Journal Pre-proof

Whipple's Disease Presenting with Bone Marrow Findings Mimicking Prefibrotic Myelofibrosis: A Diagnostic Pitfall.

Gaëlle Vertenoeil , Kaoutar Hafraoui , Patrick Collins ,
Joan Somja , Frédéric Lambert , Sophie de Worm , Yves Beguin

PII: S1201-9712(25)00493-X
DOI: https://doi.org/10.1016/j.ijid.2025.108271
Reference: IJID 108271

To appear in: *International Journal of Infectious Diseases*

Received date: 11 August 2025
Revised date: 26 November 2025
Accepted date: 28 November 2025

Please cite this article as: Gaëlle Vertenoeil , Kaoutar Hafraoui , Patrick Collins , Joan Somja , Frédéric Lambert , Sophie de Worm , Yves Beguin , Whipple's Disease Presenting with Bone Marrow Findings Mimicking Prefibrotic Myelofibrosis: A Diagnostic Pitfall., *International Journal of Infectious Diseases* (2025), doi: https://doi.org/10.1016/j.ijid.2025.108271

Whipple's Disease Presenting with Bone Marrow Findings Mimicking Prefibrotic Myelofibrosis: A Diagnostic Pitfall : **Highlights**

- First case of Whipple's disease mimicking prefibrotic myelofibrosis.
- Diagnosis confirmed by PCR for *Tropheryma whipplei* in duodenal tissue.
- Antibiotic therapy led to full clinical remission and resolution of bone marrow abnormalities.
- Emphasizes considering infections in suspected myeloproliferative neoplasms.

Title : Whipple's Disease Presenting with Bone Marrow Findings Mimicking Prefibrotic Myelofibrosis: A Diagnostic Pitfall.

Running title : Whipple's Disease Mimicking Prefibrotic Myelofibrosis.

Authors : Gaëlle Vertenoeil[1], Kaoutar Hafraoui[1], Patrick Collins[2], Joan Somja[2], Frédéric Lambert[3], Sophie de Worm[4], Yves Beguin[1].

Affiliations :

[1]Department of Hematology, University Hospital of Liège, 4000 Liège, Belgium. University Hospital of Liège is a member of the EuroBloodNet (ERN hematology network).

[2]Department of Pathology, University Hospital of Liège, 4000 Liège, Belgium.

[3]Department of Human Genetics, University Hospital of Liège, 4000 Liège, Belgium.

[4]Department of Internal Medicine and Infectious Diseases, University Hospital of Liège, 4000 Liège, Belgium.

Corresponding author : Gaëlle Vertenoeil. Gaelle.vertenoeil@chuliege.be

ORCID : 0000-0003-4129-882X

Whipple's Disease Presenting with Bone Marrow Findings Mimicking Prefibrotic Myelofibrosis: A Diagnostic Pitfall.

Abstract

Whipple's disease is a rare systemic infection that may mimic hematologic disorders. We report a case initially misdiagnosed as prefibrotic myelofibrosis based on systemic symptoms and bone marrow findings. Further investigations by PCR confirmed *Tropheryma whipplei* infection. Antibiotic therapy led to full clinical remission and resolution of bone marrow abnormalities. This case highlights the importance of considering infectious etiologies in patients with constitutional symptoms and bone marrow changes, to avoid misdiagnosis and inappropriate management.

Key words : Whipple's disease; prefibrotic myelofibrosis; constitutional symptoms.

Introduction

Whipple's disease is a rare, chronic, systemic infection caused by *Tropheryma whipplei*, with an estimated incidence of 1 to 6 new cases per 10,000,000 patients per year[1]. Although uncommon, early recognition is crucial because the infection can be fatal without antibiotic treatment. The classical form is characterized by a triad of arthralgia, diarrhea and weight loss, reflecting predominant gastro-intestinal and joint involvement.

However, the clinical spectrum is broad and many patients present with nonspecific symptoms, making diagnosis challenging. Some presentations, such as mesenteric lymphadenopathies[2] or pancytopenia[3], may mimic hematologic disorders and contribute to diagnostic delay.

