Whipple's disease presenting with false-positive HIV serology: a diagnostic pitfall

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European Journal of Medical Case Reports
Volume XX(XX):XX–XX
DOI: XXXX

ABSTRACT

Background: Whipple's disease (WD) is a rare systemic infection caused by *Tropheryma whipplei*. Its protean manifestations may mimic chronic infectious or inflammatory conditions, including HIV infection, leading to diagnostic pitfalls.

Case presentation: We report the case of a 51-year-old man presenting with a one-month history of severe weight loss, chronic diarrhea, and asthenia. Initial evaluation revealed a weakly reactive fourth-generation HIV screening assay, raising concern for HIV infection; however, subsequent HIV-1/2 nucleic acid testing was negative. Cross-sectional imaging showed diffuse small-bowel wall thickening, mesenteric lymphadenopathy, ascites, bilateral pleural effusions, and a pericardial effusion. Upper gastrointestinal endoscopy revealed friable, ulcerated duodenal mucosa with villous blunting. Duodenal biopsies demonstrated villous atrophy with periodic acid–Schiff-positive foamy macrophages, and a positive polymerase chain reaction assay for *Tropheryma whipplei* supported the diagnosis of WD. The patient received intravenous ceftriaxone followed by oral doxycycline and hydroxychloroquine, with rapid clinical improvement and no clinical evidence of relapse at six months of follow-up.

Conclusion: This case highlights WD as an important differential diagnosis in patients with unexplained multisystemic symptoms and discordant HIV test results. Weakly reactive HIV screening assays should be interpreted cautiously and confirmed before establishing a diagnosis of HIV infection. Early duodenal biopsy and timely initiation of CNS-penetrating antibiotic therapy are essential to improve outcomes and reduce relapse risk.

Keywords: Whipple disease, *Tropheryma whipplei*, false-positive reactions, HIV serodiagnosis, malabsorption syndromes, diagnostic errors, case reports.

Type of Article: CASE SERIES **Specialty:** Medicine

Received: 07 June 2026
Revised (1): XX XX XX
Accepted: 31 August 2026

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Background

Whipple's disease (WD) is a rare, chronic multisystemic infection caused by the Gram-positive actinomycete *Tropheryma whipplei*. Only a limited number of cases have been reported worldwide, predominantly among middle-aged Caucasian men from Europe and North America [1,2]. The disease manifests heterogeneously, most commonly with arthralgia, diarrhea, abdominal pain, and weight loss, but may also involve neurological or cardiac systems [2,3].

Diagnosis relies on the identification of periodic acid–Schiff (PAS)-positive foamy macrophages in duodenal biopsies, with polymerase chain reaction (PCR) serving as a useful adjunct, particularly in extra-intestinal disease [3–5]. Untreated WD is potentially fatal, but timely antibiotic therapy combining parenteral induction and prolonged oral regimens with central nervous system (CNS) penetration can ensure remission and prevent relapse [3,6].

Given the overlap of systemic manifestations with advanced HIV infection, diagnostic confusion may arise, particularly when initial serologic results are misleading. Although uncommon, false-reactive HIV serology has been well documented and should prompt confirmatory testing before HIV infection is diagnosed [7,8]. We report a diagnostically challenging case of WD that initially mimicked advanced HIV infection due to misleading reactive HIV serology - a rare but clinically significant diagnostic pitfall [7,8].

Case Presentation

A 51-year-old man was admitted for evaluation of a 1-month history of unintentional weight loss of 20 kg, asthenia, and chronic bloody, non-mucoid diarrhea, with occasional blood-streaked stools and no significant

hematochezia. He denied smoking, alcohol consumption, and high-risk sexual behavior. His medical history was unremarkable, and he was not taking any regular medication.

On physical examination, the patient appeared severely cachectic, with a body mass index of 13.8 kg/m² and a nutritional risk index of 43. He had bilateral lower-limb edema, clinically consistent with severe hypoalbuminemia, and conjunctival pallor. Neurological examination revealed mild cerebellar ataxia, mainly manifested by a slightly wide-based gait, with an Eastern Cooperative Oncology Group performance status of 3. Muscle strength, tone, reflexes, and sensation were preserved, and there were no cognitive or behavioral disturbances. The remainder of the physical examination was unremarkable, with no fever, lymphadenopathy, or cutaneous lesions.

