Exploring the Ways of “The Great Imitator”: A Case Report of Syphilitic Hepatitis

João A. Cunha Neves, Joana Roseira, Helena Tavares de Sousa, Rui Machado

Department of Gastroenterology, Centro Hospitalar Universitário do Algarve, Portimão, Portugal; Department of Biomedical Sciences and Medicine, University of Algarve, Faro, Portugal; Department of Infectious Diseases, Centro Hospitalar Universitário do Algarve, Portimão, Portugal

Keywords
Syphilis · Treponema pallidum · Syphilitic hepatitis · Secondary syphilis · Case report

Abstract
Introduction: Syphilis is a chronic infection caused by Treponema pallidum. Manifestations of this disease are vast, and syphilitic hepatitis is a rarely depicted form of secondary syphilis. Case Presentation: We report the case of a 63-year-old man with worsening jaundice, maculopapular rash and perianal discomfort. Proctological examination with anoscopy revealed a perianal gray/white area with millimetric pale granules along the anal canal. Liver function tests showed a mixed pattern. Venereal Disease Research Laboratory, T. pallidum hemagglutination assay and IgM fluorescent treponemal antibody absorbance were positive. The patient was successfully treated with a single dose of penicillin G. Discussion/Conclusion: Syphilitic hepatitis is scarcely reported in the literature. Secondary syphilis with mild hepatitis rarely leads to hepatic cytolysis and jaundice. Many signs of secondary syphilis including syphilitic hepatitis may be linked to immune responses initiated during early infection. Over the past decades, evidence has emerged on the importance of innate and adaptive cellular immune responses in the immunopathogenesis of syphilis. This report raises awareness to a clinical entity that should be considered in patients at risk for sexually transmitted diseases, who present with intestinal discomfort or liver dysfunction, as it is a treatable and fully reversible condition.

Explorando as manifestações do “Grande Imitador”: um caso clínico de hepateite sifilítica

Palavras Chave
Sífilis · Treponema pallidum · Hepatite sifilítica · Sífilis secundária · Caso clínico

Resumo
Introdução: A sífilis é uma infecção crónica provocada pelo Treponema pallidum. As manifestações desta doença são vastas e a hepatite sifilítica é uma forma de sífilis secundária raramente descrita. Caso Clínico: Apresentamos o caso de um doente de 63 anos com icterícia de agravamento
progressivo, rash maculopapular e desconforto perianal. O exame proctológico complementado por anoscopia revelou uma região perianal cinzenta-esbranquiçada com grânulos pálidos milimétricos ao longo do canal anal. Testes de função hepática revelaram um padrão misto e o Venereal Disease Research Laboratory, T. pallidum hemagglutination assay e IgM fluorescent treponemal antibody absorbance foram positivos. O doente foi tratado com sucesso com uma dose única de penicilina G. Discussão/Conclusão: São raros os casos de hepatite sifilítica descritos na literatura. Sífilis secundária com hepatite ligeira raramente conduz a citólise hepática e icterícia. Muitos dos sinais de sífilis secundária, incluindo a hepatite sifilítica, parecem estar associados a respostas imunitárias iniciadas durante o período de infecção precoce. Ao longo das últimas décadas, têm surgido evidências crescentes sobre a importância das respostas imunes inata e adaptativa na patogénese da sífilis. Este caso clínico descreve uma entidade nosológica que deve ser considerada em doentes em risco de contraírem doenças sexualmente transmissíveis, que se apresentem com desconforto intestinal ou disfunção hepática, visto tratar-se de uma condição tratável e totalmente reversível.

Introduction

Syphilis is a chronic infection caused by Treponema pallidum. Nowadays, we have a relatively complete understanding of the natural history of untreated syphilis. However, the pathogenic mechanism of T. pallidum is still not fully understood [1]. Some authors suggest that manifestations like syphilitic hepatitis (SH) are likely due to innate and adaptive cellular immune responses.

Case Report

A 63-year-old man was admitted to the Emergency Department with a 1-month history of worsening jaundice and perianal discomfort. The patient had an unremarkable medical history. He denied any medication, alcohol consumption, drug administration or unprotected sexual intercourse.

Physical examination revealed icteric skin and mucosae and a maculopapular rash on the palms, inguinal region, legs and soles (Fig. 1). Genital lesions, such as chancre, were discarded. Proctological examination revealed a perianal gray/white area and painless nodular lesions on the anal canal and distal rectum. Anoscopy confirmed millimetric pale granules along the anal canal.

Liver function tests on admission showed a mixed pattern – total/direct bilirubin of 8.3/6.9 mg/dL (normal: 0.3–1 mg/dL), aspartate aminotransferase of 105 IU/L (normal: <34 IU/L), alanine aminotransferase of 188 IU/L (normal: <44 IU/L) and alkaline phosphatase (ALP) of 670 IU/L (normal: <120 IU/L). Further investigations including hepatitis A, B and C, HIV, cytomegalovirus and Epstein-Barr serology, ceruloplasmin, α₁-antitrypsin, iron studies, smooth muscle, antinuclear and antimitochondrial antibodies were unremarkable.

