

Nearly Fatal Case of Whipple's Disease in a Patient Mistakenly on Anti-TNF Therapy

Christen Klochan, MD¹, Teresa A. Anderson, MD¹, Dusten Rose, PharmD², Rosen K. Dimitrov, MD³, and Raymond M. Johnson, MD, PhD¹

¹Department of Medicine, Indiana University School of Medicine, Indianapolis, IN

²Purdue University School of Pharmacy, Indianapolis, IN

³Department of Pathology, Indiana University School of Medicine, Indianapolis, IN

Abstract

Whipple's disease is a rare cause of chronic diarrhea and abdominal pain that may be confused with inflammatory bowel disease. We report a Whipple's case misdiagnosed as Crohn's disease in which treatment with anti-tumor necrosis factor (anti-TNF) therapy led to nearly fatal progression. Lymph node tissue obtained during laparotomy for suspected bowel necrosis stained dramatically with periodic acid–Schiff (PAS), and electron microscopy showed a bacterium consistent with *Tropheryma whipplei*. The patient made a remarkable recovery complicated only by cholestatic hepatitis, which was likely a treatment-associated inflammatory response. This case serves as a reminder that all granulomatous infections should be considered prior to initiation of anti-TNF therapies.

Introduction

Whipple's disease is a rare granulomatous infection of the gastrointestinal tract, with roughly 30 cases reported to the United States Centers for Disease Control each year. The causative agent is a fastidious, slow-growing, gram-positive actinomycete, *Tropheryma whipplei*, which was finally identified in the early 1990s using molecular biology techniques based on 16S ribosomal RNA PCR amplification.^{1,2} The illness is seen mostly in the fourth through sixth decades of life, typically presenting as chronic abdominal pain, diarrhea, weight loss, and joint complaints, with or without fevers. Pathogenesis of the infection includes invasion of the gastrointestinal mucosa, recruitment of macrophages to the lamina propria, and obstruction of local lymphatics, causing blunting of the small intestine villi and malabsorption/malnutrition. The bacteria can disseminate regionally from the small bowel to mesenteric lymph nodes, spleen, liver, and extraperitoneal organs including the joints, pleura, heart, and CNS. Untreated Whipple's disease is a fatal infection; however, once diagnosed, Whipple's disease is readily treated with ceftriaxone induction followed by prolonged oral trimethoprim/sulfamethoxazole therapy.³

It is common for patients with Whipple's disease experiencing prominent joint complaints with mild gastrointestinal tract symptoms to be initially misdiagnosed with inflammatory arthritides. In a recent large survey of confirmed cases, 50% of Whipple's patients were initially treated with immunosuppressive agents including steroids (43%) and tumor necrosis factor (TNF)-antagonists (14%) for presumed inflammatory arthritis.⁴ Analogously, there is the potential to misdiagnose Whipple's disease as inflammatory bowel disease, as chronic diarrhea with abdominal pain is a common presentation in gastroenterology clinics. Because Whipple's disease is rare and lacks a convenient diagnostic test, it may not be considered in the differential diagnosis for individual patients. Because TNF-antagonists are highly effective for treating inflammatory bowel diseases, including Crohn's dis-

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Correspondence: Raymond M. Johnson, MD, PhD, Division of Infectious Diseases, Department of Medicine, Indiana University School of Medicine, 635 Barnhill Drive, MS 224, Indianapolis, IN 46202 (raymjohn@iupui.edu)

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ease, it is foreseeable that some Whipple's patients misdiagnosed with inflammatory bowel disease will receive anti-TNF therapy. We report the first known example of this clinical scenario and the severe progression of Whipple's disease that developed while on anti-TNF therapy.

