct bilirubin and elevation of liver enzymes with a canalicular pattern. The results are detailed in Table 1. Differential diagnostic tests were performed for infectious causes of acute liver disease, which were negative: serology for HIV, hepatitis A, B and C, toxoplasmosis, cytomegalovirus and Epstein Barr. Ruled out alpha 1-antrypsin deficiency, Wilson's disease and hemochromatosis. In the investigation of autoimmune liver diseases, antibodies to non-reactive HEp-2 cells (FAN); liver/kidney antimicrosomal (anti-LKM_1) were non-reactive. Immunoglobulin IgG 1955; antimuscle smooth (ASMA) 1:40 and antimitochondria (AMA) 1:80. The tumor marker CA19.9 was 5.727. Imaging tests did not show changes that would justify a canalicular pattern lesion (contrast-enhanced tomography of the upper abdomen and magnetic resonance imaging of the biliary tract). After the presence of cholangiocarcinoma was ruled out, the hypotheses of PBC or syphilis hepatitis mimicking autoimmune liver disease were raised. Treatment for late latent syphilis was performed with three doses of benzathine penicillin 2.400.000 UI and the evolution of the laboratory results were presented in Table 1. The patient was discharged with the resolved hypothesis of syphilis mimicking primary biliary cholangitis.

Table 1 - evolution of laboratory tests.

	12/09/23	**14/09/23**	**16/09/23§**	**20/09/23**	**25/09/23¥**	**06/10/23**	**15/12/23**	**13/03/24**
AST / ALT	53/65	44/65	58/64	163/213	112/189	52/92	19/19	19/18
GGT/FAL	59/327	53/326		182/287	141/263	149/158	26/70	25/84
BT / BD	16.9/13	15.3/11.9	12.4/9.6	13.1/10	7.9/5.9	3.2/2.3	1.8/0.7	
Albumin		3.9	3.6	3.9	4.1	4.5	4.9	
Creatinine	0.66	0.64	0.75	0.8	0.75	0.92	0.96	
Total cholesterol/TAG		244.5/262					146.2/69.2	
HDL / LDL		9.3/183					47/85	

Glucose/HbA1c		74/4.4					93/4.8	
Ferritin/STI		536.42/24						
Haemoglobin	13.1		11.2	10.9	11.6	12.5	13.3	14.8
Leukocytes	9830		8480	11100	9580	10910	8790	10000
Platelets	491000		473000	439000	439000	317000	290000	303000
TSH		0.759						
Immunoglobulin IgG		1955			1896		1345	
Anti ASMA		1.:40					NR	
Anti Mitochondria		1.:80					1.:40	NR
CA 19-9		5727	346		45			
VDRL		1:256					1:64	1:4

§ First dose of benzathine penicillin on 09/17/23
¥ Third dose of benzathine penicillin on 04/10/23
Source: clinical analysis and pathological anatomy unit. Hospital das Clínicas-UFTM (2025).

4. Discussion

In 1943 Hahn described the first association between hepatitis and syphilis (Hahn, 1943). Since then, numerous similar cases have been described, until in 2004, Mullick published as a recommendation for the diagnosis of syphilitic hepatitis the following criteria: abnormal liver enzyme levels, serological evidence of syphilis with acute clinical presentation consistent with secondary syphilis, exclusion of other causes of liver damage, and improvement in liver enzyme levels with appropriate antimicrobial therapy (Mullick et al., 2004; El Mamouni et al., 2024). In recent years, numerous cases of syphilitic hepatitis, most often cholestatic, have been described (Pereira et al., 2021; Plesa et al., 2022; Orozco-Sebá et al., 2023; Terada & Sawafuji, 2024).

The disease manifests itself mainly with cholestatic pattern of enzyme elevation with normal biliary tract anatomy (Huang et al., 2018; Huang et al., 2019; Cantu Lopez et al., 2024), but one publication presents syphilis mimicking CBP with reactive antimitochondria antibody, the same pattern as the case presented here (Kern et al., 2020). The patient described by Kern had acquired immunodeficiency virus, hypertension, dyslipidemia and diabetes mellitus, comorbidities that had been treated. The present case, of an immunocompetent patient, did not have the factors that may have generated numerous differential diagnoses as described by Kern. Goldberg, in 2021, had published a case of syphilitic hepatitis in an immunocompetent patient, with elevated enzymes in a hepatocellular pattern, but with antimitochondria and antinucleus reagents. However, the main confounding variable that delayed syphilis treatment was IgM antibody positivity for Herpes simplex virus. (Goldberg et al., 2021).

Current literature suggests that there are several environmental triggers for autoimmune liver diseases, including viral and bacterial infections, and syphilis has been associated with autoimmunity through the generation of autoantibodies and altered T-cell function (Ali et al., 2022). The patient presented here had a good evolution, being ruled out the hypothesis of Primary Biliary Cholangitis, after eradication of Treponema.

In the differential diagnosis of liver diseases, syphilis is rarely considered the etiological factor of hepatocyte damage, and tests for it are very rarely performed in patients with damage to the liver parenchyma (Marcos et al., 2019; Mujumdar et al., 2022). It is important to emphasize that if the diagnosis of syphilis was not made, the patient would be prescribed Ursodeoxycholic Acid, the first option for treatment of PBC. In this context, syphilis would not be diagnosed, continuing its natural outcome.

5. Final Considerations

Cholestasis caused by Treponema pallidum is difficult to diagnose in cases that do not have other symptoms of infection. Liver involvement usually presents with nonspecific signs and symptoms. Therefore, it is essential to suspect this etiology, even while investigating the most frequent causes of structural cholestatic liver disease or other infectious diseases with liver tropism.

The present case highlights the importance of properly performed anamnesis, physical examination and adequate follow-up until the response or not to treatment, to confirm the diagnosis. It is important to include secondary syphilis among the possible causes of liver disease.

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