Here, we report the case of a patient whose initial presentation and bone marrow biopsy closely resembled prefibrotic myelofibrosis, but who was ultimately diagnosed with Whipple's disease.

Case report

A 49-year-old man was referred to the hematology department for evaluation of symptoms suggestive of a hematologic disorder, including night sweats, recurrent fever, and 10 kg weight loss over the past year. His history included seronegative polyarthritis, poorly responsive to treatment, and longstanding hyperferritinemia (> 500 ng/ml for 15 years), attributed to steatosis.

The physical examination was unremarkable. Laboratory tests showed persistent inflammation, leukocytosis, and mild thrombocytosis. A positron emission tomography (PET) scan showed intense hypermetabolism in the left colon and diffuse osteo-medullary increased uptake. A colonoscopy showed benign polyps. The bone marrow biopsy showed hypercellular marrow with mild to moderate dysplasia of megakaryocytes forming focal aggregates consistent with prefibrotic myelofibrosis (Figure 1). Next-generation sequencing (NGS) detected no common MPN associated oncogenic drivers or high-molecular-risk (HMR) mutations. Based on the morphological findings and clinical context, a diagnosis of triple-negative prefibrotic myelofibrosis was initially considered.

However, given the absence of driver mutations and the severity of constitutional symptoms and inflammatory features, an extensive workup was conducted to identify other potential etiologies, including testing for the acquired *UBA1* mutations to rule out VEXAS syndrome as well as investigations for Whipple's disease, namely polymerase chain reaction (PCR) screening on non-invasive samples (saliva and feces).

No vacuoles were observed in myeloid progenitors and *UBA1* sequencing was negative for somatic mutations. PCR tests for *Tropheryma whipplei* were positive in the fecal and saliva samples. A gastroscopy was performed, and the duodenal biopsy sample did not show intracellular bacteria within macrophages on periodic acid-Schiff (PAS) staining, while PCR analysis was positive for *Tropheryma whipplei*. A lumbar puncture to rule out neurological involvement was negative. PCR testing for the bacteria in the first bone marrow biopsy was also negative.

The patient received antibiotics comprising hydroxychloroquine (200 mg three times daily) and doxycycline (100 mg twice daily) for one year. Treatment led to rapid improvement in constitutional symptoms, including resolution of fever, night sweats, and weight stabilization.

A follow-up bone marrow biopsy performed after five months of therapy revealed a normocellular marrow with no fibrosis or dysplasia, suggesting that the previously observed hypercellularity was likely reactive rather than indicative of prefibrotic myelofibrosis. This sample's periodic acid-Schiff (PAS) staining revealed granular positivity in unclear structures, possibly representing amorphous extracellular material or degenerating macrophages (Figure 1). The PCR test on the second sample was negative.

Discussion

Infections can alter bone marrow architecture, affecting stromal and hematopoietic compartments[4]. Primary lesions include granulomas, fibrosis, lymphoid nodules, hyperplasia or hypoplasia of hematopoietic lineages, with or without dysplasia[4]. The mechanisms rely on the involvement of hematopoietic stem cells (HSCs) in the immune response, direct pathogen infection or cytokine-mediated inflammation[5].

To our knowledge, this is the first reported case of Whipple's disease mimicking prefibrotic myelofibrosis, an uncommon presentation with significant diagnostic challenges. Table 1 compares the WHO criteria for prefibrotic myelofibrosis with clinical and histologic features observed in Whipple's disease.

Beyond gastrointestinal and rheumatologic symptoms, Whipple's disease may present with hematological abnormalities. In a cohort of 191 patients with classical Whipple's disease, anemia, leukocytosis, and thrombocytosis were reported in 81%, 48%, and 56% of cases, respectively[6]. Peripheral thrombocytopenia due to platelet sequestration or immune destruction has been described in patients with blood culture-negative endocarditis and infection by *Tropheryma whipplei[7]*. Bone marrow involvement is rare but not uncommon (reviewed in[8]). The prevalence is difficult to assess because a bone marrow biopsy is not routinely performed unless hematologic disease is suspected, such as in pancytopenia[3]. Bone marrow findings include markedly increased megakaryopoiesis with hyperfragmented cells containing periodic acid-Schiff positive inclusions[8], myeloid or erythroid hyperplasia [8] or hypercellularity with noncaseating granuloma[9]. Bone marrow involvement is confirmed by periodic acid-Schiff (PAS) staining [3] or PCR[9].