Abdominal ultrasound revealed a normal liver parenchyma and biliary tree. Colonoscopy showed an indurated nodular mucosa around the rectal lumen (Fig. 2–4). Histology of the biopsied rectal mucosa revealed an unspecified inflammatory cell infiltrate.

ALP levels increased to 1,355 IU/L, and the maculopapular lesions remained unresolved. Suspecting a dermatologic disease with perianal manifestations, consultation by Dermatology was requested, along with serological tests for syphilis. Results showed a Venereal Disease Research Laboratory (VDRL) titer of 1/256, a T. pallidum hemagglutination assay (TPHA) of 1/5,120 and a positive IgM fluorescent treponemal antibody absorbance (IgM FTA-abs). At this point, the patient mentioned one unprotected heterosexual intercourse with a shared object, 2 months before the onset of symptoms.

The patient was treated with a single dose of penicillin G benzathine (2.4 million units intramuscularly). Jaundice and the rash lesions progressively subsided. Cytolysis resolved and cholestasis gradually disappeared. IgM FTA-abs results became negative, whereas VDRL and TPHA titers decreased over time.

Response to the standard regimen for early syphilis allowed the authors to confirm the diagnosis of SH.

Discussion/Conclusion

Untreated syphilitic infections may cause the widespread dissemination of T. pallidum, and approximately 25% of patients will primarily exhibit a systemic illness, representing the secondary stage of syphilis [2]. Condylomata lata are relatively common, occurring in about one third of patients suffering from syphilis. However, proctitis and hepatitis are a much less studied reflection of secondary syphilis (SS).

Regarding the absence of genital wounds, we considered the proctological lesions as the primary site of inoculation. Despite these, biopsies of the rectal mucosa failed to show spirochetes. However, it is well established that T. pallidum is impossible to visualize by direct microscopy and unable to grow in culture [1].

The frequency of SH ranges from 1 to 50% [3], but it is rarely reported in the literature. Mild hepatitis characterized by high serum ALP levels is the most frequent hepatic manifestation of SS, but it rarely leads to hepatic cytolyis and jaundice [4, 5].

Some authors report that liver biopsies of patients with SH may reveal focal necrosis, acute inflammatory inflam-
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Fig. 1. Maculopapular rash on the palms.

Fig. 2. Tubular rectum – hardened and erythematous mucosa with pale nodular lesions.

Fig. 3. Tubular rectum – hardened and erythematous mucosa with pale nodular lesions.

Fig. 4. Retroflexion in the rectum – hardened and erythematous mucosa with pale nodular lesions.

Although some authors still prefer the administration of 3 doses of penicillin G benzathine (2.4 million units intramuscularly) each at 1-week intervals [4, 8], evidence suggests a lower number of cures with a triple dose of penicillin G benzathine compared to a single dose of penicillin G benzathine [11]. Current treatment guidelines advocate a single dose of penicillin G benzathine (2.4 million units intramuscularly) as the recommended regimen for SS [11, 12].

Many signs of SS including SH may be linked to immune responses initiated during early infection [13]. Over the past decades, evidence has emerged on the importance of innate and adaptive cellular immune responses in the immunopathogenesis of syphilis [14]. The adaptive component was documented first, with the publication of experiments in rabbit models showing that the replication of treponemes at the inoculation site elicited an intense inflammatory response resembling a delayed-
type hypersensitivity reaction [13]. Immunohistochemical analysis revealed that syphilitic lesions in humans also contained cellular elements associated with adaptive immunity, including cytokine-producing Th1 cells. The contribution of innate responses to lesion development and resolution was studied both in vitro and in vivo, establishing that spirochetal lipoproteins are capable of activating macrophages via CD14 and Toll-like receptor 1/2 signaling pathways. Hence, these pathogen-associated molecular patterns are now believed to be the major pro-inflammatory agonists during spirochetal infection [15, 16]. Despite this apparent immune control, simultaneous widespread dissemination of spirochetes occurs.

Clinicians should bear in mind the possibility of syphilitic involvement in patients at risk for sexually transmitted diseases who present with intestinal discomfort or liver dysfunction, as it is a treatable and fully reversible condition.

Statement of Ethics
Informed consent was obtained from the patient for the case publication. The case was presented as a poster at the Hepathology Portuguese Scientific meeting on April 2016.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

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J.A.C.N. wrote, edited and approved the final paper and is the article guarantor. J.R. wrote, edited and approved the final paper. H.T.S. and R.M. revised the manuscript for intellectual content and approved the final paper.

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