Laboratory investigations revealed normocytic anemia with a hemoglobin level of 7.4 g/dl, lymphopenia at 940 cells/µl, hypoalbuminemia at 15 g/l, and elevated inflammatory markers, including C-reactive protein at 54.8 mg/l and procalcitonin at 1.19 ng/ml. HIV screening was performed using a fourth-generation HIV-1/2 antigen/antibody chemiluminescent microparticle immunoassay (CMIA) and was weakly reactive, with an index of 1.47 and a positivity threshold greater than 1. This low-level reactivity, just above the assay cutoff, was considered a borderline result. As an HIV-1/2 differentiation immunoassay was not available locally, HIV-1/2 nucleic acid testing was performed in the following days and was negative. No repeat HIV serologic result was documented in the available follow-up records. In this clinical context, the initial low-level reactive CMIA result was therefore considered a false-reactive screening result rather than evidence of HIV infection.

Autoimmune and oncologic screening tests were unremarkable. Interferon-gamma release assay was positive; however, two sputum examinations, including direct smear microscopy and GeneXpert testing for *Mycobacterium tuberculosis*, were negative. In our tuberculosis-endemic setting, and in the absence of clinical, radiological, or microbiological evidence of active disease, the positive interferon-gamma release assay was considered more consistent with latent tuberculosis infection than active tuberculosis. Key laboratory findings at admission are summarized in Table 1.

Abdominal computed tomography demonstrated diffuse small-bowel wall thickening measuring up to 13 mm, mesenteric lymphadenopathy, ascites, bilateral pleural effusions, and a pericardial effusion. Brain magnetic resonance imaging showed diffuse cerebral atrophy with a chronic left parietal infarct and no acute ischemic or inflammatory lesion. Lumbar puncture with cerebrospinal fluid testing for *T. whipplei* was considered after neurological evaluation. However, it was not performed during the initial hospitalization because the cerebellar ataxia was mild and isolated, without cognitive or behavioral changes, seizures, visual symptoms, or radiological evidence of active central nervous system disease. Consequently, neurological involvement by WD could not be definitively excluded.

Transthoracic echocardiography showed right ventricular dilatation with predominant right-sided heart failure, without significant mitral or aortic valvular disease or

Table 1. *Key laboratory findings at admission.*

Parameter	Value	Unit
Hemoglobin	7.4	g dl^{-1}
Platelets	100 000	cells μl^{-1}
Lymphocytes	940	cells μl^{-1}
Albumin	15	g l^{-1}
CRP	54.8	mg l^{-1}
Procalcitonin	1.19	ng ml^{-1}
Creatinine	0.57	mg dl^{-1}
LDH	461	U l^{-1}
HIV Ag/Ab CMIA	Positive 1.47	—
HIV PCR	Negative	—

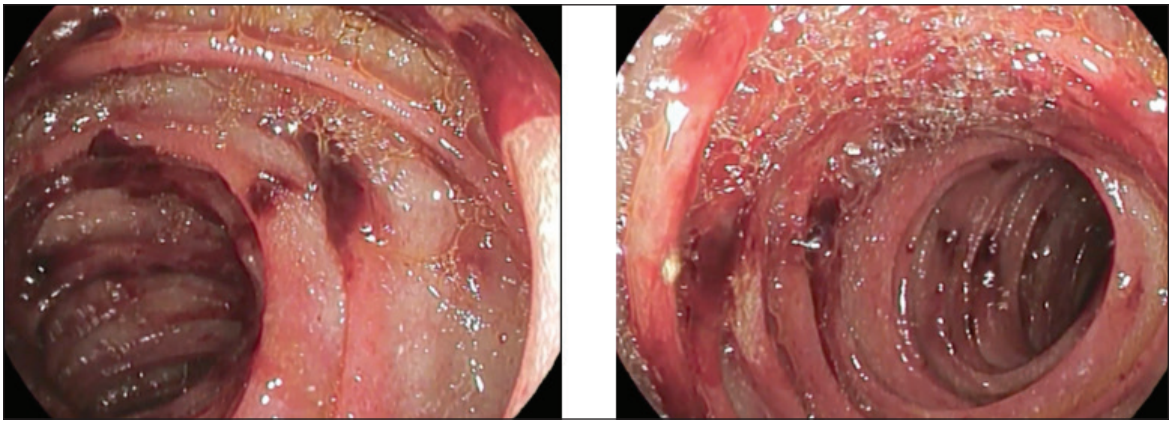

Figure 1. *Upper gastrointestinal endoscopy showing friable, ulcerated duodenal mucosa with villous blunting. These nonspecific but abnormal mucosal findings prompted multiple duodenal biopsies for histological evaluation.*

