

CASE REPORT

Fatal Whipple's disease with severe mental manifestations on relapse – case report and brief advances update

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Abstract

We present the case of a 51-year-old male admitted for asthenia, fatigability, nausea, inappetence, weight loss, watery diarrhea, lower limb paresthesia and diagnosed after further investigations with Whipple's disease (WD). The evolution was favorable under antibiotic therapy but after a period of time the patient was no longer compliant to the treatment and psychotic manifestations, general status alteration and finally the decease occurred. WD is a condition caused by *Tropheryma whipplei* (TW) bacterium in people with altered macrophage degrading capacity and it is lethal without early treatment.

Keywords: Whipple's disease, *Tropheryma whipplei*, malabsorption, central nervous system relapse, psychosis, immunopathology.

Introduction

Whipple's disease (WD) or intestinal lipodystrophy is a multiorgan infectious disease caused by *Tropheryma whipplei* (TW) Gram-positive bacterium, affecting middle-age men [1]. Clinical presentation of patients is very polymorphic, so the spectrum of the disease encompasses general (fatigability, malaise), gastrointestinal (diarrhea, abdominal pain, steatorrhea, weight loss, hepatitis, splenomegaly), skeletal (arthritis, arthralgia), cardiac (myocarditis, pericarditis, cardiac fibrosis, valvular disease, heart failure), respiratory (pleural effusion, adenopathies), ocular (uveitis, chorioretinitis, ophthalmoplegia), central nervous system (CNS) (dementia, hear impairment, reflex changes, palsy, meningitis) manifestations as well as skin hyperpigmentation, purpura and immune system alterations [2].

The bacterium is considered commensal, so it is virtually present in many persons' digestive tract but it triggers the disease only in individuals with subsequent immune changes. Many authors regard the condition as being associated with human leukocyte antigen (HLA)-B27, thus the link between WD and ankylosing spondylitis, while other recent studies infirm this link [3].

The diagnosis is usually made by demonstrating Periodic Acid–Schiff (PAS)+ macrophages with bacillus inside in small bowel lamina propria or using genetic techniques like polymerase chain reaction (PCR) to detect bacterial deoxyribonucleic acid (DNA) [4].

Without treatment, this condition is fatal within a year but with antibiotic therapy [Streptomycin, Trimethoprim–Sulfamethoxazole (TMP–SMX), cephalosporins] the cure is almost a rule, albeit there may be relapses of the disease with the cessation of medication. Complications need sometimes-specific approach [5].

Case presentation

A 59-year-old male addressed to our Service for investigation and treatment, accusing asthenia, fatigability, morning nausea with a fixed schedule, loss of appetite, important weight loss of 30 kg in the last four months, watery diarrhea, paresthesia of lower limbs. Personal pathological and heredo-collateral history was irrelevant. The patient smokes about one pack of medium tar and nicotine cigarettes per day and drinks 1–2 cup of coffee daily.

Current pathology debuted six months before addressing to our Service with the above-mentioned complaints. Meanwhile, the patient was admitted in another medical Service, where he underwent numerous paraclinical explorations, being diagnosed with hepatic hemangioma. It was also raised the suspicion of vasoactive intestinal peptide (VIP)-oma, later infirmed by the normal serotonin and 5-hydroxytryptamine levels.

Examining the patient, we found a poor nutrition state [body mass index (BMI) 17.04 kg/sqm], generalized

herpes-like eruption in remission, grade II diastolic murmur on left ventricle zone irradiating to axilla, augmented second cardiac sound on pulmonary zone, liver of normal consistence at 2 cm under right costal border, bilateral diminished osteotendinous and mucocutaneous reflexes.

From biological point of view, the patient has normochromic normocytic anemia, accelerated erythrocyte sedimentation rate (ESR), leukopenia with minimal eosinophilia and basophilia, hepatocytolysis, cholestasis without pigmentary retention (normal bilirubin), hypo-proteinemia with hypoalbuminemia and raised gamma globulins, hypertriglyceridemia, hypocalcemia, hypomagnesemia and hyperuricemia. All biological determined values are summarized in Table 1.

