CASE REPORT

WHIPPLE'S DISEASE: RARE DISORDER AND LATE DIAGNOSIS

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SUMMARY

Whipple's disease is a rare systemic infectious disorder caused by the bacterium *Tropheryma whipplei*. We report the case of a 61-year-old male patient who presented to emergency room complaining of asthenia, arthralgia, anorexia, articular complaints intermittent diarrhea, and a 10-kg weight loss in one year. Laboratory tests showed the following results: Hb = 7.5 g/dL, albumin = 2.5 mg/dL, weight = 50.3 kg (BMI 17.4 kg/m^2). Upper gastrointestinal endoscopy revealed areas of focal enanthema in the duodenum. An endoscopic biopsy was suggestive of Whipple's disease. Diagnosis was confirmed based on a positive serum polymerase chain reaction. Treatment was initiated with intravenous ceftriaxone followed by oral trimethoprim-sulfamethoxazole. After one year of treatment, the patient was asymptomatic, with Hb = 13.5 g/dL, serum albumin = 5.3 mg/dL, and weight = 70 kg (BMI 24.2 kg/m^2). Whipple's disease should be considered a differential diagnosis in patients with prolonged constitutional and/or gastrointestinal symptoms. Appropriate antibiotic treatment improves the quality of life of patients.

KEYWORDS: Whipple's disease; *Tropheryma whipplei*; Malabsorption syndromes.

INTRODUCTION

Whipple's disease is a rare multisystemic infection caused by *Tropheryma whipplei* - a gram-positive bacterium belonging to the phylum Actinobacteria and a member of the order Actinomycetales[5]. It is recognized as an important bacterial cause of malabsorption, mostly affecting middle-aged Caucasian men. Its classic clinical course has three stages: (1) nonspecific prodromal symptoms, including migratory polyarthralgia (mainly in the large joints); (2) typical abdominal symptoms: pain, diarrhea, weakness, and weight loss; and (3) generalized stage, including steatorrhea, cachexia, lymphadenopathy, hyperpigmentation, and cardiovascular, pulmonary, and neurological dysfunctions[11,14]. Laboratory tests may provide several nonspecific findings that in combination can be suggestive of diagnoses such as: hypoalbuminemia, elevated erythrocyte sedimentation rate, and anemia[8]. Diagnosis is based on the presence of typical signs and symptoms and identification of *Tropheryma whipplei* in the histopathological examination of duodenal biopsies. When there is clinical suspicion without histological findings, the use of molecular biology tests is recommended, especially polymerase chain reaction (PCR)[6]. Treatment consists of induction of antibiotic therapy followed by a maintenance regimen for a prolonged period[11].

CASE REPORT

Sixty-one-year-old Caucasian male patient admitted in March 2010 to the emergency room for investigation of 10-kg weight loss, asthenia, anemia, and intermittent diarrhea, two to three bowel movements a day, without blood, mucus or pus for about one year. His previous medical history included 10 years of prodromal symptoms associated with depression and migratory arthralgia. During this period, the patient was seen by several physicians, who could not establish a diagnosis. At admission, the patient was thin, weighing 50.3 kg (BMI = 17.4 kg/m^2), and presenting with lower limb edema and little ascites. Laboratory tests showed iron-deficiency anemia (Hb = 7.5 g/dL, ferritin = 111 ng/mL, transferrin saturation = 7.8%, serum iron = 14 ug/dL) and hypoalbuminemia (2.5 g/dL). In relation to the imaging studies, a chest X-ray revealed pericardial calcification and bilateral pleural effusion. An abdominal ultrasound showed hepatomegaly, distention of hepatic veins and inferior vena cava, and a small amount of free fluid in the abdominal cavity. A Doppler ultrasound demonstrated an ejection fraction of 40%, left ventricular contractile dysfunction, thickened aortic valve with moderate regurgitation and mild mitral valve regurgitation. Anti-HIV, HBsAg, anti-HCV, antinuclear antibodies, rheumatoid factor, and TSH were investigated and showed negative or within normal limit results. An upper gastrointestinal endoscopy showed focal enanthema of the duodenal mucosa. Biopsies were performed and

