

## Single Case

# Deep Vein Thrombosis as Initial Manifestation of Whipple Disease

Mônica Souza de Miranda Henriques Alexandre Rolim da Paz  
Ana Beatriz Person Gaertner Cibelle Ingrid Stephen Melo  
Priscyenne Lins Filgueiras Rafaella Alencar Jerome

Universidade Federal da Paraíba, João Pessoa, Brazil

## Keywords

Whipple disease · *Tropheryma whipplei* · Venous thrombosis · Vasculitis · Thromboembolic events

## Abstract

**Introduction:** Whipple disease (WD) is a rare chronic disease caused by the bacillus *Tropheryma whipplei*. Constitutive, rheumatologic, gastrointestinal, cardiac, cerebral, lymphatic, cutaneous, and ophthalmological signs are possible systemic symptoms. However, thrombotic manifestations are rarely described as “stroke-like syndrome” or arterial thrombosis. Diagnosis is based on clinical manifestations and pathological examination. Laboratory findings may include anemia, leukocytosis, and thrombocytosis. **Objective:** We report a case of venous thrombosis as initial manifestation of WD. **Case Report:** We describe the case of a 53-year-old male with iliofemoral vein thrombosis followed by intermittent diarrhea, loss of appetite, abdominal distension, and bloating. A mild malnutrition state with a weight loss of 13 kg, pallor (+/4 +), presence of lower-limb edema (+/4 +), and hypertympanic distended abdomen occurred. Laboratory tests on admission revealed anemia, positive inflammatory activity tests, and normal coagulation. Endoscopic examination showed villous edema with white dotted infiltrates in the second duodenal portion and intestinal lymphangiectasia in the terminal ileum. Pathological examination revealed numerous macrophages with positive periodic acid-Schiff inclusions. Venous Doppler ultrasound showed extensive deep thrombosis on the left lower limb and recanalization of the femoral vein in the right lower limb. The patient was treated with ceftriaxone and enoxaparin sodium, which led to an improvement of

gastrointestinal and thrombosis symptoms. **Comments:** Hypercoagulability, endothelial damage, vasculitis, and blood stasis are present in *T. whipplei* infection, which are associated with the activation of inflammatory mechanisms as well as procoagulant and thromboembolic events. WD should be part of the differential diagnosis of diseases that cause venous thrombosis of unknown origin.

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Published by S. Karger AG, Basel

## Introduction

Whipple disease (WD) is characterized by a chronic, multisystem and recurrent infection caused by the gram-positive bacillus *Tropheryma whipplei* and recognized as important bacterial cause of malabsorption. It is a rare disease whose true incidence is unknown; some studies show an incidence of 1 case/million. The occurrence is estimated to be approximately 12 cases per year [1, 2].

This disease mainly affects middle-aged Caucasian males from Europe and North America. Research has shown a higher prevalence among farmers because the bacillus has been found in the soil. *T. whipplei* can also be isolated from contaminated water, the oral cavity, and feces of healthy individuals [1–3].

The pathogenesis of WD is undetermined but appears to involve fecal-oral transmission of the bacillus. Host susceptibility, combined with a defect in cell-mediated immunity, involves the activation and interaction of macrophages with T cells, resulting in impaired phagocytosis and degradation of intracellular bacillus, allowing it to spread from the gastrointestinal tract. Although there is not a pattern of familial transmission in WD, some cases have been reported in relatives. More research is needed to clarify whether there are genetic changes that may predispose to this type of infection [1, 3].

The classic presentation consists of the triad of gastrointestinal symptoms diarrhea, weight loss, and malabsorption, which can be associated with systemic symptoms such as fever, joint pain, and neurological manifestations [4].

WD is a systemic disease with various clinical expressions, which affects in particular the small intestine. The classic disease can be divided into three phases: (a) nonspecific prodromal symptoms as arthritis, arthralgia, migratory polyarthralgia; (b) typical gastrointestinal symptoms such as diarrhea, weight loss, steatorrhea, and (c) malabsorption, which may progress to severe cachexia and abdominal lymphadenopathy. Some patients develop severe symptoms of malabsorption such as ascites and peripheral edema and generalized symptoms [3] such involvement of other organs, including heart, brain, lung, lymphatic, skin, and eye [1, 2, 5]. Hematological disorders may include anemia, leukocytosis, and thrombocytosis. However, thrombotic manifestations are poorly described in the literature, with rare reports of “stroke-like syndrome” or arterial thrombosis [6, 7].

The diagnosis should be based on clinical symptoms and pathology. In case of suspicion of WD, the immediate procedure is upper gastrointestinal endoscopy, whose most frequent findings are thickening of the mucosal folds with whitish, confluent exudates alternating with erosions and areas of friable mucosa. Histological examination, usually obtained by endoscopic duodenal biopsy, shows macrophagic infiltration containing microorganisms reactive to periodic acid Schiff (PAS). Polymerase chain reaction directed to bacterial sequences genome has high sensitivity and specificity and is indicated in atypical situations or when there is no histological confirmation. Furthermore, immunohistochemistry, the fluorescence in situ hybridization technique, culture, and serology are important tools that contribute to WD diagnosis [1].

