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Case report

Whipple's disease manifested as difficult-to-diagnose polyarthralgia: a case report and literature review

Doença de Whipple manifestada como poliartralgia de difícil diagnóstico: relato de caso e revisão da literatura

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Introduction

Whipple's disease is a rare systemic disease, described in 1907 by George Whipple at Johns Hopkins Hospital.[1] Years later, in 1961, was shown to be caused by the bacterium Tropheryma whipplei.[2] This is a mandatory intracellular organism, which inhabits mainly the gastrointestinal tract and, due to the lack of data proving its benefit to the host, can be considered a parasite.[3]

Infection by Tropheryma whipplei may be asymptomatic or present with several clinical manifestations such as fever, polyarthralgia, diarrhea, weight loss, fatigue, lymphadenopathy, pulmonary, heart, and skin involvement, and neurological disorders, such as oculomasticatory myorhythmia, oculo-facio-skeletal myorhythmia, dementia and intracranial hypertension.[4] It is a rare disease and the clinical features are extensive and varied, with absolutely variable order of appearance of symptoms, determining an extremely difficult diagnosis. Without proper antibiotic treatment, the disease invariably culminates in dissemination and is potentially fatal.[5]

Whipple's disease has an incidence that is much lower than 1:1,000,000 people, with and occurrence of 12 new cases per year worldwide being estimated. It has a correlation with cellular immunity deficiencies and HLA DRB1*13, DQB1*06 and HLA B27.[6,7] It affects mainly middle-aged men, around fifty years, with a ratio of 6:1 compared to women.[8] Complaints of migratory polyarthralgia usually precede diarrhea in many years.[9]

This article aims to report a case marked by polyarthralgia that had difficult etiological definition and delayed diagnosis, the conclusion of which was Whipple's disease and review the related literature. The patient whose case was reported in this study agreed with the publication and the Research Ethics Committee of Hospital Gaffrée and Guinle approved the study under number 631,797.

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Case report

Male, brown, 45-year-old patient, who has been married for 26 years, Brazilian from the city of Simonésia, in the state of Minas Gerais, businessman, evangelical Christian. He presented in 2006 with severe episodic right hip arthralgia that remitted with analgesics. In 2007 he presented additive, episodic and sometimes migratory arthralgia that affected the right knee joint, right sacroiliac joint, right elbow arthritis and, some months later, right ankle arthritis. During this period, the patient was seen by several physicians, who could not establish a diagnosis and prescribed painkillers, parenteral and oral anti-inflammatory drugs.

He started to have nocturnal flares of generalized non-specific pain, with dysesthesia, requiring several visits to emergency rooms with use of weak opioids between 2008 and 2009. During this period, the clinical features of additive, migratory, episodic polyarthralgia evolved to generalized polyarthritis, also affecting the sternoclavicular joint. The patient main pain complaints referred to hip and sacroiliac joints. He has taken analgesics, nonsteroidal anti-inflammatory drugs, oral corticosteroids and weak opioids with partial response.

The rheumatologist assistant chose to start therapy with a biological agent infliximab. After the second dose, he presented a fever and maculopapular rash in the dorsal region and upper limbs. Due to dissatisfaction with the results of treatment, in 2010 he sought physicians of other specialties and alternative therapies for pain relief without success.

Given the uncertainty of the case, he looked for the Internal Medicine Unit of the University Hospital Gaffrée and Guinle – UNIRIO. After history and physical examination, new complementary tests were requested (Table 1). The fact that the patient had joint complaints, consulted multiple specialists, had negative complementary tests for rheumatic diseases and presented a non-reactive PPD, although living in an endemic area of tuberculosis, was noted. This was interpreted as a possible defect of cell immunity. With this information, the diagnosis hypothesis was an articular manifestation of a systemic disease. Since HLA B27 was negative, the classic seronegative spondyloarthropathies (ankylosing spondylitis, inflammatory bowel disease, Reactive Arthritis, Psoriatic Arthritis) was less likely, but not impossible. Behçet's disease and Whipple's disease were contemplated. The patient received a written summary of the clinical features and an immediate request of upper gastrointestinal endoscopy with duodenal biopsy to specifically rule out Whipple's disease. Despite this evaluation, the patient did not follow the indications and he did not return.

In 2011, together with the articular features, he started a refractory very severe headache. Associated with the headache bursts, he developed a right hemiparesis and a left facial paralysis that remitted spontaneously. In addition, he had episodes of diarrhea with hematochezia, nausea and vomiting, resulting in significant weight loss and muscle atrophy.

In 2012, the disease progressed and the patient required hospitalization in the Intensive Care Unit (ICU) in the city of Juiz de Fora, state of Minas Gerais. He had intracranial

Table 1 – Test results performed at consultation to Internal Medicine Unit on January 8, 2010.