Table 1 – Laboratory tests: main abnormal results

Test [units]	Normal range	Current value
Hb [g/dL]	14–16	12.8
Ht [%]	37–52	35
MEV [fL]	80–97	106
MCHC [pg]	31–36	37.9
SI [mg/dL]	49–165	145
ESR [1–2 h]	5–10	26–44
RBC [elements/mL]	$4-5 \times 10^6$	3.37×10^6
WBC [elements/mL]	5000–8000	2990
Eosinophils [elements/mL]	0–3 (1–5%)	152 (5.09%)
Basophils [elements/mL]	0–1 (0–1%)	53 (1.77%)
AST [IU/L]	0–42	83
ALT [IU/L]	0–42	64
AP [IU/L]	60–306	379
GGT [IU/L]	7–50	66
TSP [g/dL]	6–8	5.7
SA [g/dL]	3.8–5.5	3.3
SGG [g/dL]	0.6–1	1.2

Test [units]	Normal range	Current value
TG [mg/dL]	45–160	173
Ca [mEq/L]	4.5–5.5	4.12
Mg [mEq/L]	1.7–2.4	1.56
SUA [mg/dL]	2.4–7	8.1

ALT: Alanine transaminase; AP: Alkaline phosphatase; AST: Aspartate transaminase; ESR: Erythrocyte sedimentation rate; GGT: Gamma-glutamyl transferase; Hb: Hemoglobin; Ht: Hematocrit; MCHC: Mean corpuscular hemoglobin concentration; MEV: Mean erythrocyte volume; RBC: Red blood cells; SA: Serum albumin; SGG: Serum gamma globulins; SI: Serum iron; SUA: Serum uric acid; TG: Triglycerides; TSP: Total serum protein; WBC: White blood cells.

Electrocardiogram (EKG) showed microvoltated complexes and first-degree atrioventricular block (Figure 1).

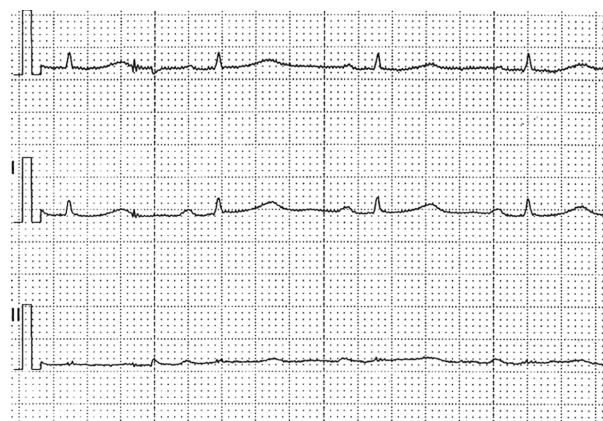


Figure 1 – EKG: microvoltated complexes and first-degree atrioventricular block. EKG: Electrocardiogram.

Upper digestive endoscopy depicted a pale yellow shaggy duodenal mucosa, with atrophic epithelium, diffuse enanthema and erythematous eroded patches from which we have taken biopsies (Figure 2).