Untreated WD can be fatal. There is good clinical and laboratory response to antibiotic therapy, although there is no consensus on the type, duration, and conduct for complications of the treatment regimen and also on how to treat serious neurological manifestations. Various treatments have been used empirically, including oral penicillins associated with streptomycins, tetracyclines, chloramphenicol, macrolides, and third-generation cephalosporins [1, 3].

The most important criterion for monitoring WD is clinical symptom improvement, which must occur during the first weeks after therapy. Follow-up investigations are recommended at 6 months, 12 months, and then yearly for at least 3 years, preferably throughout life at intervals of 2–3 years [5].

### Case Presentation

A 53-year-old farmer had a brown-colored, painful edema and hyperemia of the left calf 2 years ago. At that time, he underwent venous ultrasound Doppler, which found right and left iliofemoral thrombosis that was treated conservatively. Sequentially, intermittent diarrhea, loss of appetite, abdominal pain and distension, flatulence, asthenia, and weight loss (13 kg) occurred. Symptomatic treatment was initiated, but symptoms persisted. The patient denied smoking and important family history. On examination, he weighed 47 kg (BMI 17.46) and had a mild malnutrition status, pallor (+/4 +), presence of lower-limb edema (+/4 +), and hypotrophic muscles. He had dermatitis ocher in the lower limbs, a palpable lymph node in the right anterior cervical region, and swelling in the left thigh. Laboratory tests on admission showed anemia (hemoglobin 9.0 g, hematocrit 28.8%), leukocytes 7.400 mm<sup>3</sup> and 468,000 platelets, erythrocyte sedimentation rate 32 mm, C-reactive protein 48 mg/L, coagulation studies were normal, and coproculture and blood cultures were negative.

Colonoscopy revealed terminal ileum lymphangiectasia, and esophagogastroduodenoscopy showed villous edema and white dotted infiltrates in the second duodenal portion (Fig. 1a–d). Pathological examination revealed macrophagic infiltration containing microorganisms reactive to PAS (Fig. 2, Fig. 3). New venous Doppler pointed to extensive deep vein thrombosis of the left lower limb and recanalization signs of the femoral vein in the right lower limb. After treatment with ceftriaxone and enoxaparin, the patient has improved gastrointestinal symptoms with normalization of inflammatory activity tests and ultrasonographic signs of venous thrombosis.

### Discussion

Hypercoagulability, endothelial damage and blood stasis are components of Virchow's triad [8, 9]. It is believed that at least 2 of the 3 factors when concomitant predispose to thrombus formation [10]. The most common diseases complicating thrombosis are cancers, systemic inflammation, sepsis, heart disease, protein-losing states, infectious diseases, and the use of a central venous catheter. Among these diseases, coagulation disorders, endogenous anticoagulants systems, fibrinolysis, and complement systems are documented [11].

In infectious states, inflammation is often accompanied by alteration of stasis or disturbance of the normal hemostatic balance by procoagulant and anticoagulant mechanisms characterized by biomarkers of inflammation, coagulation, and activation of monocytes [12, 13].

Studies comparing infected and uninfected patients suggest an association of this state with cardiovascular disease. Bacteria adhesion to a thrombogenic surface can assist in the pathophysiology and explain thromboembolic events associated with infection [10, 13].

Risk factors for venous thrombosis are well defined in medical reports. Age, male gender, smoking habits, family history of stroke, dyslipidemia, and infection are predisposing factors for thrombosis [11, 14, 15].

Thrombophilic phenomena in WD are consequent to *T. whipplei* infection with the activation of the inflammatory and coagulation cascade. This case report is particularly important because of its atypical presentation of venous thrombosis as initial sign of WD preceding gastrointestinal symptoms in 2 years.

WD should be part of the differential diagnosis of diseases that cause venous thrombosis of unknown origin.

