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CASE REPORT

Whipple disease without joint involvement in a patient with chronic diarrhea and HIV seropositive partner: case report

Doença de Whipple sem envolvimento articular em paciente com diarréia crônica e parceira HIV-soropositiva: Relato de caso

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Abstract

Introduction: Whipple's disease is a rare, infectious disease caused by the bacterium Tropheryma whipplei that affects multiple organs and systems. It is difficult to identifyand frequently presents as a diagnosis of exclusion due existence of conditions causing most prevalent chronic diarrhea, as AIDS and Inflammatory Bowel Disease. **Case report**: Herein we report the clinical findings of a 38-year-old male patient, married with a HIV seropositive woman, with a four-year course of chronic diarrhea until he received a definitive diagnosis. Treatment was started with a 15-day penicillin G regimen, followed by continued trimethoprim–sulfamethoxazole 80/400mg after hospital discharge up to current days. **Conclusion:** Currently, the patient remains asymptomatic and has completed clinical remission after two years of treatment.

Keywords: Whipple's Disease. Diarrhea. Chronic Disease. Arthritis. Weight Loss.

Resumo

Introdução: A doença de Whipple é uma doença infecciosa rara causada pela bactéria Tropheryma whipplei que afeta múltiplos órgãos e sistemas. É difícil de identificar e freqüentemente se apresenta como um diagnóstico de exclusão devido à existência de condições que causam diarréia crônica mais prevalentes, como AIDS e Doença Infçamatória Intestinal. **Relato do Caso:** Aqui, relatamos os achados clínicos de um paciente do sexo masculino de 38 anos, casado com uma mulher HIV-soropositiva, com um curso de quatro anos de diarréia crônica até receber o diagnóstico definitivo. O tratamento foi iniciado com penicilina G por 15 dias, seguido de sulfametoxazol- trimetoprim 400/80 mg após a alta hospitalar até os dias atuais. **Conclusão**: Atualmente, o paciente permanece assintomático e apresentado remissão clínica completa após dois anos de tratamento.

Palavras-chave: Doença de Whipple. Diarréia. Doença Crônica. Artrite. Perda de Peso.

INTRODUCTION

In 1907, George Hoyt Whipple described the case of a 36-year-old patient with gradual weight loss, undefined abdominal symptoms and polyarthritis. The autopsy revealed polyserositis, aortic valve injury, and fat deposition on intestinal mucosa and on mesenteric lymph nodes with foam cells infiltration. That was the first description of the disease that would posteriorly take his name: the Whipple's disease (WD).[1,2]

The bacterium Tropheryma whipplei was described in 1991 from RNA 16S molecular amplification and genome sequencing obtained from autopsy samples of patients previously diagnosed with WD. In 2000, a cultivation essay was firstly well succeeded. That could relate the presence of microbe to patients' clinical manifestations.[2,3]Tropheryma whipplei is an intracellular obligate parasite that mainly indwells gastrointestinal tract. The transmission occurs by oral and fecal-oral routes. It can cause acute syndromes such as pneumonia, gastroenteritis or chronic ones (WD).[2,3,4,5]

WD is considered to be rare. There is no valid estimate of its actual prevalence. In post mortem studies, the frequency is less than 0.1%.It is most prevalent in middle-age Caucasian men[6]. Once diagnosed, patients must receive adequate treatment and close monitoring. The condition can posteriorly recur and can be fatal if not treated.

The patient's medical record was reviewed in search of information during a hospitalization period in 2014 at Walter Cantídio University Hospital and follow-up from May 2014 to November 2016 at theInfectious Diseases Service in the same hospital.

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Patient authorized publication of his case and image by free and informed consent.

CASE REPORT

The patient is a 38-year-old man, married to an HIV-infected woman, born in Tucuruí, Pará, in Northern Brazil. He came from Camocim, on the west coast of Ceará, in Brazil's Northeast, presenting chronic diarrhea between 2010 and 2014, with 5 to 7 evacuations a day, of liquid consistency and presence of blood. It was preceded by urgency to defecate and weight loss of 22 kg (48,5lbs) in the same period. There used to be some episodic improvement of symptoms with irregular use of trimethoprim–sulfamethoxazole. He denied fever or any symptoms in his joint articulations. There were no similar cases in family and he denied environmental exposure.