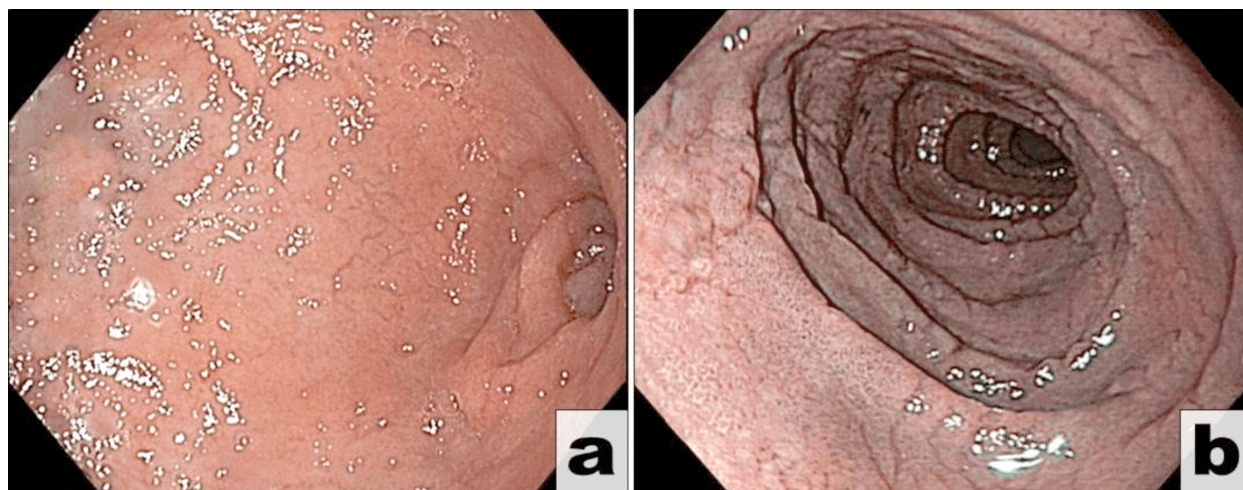


Figure 2 – Upper digestive endoscopy of duodenum: (a) Atrophic mucosa and enanthema; (b) Same aspects with enhanced-contrast narrow-band imaging (NBI).

On this occasion, enteroclysis catheter has been placed. Colonoscopy revealed no other changes except internal hemorrhoids of anus and biopsies of sigmoid mucosa were taken. Abdominal ultrasonography showed liver steatosis with left lobe hypertrophy, hemangiomas of VIth and VIIIth liver segments and a few atheromatous plaques of the aorta. Enteroclysis revealed moderate dilatation of enteral loops with flocculation of barium suspension at the ileal level (Figure 3).

Abdominal computed tomography (CT) confirmed the presence of liver hemangiomas, one of 25 mm in the VIth segment and the other, of 15 mm in the VIIth segment.

Additionally, a 14 mm cortical renal cyst and two interaortocaval lymph nodes of 7.5 mm and 14 mm respectively, along with numerous less than 1 mm left aortic and lumbar lymph nodes were revealed (Figure 4).

