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The Great Imitator Strikes Again: A Multisystemic Case of Whipple's Disease

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Abstract **Case Report**

Whipple's disease is a rare systemic infection caused by *Tropheryma whipplei* with highly variable clinical manifestations. Articular symptoms often represent the first manifestation and may precede digestive involvement for several years, which frequently leads to misdiagnosis as chronic inflammatory rheumatic diseases such as spondyloarthritis. This misdiagnosis is problematic because immunosuppressive therapies may worsen the infection by facilitating bacterial dissemination. This article reports the case of a 56-year-old man initially diagnosed with axial and peripheral spondyloarthritis. The patient presented with bilateral uveitis, inflammatory arthralgia, chronic inflammatory back pain, and digestive symptoms. Despite treatment with methotrexate, his condition progressively worsened, with severe weight loss, persistent inflammation, and pancytopenia. Because of a previous history of inadequately treated lymph node tuberculosis and a positive QuantiFERON test, intestinal tuberculosis was suspected and anti-tuberculous therapy was initiated. However, the patient's condition continued to deteriorate. Further investigations, including repeat endoscopy and duodenal biopsies, revealed PAS-positive macrophages consistent with Whipple's disease. Echocardiography also identified valvular vegetations indicating endocarditis. The final diagnosis was multisystemic Whipple's disease with articular, digestive, lymphatic, and cardiac involvement. The patient was successfully treated with intravenous ceftriaxone followed by long-term oral cotrimoxazole, leading to significant clinical improvement. This case highlights the diagnostic difficulty of Whipple's disease due to its ability to mimic other conditions such as spondyloarthritis or intestinal tuberculosis, especially in endemic regions. Histology and PCR testing are essential diagnostic tools, while cardiac evaluation is important because *T. whipplei* can cause blood culture–negative endocarditis. Early diagnosis and appropriate antibiotic therapy are crucial to improve prognosis and prevent complications or relapse.

Keywords: Whipple's disease, *Tropheryma whipplei*, Spondyloarthritis, Intestinal tuberculosis, Malabsorption syndrome, Endocarditis.

INTRODUCTION

Whipple's disease is a rare systemic infection caused by *Tropheryma whipplei*, an intracellular actinobacterium [1,2]. Its clinical presentation is notably polymorphic. Articular manifestations frequently constitute the initial symptom and may precede the typical digestive involvement by several years, thereby contributing to misdiagnoses such as spondyloarthritis or other chronic inflammatory rheumatic diseases (CIRD) [3,4]. This diagnostic confusion is particularly problematic because immunosuppressive therapies commonly used in inflammatory rheumatic disorders may worsen the course of Whipple's disease by promoting bacterial dissemination [5].

We report a case illustrating this diagnostic challenge, initially labeled as spondyloarthritis with suspected intestinal tuberculosis, before further investigations ultimately led to the diagnosis of Whipple's disease.

CASE PRESENTATION

A 56-year-old man, with a 20-year history of well-controlled epilepsy, and a past medical history of confirmed but inadequately treated lymph node

tuberculosis in 2023, presented with bilateral intermediate uveitis associated with inflammatory arthralgia evolving over 18 months, affecting the hands, knees, wrists, and ankles. He also reported chronic inflammatory lumbosciatica since the age of 40, characterized by prolonged morning stiffness, as well as episodic abdominal pain and chronic constipation.

Initial laboratory investigations revealed an inflammatory syndrome with C-reactive protein (CRP) at 95 mg/L. Pelvic radiography demonstrated stage III sacroiliitis. HLA-B27 testing was negative. A diagnosis of axial and peripheral spondyloarthritis was retained.

The etiological workup for digestive symptoms was unremarkable, including fecal occult blood testing, stool parasitology, and fecal calprotectin. Upper and lower gastrointestinal endoscopy revealed pangastritis and nonspecific duodenitis with *Helicobacter pylori* infection. Entero-CT scan did not demonstrate intestinal wall thickening.

Immunosuppressive therapy with methotrexate was initiated. The patient was considered a candidate for anti-TNF biologic therapy, which was not started. Initial articular improvement was partial.

