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Case Report

Whipple's disease: a case report

Doença de Whipple: um relato de caso

Felipe Bertollo Ferreira[1], Gabriela Azevedo Solino[2], Maria Antonia Lopes de Sousa[3], Marina Boechat Melado[4], Carla Campos Miranda[5], Matheus Zavaris Lorenzoni[6], Luciene Lage da Motta[7], Felipe Welling Lorentz[8], Ana Paula Hamer Sousa Clara[9]

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ABSTRACT: Male, 46 years old, with arthralgia, abdominal pain, weight loss, diarrhea and inappetence. An upper digestive endoscopy was performed, which showed the duodenal bulb with diffuse whitish stippling. The anatomopathological examination of the duodenum showed positive periodic acid-Schiff, confirming the diagnosis of Whipple's disease. In view of the findings, treatment with sulfamethoxazole and trimethoprim was initiated, with significant improvement in symptoms. Whipple's disease is a rare pathology, as a consequence it presents a difficult diagnosis and the ideal treatment of the pathology is still not completely elucidated. Thus, clinical studies with greater scientific impact are needed to aid in the diagnosis and define the preferential approach to the condition.

KEYWORDS: Whipple Disease; Endoscopy; Case Reports.

RESUMO: Masculino, 46 anos, com artralgia, dor abdominal, perda de peso, diarréia e inapetência. Realizado endoscopia digestiva alta que evidenciou bulbo duodenal apresentando pontilhado esbranquiçado difuso. Ao anatomopatológico de duodeno evidenciado periodic acid-Schiff positivos, firmando-se o diagnóstico de Doença de Whipple. Diante dos achados, iniciou-se o tratamento com sulfametoxazol+trimetropina, com melhora significativa dos sintomas. A Doença de Whipple é uma patologia rara, como consequência apresenta um difícil diagnóstico e o tratamento ideal da patologia ainda não é completamente elucidado. Assim, são necessários estudos clínicos com maior impacto científico para auxiliar no diagnóstico e definir a conduta preferencial diante do quadro.

PALAVRAS CHAVES: Doença de Whipple; Endoscopia; Relatos de Casos.

1. Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória (EMESCAM), Departamento de Gastroenterologia. ORCIDI 0000-0001-6833-3977; E-mail: fbertollo@hotmail.com
2. Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória (EMESCAM), Departamento de Medicina. ORCID: 0000-0001-7862-4233. E-mail: gabrielaazesolino@gmail.com
3. Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória (EMESCAM), Departamento de Medicina. ORCID: 0000-0002-6099-9464. E-mail: m.antonialopess@gmail.com
4. Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória (EMESCAM), Departamento de Medicina. ORCID: 0000-0002-2561-0345. E-mail: marinaboechatm@gmail.com
5. Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória (EMESCAM), Departamento da Residência de Clínica Médica. ORCID 0000-0002-5922-3407. E-mail: carlacamposmir@gmail.com
6. Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória (EMESCAM), Departamento da Residência de Clínica Médica; ORCID: 0000-0003-2755-5367. E-mail: matheuszlorenzoni@outlook.com
7. Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória (EMESCAM), Departamento de Patologia. ORCID 0000-0001-9643-4011. E-mail: ene.lagemotta@gmail.com
8. Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória (EMESCAM), Departamento de Gastroenterologia. ORCID 0000-0003-0333-9571. E-mail: felipelorentz@hotmail.com
9. Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória (EMESCAM), Departamento de Gastroenterologia. ORCID 0000-0001-7886-8334. E-mail: anahammer@hotmail.com

Correspondence: Felipe Bertollo Ferreira. Av. Nossa Senhora da Penha, 2190, Barro Vermelho – 29045-402 - Vitória– ES. E-mail: fbertollo@hotmail.com.

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INTRODUCTION

Chronic diarrhea, defined as diarrhea lasting longer than 4 weeks, affects about 1-5% of the adult population. Its differential diagnoses are vast, and a complete clinical history and physical examination with judicious use of complementary exams are essential for an adequate diagnosis[1].