Case Report

Our patient is a 69-year-old female with a past history of hypothyroidism, degenerative joint disease, and restless legs syndrome admitted through the emergency room with 2.5 years of waxing and waning abdominal pain, diarrhea, fatigue, and weight loss. Upper endoscopy at an outside medical center 1 year prior to admission showed patchy erythema in the duodenum. Biopsies showed villous blunting; celiac serologies were negative. Three months after the endoscopy, she was admitted to a local hospital with diarrhea, abdominal pain, and dizziness. Video capsule endoscopy showed ulcerations in the small bowel consistent with Crohn's disease. An anti-*Saccharomyces cerevisiae* antibody (ASCA) was positive. She was started on mesalamine and budesonide for presumed Crohn's disease. That therapy did not control her symptoms, so the mesalamine was changed to adalimumab, a monoclonal antibody specific for TNF-alpha.

Five months later, and 5 months prior to her current admission, she was readmitted to the local hospital with weakness, fatigue, nausea, vomiting, diarrhea, and weight loss. CT evaluation was remarkable for abdominal lymphadenopathy. A lymph node sampled by CT-guided biopsy showed granulomata with rare fungal-like organisms suggestive of histoplasmosis. Budesonide was stopped and prednisone therapy was initiated, presumably because her diarrheal symptoms were attributed to a flare of Crohn's disease. She was prescribed itraconazole, but she took this for only 2 weeks due to financial issues. Her last dose of adalimumab was approximately 1 month prior to admission to our hospital.

The patient presented to our emergency room with complaint of diarrhea, weakness, and "just not feeling right." On admission the patient was strikingly cachectic in appearance, weighing 40.7 kg (body mass index 16.2); temperature 35.0°C, blood pressure 96/56 mmHg, heart rate 72 bpm, respiratory rate 16 bpm, and O₂ saturation 100% on room air. Her abdomen was distended, soft, and minimally tender to palpation, with hypoactive bowel sounds. The remainder of her exam was unremarkable. Admission labs were grossly abnormal, especially albumin 1.4 gm/dL (normal: 3.5–5.0) and bicarbonate 12 mmol/L (normal: 22–29; see Table 1). Her admission non-contrast CT scan showed marked distention of the colon with multiple air-fluid levels. There were multiple soft tissue masses within the mesentery and retroperitoneal lymphadenopathy. A contrast CT scan was repeated 19 hours later because of worsening acido-

Table 1. Admission Laboratory Values

Laboratory Parameter	Admission Values	Normal Values
Sodium	138 mmol/L	135–145 mmol/L
Potassium	2.9 mmol/L*	3.5–5.5 mmol/L
Chloride	115 mmol/L*	98–108 mmol/L
Bicarbonate	12 mmol/L*	22–29 mmol/L
Urea nitrogen	35 mg/dL	5–20 mg/dL
Creatinine	1.5 mg/dL	0.6–1.4 mg/dL
Glucose	88 mg/dL	70–99 mg/dL
Calcium	6.3 mg/dL	8.5–10.5 mg/dL
Albumin	1.4 gm/dL*	3.5–5.0 gm/dL
Protein	4.8 gm/dL*	6.7–8.6 gm/dL
Total bilirubin	0.3 mg/dL	0.0–1.0 mg/dL
Alkaline phosphatase	87 U/L	25–125 U/L
AST	20 U/L	25–45 U/L
ALT	14 U/L	0–50 U/L
White blood cells	10.2 k/mm ³	4.5–11.5 k/mm ³
Hemoglobin	9.3 g/dL*	12–15 g/dL
Platelets	346 k/mm ³	150–450 k/mm ³

*Abnormal values. ALT=alanine aminotransferase; AST=aspartate aminotransferase.

sis and hypotension. It showed the bulky retroperitoneal and mesenteric adenopathy, diffuse thickening of the entire small bowel from the duodenum to the terminal ileum, and pneumatosis intestinalis (Figure 1). Concern for bowel compromise led to an emergent exploratory laparotomy. The bowel was intact with a pasty exudate covering the bowel and peritoneal surfaces. A 3 x 2-cm mesenteric lymph node was resected for pathology. Intraoperative brushings and frozen sections sent to surgical pathology showed granulomatous disease (Figure 2A). Acid-fast bacteria (AFB) and Grocott's methenamine silver (GMS) stains were negative for acid-fast bacilli or fungi in brushings and lymph node tissue. The patient's T-spot and *Histoplasma capsulatum* H-band M-band/complement fixation/urine antigen were negative. Based on her clinical history, the infectious disease service requested a periodic acid-Schiff (PAS) stain on lymph node tissue, which was positive (Figure 2B). Electron microscopy