In 2011, he was diagnosed in another hospital with pulmonary tuberculosis and took the 4-drug regimen (isoniazid, rifampin, pyrazinamide and ethambutol) for 6 months. In this period, not only respiratory but also gastrointestinal symptoms had complete remission, creating the hypothesis of gastrointestinal tuberculosis.
In addition, he also suffered from headaches and presented disorientation. His CT scan revealed hypodense images scattered over both brain hemispheres.Neurotoxoplasmosis was interrogated and he started treatment with sulfadiazine and pyrimethamine.

On one physical examination,he claimed upper abdominal pain on light and deep palpation.The strongly hypothesis was chronic diarrhea secondary to HIV-infection because of his history of neurotoxoplasmosis and tuberculosis treatment, in addition to his wife's HIV diagnosis. Other relevant hypotheses were inflammatory bowel disease and colonic neoplasia.

Initial laboratorial propaedeutics included complete blood count and hepatic and renal function panels (Table 1). These tests did not show any significant alteration. Then, serology for viral hepatitis A, B and C, HIV 1 and 2, PPD skin test,sputum analysis for AFB, bronchial-alveolar lavage gram stain and fungal culture, blood culture, stool culture, ova and parasite tests were requested and they all were negative (Table 2). Table 2 show cultures, tests and image studies made during hospitalization.

Colonoscopy and upper gastrointestinal endoscopy did not show any neoplasia or inflammation evidence. Subsequently, ileum biopsy revealed wide-cytoplasm cells in the lamina propria positive for periodic acid–Schiff (PAS) stain, being compatible with WD (Figure 1). The PCR for T. whipplei confirmed the diagnosis.

After etiological clarification, treatment was started with a 15-day penicillin G regimen, followed by continued trimethoprim–sulfamethoxazole 80/400mg after hospital discharge, up to current days. Then he had complete clinical remission (Figure 2).

Table 1. Laboratory findings during admission in 2014.

Exame	Valor	Parâmetro
Hemoglobin, g/dL	12,75	13,5-18,0
Hematocrit, %	36,46	40,0-54,0
VCM (fL)	94	80,0-99,0
HCM(pg)	33	27,0-32,0
Platelet,/mm3	304.200	150.000-450.000
Leukocyte counts,/mm3	7.748	4.000-10.000
Linfocyte counts, /mm3	1627	1.500-3.500
AST/GOT, IU/L	36	5-40
ALT/GPT, IU/L	68	10-49
Total bilirrubin	0,43	0,3-1,2
Direct bilirrubin	0,13	<0,2
LDH	288	<190
PPD test	Not reactor	-
C-reactive protein, mg/L	0.5	<3,0
VHS, mm	20	<8,0
INR	1,64	0,8-1,2
APTT, s	32,8	25-39
Creatinine, mg/dL	0,5	0,7-1,3
Urea, mg/dL	37	15-50
Albumin, g/dL	3,0	3,5-5,2

Table 2. Cultures, tests and image studies carried out during hospitalization in 2014.

Material/Test/Image study	Result
Feces/Culture and Stool Ova and Parasites Test by method of Lutz	Negative for enteropathogenic enterobacteriaceae
Anti HIV 1 and 2 (Elisa and western blot) / FAN	Non-reagent / Non-reagent
Feces / Specific culture for *Cryptosporidium sp*. and Stool Ova and Parasites Test by method of Lutz	Negative for *Cryptosporidium sp*.
Abdominal ultrasonography	Dilatation of intrahepatic and extrahepatic biliary ducts; vegetative lesion on gallbladder; small volume ascites.
Colonoscopy	No signs of neoplasia or inflammatory bowel disease
Ileum biopsy	Wide-cytoplasm cells in the lamina propria positive for PAS and Grocott, suggestive of ileal granulomatous disease
Anti-HBc IgG and IgM / Anti-HBs / HBsAg	Non-reagent / Non-reagent / Non-reagent
Fecal Occult Blood Testing (FOBT)	Negative
Blood / Culture	Negative
Thoracic CT	Signs of pulmonary infirmity with endobronchial dissemination pattern, pleuroparenchymal fibrosis and bronchiectasis; sings of bilateral air trapping.
Anti-gliadin IgG and IgA / Anti-tissue transglutaminase IgG / Anti-endomysium IgG and IgA / Schistosomiasis IgG	Anti-gliadin IgG: 15 and IgA: 19 / Anti-tissue transglutaminase IgG: negative Anti-endomysium IgG and IgA: both negative Schistosomiasis IgG: negative
Echocardiogram	EF = 60%. No structural or functional alterations.
Upper gastrointestinal endoscopy	Moderate enanthematous pangastritis; atrophy of second portion of duodenum.
Duodenum biopsy	Accentuated chronic duodenitis with no specificity.
C3, C4 and CH50 dosages	C3: 87, C4: 30, CH50: 121
Intestinal transit study	Apparently no alterations on stomach and duodenum; dilated loops; loss of haustrations and mucous limits; presence of liquid in jejunum.
Sputum / Acid-fast bacillus	Negative
Abdominal and pelvic CT	Normal-dimensioned gallbladder with vegetative lesion in it. The lesion is solid, endoluminal; it captures contrast media and it measures 2,2 x 2,7 x 1,7 cm. No unequivocal evidences of extension to nearby structures. Dilated common bile duct, showing abrupt thinning on distal portions, no evidence of obstructive factors
Bronchoalveolar lavage / Acid-fast bacillus	Negative
Spirometry	Moderate obstructive respiratory disorder with low FVC

