Whipple's Disease: Case Report

Doença de Whipple: Relato de Caso

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Abstract:

Whipple's disease (WD) is a rare systemic bacterial infection caused by *Tropheryma whipplei*, with an estimated incidence of one to three cases per million inhabitants. It commonly presents with persistent arthralgia, chronic diarrhea, abdominal pain, and weight loss, potentially affecting other systems, such as the neurological and cardiovascular systems. We report the case of a 41-year-old female patient with abdominal and pelvic pain, intermittent diarrhea, arthralgia, myalgia, night sweats, and unintentional weight loss of 5 kg over a short period. Initially, mesenteric lymphadenopathy raised suspicion of sarcoidosis. However, a duodenal biopsy revealed periodic acid-schiff (PAS)-positive macrophages, confirming the diagnosis of WD. The patient was treated with intravenous ceftriaxone, followed by oral trimethoprim-sulfamethoxazole (TMP-SMX) for one year. WD should be considered in the differential diagnosis of malabsorption syndromes and multisystemic diseases, given its progressive course and the potential benefit of early treatment.

Keywords: Whipple Disease/diagnosis.

Resumo:

A doença de Whipple é uma infeção bacteriana sistémica rara, causada pelo *Tropheryma whipplei*, com incidência estimada de um a três casos por milhão de habitantes. Apresenta-se frequentemente com artralgias persistentes, diarreia crônica, dor abdominal e perda ponderal, podendo envolver outros sistemas, como o neurológico e o cardiovascular. Apresentamos o caso de uma paciente de 41 anos com dor abdominal e pélvica, diarreia intermitente, artralgias, mialgias, sudorese noturna e perda de peso involuntária de 5 kg em curto período. Inicialmente, linfonodomegalias mesentéricas levantaram a suspeita de sarcoidose. No entanto, a biópsia duodenal revelou macrófagos positivos na coloração PAS, confirmando o diagnóstico de doença de Whipple. A paciente foi tratada com ceftriaxona endovenosa, seguida de TMP-SMX por um ano. A doença de Whipple deve ser considerada no diagnóstico diferencial de síndromes de má absorção e doenças multissistémicas, dada a sua evolução progressiva e o potencial benefício do tratamento precoce.

Palavras-chave: Doença de Whipple/diagnóstico.

Learning Points

1. WD presents with multisystem involvement, with a clinical picture typically characterized by weight loss, abdominal pain, chronic diarrhea, and arthralgia in most cases.
2. The diagnostic investigation should include upper gastrointestinal endoscopy, small bowel biopsy, and lumbar puncture for cerebrospinal fluid analysis.
3. The standard treatment is intravenous ceftriaxone for two weeks, followed by twelve months of TMP-SMX.

Introduction

Whipple's disease (WD) is a chronic, insidious, and multisystemic condition caused by *Tropheryma whipplei*,[1] a gram-positive bacillus from the Actinomycetales order. It predominantly affects Caucasian men between the ages of 50 and 60,[2] with an estimated prevalence of one to three cases per million,[3] being more common in individuals with exposure to soil or animals. In the classic presentation, arthralgia occurs in up to 83% of patients, often preceding the diagnosis by years and being confused with manifestations of inflammatory rheumatologic diseases.[2]

The rarity of WD epidemiologically places it as a diagnosis of exclusion in clinical investigation. However, this does not make it less important in medical clinical reasoning, as it is a potentially disabling condition for the affected patient and it is treatable, even though it requires prolonged treatment.

Case Report

A 41-year-old Caucasian female patient from the rural area of the state of Rio Grande do Sul, Brazil, who worked as a farmer but is currently on leave due to hip osteoarthritis, also presents with systemic arterial hypertension. She was referred to the Internal Medicine outpatient clinic of a tertiary hospital for investigation of sarcoidosis.

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She reported abdominal and pelvic pain associated with occasional episodes of polyarthralgia – involving hips, wrists, hands, ankles, and knees bilaterally, with mild to moderate intensity, and no identifiable precipitating or aggravating factors – diarrhea and myalgia for about two years, as well as night sweats and an involuntary weight loss of 5 kg in the past month. She denied any episodes of fever. On physical examination, there were no alterations in pulmonary auscultation, no palpable abdominal masses, no skin lesions, and no signs of arthritis in the joints. Previous exams revealed an abdominal magnetic resonance imaging (MRI) scan with numerous grouped lymphadenopathies in the mesenteric and retroperitoneal chains, measuring 19.4 x 14.1 x 9.2 cm. She had also previously undergone biopsies of the mesenteric lymph nodes and omentum, which showed non-necrotizing granulomas, the absence of caseous necrosis, and the presence of giant cells, with negative fungal and mycobacterial cultures. The granulomas were described as having a sarcoid-like pattern, suggesting sarcoidosis as a possible etiology.

