Whipple's disease in a man of North African descent : case report and brief review of the literature

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Abstract

A 62-year-old man of North African descent presented with weight loss in the past year and diarrhea for three weeks. His medical history included erosive rheumatoid arthritis, treated with methotrexate and adalimumab. Histological examination of a duodenal biopsy showed foamy macrophages in the lamina propria, with PAS-positive cytoplasmatic inclusions. These findings are compatible with Whipple's disease, a rare chronic infectious disease caused by Tropheryma whipplei, an opportunistic bacterium. It is typically seen in middle-aged Caucasian men and the immunocompromised host. The classical presentation of Whipple's disease consists of intermittent migratory arthralgia, followed by intestinal symptoms which typically occur six to seven years later. The clinical image can be very variable, and this complicates the diagnostic process. PAS-staining and PCR are the diagnostic cornerstones. In our case, treatment consisted of a prolonged cure of antibiotics: intravenous ceftriaxone for two weeks, followed by an oral maintenance therapy of doxycycline and hydroxychloroquine for at least one year. A therapeutic dilemma arose as continued anti-TNF blockade was necessary to maintain remission of the rheumatoid arthritis. Lifelong follow-up is necessary because relapse is possible. (Acta gastroenterol. belg., **2019**, 82, **83-86**).

Keywords : Whipple's disease, Tropheryma whipplei, Periodic acid-Schiff, clinical features

Introduction

Whipple's disease is a chronic infectious disease that can affect multiple organ systems (1). The etiologic agent is Tropheryma whipplei, a Gram-positive bacterium belonging to the Actinobacteria (1). It was first documented by George Hoyt Whipple in 1907 (2). We report the case of a North African man who presented to the emergency department with diarrhea and weight loss. A subsequent literature review illustrates the variable clinical features and the diagnostic challenge Whipple's disease poses.

Case Report

A 62-year-old man of North-African origin presented to the emergency department with watery diarrhea for three weeks, general weakness and 10 kg weight loss over the period of one year. Clinical examination showed diffuse muscle atrophy, loss of subcutaneous fat and slight malleolar pitting edema. There were no neurological abnormalities or active signs of arthritis.

His medical history included an erosive rheumatoid arthritis of the wrists, ankles and hips diagnosed five years ago, for which he was initially treated with methotrexate. Because of inadequate response, adalimumab was associated a couple of months later. He also received a bilateral hip replacement due to joint erosion seven years ago.

Eighteen months before admission in our gastro-enterology unit, the patient was hospitalised elsewhere with similar symptoms. Blood tests indicated inflam-mation and anemia. CT abdomen showed multiple mesenteric lymph nodes. Stool culture, ileocolonoscopy, bone marrow aspiration and biopsy gave no explanation for the patient's symptoms. Intravenous broad-spectrum antibiotics were administered for eight days, with a favorable biochemical and clinical response.

At presentation, blood tests showed elevated C-reactive protein (CRP) and leukocytosis with left shift. Iron deficiency anemia, extreme hypoalbuminemia, hypocalcemia, hypozincemia and reduced levels of lipids and fat-soluble vitamins suggested a severe malabsorption syndrome (Table 1). Blood cultures, stool cultures and HIV serology were negative.

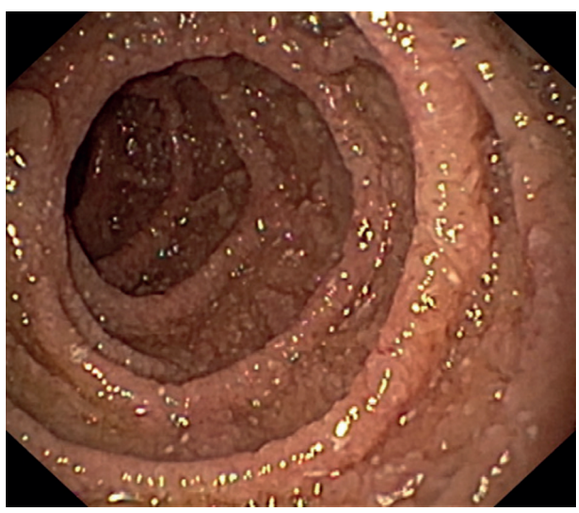

Fig. 1. — Endoscopic view of the duodenum of the patient. Macroscopic congestive mucosa, with clumsy aspect of the villi.