The clinical course was marked by worsening abdominal pain, 10 kg weight loss over five months, marked anorexia, and significant deterioration of general condition without fever. Laboratory investigations revealed pancytopenia with persistent inflammatory syndrome (CRP 109 mg/L). Bone marrow examination showed inflammatory features with normal cellularity.

Further questioning revealed recent tuberculosis exposure. Given the history of inadequately treated lymph node tuberculosis and a positive QuantiFERON test, intestinal and hematopoietic tuberculosis was strongly suspected. Digestive endoscopy could not be performed due to thrombocytopenia. Anti-tuberculous therapy was initiated and methotrexate was discontinued.

Subsequently, CRP decreased to 61 mg/L, leukocyte and platelet counts normalized, anemia persisted, and partial improvement in digestive symptoms and general condition was observed.

However, two months later, the patient continued to deteriorate with no significant response to anti-tuberculous treatment. Cervico-thoraco-abdominal CT scan revealed multiple mesenteric lymphadenopathies, centimeter and sub-centimeter in size, with fatty density and no organomegaly.

Whipple's disease was then suspected. Repeat upper gastrointestinal endoscopy demonstrated a granular ("sprinkled") appearance of the duodenal mucosa with erosive nodular antral-fundic gastritis. Duodenal biopsies showed chronic interstitial duodenitis with PAS-positive macrophage infiltration.

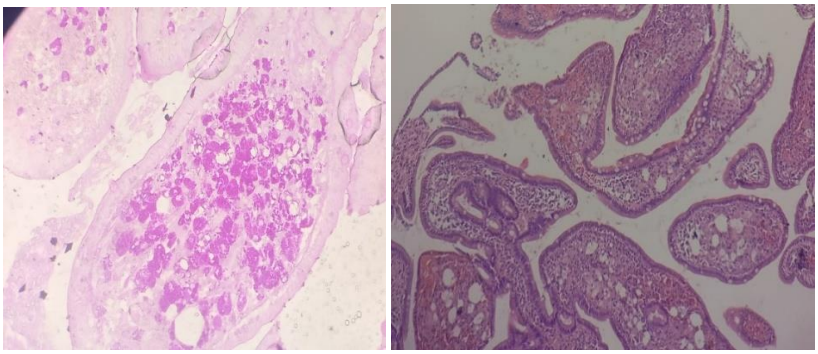

Figure 1: Histopathological examination of the duodenal biopsy shows preserved villous architecture with expansion of the lamina propria by numerous foamy macrophages. These macrophages contain finely granular cytoplasmic material, consistent with periodic acid–Schiff (PAS)-positive inclusions characteristic of Tropheryma whipplei infection. Mild inflammatory infiltrate is present within the lamina propria. These findings are highly suggestive of Whipple's disease

Echocardiography confirmed the presence of valvular vegetations. Blood cultures were negative.

The diagnosis of Whipple's disease was established, with articular, lymphatic, digestive, and cardiac involvement. The patient was treated with intravenous ceftriaxone (2 g/day for 14 days), followed by oral cotrimoxazole (800/160 mg twice daily) for 12 months.

Clinical evolution was favorable, with progressive improvement of digestive and articular symptoms, weight gain, and normalization of CRP levels.

DISCUSSION

Whipple's disease is a rare systemic bacterial infection caused by *Tropheryma whipplei*, an intracellular actinobacterium whose pathogenic mechanisms remain only partially understood [1]. First described in 1907 by George Hoyt Whipple, it is characterized by marked clinical polymorphism, making diagnosis particularly challenging [2].

Its prevalence is low but likely underestimated due to atypical or paucisymptomatic forms [3]. The natural course is typically chronic and multisystemic, predominantly affecting the small intestine, joints, central nervous system, and heart [4].

This condition represents a major diagnostic challenge because of its heterogeneous clinical presentation and frequently insidious course. The present case perfectly illustrates this deceptive nature, particularly through the initial predominance of articular manifestations mimicking spondyloarthritis.