In our case, although granular PAS positivity was detected in bone marrow samples, the PCR was negative, arguing against direct bone marrow infection.

Prefibrotic myelofibrosis is classified among myeloproliferative neoplasms and was individualized from essential thrombocythemia (ET) and primary myelofibrosis in the 2016 WHO classification . All three diseases share common driver mutations (*JAK2*, *CALR* or *MPL)* and diagnosis relies on integrated clinical, histological and molecular criteria[10]. When no driver mutation is found, cases are called "triple negative". Morphologic features like hypercellularity and megakaryocyte hyperplasia are characteristics of MPNs but can also be found in reactive settings, including infections, making the distinction challenging[4, 11].

The patient had constitutional symptoms, including fever, night sweats, and weight loss. Such symptoms occur in approximately 13% of patients with prefibrotic myelofibrosis[12]. Weight loss and fever, often with night sweats, were reported in 79% and 34%, respectively, of 113 patients with histologically confirmed Whipple's disease[13].

In our patient, the absence of driver mutations, prominence of constitutional symptoms and history of seronegative polyarthritis prompted consideration for alternative diagnoses, such as Whipple's disease, confirmed by appropriate tissue biopsy and PCR testing. PAS staining was negative on the duodenal specimen; however, only one sample was obtained, whereas 3–5 samples are recommended to minimize sampling error[1]. The diagnosis was supported by the clinical symptoms, rapid improvement following treatment, and PCR positivity in the duodenal sample.

An accurate diagnosis is critical to guide therapy, as management strategies for Whipple's disease and prefibrotic myelofibrosis completely differ. Moreover, Whipple's disease can be fatal without appropriate therapy and treatment is less effective in advanced disease[1]. Management requires a prolonged course of antibiotics. Regimens based on ceftriaxone or meropenem for 14 days, followed by co-trimoxazole for 12 months have been proposed, although concerns exist regarding *Tropheryma whipplei's in vitro* sensitivity to trimethoprim[14]. The most common combination involves doxycycline (200 mg/day) with hydroxychloroquine (600 mg/day) for 12 months, followed by lifelong doxycycline, a regimen that has recently been shown to be non-inferior to intravenous ceftriaxone followed by oral trimethoprim–sulfamethoxazole in a phase 2/3 randomized controlled trial [15] . In contrast, the treatment of prefibrotic myelofibrosis may involve cytoreductive therapy or symptom-directed anti-JAK2 treatment[10].

Our case highlights an unusual manifestation of Whipple's disease, reinforcing its reputation as a "great mimicker". It underscores the importance of integrating clinical, biological, and histological findings to achieve an accurate diagnosis and emphasizes considering infections, particularly *Tropheryma whipplei*, in the differential diagnosis of bone marrow abnormalities mimicking myeloproliferative neoplasms.

Conflict of Interest declaration: The authors declare that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

Authors Contributions : Gaëlle Vertenoeil wrote the manuscript. Yves Beguin provided revisions and critical editing of the manuscript. All authors significantly contributed to the diagnosis and/or management of the patient. All authors reviewed and approved the final version of the manuscript.

Ethical approval and patient consent: Ethical approval was not required for this case report. The patient provided written informed consent for the publication of this report and any accompanying images, in accordance with institutional and international ethical standards (including the Declaration of Helsinki).

Funding source : No funding was received for the preparation of this case report and its associated analyses.