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Table 1. — **Laboratory results at admission (MCV = mean corpuscular volume, Vit. = vitamin, INR = international normalized ratio, art. = arterial, AST = aspartate aminotransferase, ALT = alanine aminotransferase, CRP= C-reactive protein, TSH= thyroid-stimulating hormone, TTGA = tissue transglutaminase antibodies).**

Hemoglobin	6.1 g/dL	(13.5 - 17.5)	Urea	39.5 mg/dL	(15 - 49)
MCV	70.6 fL	(80 - 100)	Creatinine	1.19 mg/dL	(0.64 - 1.25)
Leukocytes	15.7 x10^9/L	(4.5 - 11)	Bilirubin	< 0.15 mg/dL	(< 1.20)
Neutrophils	90.8 %	(50 - 75)	Triglycerides	56 mg/dL	(< 150)
Thrombocytes	303 x10^9/L	(150 - 400)	Cholesterol	54 mg/dL	(< 190)
Iron	11.2 µg/dL	(2 - 3.5)	AST	15 U/L	(0 - 37)
Ferritin	19 µg/L	(41 - 400)	ALT	5 U/L	(0 - 43)
Vit. B12	493 ng/L	(> 200)	Lipase	19 U/L	(13 - 60)
Folic acid	7.72 µg/L	(> 3.88)	Albumin	15.4 g/L	(38 - 52)
INR	1.3	(2 - 3.5)	CRP	39.2 mg/L	(0 - 5)
Na^+	131 mmol/L	(136 - 145)	TSH	3.33 mU/L	(0.27 - 4.2)
K^+	4.68 mmol/L	(3.5 - 5.1)	Vit. A	15 µg/dL	(30 - 80)
Cl^-	105 mmol/L	(98 - 107)	Vit. E	0.4 mg/dL	(0.5 - 1.8)
Ca^{2+}	1.55 mmol/L	(2.2 - 2.55)	25-OH vit. D	< 3.0 µg/L	(> 30)
HCO_3^-	12.8 mmol/L	(23 - 32)	Lactate (art.)	0.8 mmol/L	(0.5 - 2.2)
Zn^{2+}	30 µg/dL	(70 - 120)	TTGA	negative	

CT thorax and abdomen visualised multiple enlarged mesenteric lymph nodes, a diffuse edematous aspect of the small intestine and a bilateral pleural effusion. Duodenoscopy revealed a macroscopic congestive mucosa with clumsy villi (Fig. 1). Histological examination of duodenal biopsies demonstrated a well-differentiated intestinal epithelium with normal villi, lymphangiectasia, fat vacuoles and foamy macrophages in the lamina propria, containing numerous PAS-positive, diastase resistant cytoplasmatic inclusions (Fig. 2). Congo red and S100 stain for amyloidosis and granular cell tumors were negative. These findings strongly suggested the diagnosis of Whipple's disease.

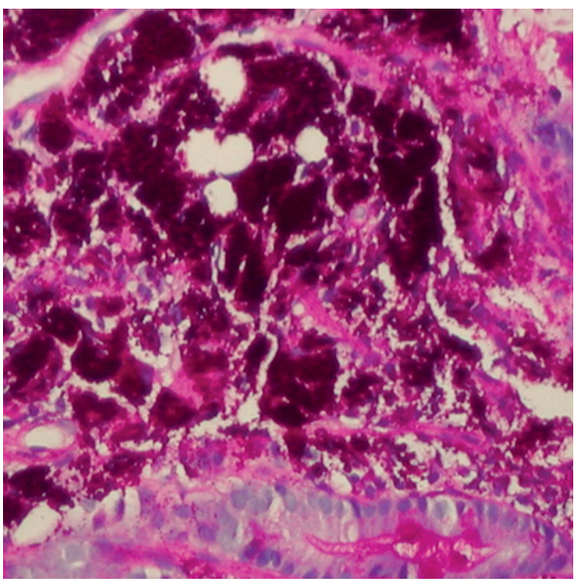

Fig. 2. — PAS diastase stain, duodenal biopsy, 200x enlarged. PAS-positive inclusions inside the cytoplasm of the macrophages.

Antibiotic treatment was initiated, consisting of daily intravenous ceftriaxone for two weeks, followed by doxycycline and hydroxychloroquine for at least one year. Transfusion of packed cells and supplementation of iron, calcium and fat-soluble vitamins (A, D and E) were provided. The patients' symptoms quickly recovered with a favorable biochemical response in the following weeks.

Discussion

Epidemiology

Whipple's disease is a rather rare disease entity, with an estimated incidence of 0.5-1 cases per million people per year (3). Men (86%) of Caucasian origin (97%) are usually affected, with a mean age of 55 years at diagnosis (3,4). To the authors' knowledge, this is one of the first case reports to document Whipple's disease in a man of North African descent (5).