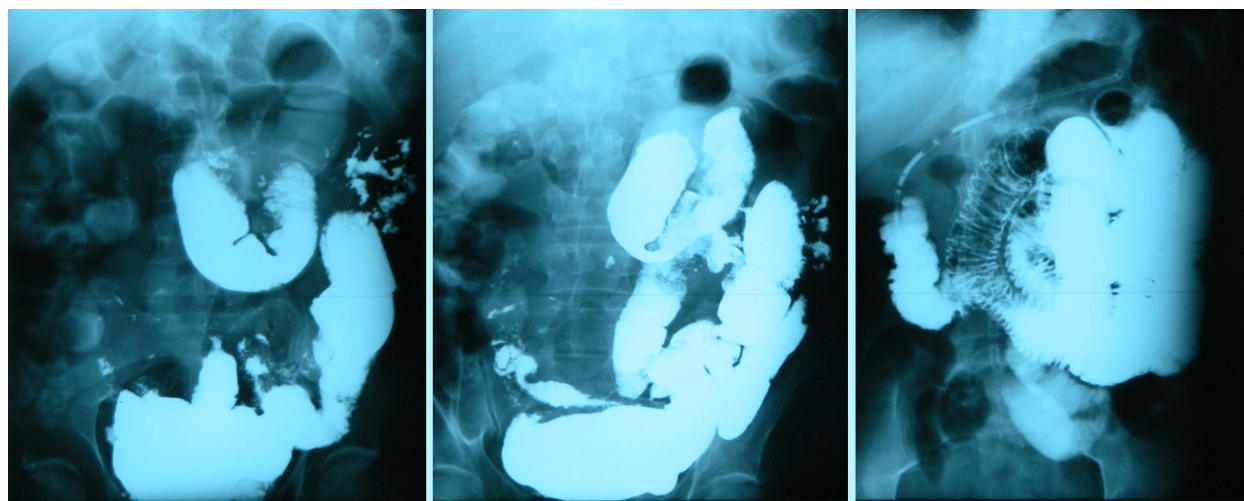


Figure 3 – Enteroclysis: dilatation of enteric loops and barium flocculation at the level of ileum.

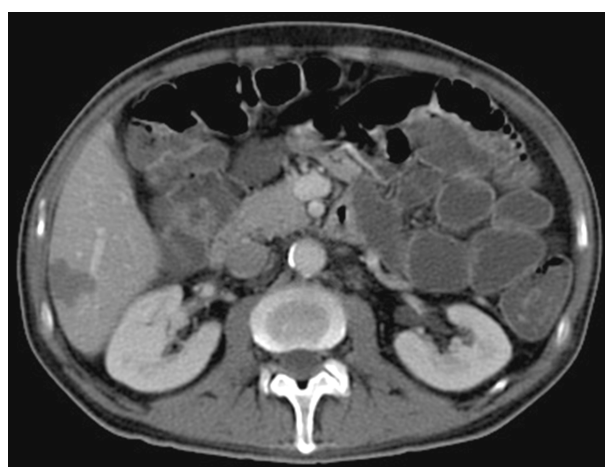


Figure 4 – Abdominal CT: liver hemangiomas, inter-aortocaval lymph nodes and aortic atheroma. CT: Computed tomography.

Duodenal biopsies from the second portion of duodenum demonstrated focal lymphangiectasias or fat vacuoles and distended macrophages diffusely scattered in mucosal lamina propria containing PAS+ (diastase-resistant) granules (Figure 5, a–c).

Sigmoid colon biopsies show marked edema of lamina propria with hypercellularity dominated also by “foamy”, PAS+ macrophages granules (Figure 5, d and e). The

phagic profile was confirmed by specific immunomarking of macrophages with D2, cluster of differentiation 56 (CD56) and leukocyte common antigen (LCA) (CD45) antibodies in both intestinal mucosa and pericolic fat (Figure 6, a–d). Within the inflammatory cellular population, the increased number of PAS+ macrophages was concurrent with decreased number of lymphocytes and plasma cells.

All these morphological features strongly suggested the presence of WD.

Consequently, we established the following diagnosis: WD, liver hemangiomas of VIth and VIIIth segments, non-alcoholic fatty liver disease, right kidney cyst, hemorrhoidal disease, abdominal aortic atheromatosis, hypomagnesemia, hypocalcemia, hypertriglyceridemia, hyperuricemia.

According to these data, the patient has been administered B group vitamins, antibiotherapy with Ceftriaxone (Cefort®) 2 g/day, one week, followed by TMP–SMX 2× 800/160 mg/day *à la longue*, together with hydroelectrolytic rebalancing. We also treated the other conditions diagnosed (calcium and magnesium supplements, fibrates, uricosuric agents).

After treatment, macrophages decreased in lamina propria but remain present elsewhere (Figure 7). Cytoplasmic inclusions became tissue ‘paper-like’ with PAS staining, resembling Gaucher cells.

