

CLINICAL NOTE

Association between Whipple's disease and *Giardia lamblia* infection

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ABSTRACT

Whipple's disease is mainly characterized by affecting the digestive system, although it can be a multisystemic process with different clinical symptoms. The bacillus causing the disease has been isolated and cultivated in 2000 and the genome sequence has been recently analyzed in 2003, which means new perspectives for its diagnosis and treatment. Giardiasis is an infestation caused by a protozoon and may cause a malabsorption syndrome or run in a subclinical way.

The case of a middle-aged male is described, who after a three-year period of migratory arthralgias, showed weight loss, diarrheas and abdominal pain, being diagnosed of Giardiasis, and after the persistent symptoms and a number of studies, was diagnosed with Whipple disease.

Nineteen cases of *Giardia*-Whipple coinfection have been described in the literature, but the reason of this association has not been found yet. The discussion on whether there is an alteration in the immunitary system which facilitates infections or, the development of an infection lead to the other one, goes on.

Key words: Whipple disease. T. Whipple. *Giardia*. Giardiasis.

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INTRODUCTION

Whipple's disease is a multisystemic disorder originated by the bacterium *Tropheryma whippelii*. This occurs

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mainly in middle-aged males, with a prevalence rate of 73% versus women (1,2). The gastrointestinal tract is the most frequently involved organ (80-90%) (3), although gastrointestinal symptoms occasionally begin after alterations in the musculoskeletal system. In fact, in one third of patients arthropathy precedes the other symptoms by several years (1,2,4,5).

Most common symptoms include: watery diarrhea, steatorrhea, colicky abdominal pain with weight loss in some cases, fever, and night sweats.

Joint symptoms are the most common extraintestinal manifestations, occurring in 90% of patients (5). Joints involved are mainly peripheral joints such as the knees, elbows, fingers, ankles, and shoulders. They are generally described as asymmetric and migratory, and deformity is rare (5). The sacroiliac area is affected in 14% of patients (4). It has also been found that about 26% of patients are positive for HLA B27, which has prompted some authors to support a genetic susceptibility in the development of the disease, which has not been demonstrated yet (1,5,6).

The lungs, heart, and eyes may become affected, as well as the central nervous system with signs such as personality changes, dementia, memory disorder, myoclonus, ophthalmoplegia, and nystagmus (1).

Regarding laboratory findings, hypochromic anemia, lymphocytopenia, thrombocytosis, increased C-reactive protein levels, vitamin deficiency, or indirect signs of malabsorption are all possible (7).

Since it affects a number of organs, manifestations can be different. Thus, it is possible to find patients with Whipple's disease and no gastrointestinal manifestations. Several cases in which neurological manifestations or arthropathy are the only symptoms have been described too (1,3,5).

As the disease is suspected on the basis of clinical findings and imaging techniques, a duodenal and/or jejunal biopsy must be performed. In the event of no diges-

tive symptoms, it would be necessary to study the synovial fluid, or even the cerebrospinal fluid if the involvement of the central nervous system predominates, where we may find the macrophages filled with PAS-positive material by means of a cyto-histological analysis. This finding shows the presence of Whipple's disease (2). An ultrastructural study can also demonstrate the presence of the bacillus.

Molecular techniques have allowed advances in the diagnosis of this disease. By amplifying genetic materials with the polymerase chain reaction (PCR) the bacillus was eventually detected in various tissues (8,9). The complete sequence of the genome has been generated and analyzed afterwards (10). However, PCR has also some limitations. Despite its high sensitivity, it lacks specificity, since the bacterium's DNA has been found in both the saliva and gastric fluid in individuals without Whipple's disease (1,11).

Raoult et al. (11,12) isolated and cultured two strain in specialized laboratories, which has proved a great advance in the understanding of this disease.

For treatment, one of the most commonly used medicines is trimethoprim-sulfamethoxazole, since it provides adequate blood-brain barrier penetration and a reduced number of neurological relapses (13-15).

Giardia is a flagellate protozoan that is more prevalent in developing countries than in developed countries. It shows a great variability in its presentation. Half of patients are asymptomatic, and in the rest it can manifest as a malabsorption syndrome (diarrhea, abdominal pain, asthenia, and weight loss) (16,17). This variation in clinical manifestations includes virulence of the *Giardia* strain involved, number of cysts ingested, age, and immune status of the patient at the time of infection (18). A greater incidence rate has been seen in patients with hypogammaglobulinemia (18,19).

The disease can be diagnosed by the identification of trophozoites or cysts, in the examination of stools. According to some authors (16), in those cases in which chronic diarrhea continues and the results of stool examination are repeatedly negative, a histological examination of duodenal biopsy samples would be advisable. Regarding the use of PCR for the diagnosis of *Giardia* we found few texts, and in those cases in which it has been done no major differences were found on stool examination (16). One of the used medicines is metronidazole, which successfully eradicates the infection (20).

CASE REPORT

A 60-year-old male who usually smokes two packs of cigarettes a day was operated on for inguinal hernia. He had been suffering from diarrhea and abdominal pain for five months now. He had lost 9 kg of body weight. The patient was diagnosed with *Giardia* infection and treated with metronidazole. He has had arthralgia since 2000,

which involve the tarsus, knees and carpus. Symptoms are described as occurring with monthly outbreaks, and disappear with analgesics and antiinflammatory drug. He was diagnosed with migratory arthritis following a palindromic pattern (RF, ANA, and HLA B27, all negative). He showed a poor nutritional condition. Cardio-pulmonary sounds were normal. He had a soft abdomen with no tender points, an inguinal hernia and no adenopathies. Laboratory results included: ESR at 1st hour 15 mm; C-reactive protein 74 mg/L; the remaining parameters were normal.

