CASE REPORT

Clinical manifestations and diagnosis of Whipple's disease: case report

Manifestações clínicas e diagnóstico da doença de Whipple: relato de caso

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ABSTRACT

Introduction: Whipple's disease is a rare multisystemic infection whose causative agent is the Gram-positive bacillus Tropheryma whippelii. It is characterized by a prolonged phase of nonspecific symptoms that delays diagnosis. The disease evolves with good response to antibiotic therapy, good clinical and laboratory evolution, however, if not properly treated it can be serious and fatal. This report describes a case of Whipple's disease with systemic manifestations. **Case report:** male patient, 60 years of age, 15 kg weight loss in one year, diarrhea, anorexia, poly arthralgia, and cutaneous-mucosa pallor. His weight was 45 kg with 18.7 body mass index. The complete propaedeutics revealed: 8.12 g/dL hemoglobin, negative viral serology and celiac disease markers; CT scan of abdomen: lymphadenopathy in mesenteric and para-aortic chains; upper gastrointestinal endoscopy revealed areas of enanthematous pangastritis and biopsy with histopathologic findings compatible with Whipple's disease, colonoscopy without alterations. Treatment was started with ceftriaxone and followed by sulfamethoxazole-trimethoprim. Patient evolved with improvement maintaining ambulatory monitoring. **Conclusion:** the Whipple's disease can be fatal if not diagnosed and treated properly. The therapeutic response is good and occurs in the first two weeks of treatment with antibiotics.

Key words: Whipple Disease; Tropheryma; Malnutrition; Diarrhea.

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RESUMO

Introdução: *a doença de Whipple é uma infecção multissistêmica rara, cujo agente causal é um bacilo Gram-positivo, Tropheryma whippelii. Caracteriza-se por fase prolongada de sintomatologia inespecífica, o que faz postergar o seu diagnóstico. A doença evolui com boa resposta à antibioticoterapia, com boa evolução clínica e laboratorial, mas se não tratada adequadamente pode ser grave e fatal. Este relato descreve um caso de doença de Whipple, com manifestações sistêmicas.* ***Relato de caso:*** *paciente masculino, 60 anos de idade, há um ano com perda de 15 kg, diarreia, anorexia, poliartralgia e palidez cutaneomucosa. Seu peso era de 45 kg e o índice de massa corpóreo de 18,7. A propedêutica completa revelou: hemoglobina de 8,12 g/dL, sorologias virais e marcadores de doença celíaca negativos; tomografia de abdome: linfonodomegalia em cadeias mesentéricas e paraórticas; endoscopia digestiva alta revelou áreas de pangastrite enantematosa e biópsia com histopatológico compatível com doença de Whipple, colonoscopia sem alterações. Iniciado tratamento com ceftriaxone seguido por sulfametoxazol-trimetoprim. Evoluiu com melhora, mantendo acompanhamento em ambulatório.* ***Conclusão:*** *a doença de Whipple pode ser fatal se não diagnosticada e tratada de maneira correta. A resposta terapêutica é boa e ocorre nas duas primeiras semanas de tratamento com antibiótico.*

Palavras-chave: *Doença de Whipple; Tropheryma; Desnutrição; Diarreia.*

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INTRODUCTION

Whipple's disease is multisystemic, rare, and caused by the Gram-positive bacillus *Tropheryma whippelii* belonging in the Actinobacteria family and Actinomycetes group.[1] There is no correct estimate of its current prevalence or incidence. They are about 1,000-1,500 described cases to the present day. The disease can occur in all age groups but affects mainly men with a mean age of 50 years old.[2-5]

It can evolve in two stages:

- with signs/non-specific symptoms such as fever and polyarthralgia;
- with signs/gastrointestinal symptoms such as abdominal pain, weight loss, chronic diarrhea; and generalized such as cachexia, lymphadenomegaly, and cardiovascular, pulmonary, or neurological alterations.[2,5]

The average duration of the initial phase of specific symptoms is six years.[3]

Laboratory findings can be nonspecific indicating anemia, leukocytosis, increase in acute phase reactants, and alterations related to mal-absorption.[2]