Epidemiological studies in France, using polymerase chain reaction (PCR) on stool samples, have indicated the presence of asymptomatic carriers and a fecal-oral route of transmission (6). Reinfections with new strains of T. whipplei after successful treatment suggest an underlying immunological predisposition in patients with Whipple's disease (6).

Clinical features

Whipple's disease can affect most organ systems, resulting in a myriad of possible presentation forms. The typical clinical manifestations of Whipple's disease are arthralgia, weight loss, diarrhea and abdominal pain (Table 2) (7).

Rheumatologic signs generally precede the intestinal symptoms by a mean period of 6 to 7 years, an interval that is often shortened when patients receive immunosuppressive drugs like inhibitors of tumor necrosis factor a (8). The large joints are predominantly affected, in the order of decreasing frequency: knees, wrists, ankles, hips, elbows, and shoulders (9). Small joints are involved far less often and never in isolation (9). Most patients have intermittent migratory joint

Table 2. — **Overview of the most important clinical features of Whipple's disease and their estimated frequency [7,14]**

Classic clinical presentation	
Weight loss	90%
Arthralgia	85%
Diarrhea	75%
Abdominal pain	60%
Frequent signs	
Hypoalbuminemia	91%
Anemia	85%
Lymphadenopathy	45%
Hyperpigmentation	45%
Fever	45%
Peripheral edema	30%
Occult blood loss	25%
Neurological signs	10-40%
Splenomegaly	15%
Hepatomegaly	10%
Ascites	10%
Ocular signs	8%

symptoms with either non-erosvie oligoarthritis or polyarthritis (9). In exceptional cases joint erosions are observed in patients with prolonged untreated Whipple's disease (9). Although rare, one should weigh in mind the possibility of Whipple's disease when initial treatment for seronegative arthritis proves to be unsuccessful, or when the symptoms ameliorate after antibiotic treatment. In our patient, however, erosive lesions and elevated anti-CCP levels were present at the onset of the joint symptoms, indicative for underlying rheumatoid arthritis rather than Whipple's disease.

The most frequent intestinal manifestations include diarrhea, steatorrhea, abdominal pain, weight loss and malabsorption, possibly leading to a severe wasting syndrome (10). Signs of hypoalbuminemia such as ascites and peripheral edema can develop (10). In the vast majority of cases the intestinal involvement leads to the final diagnosis (10).

T. whipplei is a frequent cause of culture negative endocarditis and accounts for an approximate of 6% of all cases of infectious endocarditis (11). Other organ systems are usually not involved in T. whipplei endocarditis, although a preceding history of arthralgia is possible (11). A biopsy of the affected valve is needed to confirm the diagnosis.

Central nervous system (CNS) involvement is prognostically unfavourable, with a mortality rate of 25-33% after 4 years, and severe sequelae in another 25% (8). Since neurological damage can be irreversible despite successful treatment, a rapid diagnosis is primordial (7). Possible signs are supranuclear ophtalmoplegia, cognitive dysfunction, decreased consciousness, confusion, myoclonia, epileptic seizures, upper moron neuron disease and ataxia. Psychiatric symptoms (e.g. depression and personality disorder) have also been observed (7). Involvement of the hypothalamus can lead to polydipsia, hyperphagia, changes in libido and sleep-wake cycle. (7,11). Uveitis is the most frequent ocular manifestation, usually chronic, bilateral and non-responsive to corticosteroids (3). Oculomasticatory myorhytmia is considered pathognomonic for Whipple's disease (11).

Pulmonary symptoms occur in 30-40% of cases of Whipple's disease. Pleural effusion is the most common pulmonary manifestation, followed by pulmonary nodules and interstitial lung disease (3). Whipple's disease should be considered when granulomatous mediastinal lymphadenopathies are present (3).

Diagnosis

The wide array of nonspecific symptoms and biochemical findings in Whipple's disease generates a large differential diagnosis, including inflammatory bowel disease, coeliac disease, HIV infection, tuberculosis, amyloidosis and other causes of infectious diarrhea (2).

This diagnostic conundrum is reflected by a mean interval of 7.5 years between the first clinical symptoms and diagnosis (10). Biochemical tests, medical imaging, endoscopy and histological examination are helpful in the workup.

Several combined laboratory findings may suggest the diagnosis of Whipple's disease, including elevated CRP, leukocytosis, thrombocytosis and laboratory evidence of malabsorption (11).

A quarter of the patients show endoscopic abnormalities of the small intestine suspect for Whipple's disease (10). Observations include clumsy and dilated villi, ecstatic lymph vessels, edema, signs of duodenitis, whitish deposits, polypoid changes and little aphtous ulcerations (11). In case of clinical suspicion, multiple duodenal biopsies are required to minimize sampling bias (7).