In patients with chronic diarrhea, the main distinction as to etiology is between functional and organic classification[1]. Functional disorders mainly include Irritable Bowel Syndrome. Among the organic pathologies, chronic diarrhea is frequently associated with inflammatory bowel disease, malabsorption syndromes and chronic bacterial and parasitic infections, such as *C. difficile*, *Aeromonas*, *Campylobacter*, *Giardia* and Whipple's disease[2].

Whipple's disease (WD) is a rare and difficult to diagnose condition. It is an infectious disease caused by the *Tropheryma whipplei* (TW) bacterium[3]. The disease usually courses with diarrhea in about 70% of cases, associated with weight loss, abdominal pain and arthralgia[4]. We report a case of WD in a patient treated at the Hospital Santa Casa de Misericórdia de Vitória, in Espírito Santo/ Brazil. The study was referred to the ethics and research committee and approved on 08/30/2022, with the protocol number 61404022.8.0000.5065.

CASE REPORT

This article reports the case of a 46-year-old male mechanic with no known comorbidities and no continuous medication who was admitted to Hospital Santa Casa de Misericórdia in Vitória. He reported that 6 months ago he started experiencing arthralgia in large joints, pain in the lower abdomen, unintentional weight loss of 34 kg, non-invasive daily diarrhea (Bristol 7), sensation of unchecked fever and lack of appetite. He also reported having had a cholecystectomy 7 months ago, in addition to drinking alcohol for 26 years, having stopped approximately 2 years ago and denied smoking.

On admission to the physical examination, he was pale (+/4+), without lymphadenopathy and with pain on deep palpation in the right hemiabdomen. Laboratory tests showed non-reactive serology for hepatitis B and C, syphilis and HIV and other tests seen in the Table 1.

In addition, he had an esophagogastroduodenoscopy (EGD) performed 7 months ago with evidence of moderate endoscopic enanthematous gastritis of the body and antrum.

Table 1- Laboratory tests on admission

Laboratory tests	Results	References range
Hemoglobin	10,7 g/dL	Male: 13,5 - 18 g/dL Females: 12,5 - 16 g/dL
Hematocrit	34,8%	40 a 50%
Leukocytes	9.100 mm^3	4000 - 10.000 mm^3
Plaquetas count	406.000 mm^3	150.000 - 400.000 mm^3
Erythrocyte sedimentation rate	51 mm/h	Male: 0 - 10 mm Females: 0 - 15 mm
C - reactive protein (PCR)	134,1 mg/dL	0,6 - 3 mg/dL
Fecal calprotectin	739 mcg/g	< 200 mcg/g
Serum iron	17 mcg/dL	60 - 150 mcg/dL
Ferritin	872,6 ng/mL	30 - 322 ng/mL
Transferrin saturation	9%	20 - 50%
Total iron binding capacity	200 mcg/dL	255 - 425 mcg/dL

The investigation was carried out with a request for computed tomography (CT) of the total abdomen and pelvis, which showed ill-defined nodulations and heterogeneity of diffuse mesenteric fat, with a non-specific appearance and lymph node enlargement of up to 1.6 x 1.4 cm. Colonoscopy showed mild nonspecific enanthematous ileitis, with whitish speckled lesions with a microcystic appearance; moderate enanthematous pancolitis with surface exsudate; and anatomopathological evidence showing inactive nonspecific colitis and nonspecific retitis. In the absence of a conclusive diagnosis, it was decided to investigate the small intestine by CT enterography, which suggested an incipient inflammatory process, but without a characteristic aspect.

Finally, a new EGD was performed, which showed areas suggestive of intestinal metaplasia in the antrum,

duodenal bulb with diffuse whitish stippling, apparent villous hypertrophy and an aspect that could correspond to infiltrative disease, with a similar pattern in the second portion. Pathological examination of the duodenum showed WD with absence of gastric metaplasia, absence of intraepithelial lymphocytosis, villus:crypt ratio of 3:1 (Preserved), villous enlargement, chorion with edema and moderate congestion, and intense increase in cellularity, at the expense of cells histiocytic cells containing periodic acid-Schiff (PAS) positive granules, absence of lymphoid hyperplasia and no granulomas or parasites were observed.