Figure 1 Duodenal mucosa biopsy shows histiocytes full of PAS-positive granules on lamina propria. PAS 400x

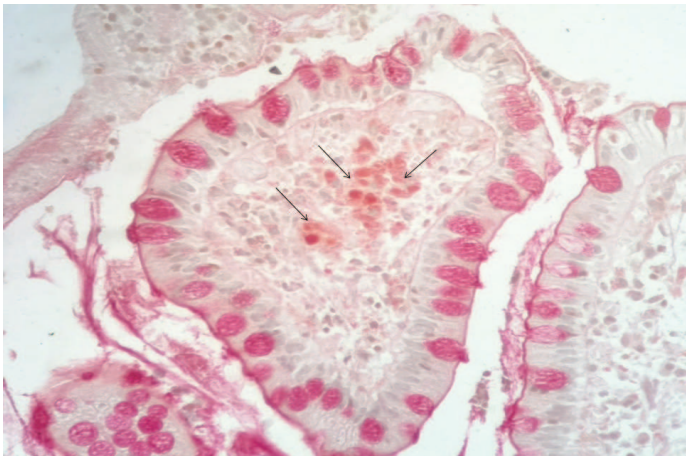
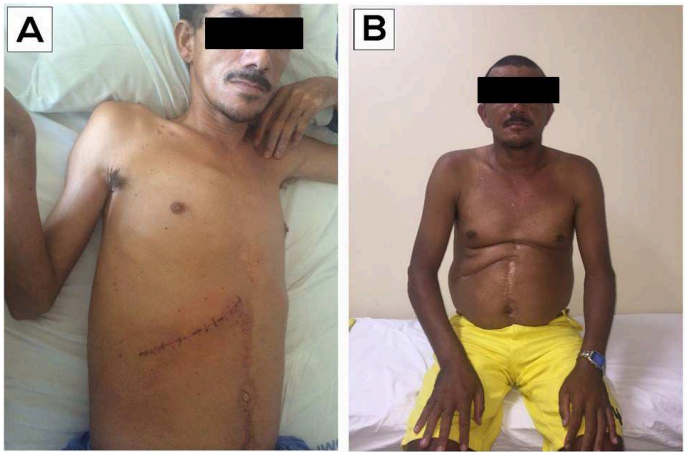


Figure 2. A: 2014, photo taken during hospital stay. B: November 2016, photo taken during medical consultation for follow-up.



DISCUSSION

WD is an infectious disease that presents a variable spectrum of presentation. It most commonly presents gastrointestinal-related symptoms: chronic diarrhea, abdominal pain, weight loss, and fatigue. Other systemic symptoms can also be present, such as fever, migratory or additive chronic arthralgia, and lymphadenopathy.[7] The reported case is interesting due to the absence of symmetric or asymmetric arthralgia and prevalence of gastrointestinal symptoms, what prompted the differential diagnosis with HIV-related immunodeficiency, colonic neoplasia, and inflammatory bowel disease. Furthermore, Tropheryma whipplei can cause different clinical presentations that vary from asymptomatic cases to pulmonary, cardiac, and cerebral disease, what makes differential diagnosis even wider.[8]