### Statement of Ethics

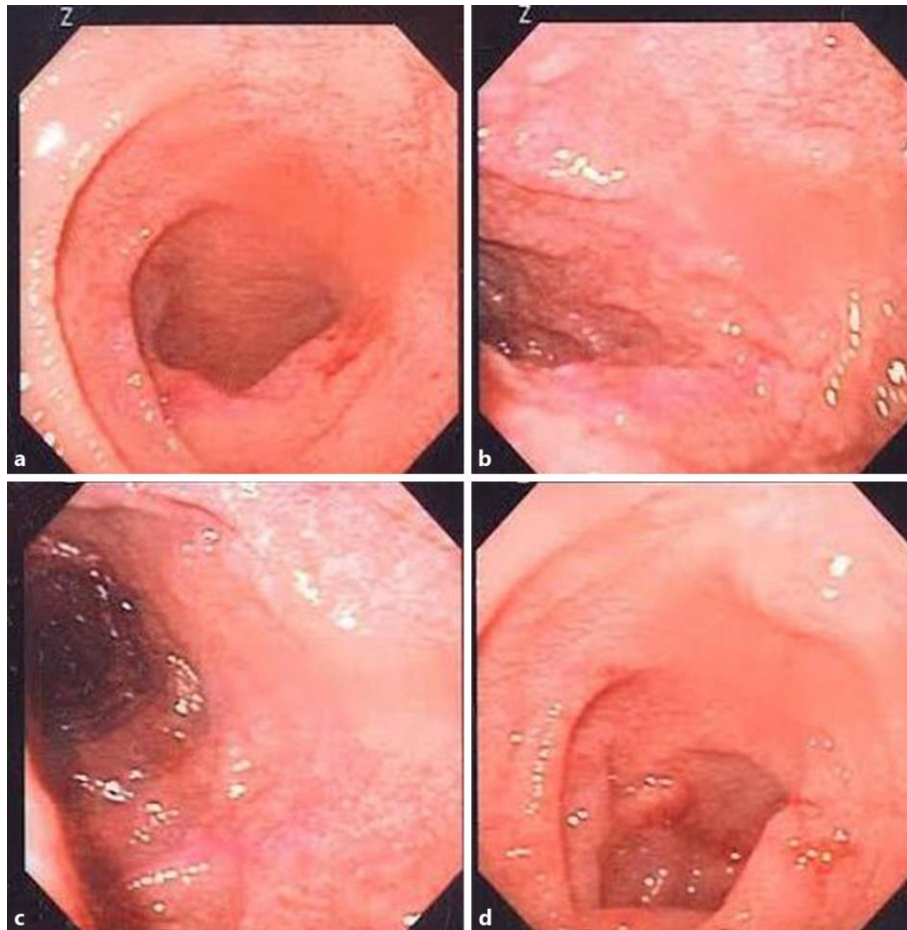
The authors have no ethical conflicts to disclose.

### Disclosure Statement

There are no potential conflicts of interest to disclose in association with this study.

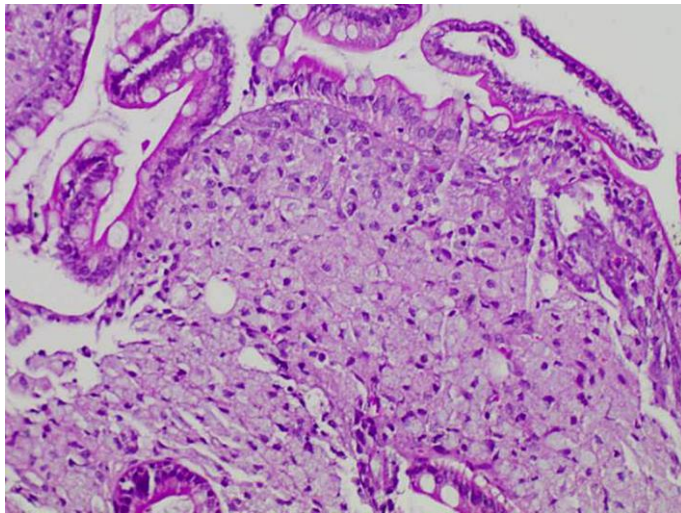
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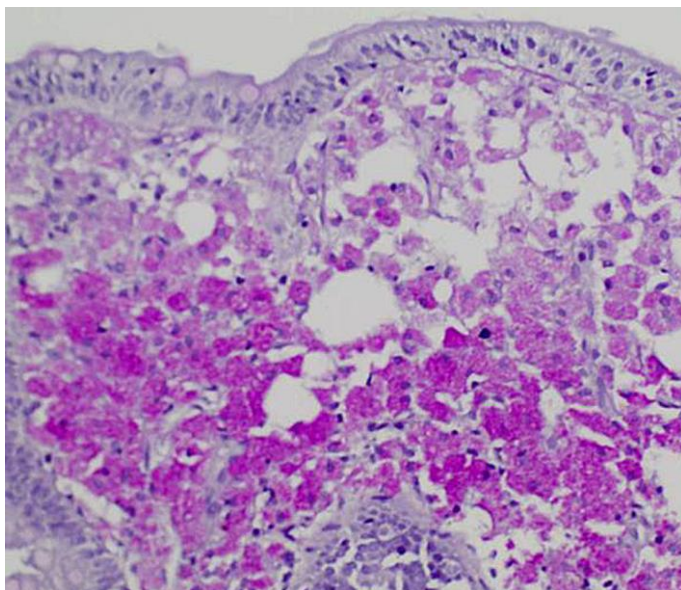


**Fig. 1.** a–d Esophagogastroduodenoscopy with reduced duodenal folds, villous edema, and white dotted infiltrates in the second duodenal portion.





**Fig. 2.** Histopathology with histiocytes diffusely infiltrating the ileal mucosa. HE. ×200.



**Fig. 3.** Histopathology with foamy histiocytes stained by PAS in the duodenum. ×200.