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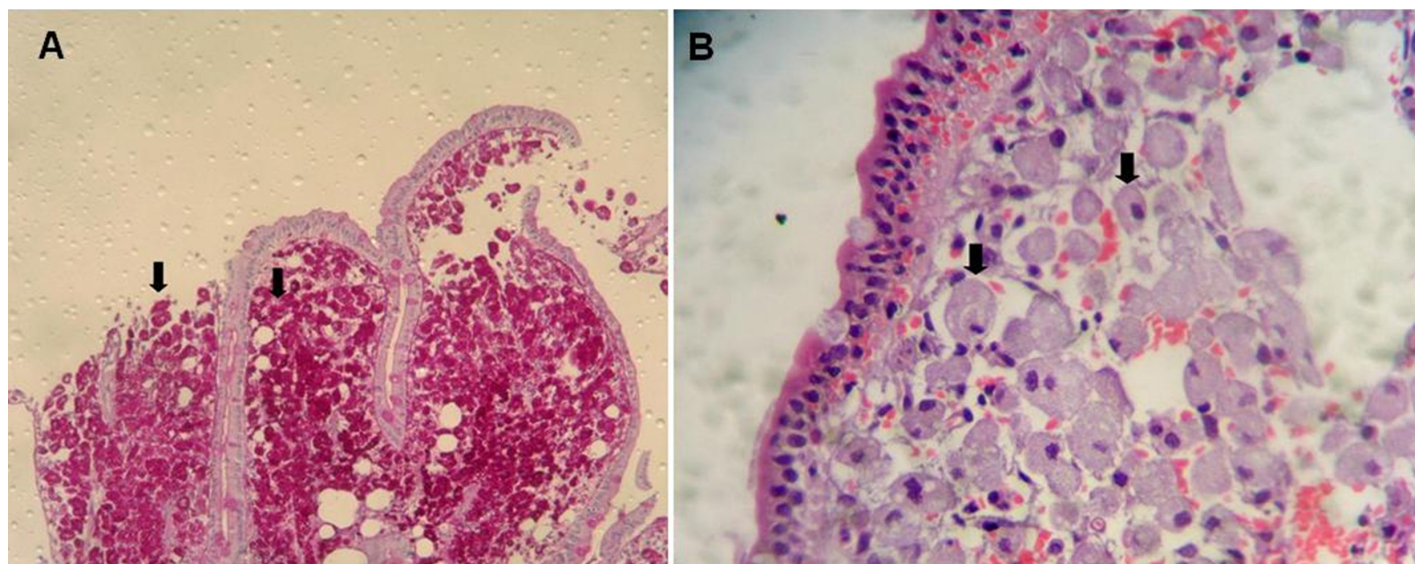
Fig. 1 - (A) Biopsy of the second portion of the duodenum, stained with periodic acid-Schiff (PAS), 10x magnification; and (B) stained with hematoxylin-eosin, 40x magnification, showing macrophages in the lamina propria.

revealed spongy macrophages in the lamina propria using hematoxylin-eosin staining and periodic acid-Schiff (PAS) staining. These findings are suggestive of Whipple's disease (Fig. 1). Given the abnormal results described above, serum and CSF PCR were requested to investigate the presence of *Tropheryma whipplei*. Serum PCR was positive for *Tropheryma whipplei*, whereas CSF PCR was negative for this bacterium. Treatment was started with intravenous ceftriaxone 2 g/day for two weeks, followed by oral trimethoprim-sulfamethoxazole 800/160 mg twice daily for a period of 12 months. It is noteworthy that after 14 days of treatment, the patient had normalization of bowel habits and started to show progressive weight increase.

After hospital discharge, the patient received outpatient follow-up for 16 months. There was significant clinical and laboratory improvement after one year of treatment. At the last follow-up visit, five months after treatment completion, the patient remained asymptomatic, with albumin level of 5.3 g/dL, Hb level of 13.5 g/dL, and weighing 70 kg.

DISCUSSION

Whipple's disease is a rare disorder. Its estimated annual prevalence is 1:1,000,000, mostly affecting middle-aged Caucasian men[5]. Some studies have shown a higher prevalence among rural residents[8,13]. *Tropheryma whipplei* is found in the soil (which could explain a higher prevalence among farmers), in sewage contaminated water, in the oral cavity and feces of healthy individuals (although there is no evidence of interpersonal transmission)[13]. There is evidence that this organism may be ubiquitous in humans, since there are studies using PCR amplification of *Tropheryma whipplei* from samples of saliva, gastric juice, and duodenal biopsies of patients without Whipple's disease[5].