Tests of January 8, 2010			
Erythrocytes (10^6 mm^3)	**4.61**	ALT (U/L)	32
Hgb (g/dL)	**12.2**	AST (U/L)	38
MCV (fL)	82	AF (U/L)	91.6
MCH (pg)	**26**	GGT (U/L)	78
MCHC (%)	**31.5**	Albumin (g/dL)	3.22
RDW (%)	15.6	Globulin (g/dL)	3.9
Leucocytes (cell/mm^3)	6900	Protein electrophoresis	Normal
Platelets (cell/mm^3)	329,000	TB (mg/dL)	0.24
ESR (mm/h)	**93**	IB (mg/dL)	0.15
CRP (mg/L)	**100**	DB (mg/dL)	0.9
PT (INR)	1.21	CK (U/L)	71.2
APTT (Rel)	1.0	Hepatitis B	Neg
Blood Glucose (mg/dL)	81	Hepatitis C	Neg
BUN (mg/dL)	42	HIV	Neg
Creatinine (mg/dL)	1.2	ANA	Neg
Uric Acid (mg/dL)	5.0	RF	Neg
Sodium (mEq/L)	134	C3 (mg/dL)	168
Potassium (mEq/L)	4.3	C4 (mg/dL)	27.4
Chloride (mEq/L)	102	HLA B27	Neg
Free calcium (mg/dL)	5.2	ANCA	Neg
Phosphorus (mg/dL)	3.9	TSH (mcUi/mL)	2.54
PPD	**Nonreactive**	Free T4	1.1

Values considered abnormal are in bold type. Hgb, hemoglobin; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, anisocytosis index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; PT, prothrombin time; APTT, Activated Partial Thromboplastin Time; PPD, tuberculin purified protein derivative; ALT, alanine transaminase; AST, alanine transaminase; AF, alkaline phosphatase; GGT, gamma-glutamyl transferase, TB, total bilirubin; DB, direct bilirubin; IB, indirect bilirubin; CK, creatine kinase; ANA, antinuclear factor; RF, rheumatoid factor; ANCA, antineutrophil cytoplasmic antibodies.

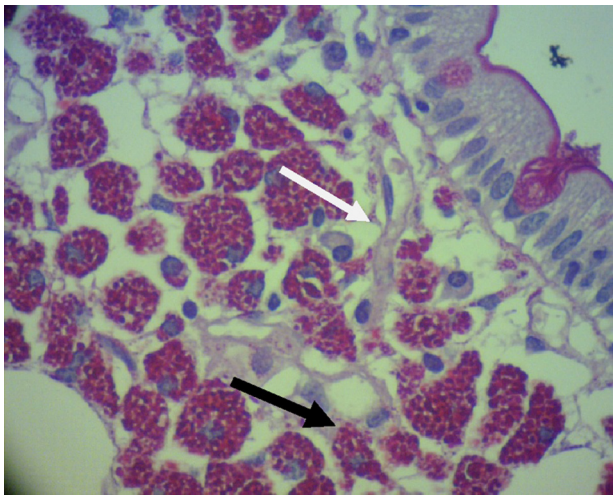

Fig. 1 – Specimen collected by duodenal biopsy. Periodic Acid–Schiff (PAS) staining. Marked accumulation of PAS-positive macrophages (white arrow) on submucosa and presence of fibrosis (black arrow) suggesting a chronic process.

hypertension due to cerebral edema, confirmed by magnetic resonance imaging (MRI) associated with dyspnea on minimal exertion, paroxysmal nocturnal dyspnea, prerenal failure, pleural effusion and generalized edema consistent with congestive heart failure. The echocardiography showed a mitral valve vegetation and insufficiency. The medical team who conducted the case requested an upper gastrointestinal endoscopy with duodenal biopsy for Whipple's disease investigation after reviewing information collected in the consultation at the Internal Medicine Unit in 2011. Histopathological specimen examination and polymerase chain reaction (PCR) were performed at the Pasteur Institute in France (Fig. 1), which confirmed Tropheryma whipplei. The primer oligonucleotide sequence used was pW3FE (5′-GGA ATT CCA GAG ATA CCC GCC GCC CAA-3′) and pW2RB (5′-CGG GAT CCC ATT CGC TCC ACC TTG CGA-3′).[10]

In view of the diagnosis, therapy was initiated with trimethoprim-sulfamethoxazole, soon interrupted due to severe gastrointestinal intolerance. Therapy was replaced with doxycycline 100 mg orally 2 tablets bid and hydroxychloroquine 600 mg orally once a day. The patient showed dramatic clinical improvement and was discharged for outpatient monitoring.