In view of the histopathological findings in the EGD and compatible clinical findings, the diagnosis of WD was established, and treatment with sulfamethoxazole-trimethoprim was initiated, with significant improvement in symptoms after starting treatment. New EGDs were performed 2 and 5 months after the start of treatment, and both clinical improvement of the patient and improvement in the endoscopic pattern were visualized.

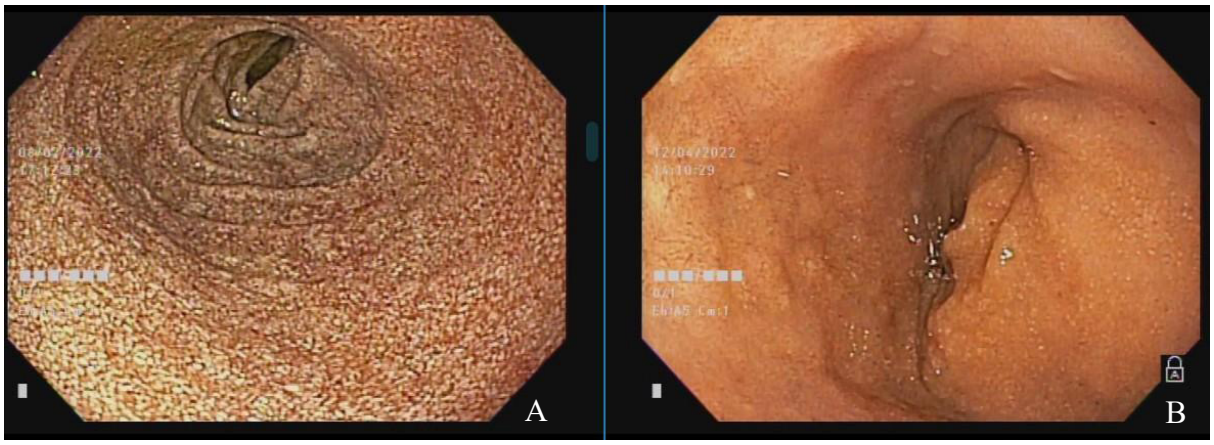

Figure 1 - EGD on follow-up. A - Previous to the treatment demonstrating yellow, shaggy mucosa alternating with erythematous mucosa in the duodenum. B - 2 months after treatment with partial improvement in the duodenal mucosa.

