

Whipple's disease, a rare malabsorption syndrome of late diagnosis.

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Abstract

Whipple's disease is a rare, chronic bacterial illness with multisystemic involvement, caused by *Tropheryma whipplei*. Due to its multiform presentation and rarity it is often misdiagnosed. The standard method concerning diagnosis is the detection of PAS (periodic acid- Schiff) positive macrophages in affected tissues. Immunohistochemical staining and PCR (polymerase chain reaction) increase the sensitivity and specificity of conventional methods. Long term antibiotic therapy provides a favourable outcome in the majority of cases. The authors describe a case of a patient with Whipple's disease in a progressive stage.

Keywords: Whipple's disease. Malabsorption syndrome. *Tropheryma whipplei*

Palabras clave: Enfermedad de Whipple. Síndrome de malabsorción. *Tropheryma whipplei*

Introduction

The Whipple's disease is a rare multisystemic infection caused by *Tropheryma whipplei*, a gram positive bacterium which is taxonomically closely related to the group of *Actinomyces* and *Mycobacteria*¹. It is an important cause of infectious malabsorption syndrome that affects about 1 in 1 000 000 people, being affected mainly men 40 to 50 years². Its pathogenesis is linked to a defect of the impaired function of the macrophages³. *Tropheryma whipplei* preferably reaches the small intestine at the jejunum level causing malabsorption.

Its classic clinical course has three stages: (1) nonspecific prodromal symptoms, including migratory polyarthralgia (mainly in the large joints) that can precede illness for 10 years; (2) typical abdominal symptoms: pain, diarrhea, weakness and weight loss and; (3) generalized stage that includes steatorrhea, cachexia, lymphadenopathy, hyperpigmentation and cardiovascular, neurological and pulmonary disfunctions^{4,5}.

Early diagnosis is difficult to achieve because it is a disease with systemic repercussions and nonspecific symptoms. Laboratory tests may provide several nonspecific findings that in combination can be suggestive of the diagnosis such as: hypoalbuminemia, elevated erythrocyte sedimentation rate and anemia⁶. Thus, the specific immediate diagnosis can be performed through endoscopy where there is a thickening of mucosal folds with whitish exudates and mucosal erosions. The polymerase chain reaction (PCR) can be used to identify the presence of the bacteria in the tissue biopsy to confirm the diagnosis⁷. Treatment consists of induction of antibiotic therapy followed by maintenance regimen for a long period⁴.

Case report

A fifty four year old female caucasian patient was admitted to the emergency room for investigation of a 17 kg weight loss with asthenia, anemia and intermittent diarrhea without blood, mucus or pus for about one year. Her previous medical history included 2 years of lumbago pain with mechanical characteristics. At the admission, the patient was thin, weighing 32 kg (BMI= 13.3 kg/m²), presented lower limb edema and skin hyperpigmentation of the entire body mostly the sun exposed areas (fig 1).

Fig. 1. Patient before the treatment for Whipple's disease.



Unremarkable pulmonary, cardiac and abdominal examination. Laboratory tests showed iron deficiency anemia (hemoglobin = 6.5 g/dL, ferritin = 26.6 ug/L, transferrin saturation = 4%, serum iron = 7 ug/dL), hypokalemia of 2.4 mmol/L, hypoalbuminemia (1.3 mg/dL), a deficiency of folat acid (3.06 nmol/L) and an elevated erythrocyte sedimentation rate of 75 mm/h. In relation to the imaging studies an abdominal ultrasound showed a small amount of free fluid in the abdominal cavity. Anti-HIV antibodies, antinuclear antibodies, rheumatoid factor, serum cortisol and thyroid-stimulating hormone (TSH) were investigated and showed to be negative or within the normal limit ranges. Stool search for parasites was negative, and steatocrit was normal. The antibodies for celiac disease were negative. The patient underwent a colonoscopy which was normal. An upper endoscopy showed a focal duodenal whitish exsudat. Biopsies were performed and revealed many spongy macrophages in the lamina propria, with diffuse and nodular distribution and positive cytoplasmatic staining with periodic acid-Schiff (PAS) staining with negative Ziehl-Neelsen staining, compatible with Whipple's disease. In the absence of molecular biology test to further confirm the diagnosis, it was began treatment with intravenous ceftriaxone 2g/day for two weeks, with normalization of the bowel habits and progressive improvement of the general condition of the patient. After discharge, the patient was continued on sulfamethoxazol and trimethoprim for a year and supplements of folat acid and iron. The medication was discontinued after a year and the patient nowadays is asymptomatic, with normal albumin level, Hb level of 11.2 g/dL and weighing 65 kg (fig 2).