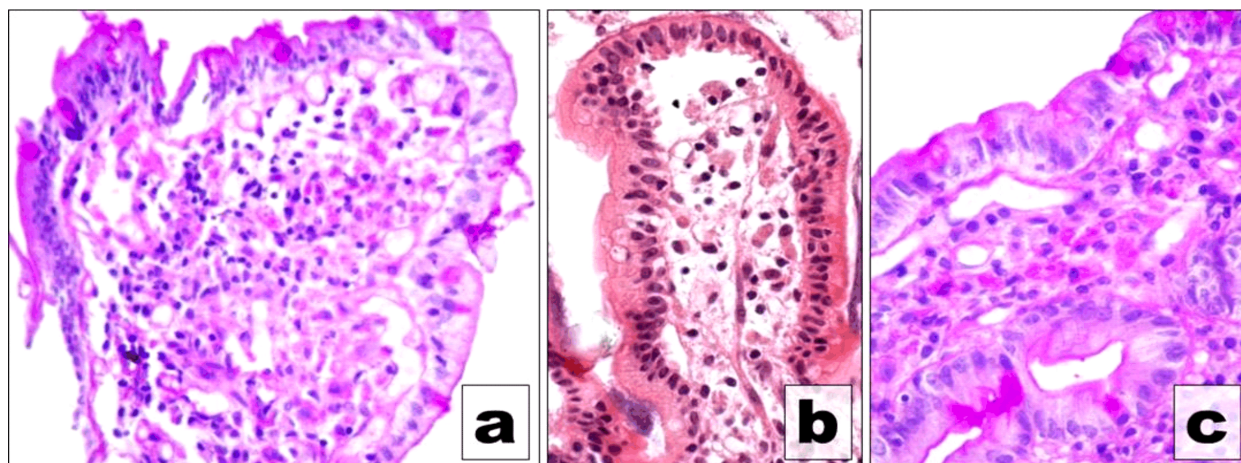


Figure 5 – Duodenal biopsy. HE staining: (a) ×40; (b) ×100. PAS staining: (c) ×200. HE: Hematoxylin–Eosin; PAS: Periodic Acid–Schiff.