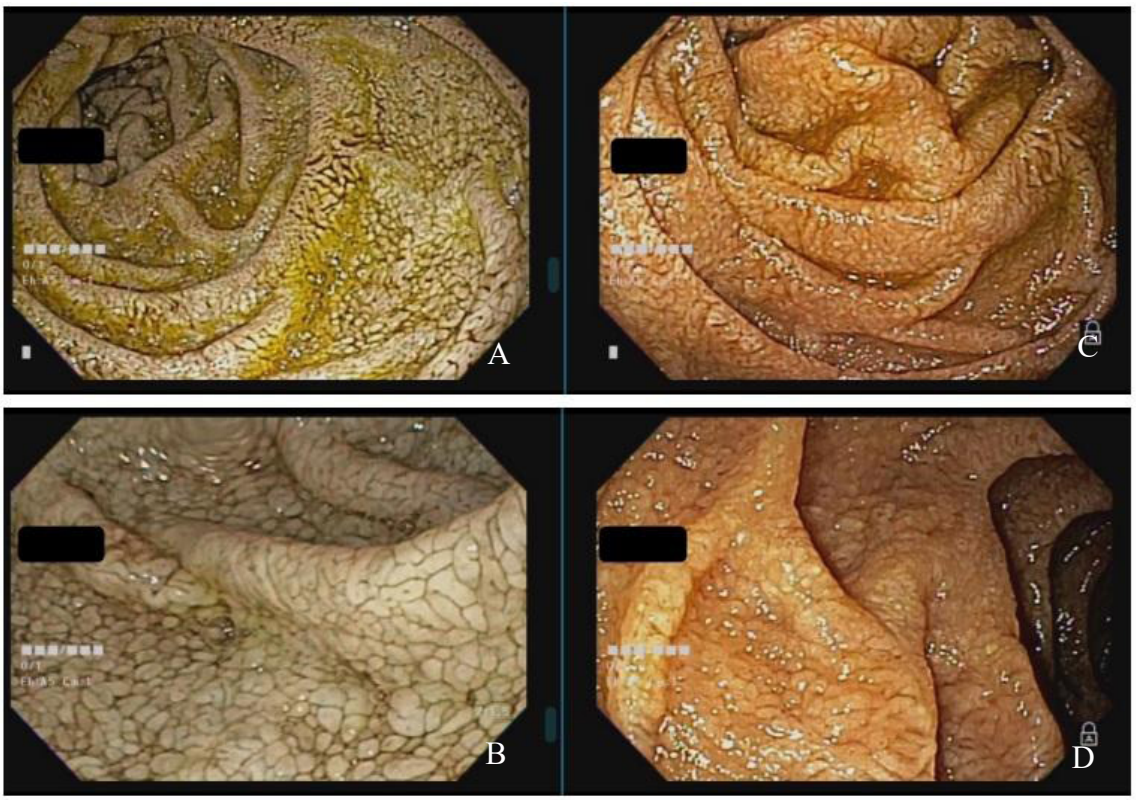

Figure 2 - EGD on follow-up. A and B - Previous to the treatment image shows patchy white plaques and duodenal villi clearly visualized. C and D - 2 months after treatment still remains with the alterations.

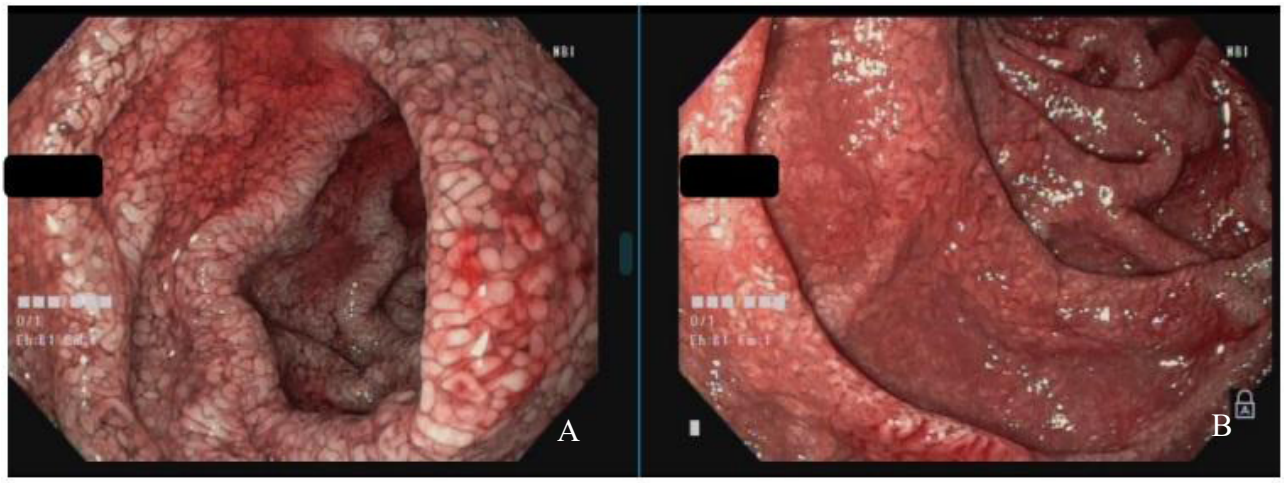

Figure 3 - EGD on follow-up. A- Narrow-band imaging (NBI) previous to the treatment with villous hypertrophy, which is edematous and slightly flattened. Alterations on microvasculature were not observed. B - NBI 2 months after treatment remains with the abnormality but less intense.