This presentation is widely reported: in 70–90% of cases, inflammatory arthralgia or arthritis precedes digestive manifestations, sometimes by several years [5,6]. These symptoms, often migratory, non-erosive, and recurrent, may be mistaken for spondyloarthritis or undifferentiated polyarthritis, as observed in our patient.

Lack of improvement under anti-TNFα therapy, or even clinical worsening, is now recognized as an important clue suggesting underlying Whipple's disease [7].

The second source of diagnostic error arises from digestive manifestations. The coexistence of abdominal pain, persistent inflammatory syndrome, progressive weight loss, and nonspecific endoscopic findings may easily suggest intestinal tuberculosis, particularly in endemic regions such as the Maghreb [8].

The occasional presence of granulomas on biopsy, reported in certaine case of Whipple's disease, further contributes to its mimicry of tuberculosis or Crohn's disease [9]. In our case, inappropriate anti-tuberculous therapy not only delayed the correct diagnosis but likely contributed to disease progression.

Histological examination remains a cornerstone of diagnosis, based on the identification of PAS-positive macrophages within the duodenal mucosa [11]. However, this technique has limitations, as PAS-positive macrophages may also be observed in other infectious or inflammatory conditions, creating a risk of false-positive results [12].

For this reason, specific PCR testing for *Tropheryma whipplei* has become an essential diagnostic tool, significantly improving sensitivity and specificity, particularly in atypical and extra-digestive forms [13].

A distinctive feature of our case is the presence of endocarditis, a well-described but often underestimated cardiac manifestation of Whipple's disease. *T. whipplei* endocarditis, long considered exceptional, is now recognized as an emerging cause of blood culture–negative endocarditis, particularly in patients presenting with unexplained systemic manifestations [6,7].

It is characterized by the absence of prior valvular risk factors, often subtle clinical presentation, and diagnostic difficulty due to negative blood cultures. In such cases, PCR testing of valvular tissue or blood is essential for etiological confirmation [8].

In our patient, the concomitant identification of chronic articular involvement, suggestive digestive manifestations, and silent endocarditis underscores the systemic nature of the infection. This association highlights the importance of systematic cardiac screening, particularly echocardiography, in any patient with suspected or confirmed Whipple's disease.

Several studies report that endocardial involvement may precede or accompany other manifestations and may even represent the initial presentation of the disease (9). Recognition is crucial, as untreated endocarditis increases the risk of embolic complications and may compromise therapeutic response.

The favorable outcome following appropriate antibiotic therapy confirms the effectiveness of early treatment. Nevertheless, the presence of endocarditis requires prolonged therapy and close cardiological follow-up to prevent relapse, reported in 17–35% of cases depending on the series [1,6].

This case illustrates not only the ability of Whipple's disease to mimic spondyloarthritis and intestinal tuberculosis but also the necessity of considering *T. whipplei* endocarditis in cases of blood culture–negative or atypical endocarditis. Early recognition of these multisystemic manifestations directly impacts prognosis.

The favorable evolution observed after initiation of antibiotic therapy is consistent with the literature: prolonged treatment combining an induction phase with third-generation cephalosporins followed by long-term oral therapy (TMP-SMX) achieves sustained remission in most cases [8,15]. However, the risk of relapse remains significant, particularly in cases with neurological involvement, thus requiring long-term monitoring.

Conclusion

The misleading clinical presentation of Whipple's disease frequently leads to misdiagnosis, particularly when it manifests as prolonged inflammatory arthritis or blood culture–negative endocarditis.

Our case highlights the importance of early use of molecular techniques and histology to confirm *Tropheryma whipplei* infection and to avoid inappropriate treatments that may worsen disease progression.

The rapid improvement observed under appropriate antibiotic therapy reinforces the need to include Whipple's disease in the differential diagnosis of atypical systemic presentations, especially when articular, digestive, and cardiac manifestations coexist.

Earlier recognition allows optimization of management and prevention of complications related to this multisystemic infection.

Competing Interests

The authors declare that they have no competing interests, and all authors confirm accuracy.

Authors' Contributions

All the authors made a substantial intellectual contribution, read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images.

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