Bibliography

[1]Dolmans RA, Boel CH, Lacle MM, Kusters JG. Clinical Manifestations, Treatment, and Diagnosis of Tropheryma whipplei Infections. Clin Microbiol Rev. 2017;30(2):529–55.
[2]Chizinga M, Schiliro D, Mullin B, Barrie R. Mesenteric lymphadenitis as a presenting feature of Whipple's disease. IDCases. 2017;9:50–2.
[3]Tun NT, Shukla S, Krishnakurup J, Pappachen B, Krishnamurthy M, Salib H. An unusual cause of pancytopenia: Whipple's disease. J Community Hosp Intern Med Perspect. 2014;4(2).
[4]Diebold J, Molina T, Camilleri-Broët S, Le Tourneau A, Audouin J. Bone marrow manifestations of infections and systemic diseases observed in bone marrow trephine biopsy review. Histopathology. 2000;37(3):199–211.
[5]Glatman Zaretsky A, Engiles JB, Hunter CA. Infection-induced changes in hematopoiesis. J Immunol. 2014;192(1):27–33.
[6]Günther U, Moos V, Offenmüller G, Oelkers G, Heise W, Moter A, et al. Gastrointestinal diagnosis of classical Whipple disease: clinical, endoscopic, and histopathologic features in 191 patients. Medicine (Baltimore). 2015;94(15):e714.
[7]Olivier M, Licitra C, Field Z, Ge L, Hill D, Madruga M, et al. Thrombocytopenia and endocarditis in a patient with Whipple's disease: case report. BMC Infect Dis. 2020;20(1):71.
[8]Walter R, Bachmann SP, Schaffner A, Rüegg R, Schoedon G. Bone marrow involvement in Whipple's disease: rarely reported, but really rare? Br J Haematol. 2001;112(3):677–9.
[9]Kröber SM, Kaiserling E, Horny HP, Weber A. Primary diagnosis of Whipple's disease in bone marrow. Hum Pathol. 2004;35(4):522–5.
[10]Rumi E, Sant'Antonio E, Boveri E, Pietra D, Cavalloni C, Roncoroni E, et al. Diagnosis and management of prefibrotic myelofibrosis. Expert Rev Hematol. 2018;11(7):537–45.
[11]Thiele J, Kvasnicka HM, Müllauer L, Buxhofer-Ausch V, Gisslinger B, Gisslinger H. Essential thrombocythemia versus early primary myelofibrosis: a multicenter study to validate the WHO classification. Blood. 2011;117(21):5710–8.
[12]Mudireddy M, Shah S, Lasho T, Barraco D, Hanson CA, Ketterling RP, et al. Prefibrotic versus overtly fibrotic primary myelofibrosis: clinical, cytogenetic, molecular and prognostic comparisons. Br J Haematol. 2018;182(4):594–7.
[13]Lagier JC, Lepidi H, Raoult D, Fenollar F. Systemic Tropheryma whipplei: clinical presentation of 142 patients with infections diagnosed or confirmed in a reference center. Medicine (Baltimore). 2010;89(5):337–45.

[14]Lagier JC, Fenollar F, Lepidi H, Giorgi R, Million M, Raoult D. Treatment of classic Whipple's disease: from in vitro results to clinical outcome. J Antimicrob Chemother. 2014;69(1):219–27.
[15]Moos V, Krüger J, Allers K, Moter A, Kikhney J, Kühl AA, et al. Oral treatment of Whipple's disease with doxycycline and hydroxychloroquine versus intravenous therapy with ceftriaxone followed by oral trimethoprim-sulfamethoxazole in Germany: a phase 2/3, prospective, open-label, randomised, controlled, non-inferiority trial. Lancet Infect Dis. 2025;25(7):788–800.