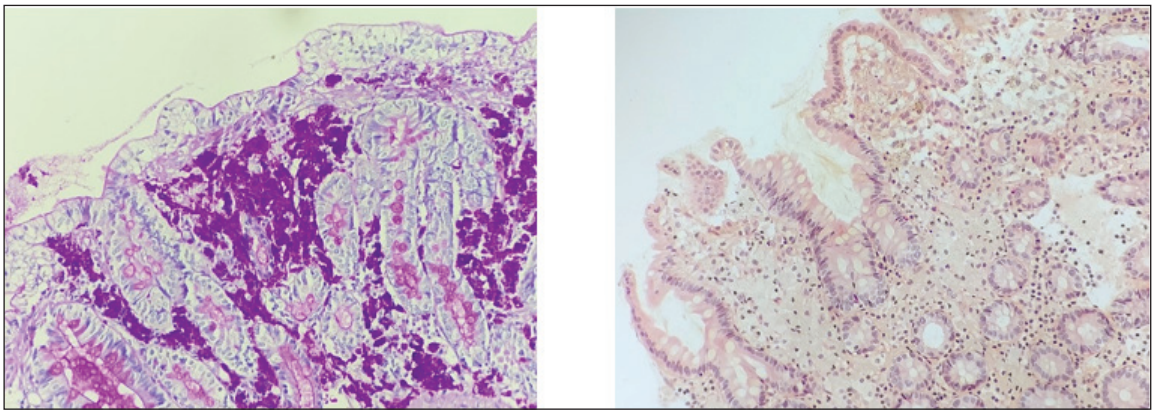

Figure 2. *Duodenal biopsies showing villous atrophy and expansion of the lamina propria by foamy macrophages containing periodic acid–Schiff-positive inclusions, consistent with WD.*

valvular vegetations. In the setting of concomitant pleural and pericardial effusions, cardiac involvement related to WD, including myocarditis or endocarditis, was considered. However, cardiac magnetic resonance imaging was not available during hospitalization, and no definitive evidence of myocardial or valvular involvement was obtained.

Upper gastrointestinal endoscopy revealed friable, ulcerated duodenal mucosa with villous blunting (Figure 1).

Histological examination of the duodenal biopsies showed villous atrophy and expansion of the lamina propria by foamy macrophages containing periodic acid–Schiff-positive inclusions, strongly supporting WD (Figure 2). Polymerase chain reaction testing for *T. whipplei* was reported as positive and provided additional support for the diagnosis. However, the available records did not specify the specimen type or assay platform and did not provide a cycle-threshold value or copy-number result. The molecular result was therefore interpreted as a qualitative supportive finding rather than as standalone diagnostic confirmation. Although *Mycobacterium avium* complex infection and histoplasmosis may also produce foamy macrophages, specific acid-fast and fungal stains or pathogen-directed molecular tests were not documented in the available pathology records. Nevertheless, the combination of characteristic PAS-positive duodenal macrophages and a positive molecular assay for *T. whipplei* strongly favored the diagnosis of WD.

The patient was treated with intravenous ceftriaxone 2 g once daily for 4 weeks, followed by oral doxycycline 200 mg daily and hydroxychloroquine 200 mg three times daily, planned for a total treatment duration of 18 months. Clinical improvement was observed shortly after treatment initiation, with progressive resolution of diarrhea. At 3 months, the patient had regained 10 kg, lower-limb edema had resolved, inflammatory markers had normalized, and cerebellar ataxia had partially improved. Follow-up consisted of regular clinical and neurological assessments and serial laboratory testing, including complete blood count, albumin, and inflammatory markers. At 6 months, the patient remained clinically stable, without recurrent diarrhea or other clinical evidence of relapse. Exact body weight, albumin concentration, and inflammatory-marker values at 6 months were not available in the follow-up records. No scheduled repeat upper gastrointestinal endoscopy or follow-up *T. whipplei* PCR was documented during the first six months. Repeat echocardiography and thoracic imaging were also unavailable; therefore, the evolution of the right ventricular dilatation and the pleural and pericardial effusions could not be objectively assessed.