After infection, the bacterium invades the whole body, including the intestinal epithelium, lymphatic and capillary endothelium, synovium, heart, lungs, liver, brain, eyes, and skin. There is failure of immune response to *Tropheryma whipplei* in these sites, suggesting that such

deficiency has a role in the occurrence of the disease[8]. Several immune system abnormalities have been associated with Whipple's disease. These alterations may be transient during the exacerbation period or even typical of the host of the bacterium. Among the innate abnormalities, the association of Whipple's disease with the human leukocyte antigen (HLA) has been described since 1979[15,24], when the association with HLA B27 was demonstrated even in the absence of ankylosing spondylitis[15]. Approximately 26% of patients have the HLA class I histocompatibility antigen and HLA B27 three to four times higher than expected, although this characteristic is not found in all populations studied[8,9,13]. Because of the low incidence of the disease, this association has been studied only in small case series, generating conflicting data[1].

This immune deficiency appears to be specific, because the patients are not predisposed to infection with other bacteria. In addition, IgG antibodies against *Tropheryma whipplei* are detected in approximately 70% of healthy individuals. Whipple's disease is rare, but apparently *Tropheryma whipplei* is not[8].

The classic disease can be divided into three stages: (1) nonspecific prodromal symptoms, mainly joint manifestations (e.g., arthritis, arthralgia, migratory polyarthralgia); (2) gastrointestinal symptoms such as diarrhea, weight loss, and weakness; and (3) generalized symptoms, including anemia, steatorrhea, hypoalbuminemia, and neurological and/or cardiovascular manifestations[11,14]. The most frequent extra-intestinal manifestations are joint disease and constitutional symptoms (mainly weight loss, which is present in more than 2/3 of cases in some series). However, the following systems may also be affected in some way during the course of the disease in order of frequency: central nervous system (CNS), cardiovascular system, mucocutaneous system, pleuropulmonary system, and vision[13]. The mean time between the onset of prodromal symptoms and the advance stage is approximately six years[8,10]. However, despite this being the most common sequence, there are cases of isolated Whipple's disease without gastrointestinal disorders[5]. Approximately 15% of patients do not have typical symptoms and signs of the disease[8,10].

Therefore, the Whipple's disease should be considered a differential diagnosis in many clinical situations: malabsorption with involvement of the small intestine (tropical sprue, celiac disease, sarcoidosis, and lymphoma), inflammatory rheumatic disease (seronegative arthritis), Addison's disease, conjunctive tissue disease, and a variety of neurological diseases. Patients receiving immunosuppressive therapy, such as corticosteroids and tumor necrosis factor antagonists, may have a faster clinical progression of Whipple's disease[8].

The central nervous system (CNS) may be affected in up to 50% of patients in combination with the gastrointestinal tract or even alone[5,12,17]. CNS manifestations are characterized by slowly progressive dementia, ophthalmoplegia, headache, myoclonus, hypothalamic dysfunction, and a pathognomonic movement - oculofacial-skeletal myorhythmia, dementia, ophthalmoplegia, and myoclonus are the most common[1,17]. Some of the most unusual symptoms are seizures and signs similar to ischemic brain syndrome[2,22]. Despite the intense gastrointestinal symptoms, our patient did not have any neurological manifestations or positive CSF PCR.

The most common gastrointestinal symptom of Whipple's disease is weight loss, often associated with diarrhea. Abdominal pain, hepatosplenomegaly, and, occasionally, hepatitis may occur. Ascites has been reported in 5% of patients[8].

Joint involvement is the most common extra-intestinal symptom, occurring in approximately 65-90% of patients with classic disease, and it usually precedes gastrointestinal symptoms in up to 63% of affected individuals[8,19]. Intermittent migratory arthralgia and/or arthritis are the most common manifestations, usually in combination with polyarthritis, affecting the peripheral joints[8,20].

Cardiac involvement is a common manifestation in Whipple's disease and it is usually present with endocardial or valvular disease or, rarely, congestive heart failure[13]. After a long duration of nonspecific symptoms, our patient reached the generalized stage of the disease with uncommon manifestations such as pleural effusion, ascites, and heart failure.