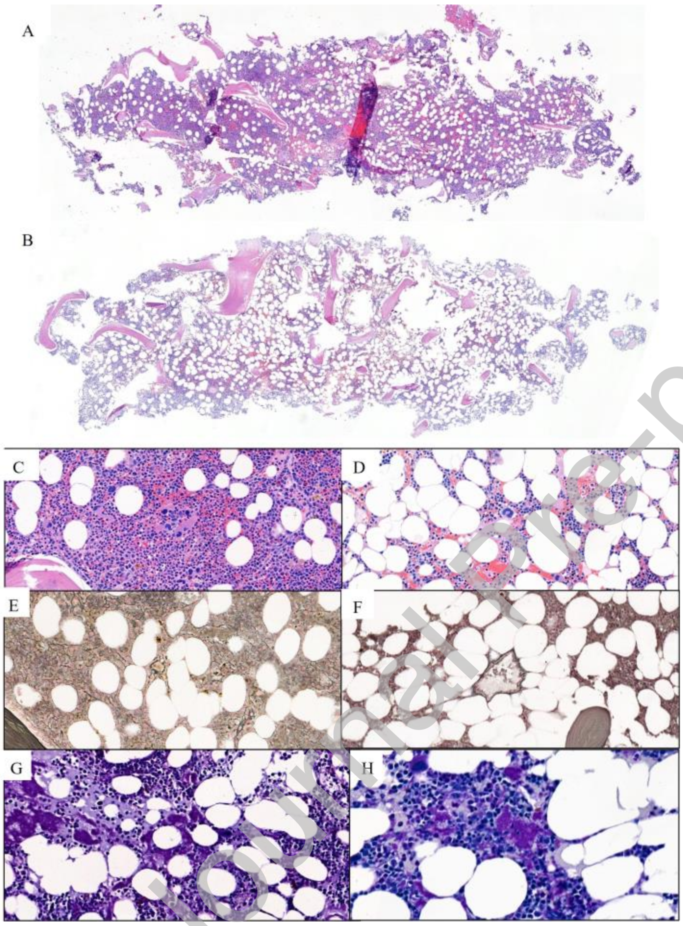

Figure 1.

Bone marrow biopsy images before treatment (A, C, E, G) and five months after treatment (B, D, F, H), illustrating a reduction in cellularity following therapy. Images A and B show the biopsy at low magnification. Images C and D show a cluster of megakaryocytes with hypolobulated nuclei in the initial sample (C), while the post-treatment sample (D) displays normal megakaryocytes. Images E and F show the FOOT reticulin staining, both indicating MF-0 fibrosis. Images G and H show PAS staining. In both samples, PAS highlights a granular positivity within structures that are difficult to identify (extracellular amorphous material vs. macrophages).

Table 1.

2022 WHO criteria for prefibrotic myelofibrosis, with emphasis on bone marrow features and clinical findings observed in prefibrotic myelofibrosis and Whipple's disease.

2022 WHO criteria for prefibrotic myelofibrosis (requires all three major criteria and at least one minor criterion)	Prefibrotic myelofibrosis	Whipple's disease
Major criteria		
1. Presence of megakaryocytic proliferation and atypia, without reticulin fibrosis > grade 1, accompanied by increased age-adjusted bone marrow cellularity, granulocytic proliferation and often decreased erythropoiesis.	**Bone marrow findings (11) :** • hypercellularity • pronounced proliferation of granulopoiesis and reduction of erythroid precursors • megakaryocytic hyperplasia with Mk characteristics : - megakaryocytes forming tight clusters near trabecular bone or marrow sinuses. - size varies, with some large forms (not as giant as in ET). - high nuclear-to-cytoplasmic (N:C) ratio, reduced nuclear lobation, and abnormal chromatin condensation, creating a "cloud-like" appearance. • no or no significant increase in reticulin fibers	**Bone marrow findings (3, 8, 9) :** • hypercellularity • granulocytic hyperplasia • atypia of megakaryocytes • Increase in reticulin fibers not described
2. Not meeting WHO criteria for ET, PV, BCRABL1+ CML, myelodysplastic syndromes, or other myeloid neoplasms.		
3. Presence of *JAK2*, *CALR*, or *MPL* mutation or, in the absence of these mutations, presence of another clonal marker, or absence of reactive myelofibrosis	90% of patients	0% of patients
Minor criteria (confirmed in 2 consecutive determinations)		
1. Anemia not attributed to a comorbid condition	Hb < 10 g/dl in 24% of patients (12)	81% of the patients (6)
2. Leucocytosis > 11 x 10^9/L	Leucocytes > 25 x 109/L in 11% of patients (12)	Leucocytosis in 48% of patients (6)
3. Palpable splenomegaly	54% of patients (12)	3% of patients (13)
4. LDH increased to above upper normal limit of institutional reference range	% unknown	% unknown

Declaration of Interest Statement

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The author is an Editorial Board Member/Editor-in-Chief/Associate Editor/Guest Editor for this journal and was not involved in the editorial review or the decision to publish this article.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:
