Multifocal secondary amyloidosis and Whipple disease: a case report

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ABSTRACT

Background: Whipple disease (WD) is an exceedingly rare disease. Despite its rarity, there has been a longstanding allure with this disease. The classic form manifests with arthralgia, weight loss, abdominal pain, and diarrhea. However, the infection may involve other organs causing a great diversity of symptoms.

Case Presentation: We report a case of a patient presenting to the emergency room with weight loss, abdominal pain and diarrhea. Duodenal biopsies revealed periodic acid Schiff-positive macrophages and *Tropheryma whipplei* was detected on a cervical lymph node. Diagnosis of WD was established. The patient also had multifocal secondary amyloidosis. We started the patient on a standardized antibiotic regimen for 1 year. Clinical improvement was seen early during the treatment.

Conclusion: This case is an example of the protean nature of WD. To the authors' knowledge, this is the first case report on WD with multifocal secondary amyloidosis affecting several digestive organs.

Keywords: Whipple disease, *Tropheryma whipplei*, PAS-positive macrophages, secondary amyloidosis, case report.

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Background

Whipple disease (WD) is extremely uncommon with an incidence of less than 1 per million and fewer than 1,000 cases reported worldwide [1]. The disease is caused by *Tropheryma whipplei*, a Gram-positive bacillus ubiquitous in the environment. It is not known how people become infected with the bacteria although transmission is probably orofecal or oro-oral [2]. WD appears to predominantly affect white males of European ancestry, aged 40-60 years, suggesting an underlying genetic predisposition to the disease [1,3]. Indeed, WD has been recently associated with human leukocyte antigen B27 haplotype [4].

The disease is a multisystemic process with four cardinal clinical manifestations: arthralgias, weight loss, diarrhea, and abdominal pain [5].

Overall, intestinal symptoms are the most prevalent among WD patients, followed by rheumatological symptoms [2]. Nevertheless, other organs are known to be potential targets for *T. whipplei*. Cardiac involvement is reported in up to 55% of cases, with pericarditis and blood culture-negative endocarditis being more frequent [1]. Skin hyperpigmentation is relatively common, being reported in up to 45% of WD cases [4]. Lymphadenopathy, predominantly of mesenteric and mediastinal nodes, has been reported up to 60% of cases making WD a differential diagnosis for lymphoproliferative diseases [6]. Pulmonary involvement occurs in an estimated 30%-40% of patients with WD, mainly as pleural effusion, chronic cough, interstitial-lung disease-like presentation, and pulmonary hypertension [6]. Both ocular and neurological involvement are seen in less than 20% [7]. Kidney involvement was reported only on a few occasions and typically occurs late in the course of the disease [8-11].

The diagnosis of WD is made with a biopsy of the intestine and the identification of *T. whipplei* [12]. Current diagnostic criteria require positive results for periodic acid Schiff (PAS) positive foamy macrophages in the small bowel biopsy. If negative, diagnosis can also be reached by showing positive results in two of the following: i. PAS staining showing foamy macrophages in a biopsy specimen of involved tissues; ii. PCR Detection of *T. whipplei* or detection of the specific 16S rRNA of the bacterium; and iii. Immunohistochemical staining with *T. whipplei* antibodies [12].

Without treatment, WD is ultimately fatal [1]. The basis of treatment is antibiotic therapy. Because of the possibility of central nervous system (CNS) involvement, the use of antibiotics that penetrate the blood-brain barrier

is desirable [12]. One recommended regimen for the initial phase is ceftriaxone 2 g daily or penicillin G 2 million units every 4 hours. The usual duration for the initial phase is 2 weeks, followed by the maintenance phase with trimethoprim 160 mg-sulfamethoxazole 800 mg twice daily for 12 months. Long courses are usually necessary to prevent relapses that can occur even years after treatment, with an estimated incidence of up to 30% of the cases [13].

Secondary amyloidosis is a late complication of chronic inflammatory disorders associated with a sustained acute-phase response [14]. Deposits of amyloid fibrils can lead to the disruption of structure and function of tissues and organs [14]. In WD, secondary amyloidosis has only been sporadically described [8-11,15-17]. This is, to our knowledge, the first report of secondary amyloidosis found in several digestive organs in a patient diagnosed with WD.

