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*OBSERVATION*

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# *Tropheryma whipplei* infection

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## Abstract

Whipple's disease was initially described in 1907. Over the next century, the clinical and pathological features of this disorder have been better appreciated. Most often, weight loss, diarrhea, abdominal and joint pain occur. Occasionally, other sites of involvement have been documented, including isolated neurological disease, changes in the eyes and culture-negative endocarditis. In the past decade, the responsible organism *Tropheryma whipplei* has been cultivated, its genome sequenced and its antibiotic susceptibility defined. Although rare, it is a systemic infection that may mimic a wide spectrum of clinical disorders and may have a fatal outcome. If recognized, prolonged antibiotic therapy may be a very successful form of treatment.



**Key words:** *Tropheryma whipplei*; Small intestinal malabsorption; Abdominal lymphadenopathy; Periodic acid-Schiff staining; Whipple's disease

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## INTRODUCTION

Whipple's disease was first described in 1907. It required almost 100 years before the responsible organism, *Tropheryma whipplei* (*T. whipplei*) was cultivated, its genome sequenced and its antibiotic susceptibility defined[1-5]. Detailed and authoritative reviews regarding the disease have also recently appeared[6,7]. Whipple's disease is known to mimic a wide spectrum of medical conditions, and yet, only 1500 cases or so have been described to date in the literature. Most expert clinicians, including specialist gastroenterologists, never see a single case over the course of their entire careers, however this disease is a principal bacterial cause of chronic malabsorption. As such, recognition of Whipple's disease should not be minimized since timely treatment might impact on the outcome of this potentially fatal disorder.

## ORGANISM AND HOST FACTORS

Whipple's disease often affects middle-aged Caucasian men (but not exclusively), causing weight loss, arthralgia, diarrhea, steatorrhea and abdominal pain. Occasionally, other atypical presentations may occur due to involvement of the heart, lungs or central nervous system. The responsible organism is rod-shaped and can be seen in many different ultrastructural forms present in cells and extracellular spaces[8,9]. Usually, the organism is detected within macrophages of the lamina propria of the small intestine and its lymphatic drainage. The organisms, however, may also occur in epithelial cells as well as cells of the immune system. Because of genetic heterogeneity, some strains are non-pathogenic or may cause atypical clinical presentations such as an isolated infectious form of endocarditis[10]. Using a polymerase chain reaction (PCR) method, researchers found *T. whipplei* occurring in the environment and it has been documented in sewage water, fecal material and in sewage plant workers without Whipple's disease[11,12]. There may be a selective immune defect in host T-cells (or macrophages) that leads to Whipple's disease, or alternatively, these immune defects may be secondary and caused by *T. whipplei* itself[13].

## CLINICAL AND LABORATORY FEATURES

Table 1 displays common clinical and laboratory features of *T. whipplei* infection. In some cases, there is a "prodromal phase" with fever and isolated joint manifestations, including arthralgia, preceding any gastrointestinal symptoms[14,15]. These joint symptoms

**Table 1 Clinical and laboratory changes in *T. whipplei* infection**

| Clinical and laboratory changes | % |
|---|---|
| Clinical | |
| Weight loss | 90 |
| Diarrhea | 80 |
| Joint pain | 70 |
| Abdominal pain | 55 |
| Lymphadenopathy | 50 |
| Skin hyperpigmentation | 40 |
| Neurological changes | 30 |
| Laboratory | |
| Low serum carotene | 95 |
| Low serum albumin | 90 |
| Anemia | 75 |
| Elevated sedimentation rate | 70 |