In the present case report, the patient had clinical and laboratory manifestations consistent with Whipple's disease, and the biopsy of the second portion of the duodenum showed typical findings, which confirmed the diagnosis.

Because of its broad spectrum of clinical manifestations, Whipple's disease is very similar to other chronic inflammatory diseases[5,8]. This factor added to its low incidence in the general population makes the diagnosis difficult, usually leading to a late diagnosis. In the case described herein, our patient had prodromal symptoms for a period of 10 years. His diagnosis was only established after the onset of the abdominal symptoms and the malabsorption syndrome.

Diagnosis is often made based on a biopsy of small intestine or proximal jejunum, as these regions are commonly affected in symptomatic patients, even in the early stage of the disease. The infiltration of the lamina propria of the small intestine by macrophages filled with bacilliform bodies, positive PAS, and diastase-resistant structures, accompanied by dilated lymphatic ducts, are specific and diagnostic aspects of Whipple's disease[5].

In some cases, the diagnosis is established without the presence of classic signs when typical histological lesions are found in duodenal biopsies stained with PAS[10]. Nevertheless, the presence of macrophages with positive PAS material is not completely specific for Whipple's disease, since macrophages are also found in patients with infections caused by *Mycobacterium avium-intracellulare*, *Rhodococcus equi*, *Bacillus cereus*, *Corynebacterium*, *Histoplasma*, or certain types of fungi. Failure to obtain positive intestinal biopsies does not invalidate the diagnosis because the disease can be restricted to the submucosa and, therefore, it may not be diagnosed by a biopsy of the mucosa[13].

Thus, the diagnosis should be made based on clinical and endoscopic suspicion, and confirmed by duodenal biopsy, associated with molecular biology methods (PCR), immunohistochemistry and serological methods[5,24]. PCR is an important diagnostic tool for this disease because it has high sensitivity and specificity and it is useful mainly in typical cases and/or when there is the possibility of histological confirmation of the diagnosis[23]. Nevertheless, PCR for *Tropheryma whipplei* in the serum is not a useful test for the diagnosis once a negative result does not exclude the diagnosis. On the other hand, false positive results in PCR can be seen in cases of intestinal colonization by *T. whipplei*. That's why some authors recommend that the diagnosis should be established based on the combination of two positive tests, usually the histological analysis of duodenal biopsy with PAS staining, along with PCR or immunohistochemistry[25].

Electron microscopy has contributed in a decisive way, since 1961, for the detection of the bacillus. Although electron microscopic examination is considered "gold standard" for confirmation of diagnosis[8], it is a more expensive and demanding method since it involves complex laboratory procedures, which are not always available. Therefore, electron microscopy is only used to clarify those cases where PCR and/or histology provide doubtful results[23].

Immunohistochemistry is a tool that can help establish the diagnosis with good sensitivity[8,23]. This technique improves the histologic examination using *T. whipplei*-specific antibodies showing greater sensitivity than PAS staining, being able to identify *T. whipplei* using immunohistochemistry on tissues in which PAS staining provided negative results[4,16].

When the diagnosis of Whipple's disease is established, the cerebrospinal fluid should be tested with PCR, even in the absence of neurological signs, it has important implications for therapy and prognosis[8,24]. In patients with CNS involvement, CSF is usually normal or shows mild pleocytosis, while the PCR result is usually positive[18,26].

Antibiotic therapy should be started early, preferred medications that have good penetration into the central nervous system, preventing neurologic relapses, given the frequent involvement of the CNS and the fact that this is the most frequent site of relapses[5,8,9,23,24]. If not treated, Whipple's disease can have a fatal outcome[5,8,11,24]. Thus, the antibiotic selection was based on the fact that trimethoprim/sulfamethoxazole is an antibiotic that crosses the blood-brain barrier, with probability of being effective in the CNS involvement. Various antibiotic regimens have been tried, from chloramphenicol to tetracyclines, penicillin alone, penicillin and streptomycin, ampicillin, erythromycin, third generation cephalosporins[5,8,23,24]. Some studies suggest initial treatment

with penicillin and streptomycin intravenously for two weeks. Another possible regimen is ceftriaxone (2 g intravenous/day) during the first two weeks followed by oral administration of trimethoprim/sulfamethoxazole for one year[5,8,24].