For the initial evaluation, general laboratory tests were requested, with emphasis on: HIV antigen and antibody screening – non-reactive; HBsAg – reactive, anti-HCV antibodies – non-reactive, anti-HAV IgM antibodies – non-reactive, and anti-HAV IgG antibodies – reactive –, alanine aminotransferase 66 U/L (reference value [RV] < 34 U/L), aspartate aminotransferase 54 U/L (RV 11-43 U/L), gamma-glutamyl transferase 202 U/L (RV < 38 U/L), and alkaline phosphatase 389 U/L (RV 46-122 U/L). A computed tomography (CT) scan of the abdomen was also requested, which showed multiple lymphadenopathies with centres of low density, with attenuation similar to fat, in various abdominal sites, associated with apparent prominence of the mucosal folds in the jejunal loops and mild splenomegaly. These radiological findings, combined with the clinical picture, raised suspicion of celiac disease and Whipple's disease as differential diagnoses, in addition to extrapulmonary sarcoidosis.

During follow-up, an upper gastrointestinal endoscopy was performed, revealing whitish plaques in the duodenal region, where multiple core biopsies were taken. The biopsies showed minimal reactive gastropathy, negative *Helicobacter pylori* tests, and histopathological findings compatible with Whipple's disease. The material was subjected to Ziehl-Neelsen staining for acid-fast bacilli, which was negative; Grocott staining for fungi, also negative; and PAS staining, which was positive in interstitial macrophages (Fig. 1), confirming the diagnosis of WD. In this context, the patient was electively hospitalized to begin intravenous treatment and undergo a lumbar puncture, as well as a brain MRI to evaluate for central nervous system involvement. The brain MRI did not show any characteristic findings. The cerebrospinal fluid had hypoglycorrhachia, with no other alterations. Polymerase chain reaction (PCR) for *T. whipplei* was not available at the hospital.

During hospitalization, the patient started treatment with intravenous ceftriaxone 2000 mg/day, maintained for five days without complications. Since the patient did not present any other clinical concerns, the attending team contacted the Municipal Health Department of her city of origin to arrange for continued administration of intravenous ceftriaxone, until the total treatment duration of two weeks was completed. As is known, after two weeks of ceftriaxone therapy, the use of trimethoprim 160 mg + sulfamethoxazole 800 mg, twice daily for one year, is required. Therefore, the patient, the Municipal Health Department, and the hospital where the patient would be received were all informed about the need for follow-up with this additional antimicrobial regimen. The antibiotic therapy selected for this patient was based on an antimicrobial regimen that covers the form of the disease with central nervous system involvement, given that PCR testing for *Tropheryma whipplei* could not be performed, thereby precluding the exclusion of neurological compromise.

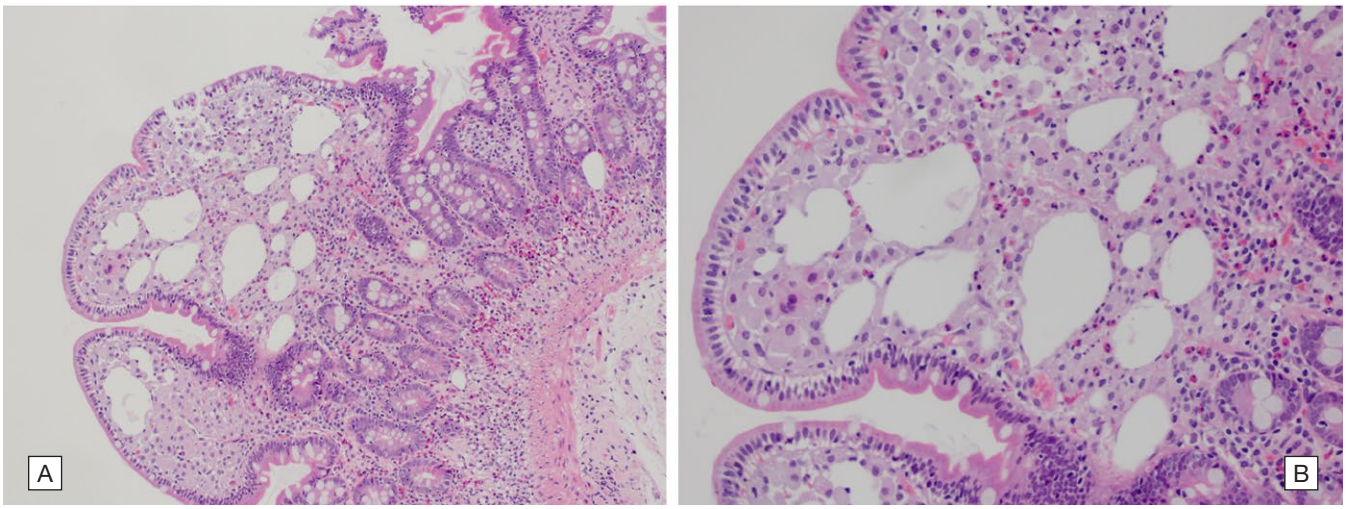

Figure 1: Histopathological findings: **[A]** - Haematoxylin-eosin (HE) staining at 100x magnification; **[B]** - HE staining at 200x magnification.