The diagnosis can be based on specific histopathological alterations in duodenal biopsy or through molecular biological methods.[4,5] Treatment should be implemented with antibiotic therapy and outpatient follow-up because of the risk of recurrence, with evaluation of laboratory tests and endoscopy for complete control.[3-9]

CASE REPORT

RBM, male, 60 years old, admitted to the internal medicine service at the University Hospital of the Federal University of Juiz de Fora in July of 2012 due to weight loss of 15 kg for about one year. He reported watery, bulky, without mucus, pus, or blood, and with food debris diarrhea, with no association with nociceptive abdomen episodes, lasting about four days and frequency of eight evacuating episodes/day, self-limited, interspersed with periods of normal bowel movements. He also presented anorexia, asthenia, and evening fever (39 °C). No history of steatorrhea or tenesmus. In March of 2012, during periodic assessment tests, anemia was identified with RBC count of: 3.14 x 10^6/uL, hemoglobin of 8.12 g/dL, hematocrit: 24.7%, VCM 78.8 fl, HCM 25.8 pg, and 18% RDW. Thus, propaedeutic evaluation was initiated.

He also reported episodes of migrating polyarthralgia, intermittent, mainly affecting knees and elbows with no signs of arthritis. History of ischemic cardiomyopathy. He lost weight (weight 45 kg, body mass index: 18.7 and pallor (2+/4+).

He presented microcytic hypochromic anemia, with low serum iron and transferrin saturation index, and normal ferritin. The WBC was within normal levels. Markers for celiac disease (endomysium IgA and IgG, anti-gliadin IgA and IgG, and antitransglutaminase) were negative. Table 1 summarizes the exams performed during the initial evaluation.

Table 1 - Exams performed during hospitalization

Exams	Results	Reference values
Hemogram	Hemoglobin: 9.07 Erythrocytes:3.49 x 10^6 Hematocrit:27.41 VCM:78.5 HCM:26.5 RDW:16.9 Leukocytes:5.86x10^3 Platelets: 210.000	13.0 to 17.5 g/dL 4.5 to 5.5 million/µL 40 to 50% 80 to 100 fL 27 to 32 pg 11.5 to 14.6% 4.0 to 11.0x10^3/µL 150 to 450 x 10^3/µL
Parasitological feces exam (3 samples)	Negative	–
Serum iron	22	59 a 158 mcg/dl
Index of saturation of transfemina	16	20 a 50 %
Anti HIV 1 and 2	Negative	–
Antinuclear factors (ANA)	Negative	–
Anti HTLV	Negative	–
Femitin	127	30 to 200 µ g/L
Sudam III Test	Negative	–
VDRL	Non-reagent	–
TSH	3.98	0.3 to 4.0 m UI/L
Free T4	0.88	0.7 to 1.5 ng/dL
Aspartate aminotransferase	18	15 to 46 U/L
Alanate aminotransferase	12	13 to 69 U/L
Gamma glutamyl transferase	34	7 to 58 U/L
Alkaline phosphatase	84	38 to 126 U/L
C-reactive protein	14.78	Less than 10 mg/L
Hemosedimentation speed	110 (1st hour)	Less than 15 mm
Urea	25	19 to 43 mg/dL
Creatinine	0.73	0.66 to 1.25 mg/dL

During hospitalization, he had four episodes of watery and bulky diarrhea, without mucus, pus, or blood, but with food debris. He was treated with symptomatic drugs, and also with iron III hydroxide to correct the iron deposit deficit.

Ultrasonography and computed tomography (CT) of the abdomen were normal with lymphadenopathy in mesenteric and para-aortic chains, respectively.

Considering the possibility of disease with involvement of the small intestine, intestinal transit, high digestive endoscopy (EDA), and colonoscopy with biopsies were performed.

The intestinal transit was normal, and EDA showed light enanthematous pangastritis; five fragment biopsies of the duodenum were conducted. Colonoscopy did not show macroscopic alterations; rectal, colon and terminal ileum biopsies were performed.

The histopathological examination of biopsy fragments revealed clusters of histiocytes with cytoplasm rich in periodic acid-Schiff (PAS) positive granules in the ileal and duodenal mucosa, these findings are consistent with Whipple's disease. Debris of bacteria phagocytosed by macrophages was not found (Figures 1 and 2).