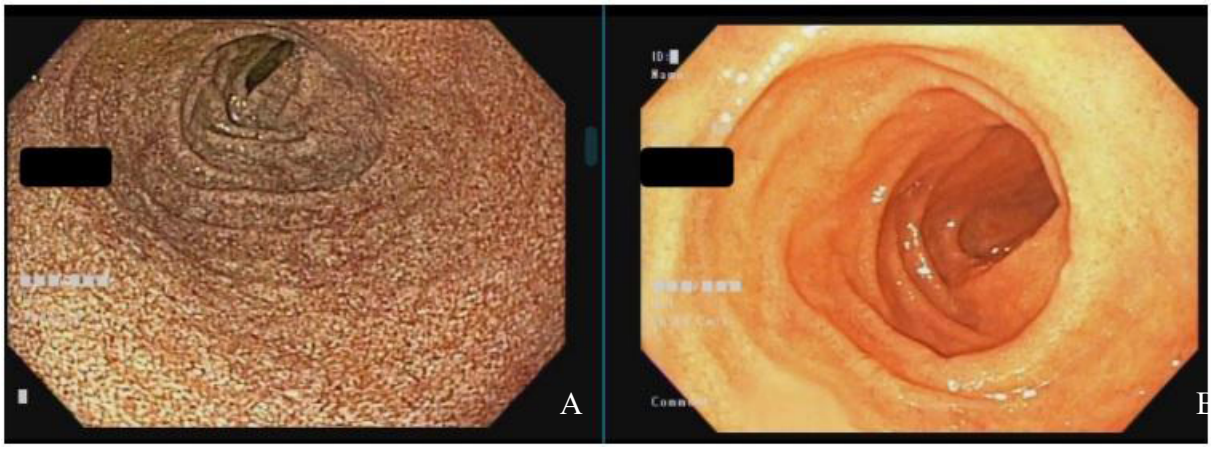

Figure 4 - EGD on follow-up. A- Previous to the treatment demonstrating yellow, shaggy mucosa alternating with erythematous mucosa in the duodenum. B - 5 months after treatment with important improvement in the duodenal mucosa.

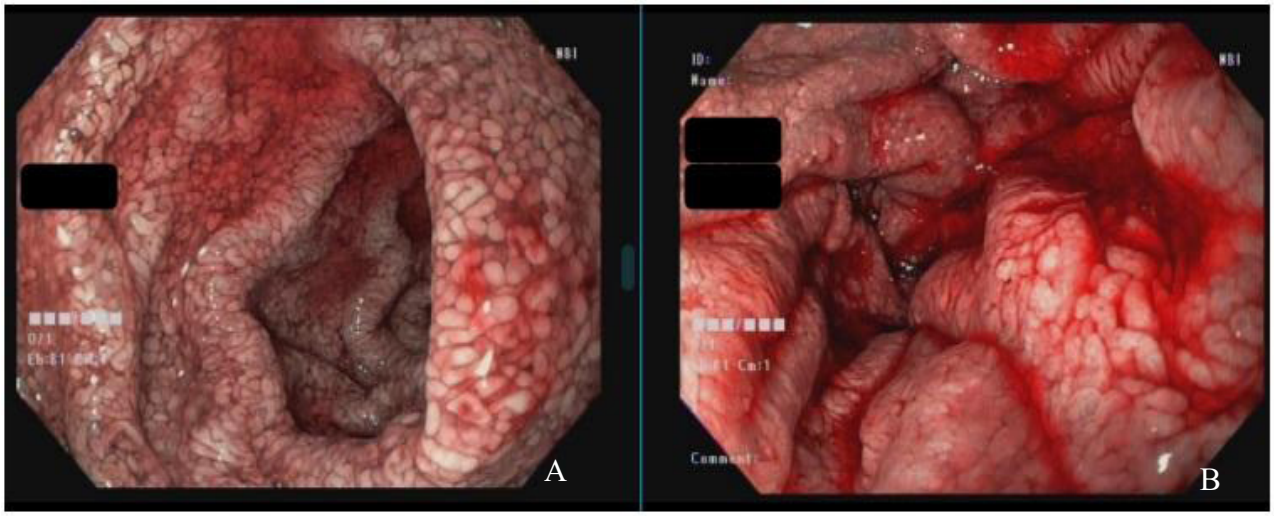

Figure 5 - EGD on follow-up. A- Narrow-band imaging (NBI) previous to the treatment with villous hypertrophy, which is edematous and slightly flattened. Alterations on microvasculature were not observed. B - NBI 5 months after treatment remains with the abnormality but less intense.