Case Presentation

A 56-year-old man with a 2 years-evolution of normocytic/normochromic anemia, under no daily medication, presented to the emergency room with complaints of diarrhea of multiple watery stools per day, abdominal cramping, skin darkening and a 14 kg unintentional weight loss (13% of patient total weight) within the previous month. There was no history of fever or night sweating. Physical examination revealed muco-cutaneous pallor and dehydration, diminished breath sounds with crackles, and symmetric lower limb edema. Neurological examination did not show signs suggestive of CNS affection. Blood tests on admission revealed a normocytic normochromic anemia (hemoglobin 11.4 g/dl, elevated reactive C protein (8.55 mg/dl), acute renal injury (creatinine 1.23 mg/dl), hyponatremia (129 mg/dl) and hypoalbuminemia (2.1 mg/dl). Biochemical analysis of urine showed a proteinuria of 300 mg/dl. Human immune deficiency virus, hepatitis B/C virus, cytomegalovirus, and Epstein-Barr virus testing were negative. Autoimmune markers were also negative. Microbiological sampling of the stool and blood demonstrated no organisms on smear or culture. Cutaneous biopsy shown irregular hyperplasia and melanic pigmentation of basal cells without inflammatory infiltrates. Abdominal computed tomography (CT) scan revealed multiple enlarged retroperitoneal lymph nodes and mild splenomegaly (Figure 1). At this stage, lymphoproliferative disease could not be ruled out and a bone marrow biopsy was performed showing increased marrow iron suggestive of chronic disease, with no further clinically relevant findings. Biopsy of an inguinal lymph node was inconclusive. Thoracic CT scan revealed axillary and mediastinal lymphadenopathy and a small volume pleural effusion.

Upper endoscopy and colonoscopy were performed with standard biopsies. The histological findings were characteristic of WD. Microscopically, the duodenal

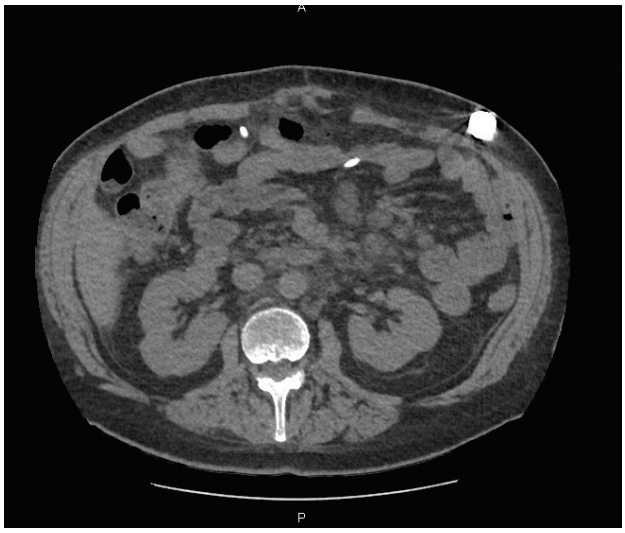

Figure 1. *Abdominal-pelvic CT-scan in axial sections revealing multiple mesenteric and retroperitoneal adenopathies.*

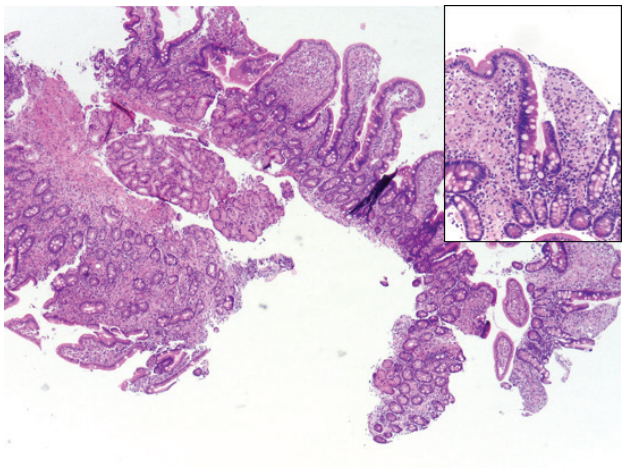

Figure 2. *Duodenal biopsy featuring distortion of villous architecture (hematoxylin-eosin, original magnification ×40). Inset: distension of villi due to macrophage infiltrates in the lamina propria (hematoxylin-eosin, original magnification ×100).*

biopsy featured a prominent infiltrate of plumped macrophages with granular cytoplasm which filled the lamina propria, distorting the overlying villous architecture (Figure 2). PAS stain highlighted these histiocytes packed with coarse granules in their cytoplasm (Figure 3). Histiocytes of identical appearance and epithelioid non-caseating microgranulomas were also identified in an involved regional lymph node (Figure 4). Ziehl-Neelsen stains were negative, excluding *Mycobacterium avium-intracellulare*. At this stage, a second attempt of lymph node biopsy was performed at a cervical node and *T. whipplei* was detected by PCR.

