Unintentional weight loss as presenting form of Whipple's disease. Role of PET-CT scanning and review of the literature

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INTRODUCTION

Whipple's disease (W.D.) is a multisystemic chronic infectious disorder first described in 1907 by Dr. George Hoyt Whipple[1]. The disease is very rare, with an annual incidence of 1 per 1.000.000 inhabitants[2]. It not only involves malabsorption from gastrointestinal involvement but also affects other systems like the joints, cardiovascular system and central nervous system[3]. The etiological agent, *Tropheryma whipplei* (*T. whipplei*) was first described in 1992. It is a gram-positive actinomycete, periodic acid-Schiff-positive (PAS) and acid-fast negative[4]. It contains polysaccharides that stain positive with PAS. The foamy rosy appearance of macrophages inside the intestinal mucosa determines an extensive involvement of the lamina propria[2] and, in this sense, the name of the etiological agent comes from the Greek "Trophy" (food), and "Eryma" (barrier), that means obstacle to absorption of food[5].

The authors describe a case of W.D. presented as isolated weight loss and review the literature focusing on the role of PET-CT scanning as a diagnostic tool.

CASE REPORT

A 68 years old man was referred to the outpatient consultation because of unintentional weight loss. He had lost 10 kg in a period of three months. The patient tried to lose weight on a diet and doing some exercise. He stopped both after suffering an influenza infection, but the weight loss continued. He was a retired man and referred a history of hypertension, hyperuricemia, and atrial fibrillation. There was no history of fever, arthralgia, nausea, vomiting, abdominal pain, diarrhea, or bleeding.

On physical examination, the patient was afebrile and vital signs were normal. Neurological examination, digestive system and joints were normal.

Serum biochemistry, leucocyte count, platelet count, as well blood coagulation was normal. Mild anemia (Hb 12.8 g/L) was found with normal serum ferritin level, and iron level. Anti-tissue transglutaminase antibodies (ATGT) were negative. An abdominal ultrasonographic study, upper endoscopy and colonoscopy were normal.

After this initial evaluation the patient referred no associated symptoms but continued losing weight. A positron emission tomography/computed tomography (PET-CT) scan was performed (Figure 1) showing enlargement of several abdominal and inguinal hypodense lymph nodes suggesting the radiologic appearance of the cavitating mesenteric lymph node syndrome. A core needle biopsy from the inguinal lymph node was reported as normal. Duodenal biopsy with investigation of coeliac disease and W.D. was performed showing thickening of the intestinal villi and foamy macrophages containing numerous granular intracytoplasmic inclusions PAS positive (Figure 2). Special staining for acid-fast bacilli and fungi were negative. There was no evidence of malignancy. Polymerase chain reaction (PCR) assay targeting the 16S rRNA gene of *T. whipplei* showed a positive result in the duodenal biopsy.

Antibiotic treatment using ceftriaxone (2 g/day intravenously at home) was given for 2 weeks. This initial therapy was followed by long term trimethoprim-sulfamethoxazole (TMP-SMZ; 160/800 mg twice a day). Currently he continues to take TMP-SMZ on a regular basis.

Figure 1. PET-CT scan. Panel A shows enlarged mesenteric lymph nodes and Panel B an inguinal enlarged lymph node. Biopsy of the inguinal lymph node was made showing no pathological findings.