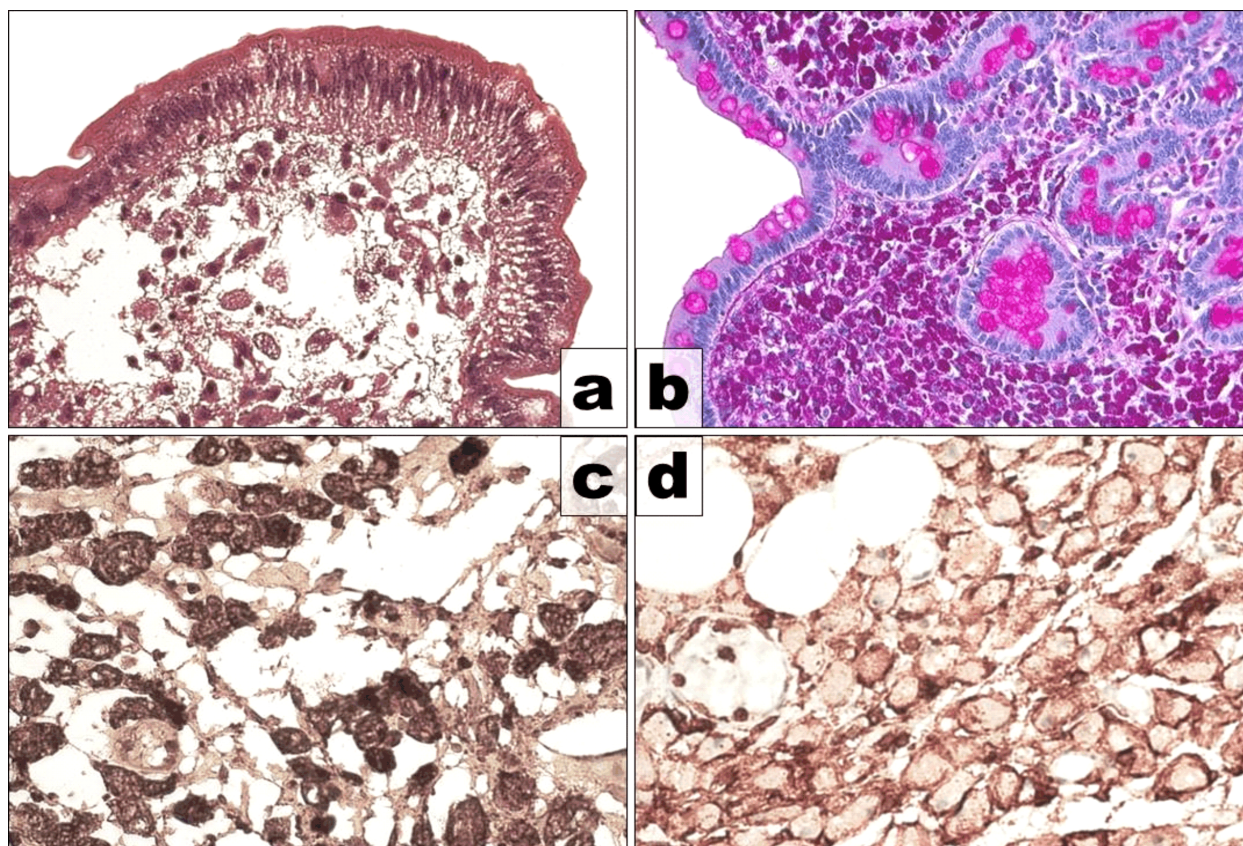


Figure 6 – Colon biopsy: (a) Anti-D2 antibody immunostaining, $\times 200$; (b) PAS staining, $\times 200$. **Pericolic fat biopsy:** (c) Anti-CD56 antibody immunostaining, $\times 400$; (d) Anti-LCA antibody immunostaining, $\times 400$. PAS: Periodic Acid–Schiff; CD56: Cluster of differentiation 56; LCA: Leukocyte common antigen.

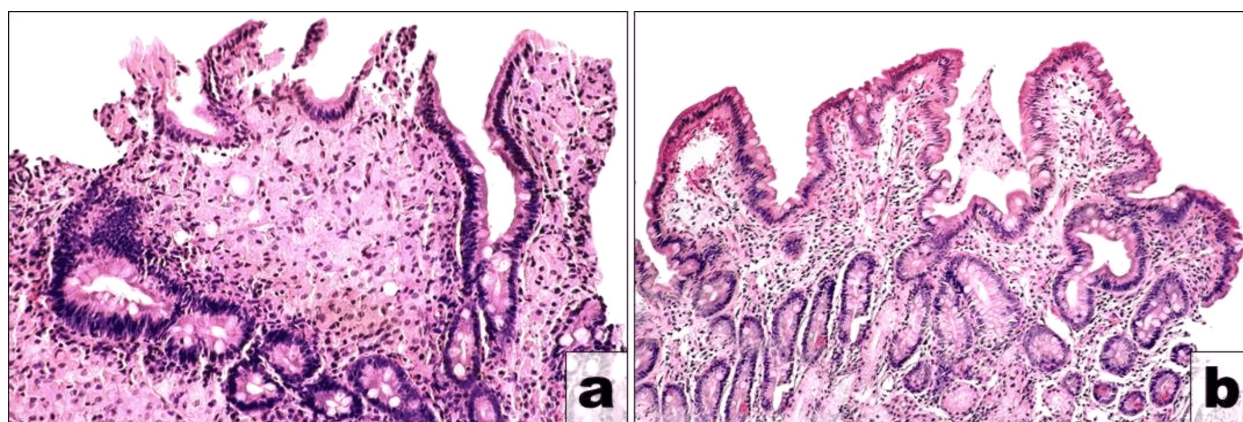


Figure 7 – Duodenal biopsy: (a) Before treatment; (b) After treatment. HE staining: (a and b) $\times 40$.