After diagnosis was established and due to previously known cardiovascular involvement in WD, a transthoracic echocardiogram was performed revealing a blood-culture negative endocarditis, with no stigmata of infective endocarditis. Also, due to the initial finding of sub-nephrotic

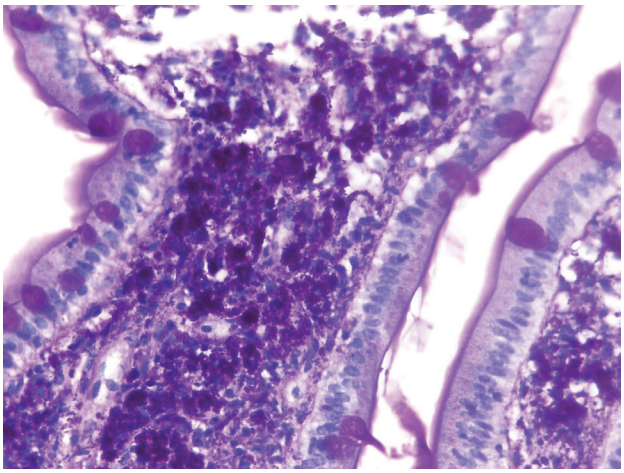

Figure 3. *Expansion of the lamina propria by PAS-positive macrophages (original magnification ×400).*

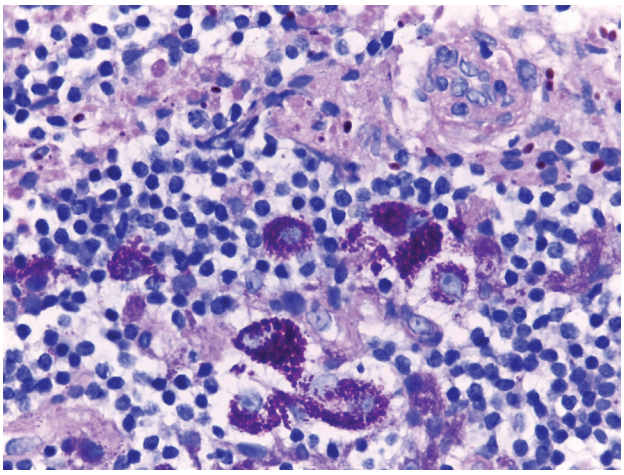

Figure 4. *Mesenteric lymph node with PAS-positive histiocytes (original magnification ×400).*

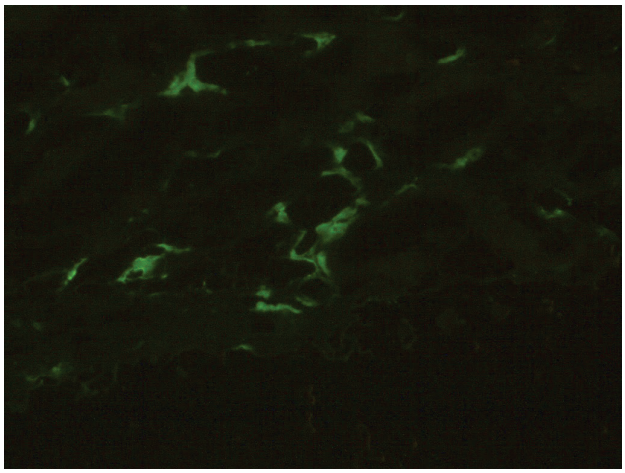

Figure 5. *Kidney biopsy with serum amyloid A deposits (Immunofluorescence, original magnification ×400).*

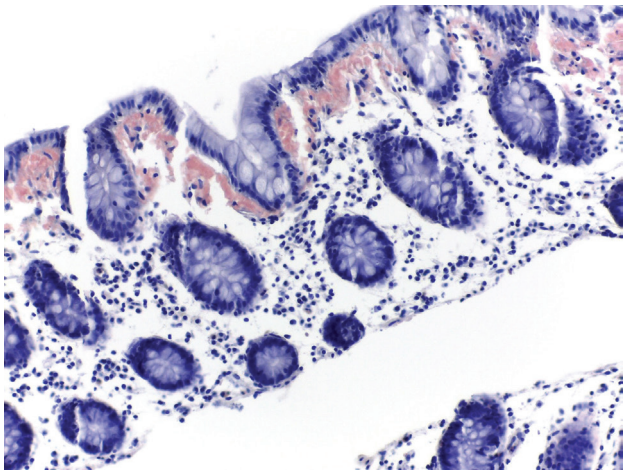

Figure 6. *Superficial subepithelial "band-like" amyloid deposits in large bowel biopsy (Congo red stain, original magnification ×100).*

proteinuria, a work-up to further investigate patient renal function was established. Both 24-hours proteinuria and protein/creatinine ratio were 20-fold higher than the maximum of the normal range, reaching a proteinuria peak value of 9 g/24 hours during hospitalization. An urgent kidney biopsy was performed revealing glomerular and arteriolar serum amyloid A deposits compatible with secondary amyloidosis (Figure 5). Similar findings were observed in colonic (Figure 6) and gastric mucosa biopsies.