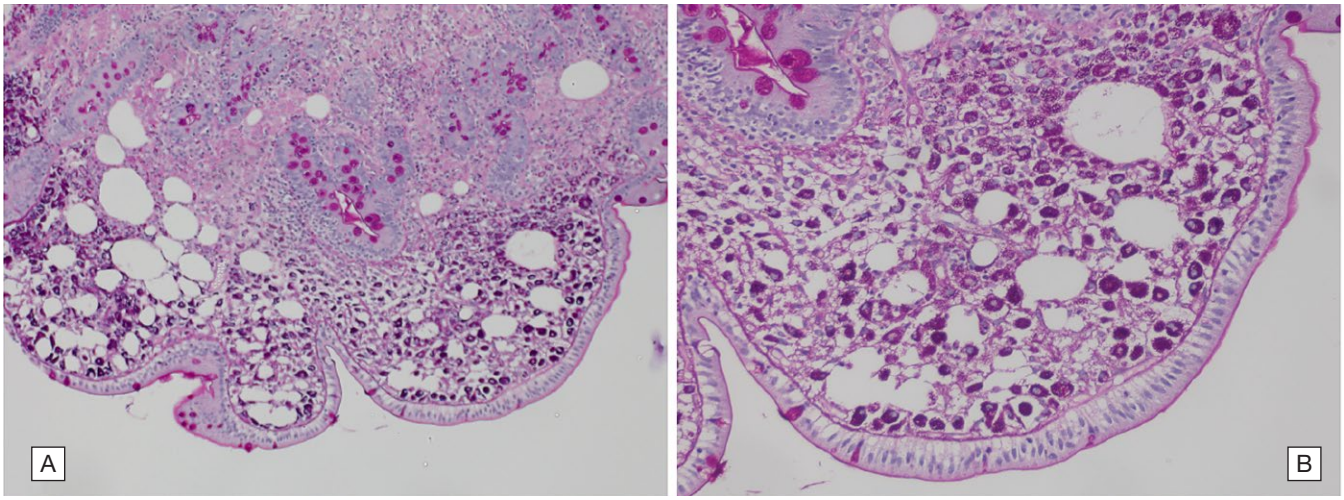

Figure 2: Histopathological findings: **[A]** - PAS staining, showing PAS-positive subepithelial macrophages at 100x magnification; **[B]** - PAS staining, showing PAS-positive subepithelial macrophages at 200x magnification.

The patient reported partial improvement of symptoms after two months of treatment, except for persistent mild arthralgia, worse in the hip and ankles. Follow-up will be conducted through outpatient visits at the tertiary care hospital, where the diagnosis was established, scheduled every three months.

Discussion

Whipple's disease (WD) is a rare, multisystemic inflammatory disease. However, despite its low prevalence, it should be considered as a differential diagnosis, for example, in cases of unexplained persistent diarrhea, when accompanied by unintended weight loss and abdominal pain, with or without arthralgia – joint involvement is observed in 68% of patients.[4] There may be cardiac, dermatologic, pulmonary, and neurological involvement, which is characterized by the classic triad: dementia, supranuclear ophthalmoplegia, and myoclonus.[5] In the described case, the patient's gender and age were less characteristic epidemiologically; however, among diagnosed patients, 35% were farmers and 66% had occupational exposure to soil or animals,[6] increasing the diagnostic probability due to the patient's occupational exposure. Therefore, it is crucial to consider WD in diagnostic hypotheses due to the possibility of identifying a disease that has available treatment and the potential for a cure if detected early.

For diagnosis, upper gastrointestinal endoscopy and small intestine biopsy are performed in patients with gastrointestinal symptoms, aiming to identify *T. whipplei*. In the absence of these symptoms, samples from affected areas, such as synovial fluid or cerebrospinal fluid,[7] are analysed. Tests include histology with PAS staining, polymerase chain reaction (PCR), and immunohistochemistry.[8] The presence of PAS-positive macrophages in the intestinal biopsy confirms the diagnosis, and PCR for *T. whipplei* in cerebrospinal fluid is recommended for all diagnosed patients, regardless of the presence of neurological symptoms.[9] A 2015 systematic review of 41 patients diagnosed with WD identified about 20% with neurological symptoms and around 50% with cerebrospinal fluid (CSF) PCR positive for *T. whipplei*.[10] In general, the chances of neurological involvement progressively increase over time and are associated with a worse prognosis.[11] Thus, suspicion and diagnostic investigation are extremely important to ensure better outcomes. In the case of this patient, there was a limitation due to the unavailability of CSF PCR testing at the hospital, as well as logistical difficulties in referring the patient to locations that could perform the analysis.

Treatment includes intravenous antibiotics such as ceftriaxone, followed by oral TMP-SMX for 12 months, with clinical improvement observed within the first few weeks.[10] ■

Contributorship Statement

GDM e GTR - Drafting of the Case Report and Discussion
LPF e GMC - Drafting of the Abstract and Introduction.
HLB - Drafting of the Case Report and revision of the manuscript.
All authors approved the final version to be published.

Declaração de Contribuição

GDM e GTR - Redação do Caso Clínico e Discussão.
LPF e GMC - Redação do Resumo e Introdução.
HLB - Redação do Caso Clínico e revisão do manuscrito.
Todos os autores aprovaram a versão final a ser publicada.

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