A chest PA showed no remarkable findings. In the barium enema a dolichosigma with some isolated diverticula was seen. Ultrasounds revealed an increased caliber in intestinal loops, and a thickening of both the wall and enteric folds. A small-bowel transit showed a diffuse thickening of the duodenal-jejunal fold with a nodular pattern. Upper gastrointestinal endoscopy showed some isolated erosions in the antrum (Fig. 1). Likewise, on the 2nd duodenal portion, the mucosa was highly hyperemic and edematous, with a white-yellowish punctate miliaria with a patchy distribution. The histological analysis showed a thickening of villous folds in the duodenum, with their lamina propria being characterized by a massive macrophage infiltration with a PAS-positive, diastase-resistant material. A Ziehl-Nielsen stain was negative. The patient was then diagnosed with Whipple's disease (Fig. 2). Stool examination: positive to *Giardia lamblia*.

On these findings, we started treatment with trimethoprim-sulfamethoxazole at a dose of 160/180 mg twice a



Fig. 1.- Small-bowel transit: a diffuse thickening of the duodenal-jejunal fold may be seen.

Tránsito intestinal: se aprecia una dilatación de las asas duodenales y yeyunales con engrosamiento de sus pliegues.

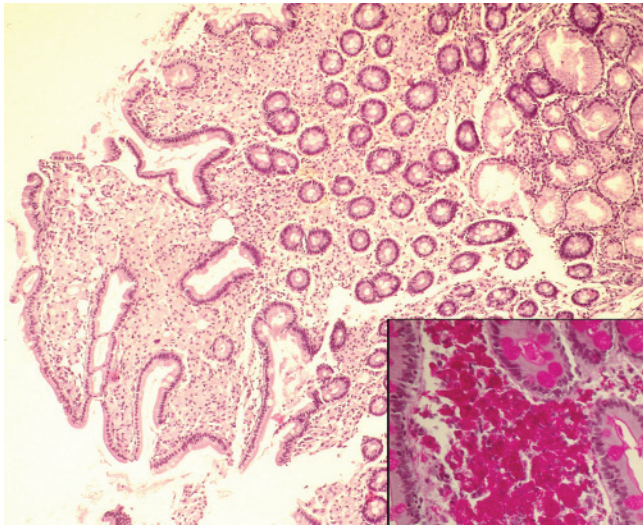


Fig. 2.- The lamina propria is occupied by histiocytes with a wide, acutely granular cytoplasm (HE 200X). The cytoplasm of macrophages is PAS-positive.

Lámina propia dilatada y ocupada por histiocitos de citoplasma amplio, finamente granular y eosinófilo (HE 200X). Detalle: los citoplasmas de estas células son fuertemente PAS-positivos (PAS 200X magnificación original).

day for a year and metronidazole 500 mg three times/day for ten days. Within two months of treatment onset abdominal pain had vanished, and the patient gained 4 kg of body weight. Four months later he kept asymptomatic, and had put on weight 10 kg.

DISCUSSION

Some studies have suggested that Whipple's disease may develop in cases with immunodeficiency or immunosuppression, or in association with other infections, including *Giardia lamblia* (16,21-23) as was our case.

In a recent study by Fenollar et al. (16), they found 4 cases of Whipple's-*Giardia* coinfection. These authors performed a study to establish the prevalence of giardiasis in 25 patients with Whipple's disease. They researched duodenal biopsy samples for all 25 patients in order to find *Giardia*. Five biopsy samples out of 25 had been collected before the diagnosis of Whipple's disease. Six duodenal biopsy samples had been collected before therapy onset, and the rest once the therapy was started. After the results had been analyzed, they found a greater prevalence of Giardiasis in patients with Whipple's disease than those in the control group, with a statistically significant difference (16).

These authors reviewed cases of Whipple's-*Giardia* coinfection as previously described in the literature. Thirteen out of 15 cases found with coinfection were diagnosed with Whipple's disease due to the presence of PAS-positive macrophages in the duodenal and/or jejunal biopsy; in another case, in the biopsy of a cardiac valve,

and in the last case in mesenteric adenopathies. Infection by *Giardia* was diagnosed using a histological analysis too. In the 19 cases found (4 diagnosed by them and 15 identified in the literature) the most common symptoms were diarrhea, arthralgia, and loss of weight (16,24-26). Since few cases of coinfection have been described, researchers have no explanation on the association between these two diseases, although several hypotheses have been proposed. Thus, a greater prevalence of *Giardia* infection rates has been described in patients with hypogammaglobulinemia versus immunocompetent individuals (18,19). Defects of the immune system in patients with Whipple's disease have also been described. Particularly the ability of macrophages and T-lymphocytes to become activated seems to be affected (27). A reduction in CD11b expression within macrophages has been seen, which has an important role in antigen processing and serves as a facilitator of phagocytosis (5). Marth et al. (28,29) observed a reduced production of monocyte-related IL-12 in these patients, a cytokine which is important in the regulation of cell-mediated immune responses. These changes may result in a defect regarding phagocytosis and the intracellular degradation of the bacillus (28). A defective immune system might likely favor the development of both diseases. On the other hand both organisms abide in sewage water (3,8,16), but no common source of infection has been found yet. The fact that the development of the one infection allows the development and propagation of the other infection remains to be proven (16). Due to the fact that both diseases show different clinical signs, when suspecting the presence of any of them we must follow the necessary techniques to achieve an early diagnosis for the other condition and then initiate treatment.

In the case of Whipple's disease, new findings will allow a greater knowledge on its pathogenesis, as well as the design of new diagnostic tests, all of which will lead us to a complete understanding of the disease.

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