PAS-positive, diastase resistant foamy macrophages visible in the lamina propria of biopsies from the duodenum and jejunum are the histological signature of Whipple's disease (Fig. 2) (4). Other microscopic observations are the presence of fat vacuoles and lymphangiectasia (12). Histological examination of duodenal biopsies with additional PAS-stain is positive in 95% of cases with intestinal signs (10). However, the presence of PAS-positive inclusions is not 100% specific for Whipple's disease, as they are also seen in association with other infectious agents, such as Mycobacterium avium intracellulare, Rhodococcus equi, Bacillus cereus, Histoplasma or fungi (1). Furthermore, in patients without intestinal symptoms, the sensitivity is only 48% (10). PAS-positive macrophages may also be detected in cerebrospinal fluid, lymph nodes, synovial tissue, cardiac valves, and bone marrow (4).

PCR and immunohistochemistry provide an additional diagnostic value in unclear cases. These techniques can detect T. whipplei in samples from a variety of tissue types and body fluids (11). It should be noted that PCR or immunohistochemistry is the preferred technique to evaluate CNS involvement, because PAS-stain is more easily misinterpreted (7). PCR on cerebrospinal fluid is positive in 27% of cases without

neurological signs, which rises to 76% in patients with neurological symptoms (10). A disadvantage of PCR and immunohistochemistry in the diagnosis of Whipple's disease is the limited availability.

Cultivation of T. whipplei cannot be considered as a routine diagnostic approach, because it is limited to specialized laboratories and takes several months to obtain results (7). Serology is not useful for clinical diagnosis in Whipple's disease, since antibodies are detectable in both patients with Whipple's disease and in healthy controls (7).

Treatment

Prospective studies regarding therapy of Whipple's disease are scarce. The rationale of the treatment is to obtain a bactericidal dose for a sufficient time, to eradicate T. whipplei and avoid potential relapse. A German randomized study including 40 patients from Central-Europe observed clinical and histological remission in all patients after treatment (13). Treatment consisted of intravenous ceftriaxone or meropenem for two weeks, followed by oral maintenance therapy with trimethoprim-sulfamethoxazole for a year (13). One relapse was observed after a mean follow-up of 89 months (13).

Genetic analysis of T. whipplei showed a lacking coding sequence for dihydrofolate reductase, the target of trimethoprim (1). Indeed, a French study showed in vitro resistance of T. whipplei for trimethoprim (14). As resistance for sulfamethoxazole has been increasingly reported, use of trimethoprim-sulfamethoxazole is no longer recommended as first choice for this indication (3). A combination of doxycycline and hydroxychloroquine proved to be bactericidal in vitro: hydroxychloroquine, an alkalinizing agent, increases the effectiveness of doxycycline (15). A clinical study confirmed the in vitro findings, as all 14 patients who received maintenance therapy with trimethoprim-sulfamethoxazole developed treatment failure (15). A combination of doxycycline and hydroxychloroquine was more effective: none of the 13 patients underwent treatment failure after one year of therapy (15). Subsequently, 22 patients received lifetime prophylaxis with doxycycline: one relapse (possibly due to non-compliance) was observed after a mean follow-up of 20 months (15). Although unclear, the distinct discrepancies between these studies may be due to geographical heterogeneity of the antibiotic susceptibility of T. whipplei (14).

The current treatment recommendation comprises two phases. Intravenous ceftriaxone (2 g, once daily) or meropenem (1 g, three times a day) is administered for two weeks (13), followed by an oral combination therapy of hydroxychloroquine (200 mg, three times a day) and doxycycline (100 mg, two times a day), for at least one year (15). Lagier et al. prefer lifetime prophylaxis with doxycycline after successful therapy, based on the presumed immunological predisposition of the host for Whipple's disease (15). In cases of CNS involvement, additional therapy with oral sulfadiazine (500 mg, 4-8 tablets a day) or oral trimethoprim-sulfamethoxazole (800 mg, daily) is recommended (7). Inhibitors of tumor necrosis factor a and other immunosuppressants should be avoided if possible, since several publications have reported a positive association of immunosuppressive therapy and the incidence, exacerbation and relapse of Whipple's disease (8). Relapse can lead to irreversible and fatal complications, especially in patients with CNS involvement. Furthermore, previous immunosuppressive therapy is a risk factor for developing immune reconstitution inflammatory syndrome during initial treatment (8). In our case, adalimumab was continued by the treating rheumatologist, given the initial fulminant and erosive course of the rheumatoid arthritis. Prolonged use of antibiotic prophylaxis, as described above, could be a valuable option in immunocompromised patients (15). Lifelong follow-up is necessary because relapse is possible. There are reports of relapse 20 years after successful therapy (6).

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