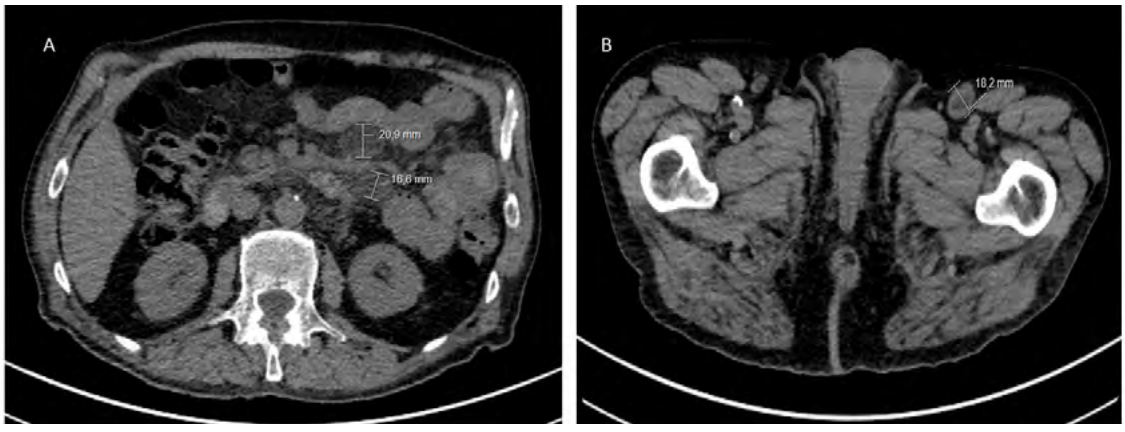

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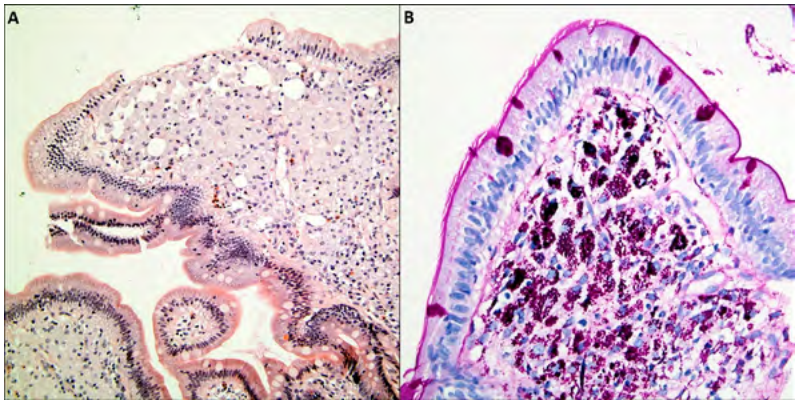
Figure 2. Duodenal biopsy. Panel A shows thickening of the intestinal villi and foamy macrophages (H&E, original magnification x 20). PAS stain (Panel B) reveals the presence of numerous granular intracytoplasmic inclusions PAS positive, diastase resistant (PAS-D, original magnification x 40).



DISCUSSION

This case deals with a rare disease presenting with unexplained unintentional weight loss. Non-malignant organic disorders, mainly digestive diseases are the most frequent cause of unintentional weight loss[6]. Malabsorptive diseases like W.D. are a possible underlying etiology.

Epidemiologically, W.D. is linked to a fecal-oral transmission, particularly in male patients that work with animals[7] affecting mainly patients from Europe and North America. It is very rare in the native African and Asian populations[8]. After introducing PCR testing as a tool for diagnosis of W. D., the annual incidence rate has been estimated to be between 1 and 6 new cases per 10.000.000 persons per year worldwide[9].

Asymptomatic carriers of *T. whipplei* represent a large reservoir from which other humans might be colonized. Most carriers develop protective response that prevents spread of the bacterium through the body, but carriage can last for several years[10]. *T. whipplei* has been found in numerous biological samples including urine, blood, saliva, stool, skin, lymph node, synovial fluid, skeletal muscle, myocardium, cardiac valve, lung, bronchoalveolar fluid, liver, spleen, stomach, small bowel, colon, larynx, maxillary sinus, aqueous humor, brain, and cerebrospinal fluid[11,12].

Relatives of chronic W.D. patients have a higher chance of carrying the bacterium either because of human to human transmission or because they are infected by the same environmental source[13]. Although it is assumed that the bacterium is acquired during childhood[14], only a limited number of carriers develop W.D. In this sense, it seems that host, bacterial, and environmental factors may all contribute to the pathogenesis[14]. Probably, subjects who do not develop a protective immune response are prone to development of classical W.D.[1].

The most frequent and common symptoms involve the gastrointestinal system (75-95%)[2,16]. Diarrhea is the most common complaint in patients affected from W.D.[17] frequently associated with malabsorption[18]. Weight loss is the second most important manifestation[17] commonly associated with other symptoms but isolated weight loss is very rare. A patient with W.D. associated weight loss can lose up to 15 Kg in one year. Weight loss is less common in patients under 40 years. It is most common in males 40-50 years old[7,19]. When weight loss is a predominant feature of the disease, cachexia may result both from anorexia and nutritional deficiency due to malabsorption[16].