Discussion

Whipple's disease has a variable presentation of polyarthralgia, including symmetric and asymmetric forms of intermittent nature, sometimes being migratory or additive. Joint involvement is present in over 90% of cases and can precede the exuberant manifestation of the disease in about a decade.[11]

The patient presented the polyarticular arthritis features about five years before the severe illness. During the initial period, he had consultations with multiple internists and rheumatologists without a specific diagnosis, also undergoing immunosuppressive therapies (infliximab) that worsened the disease. The search for pain relief was added to the frustration of not receiving an accurate diagnosis, including seeking alternative therapies. When he was seen at our clinic, some details called our attention. The first was the fact that experts, even ordering an extensive list of tests, could not provide a clear diagnostic definition, what reinforced the hypothesis that this was a joint disease probably related to a rare systemic disease, possibly indirectly related to rheumatology.

Other relevant information was the absence of symptoms such as chronic diarrhea (inflammatory bowel disease), lesions suggestive of psoriasis or any other skin involvement (psoriasis, SAPHO or Behcet's disease), no history of sexually transmitted diseases (Reactive Arthritis), features that are non-excluding when considering that the articular manifestation may precede other symptoms. The negative HLA B27 was valued because of its known correlation with seronegative spondyloarthropathies.[12]

Finally, we highlight the fact of PPD not being reactive, something possible, but unusual in a resident of a highly endemic tuberculosis region. The non-reactive PPD lead us to think of cellular immunity changes, not linked to AIDS, given that HIV test was negative. The hypothesis of Whipple's disease was suggested,[13–15] but the patient did not return to the outpatient's clinic with the upper gastrointestinal endoscopy and duodenal biopsy that had been requested. Abandonment was attributed to the patient's lack of trust in the ability of medicine to solve the problem of chronic pain. The case has evolved into a typical form of a complex clinical syndrome related to Whipple's disease.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Whipple GH. A hitherto undescribed disease characterized anatomically by deposits of fat and fatty acids in the intestinal and mesenteric lymphatic tissues. Bull Johns Hopkins Hosp. 1907;18:382–91.
2. Chears WC, Ashworth CT. Electron microscopic study of the intestinal mucosa in Whipple's disease: demonstration of encapsulated bacilliform bodies in the lesion. Gastroenterology. 1961;41:129–38.
3. Wilson KH. Whipple disease research accelerates. J Infect Dis. 2011;204:4–5.
4. Dobbins WO III. Whipple's disease. Mayo Clin Proc. 1988;63:623–4.
5. Guthikonda B, Rouah E, Krishnan B, Powell SZ, Goodman JC, Gopinath SP, et al. Whipple disease of the central nervous system: an unusual occurrence in association with acquired immune deficiency syndrome. J Neurosurg. 2010;112:983–9.
6. Martinetti M, Biagi F, Badulli C, Feurle GE, Muller C, Moos V, et al. The HLA alleles DRB1*13 and DQB1*06 are associated to Whipple's disease. Gastroenterology. 2009;136:2289–94.
7. Feurle GE. Association of Whipple's disease with HLA-B27. Lancet. 1985;325:1336.
8. Fleming JL, Wiesner RH, Shorter RG. Whipple' disease: clinical, biochemical, and histopathologic features and

assessment of treatment in 29 patients. Mayo Clin Proc. 1988;63:539–51.
9. Tan TQ, Vogel H, Tharp BR, Carrol CL, Kaplan SL. Presumed central nervous system Whipple's disease in a child: case report. Clin Infect Dis. 1995;20:883–9.
10. Fenollar F, Fournier P, Raoult D. Quantitative detection of Tropheryma whipplei DNA by real-time PCR. J Clin Microbiol. 2002;40:1119–20.
11. Durand D, Lecomte C, Cathedras P, Rousset H, Godeau P. Whipple's disease. Clinical Review of 52 cases. The SNFMI Research Group on Whipple's disease. Societe Nationale Francaise de Medecine Interne. Med Tropheryma Whipplei. 1997;76:170–84.
12. McHugh NJ. Other seronegative spondyloarthropathies. Medicine. 2010;78:190–3.
13. Dobbins WO III. Is there an immune deficit in Whipple disease? Dig Dis Sci. 1981;26:247–52.
14. Kent SP, Kirkpatrick PM. Whipple disease. Immunological and histochemical studies of eight cases. Arch Pathol Lab Med. 1980;104:544–7.
15. Groll A, Valberg LS, Simon JB, Eidinger D, Wilson B, Forsdyke DR. Immunological defect in Whipple's disease. Gastroenterology. 1972;63:943–50.