Before starting the patient on antibiotic therapy, a lumbar puncture was performed with cerebrospinal fluid showing inflammatory cell responses with no PAS-positive macrophages. We started the patient on a standardized antibiotic regimen of ceftriaxone 2 g a day for the first 2 weeks and then trimethoprim/sulfamethoxazole (TMP-SMX) 960 mg twice a day for 1 year. Clinical improvement was seen on the 7th day of treatment, with proteinuria decreasing to subnephrotic levels. Within 1 month of the planned year-long treatment regimen, complete resolution of abdominal complaints was obtained.

Discussion

WD is a chronic systemic infection caused by *T. whipplei*, resulting in a variable clinical presentation, including intestinal and extra-intestinal symptoms [1].

It is known that *T. whipplei* is present in the environment and has also been found in healthy carriers. A higher incidence of the infection among breeders and sewage workers has been reported, suggesting an occupational or environmental method of transmission [5]. In the case we report, the patient had no contact with livestock, residual water or sewers.

Diagnosis of WD is suspected most of the time on the basis of the appearance of gastrointestinal symptoms with rheumatologic manifestations usually preceding intestinal symptoms [2]. In hindsight, our patient had a presentation consistent with WD: European male, fifth decade of life, with diarrhea, weight loss, and skin pigmentation. We were able to diagnose WD both from duodenal biopsies with PAS-positive macrophages and *T. whipplei* detected on a cervical lymph node.

Besides WD classic manifestations, cardiac disease may also occur. Patients with WD endocarditis usually have no previous heart disease and are most often apyretic, with negative blood cultures [1]. This was the case of our patient who developed endocarditis without symptoms or signs suggestive of cardiac disease.

Even less common WD presentations include pleuropulmonary, renal and endocrinological manifestations [6-13]. In the case we report, thoracic CT scan revealed a small volume pleural effusion and multiple axillary and mediastinal lymphadenopathies. Proteinuria was identified at an early-stage and immunofluorescence of kidney biopsy samples revealing subepithelial type A amyloid deposits. Similar deposits were found in biopsy samples collected from gastric and colonic mucosa.

Aside from kidney [8,9,10,11,17], secondary amyloidosis in other locations in WD patients has only occasionally been described during life [14] and at autopsy [16,17]. Sander described the first link between WD and amyloidosis in a WD patient [17]. Farr et al. [15] reported a case of WD patient with amyloid fibers found in rectal and knee synovial. Schmid et al. [16] identified amyloid deposits in the heart of a WD patient that died suddenly of a heart attack. To the authors' knowledge this is the first report of secondary amyloidosis affecting several digestive organs in the context of WD.

It is possible that the chronic inflammatory stimulus of WD works as a trigger for the development of secondary amyloidosis. In fact, Sander [17] proposed that the elaboration of amyloid might be induced by antigenic stimulation by the microorganisms found locally. The prognosis of secondary amyloidosis is poor with a median survival after diagnosis of 133 months [14]. However, successful treatment of the underlying inflammatory disease may be beneficial.

Further studies are needed in order to conclude a causal association between *T. whipplei* presence and amyloid deposits.

Conclusion

WD is a rare chronic multisystemic bacterial disease that is potentially fatal, but responds dramatically to antibiotic treatment, thus early diagnosis is mandatory. Diagnosis of WD relies on clinical suspicion and an effective cooperation between several medical specialties.

What is new?

WD is an extremely rare disease and, to our knowledge, this is the first case report on WD with multifocal secondary amyloidosis affecting several digestive organs.

List of Abbreviations

CNS	Central nervous system
CT	Computed tomography
PAS	Periodic acid Schiff
PCR	Polymerase chain reaction
TMP-SMX	Trimethoprim/sulfamethoxazole
WD	Whipple disease

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this case report.

Funding

None.

Consent for publication

Written informed consent was taken from the patient.

Ethical approval

Ethical approval is not required at our institution for publishing an anonymous case report.

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Summary of the case

1	**Patient (gender, age)**	Male, 56 year old
2	**Final diagnosis**	WD with multifocal secondary amyloidosis
3	**Symptoms**	Diarrhea, abdominal cramping, skin darkening, weight loss
4	**Medications**	Ceftriaxone 2 g a day for the first 2 weeks + TMP-SMX 960 mg twice a day for 1 year
5	**Clinical procedure**	Skin, lymph nodes, thyroid, bone marrow and kidney biopsies
6	**Specialty**	Internal Medicine