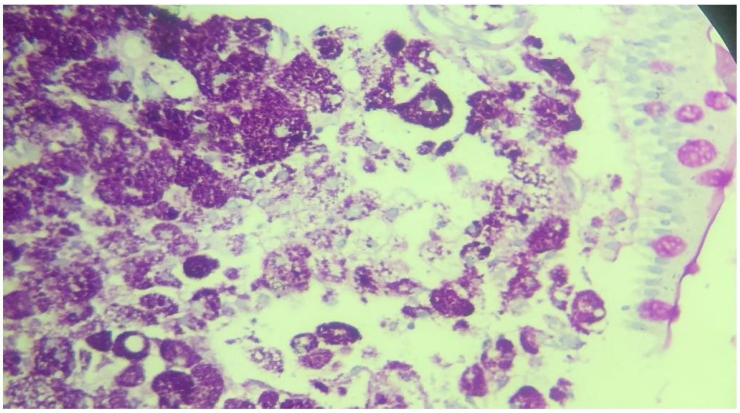

Figure 6 - Histopathologic findings at diagnosis. Periodic acid-Schiff (PAS) staining (x20). Presence of PAS positive macrophages in the chorion.

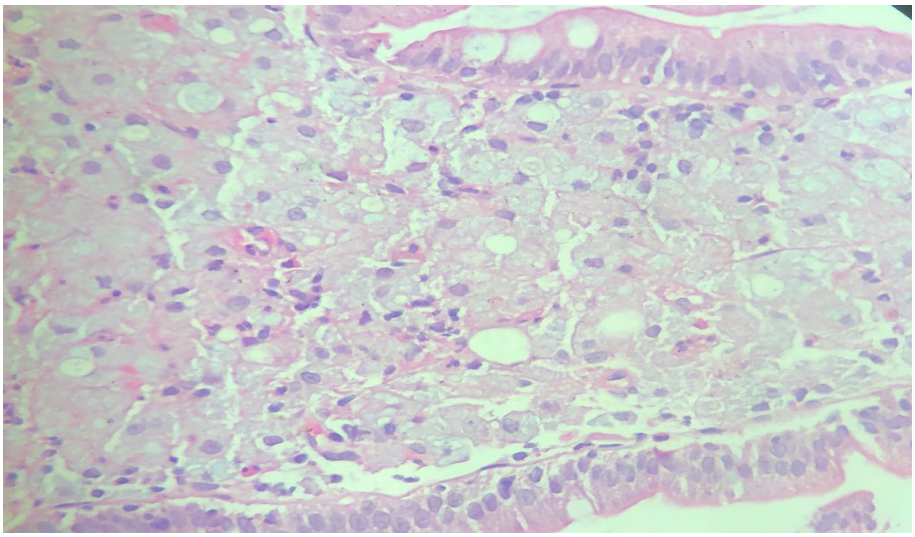

Figure 7 - Histopathologic findings 5 months after treatment. Hematoxylin and eosinn (HE) staining (x40). Presence of foamy macrophages.

DISCUSSION

WD is a chronic infectious disease caused by TW, a gram-positive bacillus with low virulence and high infectivity[5,6]. It is a rare multisystem pathology, with an average of 30 reported cases per year since 1980, which implies a difficult diagnosis. of the disease[7].

It is believed that the main route of transmission is fecal-oral associated with a genetic predisposition of the host, since not all people who have contact with the bacillus manifest the disease[5,7]. In some patients it is possible to observe the representation of the HLA - B27, however, little is known about its exact role in the pathogenesis of the disease and it would be expected that with better knowledge of the organism's genetic sequencing answers would be found[5,8].

The clinical presentation of classic WD usually has an insidious onset and includes symptoms such as weight loss, chronic diarrhea, joint symptoms, fever, abdominal pain, and malabsorption[7], as seen in the reported patient who had all the classic symptoms of the disease. Cerebrospinal fluid (CSF) infection can affect 10% to 40% of patients with classic symptoms, who may develop neurological or psychiatric symptoms, but may also remain asymptomatic[5,6]. Laboratory findings are associated with chronic inflammation and malabsorption, being characteristic the presence of anemia, leukocytosis, thrombocytosis, high CRP, in addition to hypoalbuminemia, vitamin deficiency and high prothrombin time[6], this patient had normocytic and normochromic anemia, elevated CRP and hypoalbuminemia.