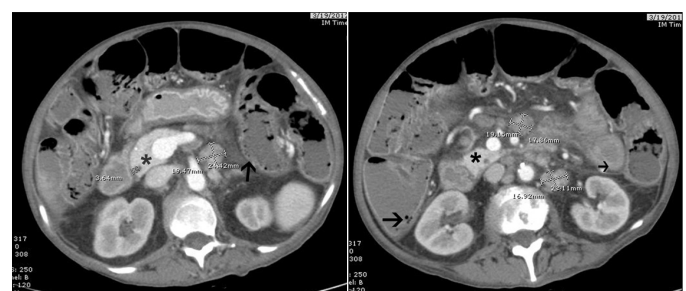


Figure 1. CT scan of the abdomen with lymphadenopathy (rulers), abnormal mesenteric soft tissue (*), thickened small bowel wall (small arrow), and pneumatosis intestinalis (large arrows).

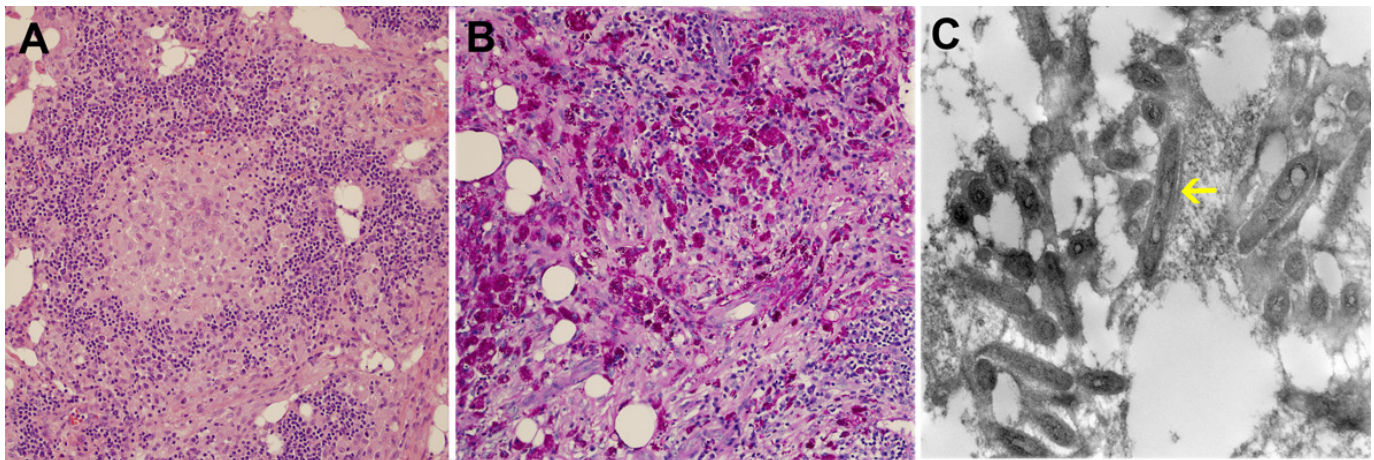


Figure 2. (A) H&E staining of peritoneal cavity brushings (200 x magnification). (B) PAS staining of mesenteric lymph node tissue (200 x magnification). (C) Electron microscopy of lymph node tissue (43,600 x magnification). Yellow arrow highlights a rod-shaped bacterium consistent with *Trophyrema whipplei*.

demonstrated aggregates of rod-shaped bacteria consistent with *Trophyrema whipplei* (Figure 2C). There was no evidence of malignancy on histopathology or flow cytometry.