may be migratory in type and rheumatoid-factor-negative. Large joints may be involved more often than small joints alone and there may be treatment resistance to antirheumatic drugs. Duodenal biopsies may be negative, but synovial fluid and biopsies examined using PCR, immunohistochemistry or electron microscopy may reveal the diagnosis[16]. Diarrhea, weight loss and malabsorption associated with low serum carotene may occur[14,15]. Anemia with an elevated sedimentation rate may develop. Peripheral edema with hypoalbuminemia and ascites (associated with protein-losing enteropathy) may develop later in the clinical course. Endoscopic changes may be noted in some, but not all, patients and have recently been illustrated by Armelao *et al*[16]. Essentially, duodenal folds appear thickened and erythematous and yellow-white plaques may be seen. Duodenal biopsies are still the basis for diagnosis in the majority of cases and have been illustrated well elsewhere[17]. The histological features can be readily appreciated on standard hemotoxylin-eosin-stained sections of mucosal biopsies as massive infiltration of the lamina propria with foamy macrophages. These macrophages contain the organism. A periodic acid-Schiff (PAS) stain will confirm the suspected diagnosis. Rarely, the infiltrate may be limited to the submucosa. Lamina propria plasma cells and lymphocytes are not increased; indeed, with extensive macrophage infiltration, they may appear to be decreased. Small collections of fat may also be present in the lamina propria (thus, the term intestinal lipodystrophy coined by Whipple) and the overlying villus epithelium may appear vacuolated because of fat accumulation[17]. In part, this may reflect obstruction of lamina propria lacteals and regional lymphatics by lymph node involvement[17]. After treatment, the bacilli may disappear and the macrophage numbers become reduced, but both may persist for years[17].

Approximately a quarter of patients with Whipple's disease develop neurological changes, and some, despite treatment, are irreversible[18,19]. Neurological change may be the initial clinical feature, and rarely may occur in isolation[19-21]. Cognitive manifestations, such as dementia, are common. Altered ocular movements may occur, including a progressive form of supranuclear ophthalmoplegia. Headache, psychiatric changes, focal or generalized seizures and ataxia are frequent. Even without neurological symptoms, cerebrospinal fluid infection may be defined by PCR analysis[22]. Ocular involvement may include uveitis, retinitis and optic neuritis with papilloedema[23]. Historically, the disorder has been recognized as a form of culture-negative endocarditis. Diagnosis by valve explantation has been recorded[10,24].

Laboratory diagnosis of *T. whipplei* infection is still largely based on duodenal biopsy. Foamy macrophages in the lamina propria are seen that are PAS-positive, but diastase-resistant. Possibly, this positive staining reaction is related to the inner membrane of the polysaccharide bacterial cell wall. A Ziehl-Nielsen stain (most typically used for mycobacteria species) is negative. Other sites, e.g. lymph nodes, may also yield a classic PAS-positive staining reaction in the macrophages. PCR has a high sensitivity and specificity but is not recommended for screening because healthy carriers with a positive PCR have been noted. Recent studies using quantitative PCR on saliva and fecal materials make a case for a role of PCR in initial evaluation[25], followed by more invasive biopsy evaluation. Immunostaining with specific *T. whipplei* antibodies may reveal the organism in PAS-negative tissues[26]. Other biomarker methods are being explored[27].

## TREATMENT

Before antibiotic treatment, a fatal course was often recorded. Later, tetracycline was often used, but recurrence was common and more recent treatment recommendations have been based on antibiotics that are capable of crossing the blood-brain barrier. Recent recommendations suggest that a 2-wk course of intravenous ceftriazone to achieve high cerebrospinal fluid levels, followed by twice daily cotrimoxazole for 1 year is very effective[7]. Most recover completely, although central nervous system symptoms may not resolve[7]. Others have suggested trimethoprim-sulfamethoxazole twice daily for 1-2 years[6]. Interestingly, treatment may be successful even if the diagnosis is established many decades after the onset of symptoms[28].

If ceftriaxone hypersensitivity is evident, then induction has been recommended with penicillin, cephalosporins, carbapenems, or chloramphenicol[7]. As an alternative to long-term cotrimoxazole, combination doxycycline and hydroxychloroquine have been recommended[7].

Recurrent neurological changes in Whipple's disease have a poor prognosis, and use of interferon gamma therapy has been described[29].

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