The diagnosis should be considered in all patients who present with the cardinal symptoms of the disease, after excluding differential diagnoses. For diagnostic confirmation, the test of choice is EGD with small bowel biopsies, with at least 5 samples from different portions

of the duodenum, which will be subjected to PAS staining and/or specific CRP testing for TW, although the latter is not available in all locations[5-8]. The patient reported above underwent EGD with multiple duodenal biopsies, which were later submitted to PAS staining. It should be noted that TW-specific CRP is not an exam available in our locality. If the diagnosis is confirmed, lumbar puncture with analysis of the cerebrospinal fluid is recommended in order to rule out the involvement of the Central Nervous System (CNS), since many patients can be asymptomatic from a neurological point of view and their complications can be catastrophic[8,9].

Macroscopy shows duodenal mucosa with a yellowish appearance, with whitish plaques and signs of erythema, with edema and dilated lymphatic vessels[5,9]. Despite the great help of imaging tests, the diagnosis is confirmed through duodenal biopsies. Histopathological examination reveals enlargement of the lymphatic vessels, disarrangement of the villi architecture and the presence of numerous macrophages containing glycoprotein granules, positive PAS in the lamina propria[5,9,10]. The finding of vacuoles with a foamy appearance in the cytoplasm of macrophages infiltrating the lamina of the small intestine and containing large amounts of PAS-positive material on histological detection is the standard diagnostic method[7].

Due to the rarity of cases, the ideal management of WD is still uncertain. For patients with chronic WD, treatment includes an initial phase with administration of intravenous antibiotics for a period of two weeks, which may be used Ceftriaxone or Meropenem, agents that penetrate the blood-brain barrier. Then, oral maintenance therapy with trimethoprim-sulfamethoxazole for at least 12 months is recommended[5,8,9]. In patients with CNS manifestation, the initial phase treatment time can be extended by up to four weeks, and the addition of corticosteroid therapy with prednisone is recommended[5]. In the case reported here, the recommended treatment was started with trimethoprim-sulfamethoxazole and a significant improvement in clinical symptoms and endoscopic findings was observed 5 months after starting therapy.

After the initiation of adequate treatment, the response usually occurs within 7 to 21 days[11]. Clinical improvement is the main criterion for evaluating the response to treatment, and the follow-up of these patients should be performed with biannual EGD. However, it is already known that despite a good clinical response, histological remission is not achieved by many patients, and they may remain with positive PAS for years, but the intensity and number of viable intracellular bacteria should reduce[5,8].

CONCLUSION

WD is a rare infectious pathology and, due to the different clinical and endoscopic manifestations, it is difficult to diagnose. At endoscopy, patients can manifest different forms of presentation, including the absence of macroscopic changes, and it is extremely important to perform biopsies in the presence of cardinal symptoms of WD. Furthermore, due to the few studies in the literature related to WD, the initial management and optimal treatment of the pathology are not yet fully elucidated. Thus, it is concluded that clinical studies with greater scientific impact are needed to assist in the diagnosis and define the preferred conduct in the face of WD.

Authors' contributions: Felipe Bertollo Ferreira: teve a ideia do estudo e realizou a revisão crítica do manuscrito. Gabriela Azevedo Solino: escreveu, revisou e editou o manuscrito. Maria Antonia Lopes de Sousa: escreveu, revisou e editou o manuscrito. Marina Boechat Melado: escreveu, revisou e editou o manuscrito. Luciene Lage da Motta: análise histopatológica e realizou a revisão crítica do manuscrito. Matheus Zavaris Lorenzoni: escreveu, revisou e editou o manuscrito. Carla Campos Miranda: escreveu, revisou e editou o manuscrito. Felipe Welling Lorentz: realizou a endoscopia digestiva alta e realizou a revisão crítica do manuscrito. Ana Paula Hamer Sousa Clara: realizou a endoscopia digestiva alta e realizou a revisão crítica do manuscrito.

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