Discussion

WD is a rare multisystemic infection that predominantly affects middle-aged Caucasian men [1,2]. Its gastrointestinal, rheumatologic, neurological, and cardiac manifestations may mimic inflammatory bowel disease, abdominal tuberculosis, lymphoma, or advanced HIV infection, leading to diagnostic delay [2,3]. In our patient, the principal diagnostic pitfall was a weakly reactive HIV screening result that initially redirected clinical reasoning despite a syndrome compatible with WD. Right ventricular dilatation associated with pleural and pericardial effusions also raised concern for cardiac involvement; however, in the absence of cardiac magnetic resonance imaging and follow-up cardiac imaging, these findings could not be definitively attributed to WD.

HIV screening assays prioritize sensitivity and may yield false-reactive results. In the present case, the low-level reactive fourth-generation X` was not supported by subsequent HIV-1/2 nucleic acid testing, which was negative, and no repeat serologic result was documented during follow-up. This discordance prompted reassessment rather than a diagnosis of HIV infection [7–9]. Because an HIV-1/2 differentiation immunoassay was unavailable locally, confirmation relied on nucleic acid testing, illustrating how limited access to confirmatory algorithms

may prolong diagnostic uncertainty [8–10]. False-reactive fourth-generation assays have also been reported in other clinical contexts [11].

Diagnosis was supported by the combination of characteristic duodenal histology and a positive molecular result for *T. whipplei*. PAS-positive foamy macrophages in duodenal biopsies are highly suggestive, whereas PCR improves diagnostic specificity but should be interpreted in context because asymptomatic carriage may occur [3–6,12,13]. In this case, the available records did not specify the specimen source, assay platform, or quantitative parameters; the PCR result was therefore considered qualitative supportive evidence rather than standalone confirmation.

Early recognition is essential because untreated WD may be fatal [1,3]. Treatment generally combines parenteral induction with prolonged CNS-penetrating oral therapy, including doxycycline plus hydroxychloroquine [1,3]. Neurological recovery may be incomplete, and in our patient, the mild cerebellar ataxia remained a possible manifestation because cerebrospinal fluid analysis and *T. whipplei* PCR were not performed. Long-term clinical, laboratory, and, when available, endoscopic or molecular surveillance is therefore important [5,6]. Empirical immunosuppression should be avoided because it may worsen unrecognized WD [14,15]. Overall, this case underscores that discordant HIV screening should prompt confirmatory testing before HIV infection is diagnosed [7–9], while early duodenal biopsy supported by molecular testing can establish WD and allow timely therapy [1,3–6].

Conclusion

WD should be considered in patients with unexplained weight loss, chronic diarrhea, and multisystem involvement, particularly when the clinical presentation suggests advanced HIV infection but confirmatory testing is negative. Weakly reactive HIV screening results should be interpreted cautiously and confirmed before establishing a diagnosis of HIV infection. Early duodenal biopsy, supported by molecular testing when available, allows timely diagnosis and initiation of appropriate CNS-penetrating antibiotic therapy, thereby improving outcomes and reducing the risk of relapse.

Whats new?

This case highlights a rare diagnostic pitfall in which a weakly reactive fourth-generation HIV screening assay initially misdirected clinical reasoning toward advanced HIV infection, while confirmatory HIV PCR was negative. The manuscript emphasizes that discordant HIV results should prompt confirmatory testing and careful reassessment of alternative diagnoses. In patients with severe weight loss, chronic diarrhea, and multisystem involvement, early duodenal biopsy may allow timely diagnosis of Whipple's disease and avoid delays in appropriate antimicrobial therapy.

List of abbreviations

CMIA	chemiluminescent microparticle immunoassay
CNS	central nervous system
CRP	C-reactive protein
ECOG	Eastern Cooperative Oncology Group
HIV	human immunodeficiency virus
LDH	lactate dehydrogenase
PAS	periodic acid–Schiff
PCR	polymerase chain reaction
WD	Whipple's disease

Declarations

Conflict of Interest

The authors declare that they have no conflict of interest regarding the publication of this case report.

Funding

This research received no external funding.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Ethical Approval

Ethical approval was not required at our institution for the publication of this anonymized case report.

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Summary of the case

1	**Patient (gender, age)**	Male, 51 years old
2	**Final diagnosis**	Whipple's disease caused by *Tropheryma whipplei*
3	**Symptoms**	Severe weight loss, chronic diarrhea, asthenia, cachexia, lower-limb edema, anemia, and mild cerebellar ataxia
4	**Medications**	Intravenous ceftriaxone, followed by oral doxycycline and hydroxychloroquine
5	**Clinical procedure**	Upper gastrointestinal endoscopy with duodenal biopsies; histology with PAS-positive foamy macrophages; PCR confirmation
6	**Specialty**	Hepato-gastroenterology/Gastroenterology