Clinical presentation is highly polymorphic. There has been described four commonly recognized patterns: classic W.D., localized chronic infections, acute infections, and carriage[13,20]. Symptoms tend to develop in three phases. An early phase with symptoms of infection such as fever, arthritis or arthralgia. A middle phase with diarrhea and weight loss, and a late phase where almost every organ can be involved, mostly the eyes, heart, and central nervous system[21]. Pathophysiology of gastrointestinal affectation is due to bacterial overgrowth and diffuse edema and exudates inside the intestinal wall and mucosa[22].

Polyarthralgia due to chronic polyarthritis with migrant involvement of distal joints is common (65-90%) and can evolve to spondylitis[5,23]. The cardiovascular system is affected in 17-55% of the cases being endocarditis the most frequent feature[2,22]. The central nervous system can be involved around 10-43% in patients with W.D. Neurological manifestations can be the result of a relapse of previously treated classic W.D., neurological involvement in untreated W.D., or an isolated neurological symptom[24].

Important diagnostic support is provided by the molecular diagnosis with PCR giving a determination of the nucleotide sequence of the 16S RNA gene of *T. whipplei*. This test have a high sensitivity (59-95%) but low specificity (45-71%), depending from the PCR assay performed[11,16]. PCR also allows to evaluate the degree of patient response to antibiotic therapy and perform a differential diagnosis with other bacteria such as *Mycobacterium complex*, *Corynebacterium spp*, *Rhodococcus equi*, or *Histoplasma sp*[16].

Both diagnostic tests, PCR and PAS positive, allow also the differentiation with malabsorptive disorders such as celiac disease, lymphoma, Crohn's disease or amyloidosis[25]. Never-

theless, histology (PAS positive) and PCR may show discordant results especially because PCR sensitivity is higher than histology. A possible explanation for this discrepancy has been related to an uneven distribution of the bacterium within the gut[26]. Although intestinal tissue PCR has been traditionally ordered as a confirmatory test after PAS staining in classical disease, it can be also performed in non digestive samples such as synovial fluid, cerebrospinal fluid, cardiac tissue or blood[27]. Of note, some authors have proposed a strategy for diagnosing W. D. using PCR in stool or saliva samples. When positive, more invasive samples such as blood, or others according to clinical findings should be preformed[28].

PET-CT scanning is commonly used in the assessment of patients with suspected occult inflammation, primary malignancy, or in the evaluation of metastatic disease. Cavitating mesenteric lymph node syndrome (CMLNS) is a complication of celiac disease (chronic enteropathy characterized by intolerance to gluten ingestion) that is documented but poorly understood. Patients with CMLNS often present with weight loss that is refractory to treatment, fatigue, and diarrhea associated to clinical signs and laboratory findings of hyposplenism. Computed tomography shows multiple cystic mesenteric masses with a central low attenuation area caused by the presence of fluid and/or adipose material in the central cavity of the mesenteric lymph node[29]. Differential diagnosis should be made with cystic lymphangiomas, mesenteric lymphangiomas, tuberculosis, metastatic germ cell tumors, or lymphomas[16,25,30].

Peripheral lymphadenopathy is frequent in W.D. ranging from 40 to 60% of cases[31]. From a clinical point of view, they are indistinguishable from lymphadenopathy due to sarcoidosis, lymphoma or other infectious diseases such as tuberculosis. Mesenteric lymphadenopathy is also common and can evolve to chronic constipation and eventually intestinal obstruction[22]. The mesenteric and retroperitoneal lymphadenopathy can aggravate the lymphatic stasis and associated edema of the intestinal mucosa leading to malabsorption and diarrhea[31].

Diagnostic tools include upper endoscopy with duodenal biopsy that evidences thickening of the intestinal wall, lymphatic occlusion of vessels, lipid deposit in the lamina of the wall, and foamy macrophages with vesicles PAS-positive that can contain bacteria or remnants of bacteria. PCR testing can be positive for *T. whipplei* DNA.

Treatment with parenteral ceftriaxone, 2 gr daily, followed by prolonged antibiotic therapy with Trimethoprim and Sulfomethoxazole for 1 to 2 years guarantees the remission of the disease and prevents relapse[5.] Antibiotic treatment reduces clinical symptoms in 1-4 weeks. Regarding to follow up, gastroscopy with duodenal biopsy within 6 to 12 months from the onset of therapy should be made. When the PAS-positive macrophages research is negative, antibiotic treatment can be stopped.[16,25]

In patients with mesenteric or retroperitoneal lymphadenopathy and unintentional weight loss, a possible underlying W.D. should be investigated.

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