Moos et al. (2011) realized a literature review and pointed out the most common clinical findings for the disease: weight loss (90%), hypoalbuminemia (90%), diarrhea (80%), arthralgia (80%), lymphadenopathy (55%), abdominal pain (45%), skin pigmentation (40%), fever (35%), and neurological sings (30%). Classical clinical findings on WD are gastrointestinal symptoms and arthralgia.[10]

The presence of headache and disorientation could suggest nervous system involvement of the disease. About 10 to 20% of the casespresent associated neurological symptoms. Central nervous system involvement is not common in immunocompromised individuals[7]. Most common presentations of neurological involvement are headaches and cognitive dysfunction. Rarely there can be present insomnia, ataxia, and meningitis.[10] Isolated Central Nervous System involvement can occur in about 5% of WD cases[5]. Another valid hypothesis could be neurotoxoplasmosis recurrence. Malnutrition and malabsorption state could possiblyhave generated the immunocompromising necessary for the onset of the disease. Computed tomographyof skull would be the exam necessary for elucidation of etiology.

Cardiac system involvement: endocarditis and mitral valve infections, in addition to other rare conditions, such as skin hyperpigmentation and uveitis, can also be present as WD symptomatology.[5] Therefore, diagnosing this disease becomes a challenge due to its multiplicity of possible symptoms. However, in case of suspicion of WD, the presence of thickened duodenal and jejunal folds and whitish exudate on upper gastrointestinal endoscopy allow to consider it as a diagnostic hypothesis.[5] Histopathology and serum tests, bacterial culture, PCR, and unspecific laboratory findings are also methods that can show some evidences of the disease.[2,5,8] Histology (PAS) is the gold standard test for diagnosing WD.PCR is used in combination with histology for routine diagnosis.[5,6]

Laboratory researches on WD can also reveal anemia, lymphocytopenia, thrombocytosis, eosinophilia, hypoalbuminemia, and altered liver tests. As a malabsortive syndrome, it is possible to observe a decrease in serum concentrations of some substances due to protein and fat elimination in feces (protein-losing enteropathy and steatorrhea)[5].During chronic stage, there is a steady worsening ofthe patient's clinical condition. Upon effective treatment,most of the clinical parameters should normalize. However, there are patients that cannot be cured[5,6,10]. Nevertheless, the association between Whipple's disease and the presence of markers such as HLA DRB1 * [13], DQB1 * 06 and HLA B27 is described. These markers are related to deficiency of cellular immunity and a pertinent investigation was not requested during hospitalization.[8]

The optimal choice of antibiotic and duration of treatment for WD has been debated for many years. Treatment recommendations are to start with an initial 2-week antibiotic treatment followed by long-term maintenance therapy. In the reported case, the absence of treatment could have led patient to death. Before antibiotics advent, this disease was invariably fatal.[6] However, the disease has good prognosis even with late diagnosis and therapy[2]. In addition, recurrences are common even when the first treatment is efficient or when an antibiotic isable to cross the blood-brain barrier, as ceftriaxone, is not chosen to form the first therapeutic scheme.[5,10,11]

The use of Meropenem, ceftriaxone or Benzyl penicillin in induction therapy, followed by Trimethoprim-Sulfamethoxazole for one year is described[11]. Fenolar et al.(2014) propose the use of hydroxychloroquine and doxychloroquine as aninduction therapy followed by a maintenance therapy with Doxychloroquine for one year.[11,12]

The reported case follows the treatment proposed by Singer in 1998, with an inductive therapy with Benzyl penicillin or Streptomycin, associated with Trimethoprim-Sulfamethoxazole for one year.[13]

Although WD presents a systemic impact, its main symptoms are gastrointestinal complaints, weight loss, and symmetric or asymmetric polyarthralgia, even if these symptoms are not pathognomonic conditions. Therefore, in face of a clinical picture presented as abdominal pain, lack of appetite, diarrhea, and emaciation, it is necessary to consider WD as a differential diagnosis.

It is possible to diagnosis WDbyusing the gold standard test (Histology); but other tests like PCR may be necessary, as exemplified by the case, whose clarifying was based on histopathology, PCR and clinical improvement during two years of treatment with trimethoprim-sulfamethoxazole (2014-2016). With appropriate treatment it is possible to reach heal of WD. However, clinical relapse can occur, what may evoke the necessity of other antibiotics.[10,11,14]

The related case turned out to be onerous, because there was high expenditure during medical stay and multidisciplinary work as an effort to reach diagnostic elucidation

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