Whipple's disease is an infectious disease with an excellent clinical response within a few weeks after initiation of antibiotic therapy[5,8,23]. The typical evolution of the treatment is the improvement of the classic symptoms (such as arthralgia and diarrhea) within two weeks after appropriate treatment is initiated. However, about 9-15%[15] of patients develop failure during or relapse after treatment with trimethoprim-sulfamethoxazole[8]. Jarisch-Herxheimer reaction has been reported after initiation of antibiotic therapy, with symptoms similar to systemic inflammatory response syndrome, especially in patients with CNS disease or receiving immunosuppressive therapy[17].

According to different studies, the decision to discontinue therapy seems to depend on clinical and laboratory remission, as well as on decreased amount of PAS-positive macrophages and absence of free bacilli in follow-up biopsies after apparent clinical remission[5,23]. Also in relation to this fact, there are doubts related to the number of biopsies needed for a strict follow-up, as well as regarding the time interval between each procedure. Usually, if there is good clinical response, biopsy may be repeated six and twelve months after diagnosis, although some studies suggest longer time intervals[5].

Conversely, there is evidence that PAS-positive macrophages may remain in the lamina propria for several years after complete clinical remission, representing degraded bacterial material, which might cause a positive test result after treatment show a false positive result instead of a relapse[5,23]. Thus its validity in monitoring the disease is controversial. However, it has a 100% negative predictive value, meaning that the most important use of PCR seems to be to confirm the diagnosis after histology and exclude disease relapse after apparently effective therapy despite histological changes. Thus a negative PCR may exclude disease relapse (100% negative predictive value), whereas the visualization of intact bacilli by means of electron microscopy may be a sign of active disease[5]. In cases with neurological manifestations, antibiotic therapy should only be discontinued when the PCR is negative in the CSF and the duodenum[23].

In addition, all patients should be monitored for life because relapses may occur after long-term remission with severe involvement of the CNS[1,15].

Relapses of Whipple's disease may appear several years after cessation of therapy, even when the initial treatment was considered effective. Even with an appropriate clinical treatment, there are reports of clinical relapse in about 2-33% of cases after a mean period of five years, and the CNS is the most frequent site involved[8]. It occurs most frequently in patients with CNS involvement and in patients treated with a single type of antibiotic or with antibiotics that do not cross the blood brain barrier (such as tetracycline or oral penicillin)[1,23].

In cases of failure or relapse, other antibiotic regimens are suggested. In patients without neurological involvement, doxycycline (100 mg twice a day) in combination with hydroxychloroquine (600 mg/day) without induction could be used. In patients with neurologic manifestations or positive CSF PCR, the regimen mentioned above may be associated with sulfadiazine[7,24].

RESUMO

Doença de Whipple: patologia rara e de diagnóstico tardio

Doença de Whipple é uma rara infecção sistêmica causada pelo *Tropheryma whipplei*. Caracteriza-se por fase prolongada de sintomas inespecíficos, levando longo período até o seu diagnóstico. Sem tratamento, pode ser grave e fatal, mas com antibioticoterapia tem ótima resposta clínica e laboratorial. Relatamos o caso de paciente masculino, 61 anos, internado por astenia, anorexia, diarréia intermitente e perda de 10 kg em um ano. Apresentava-se com hemoglobina (Hb) 7,5 g/dL, albumina de 2,5 mg/dL, peso 50,3 kg (IMC 17,4). Endoscopia digestiva alta com áreas de enantema focal da mucosa duodenal e biópsia compatível com doença de Whipple. O diagnóstico foi confirmado com PCR sérica positiva, sendo instituído tratamento com ceftriaxone seguido de sulfametoxazol-trimetropim. Após um ano de tratamento, encontrava-se assintomático, com Hb 13,5 g/dL, albumina sérica de 5,3 mg/dL e peso de 70 kg. Doença de Whipple deve fazer parte da lista de diagnósticos diferenciais em pacientes com sintomas constitucionais e/ou com queixas gastrointestinais com evolução prolongada. O tratamento antibiótico pode curar a infecção, recuperando a qualidade de vida do paciente.

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