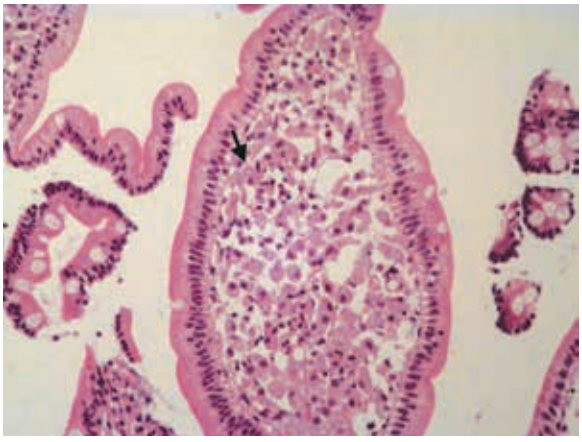

Figure 1 - Biopsy of duodenal mucosa – Duodenal mucosa exhibiting, in the lamina propria, numerous macrophages with granular cytoplasm with PAS positive inclusions. HE 100x.

Due to the diagnostic confirmation of Whipple's disease, a lumbar puncture was performed to collect cerebrospinal fluid, which showed no alterations (cytometry – one red cell and one nucleated cell; 115 umol/L chloride, 60 mg/dL glucose; 64.6 mg/dL total protein, and colorless and clear liquor). The polymerase chain reaction (PCR) test for *Tropheryma whippelii* was requested but due to laboratory technical problems it was not performed. Treatment with intravenous ceftriaxone (2 g twice daily) for 14 days was initiated, followed by sulfamethoxazole/trimethoprim (800 + 160 mg) twice daily for at least 12 months, and referral to the internal medicine clinic for clinical control.

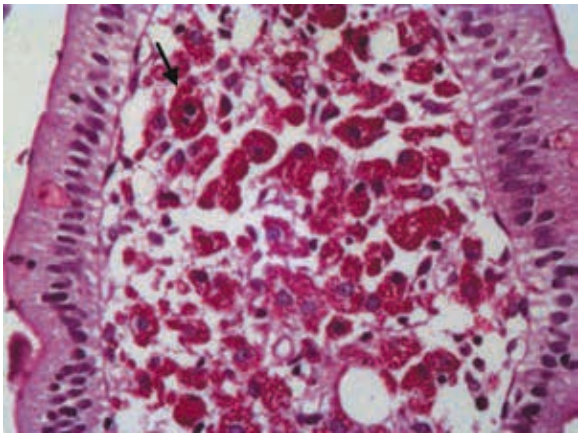

Figure 2 - Biopsy of duodenal mucosa – Histochemistry for periodic acid-Schiff (PAS) reveals macrophages with cytoplasm rich in PAS positive granules. PAS 200x.

The patient showed adherence and adequate response to treatment. After one year, he gained weight (20kg) and showed remission of previous symptoms. In the control EDA (one year after initiation of treatment) histiocytes clusters containing cytoplasm with PAS-positive granules were visualized in the duodenal mucosa.

DISCUSSION

The first case of Whipple's disease (WD) was described by George Hoyte Whipple in 1907.[2,3] Despite some advances about the disease; there is still much to clarify regarding its epidemiology and habitat.[2-6]

Some studies suggest high prevalence in rural residents. The bacillus can be found in soil, sewage water, oral cavity, and feces of healthy subjects.[2,5,6] Moreover, there is evidence that this microorganism can be ubiquitous in humans based on studies using PCR that allows the identification of *T. whippelii* in saliva and gastric samples and duodenal biopsies from individuals without Whipple's disease.[2,6]

DW is rare. However, its real incidence is not known.[3] Some studies suggest a worldwide occurrence of approximately 12 new cases/year though this number certainly represents an underestimation of the total number of cases.[4] Approximately 80 % of affected individuals are males, mostly Caucasians. The average age of diagnosis is 49 years, but the disease can occur at any age.[1-6]

The disease is characterized by two stages: a prodromal stage marked by multiple symptoms associated with chronic nonspecific findings such as

arthralgia and arthritis. The other stage is marked by weight loss, diarrhea, and other systemic manifestations depending on the site of involvement.[1,3]