Discussion

Whipple disease is a rare disorder that affects more men than women, generally middle aged¹. There is evidence that the *Tropheryma whipplei* may be ubiquitous in humans, since there are studies using PCR amplification of this or-

Fig. 2. Patient after a year of treatment for Whipple's disease.



ganism from samples of saliva, gastric juice and duodenal biopsies of patients without Whipple's disease⁸. There seems to be a failure of the immune response to *Tropheryma whipplei*, suggesting that such deficiency has a role in the occurrence of this disease.

Gastrointestinal manifestations typically of a malabsorption syndrome, occur in about 70% of the cases of Whipple's disease. The weight loss is on average 11 kg (range : 3-36 kg)⁹ and diarrhea is usually watery and occurs episodically with colic pain. A pure statorrhea is rather rare¹⁰.

The most frequent extra-intestinal manifestations are joint disease and constitutional symptoms, mainly weight loss, as verified in this patient and that is present in more than 2/3 of cases in some series. The following systems may also be affected in some way during the course of the disease in order of frequency : central nervous system, cardiovascular system, mucocutaneous system, pleuropulmonary system and vision¹¹.

Therefore the Whipple's disease should be considered a differential diagnosis in many clinical situations: malabsorption with involvement of the small intestine (celiac disease, sarcoidosis and lymphoma), inflammatory rheumatic disease (seronegative arthritis), Addison's disease, conjunctive tissue disease and a variety of neurological disease.

Because of its broad spectrum of clinical manifestations added to its low incidence in the general population makes the diagnosis difficult, usually leading to a late diagnosis. In this case the diagnosis was only established in a progressive stage with a malabsorption syndrome and skin pigmentation which suggests a severe case of Whipple's disease. Skin hyperpigmentation is present in about 40% of the patients, it may occur as a consequence of vitamin D malabsorption, which may induce compensatory secondary hyperparathyroidism leading to enhanced MSH and ACTH production¹². In addition to this *Tropheryma whipplei* infection may induce hypothalamic dysfunction and adrenal gland insufficiency¹³.

Upper endoscopy with intestinal biopsy and PCR, if necessary, are the most effective method of investigation. Histologically, there are infiltrates comprised by macrophages with granular cytoplasm, showing inclusions which stain positive with periodic acid-Schiff (PAS), and phagocytosed bacteria. The presence of macrophages with positive PAS material is not pathognomonic of the disease and can occur in cases of infection of *Mycobacterium avium complex*, *Rhodococcus equi*, *Bacillus cereus*, *Corinebacterium* and Histoplasma. The Ziehl-Neelsen staining is useful for differentiation of infections caused by alcohol resistant acid bacilli.

The PCR technique has a high sensitivity but low specificity, therefore it is only indicated for people who have characteristic symptoms of Whipple's disease. Whipple's disease was invariably fatal before the advent of antibiotics⁶. However the recommendations are not based on therapeutic trials or the susceptibility of *Tropheryma whipplei* to various antimicrobial agents, they favour antibiotics that are capable of crossing

the blood –brain barrier, such as trimethoprim-sulfamethoxazole^{6,10}. There is no consensus on the type and duration of the antibiotic treatment. The mostly recommended treatment is oral administration of 160 mg trimethoprim and 800 mg of sulfamethoxazole twice a day during a year, usually preceded by parenteral administration ceftriaxone (2 g daily during two weeks^{6,10}.

For some authors, the control of the disease progression and prognosis should be carried out from monitoring the patients with the realization of upper endoscopy with duodenal biopsy at 6 and 12 months of treatment¹⁴. We know that Whipple's disease relapses and very frequently may occur several years after diagnosis. Therefore clinical follow-up should be maintained for 10 years because the risk of late recurrence is high¹⁵. In the present case report, the patient had compatible symptoms and additional tests suggesting Whipple's disease, confirmed with endoscopy and biopsies with progressive improvement and improving her quality of life after the recommended treatment.

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