Discussions

We presented the case of a fatal WD in a 59-year-old Caucasian male, who presented weight loss, fever, arthropathy and diarrhea, at the admission with favorable evolution, followed by CNS relapse, progressive deterioration and death. From the beginning, we must advert that there were some exploratory and therapeutic shortcomings. Investigations like electron microscopy, PCR, HLA-B27, IgG titer were not performed, some of them not being available in our Service. On the other hand, we concluded the diagnosis with help of intestinal biopsy, which showed the classical aspect, and we were aware of the fact that PCR proved to be negative in some cases [6] and IgG – TW has the same level in people with WD and in control subjects, as the bacterium is considered commensal.

Data regarding bacteria reservoir are not conclusive although histological ulcerative colitis in dogs is induced by TW and there is no evidence of animal to human or human-to-human transmission [7].

Some authors consider that gastroscope disinfection is not sufficient to prevent the transmission as TW can be found in dental plaque and gingival pockets too. In spite of the fact that TW is found ubiquitary and there could be human-to-human transmission, the disease is very rare, with an incidence of 12 new cases per year [5, 8]. In 2009, for instance, there were four new cases in a population of seven million individuals [9].

Immunological changes and responses are credited to determine some individuals to develop the disease, including downregulation of cytokine genes, reduced number of CD4 lymphocytes with lowering of CD4/CD8

ratio, lessening of mitogen response and antigen-degrading capacity, and decline of CD11b, complement receptor (CR) 3, interferon-gamma (IFN- γ) and interleukin-12 (IL-12) production by monocyte/macrophage system, which is also related with relapses [10, 11].

There are PAS– and PCR– relapses that can be suggested by magnetic resonance imaging (MRI) and CT changes.

Usually, relapses comprise CNS manifestations with less severe gastrointestinal complaints with poor prognosis, issues are also encountered in our case [12]. A particularity of our patient was the presence of PAS+ macrophages in sigma biopsies, having in mind that stomach, colon or liver involvement is rare [13].

Rectum may contain PAS+ macrophages in normal individuals, so rectal biopsies have no diagnostic value. PAS+ macrophages may be present in other disease but clinical presentation is different and macrophages in WD could persist during the recovery period [14].

The second important issue is the therapeutic approach, which is not well defined and still empirical due to the lack of data and clinical trials and related to the scarcity of cases [1]. We started therapy with drugs accepted for WD but relapse still intervened. For these cases, IFN- γ (Actimune®) 150 mcg three times a week is the accepted choice but the product was not available in our country. We found in literature little data regarding possible drug resistance of TW, phenomenon explained by culture resistance and thus the difficulty of achieving an antibiogram [15] but we also have to take into account a demonstrated *in vitro* resistance to TMP–SMX [16].

The majority of authors suggest that the treatment of the condition should be as we proceeded in our case, while other investigators consider that TMP–SMX is not the best choice [13] and that Doxycycline and Hydroxychloroquine should be administrated instead [8, 17]. More recent data reconfirm TMP–SMX as the gold standard, since under Doxycycline and Hydroxychloroquine scheme the relapses are frequent [18, 19].

Concerning cardiac involvement, we studied recent literature and found no case of atrioventricular block in WD (www.uptodate.com). We suspect that this change is related to TW infection, considering that the EKG from a year before the onset of the disease showed no alteration.

✉ Conclusions

WD is a rare disorder caused by TW in susceptible individuals. The evolution is lethal without treatment and normally, under antibiotic therapy, complete clinical and morphological resolution is achieved. In some cases, there may be relapses with less gastrointestinal manifestation and more severe CNS involvement. In the circumstances of an unexplainable malabsorption syndrome, a possible

WD should be considered in spite of the scarcity of cases. The landmark of the disease is the presence of PAS+ macrophages in the lamina propria of duodenal mucosa.

Conflict of interests

The authors declare that they have no conflict of interests.

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