The clinical manifestations are varied. In most cases, there is involvement of the small intestine with diarrhea being the major clinical manifestation, followed by weight loss with the characterization of malabsorption syndrome. Other common manifestations are abdominal pain, fever, and lymphadenopathies.[2,3,6]

The involvement of joints causes arthralgia and/or arthritis, which are the most common extra-intestinal symptoms in DW occurring in 65 to 90% of patients. They may precede diagnosis for several years, and are usually symmetrical, migratory, and of short duration.[1,2]

The involvement of the central nervous system (CNS) associated with Whipple's disease may occur in the absence of gastrointestinal manifestations.[3,8] The most frequent neurological alterations in DW are cognitive changes, eye movement disorders, ophthalmoplegia, movement disorders (particularly myoclonus), and hypothalamic changes.[1,3,5,8] The patient reported in this case did not have neurological disorders.

In addition to these symptoms, the disease can affect the cardiovascular system with valvular alterations. The skin can show hyperpigmentation; ocular manifestations such as uveitis and coriorretinite may be present.[2,3] Laboratory abnormalities are common: anemia, thrombocytosis, hypoalbuminemia, and elevated acute phase reactants such as C-reactive protein.[3]

Whipple's disease should be part of the differential diagnosis in various clinical situations: disabsortive diseases affecting the duodenum and proximal ileum (tropical sprue, celiac disease, sarcoidosis, and lymphoma) and rheumatic diseases (seronegative arthritis).[3]

EDA can reveal changes in the intestinal mucosa, particularly in the post-duodenal bulbar region, extending to other segments of the small intestine. The most common alterations are the thickening of mucosal folds with whitish confluent exudates alternating with erosions, and areas of friability in the mucosa.[4]

The diagnosis is based on duodenal or proximal jejunum biopsy, as these regions are the most affected in symptomatic patients.[1] The infiltration of the lamina propria in the small intestine by macrophages containing bacilliform structures that are PAS positive and resistant to diastase, accompanied by lymphatic expansion, are specific aspects of the Whipple's disease.[2,3,10,11] Cells with PAS positive material can result from other infectious agents such as *Mycobacterium avium* complex, *Rhodococcus*, *Bacillus cereus*, *Corynebacterium*, and certain fungi such as histoplasma.[5,11,12]

Electron microscopy is used to identify *T. whippley* since 1961.[2] However, it is a complementary diagnostic means that is not present in all hospitals and require complex and lengthy laboratory methods for sample preparation. Therefore, that option is currently reserved for cases where the PCR and/or histology results are questionable. In this disease, PCR is an important diagnostic tool because it presents great sensitivity and specificity, especially useful in cases with atypical manifestations and/or when the diagnosis cannot be confirmed histologically.[1,3] Once diagnosed, the cerebrospinal fluid should be tested with PCR, even in the absence of neurological symptoms because of the importance of treatment and disease prognosis.[2]

Antibiotic therapy should be initiated as early as possible, with preference to drugs that can cross the blood-brain barrier.[1,3,9] The initial treatment should be conducted for 14 days, initially with intravenous antibiotics, and replaced by mouth for 1-2 years.[1,3] Some antibiotic schemes have been tried such as penicillin alone, penicillin and streptomycin, ampicillin, erythromycin, and third generation cephalosporins.[8] Another possibility is the initial intravenous treatment with penicillin and streptomycin for two weeks. There is also the scheme with ceftriaxone (2 g iv/day) for the first two weeks, followed by oral administration of trimethoprim/sulfamethoxazole for one year.[2,8] The therapeutic response is rapid and often occurs in the first two weeks of treatment.[5,9]

Even with the proper treatment, the disease can recur in 2-33% of patients within five years.[2] Recurrence is characterized mainly by neurological involvement.[1] In cases of treatment failure, another antibiotic regimen should be considered.[3] Patients must be frequently monitored to evaluate the therapeutic response. Clinical manifestations usually improve, and PCR becomes negative in a few weeks. The histopathological alterations may remain for a few years.[11-13]

CONCLUSION

Whipple's disease is rare, systemic, and can be fatal if not treated properly. Because it shows varied clinical presentation, it is not always diagnosed, resulting in harm to patients. It shows good response when treated properly. The clinical evolution must

be monitored throughout therapy to confirm the response to treatment, and for several years after the end of treatment, in order to identify late recurrences.

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