The patient was treated with ceftriaxone 2 gm daily for 2 weeks, followed by oral trimethoprim/sulfamethoxazole therapy, dose-adjusted for mild renal insufficiency to 400/80 mg orally 3 times daily. The patient recovered dramatically. She had a transient increase in alkaline phosphatase from its admission value of 87 U/L to a peak value of 525 U/L at 3 weeks into antibiotic therapy, dropping down to 244 U/L at 4 weeks, and 204 U/L at 6 months of antibiotic therapy. A 4-month follow-up CT scan showed a roughly 50% decrease in the size of all intraperitoneal lesions. Her lab abnormalities of anemia, acidosis, and hypoalbuminemia resolved. Four months after discharge, her weight was 54.9 kg, up from 40.7 kg, close to her baseline weight 3 years earlier. Her diarrhea and joint pains resolved; her only residual complaint was her previously diagnosed restless legs syndrome.

Discussion

While there are several case reports of Whipple's disease patients initially misdiagnosed with inflammatory arthritides and receiving TNF-antagonist therapies,⁵⁻⁹ to our knowledge this is the first reported case of a patient initially misdiagnosed with Crohn's disease. Our patient had a severe case of Whipple's disease due to either the 10-month duration of anti-TNF therapy preceding Whipple's diagnosis, a significant infection at the time of anti-TNF therapy initiation, or possibly both. Because the patient's diarrhea and abdominal pain syndrome resolved completely with ceftriaxone followed by trimethoprim/sulfamethoxazole, it is highly unlikely that she has underlying Crohn's disease.

Though difficult to prove, it is generally thought that anti-TNF therapy worsens the clinical course of Whipple's dis-

ease. A study of non-steroidal anti-inflammatory drugs versus conventional immunosuppression (corticosteroids, azathioprine, methotrexate, etc.) in Whipple's patients initially treated for inflammatory arthritis showed that immunosuppressive therapy accelerated the disease in the form of earlier development of diarrhea.¹⁰ Our patient's clinical course is consistent with that general impression. Histopathology suggests that macrophages are critical in the host immune response to *Trophyrema whipplei* infections. TNF-alpha is critical for macrophage killing of intracellular pathogens,^{11,12} and has been shown to facilitate granuloma formation for the containment of intracellular pathogens such as *Mycobacterium* and *Histoplasma*.^{13,14} Disruption of granuloma formation is one hypothesis for the infectious complications of anti-TNF therapies.

An interesting feature of our patient's clinical course was a dramatic asymptomatic elevation in her alkaline phosphatase level after starting antibiotic therapy. Based on the extent of infection in her abdomen and hepatomegaly seen on CT, it is possible that the liver was also involved with the infection. Alternatively, treatment-induced inflammatory syndromes can be seen in Whipple's disease patients.¹⁵ Our patient's cholestatic liver injury may be a treatment-induced inflammatory syndrome. Her alkaline phosphatase continued to decline through 6 months of trimethoprim/sulfamethoxazole therapy, largely ruling out drug-related toxicity. However, the alkaline phosphatase was never fractionated, gamma-glutamyl transferase was never obtained, and a liver biopsy was not performed, so the true etiology cannot be proven.

Advent of non-invasive endoscopy (video capsule) and serologic testing for inflammatory bowel diseases (e.g., the Prometheus® IBD7 panel [Prometheus Laboratories, Inc., San Diego, CA]) has the potential for non-histopathology-based

diagnosis of inflammatory bowel diseases. However, as this case report demonstrates, a non-histology-based diagnostic approach is problematic. There is a long differential diagnosis for small bowel ulcerations seen on capsule endoscopy. Positive serologic testing for inflammatory bowel disease is helpful in cases with a high pre-test probability, and can be helpful in distinguishing between Crohn's disease and ulcerative colitis, but it is not diagnostic of either disease. A retrospective study in a pediatric abdominal pain/diarrhea/weight loss cohort showed that the IBD7 panel had a positive predictive value of 63%.¹⁶ In our case, a non-diagnostic EGD duodenal biopsy (without PAS staining) was followed up by video endoscopy and serology to give an errant diagnosis of Crohn's disease. Even with biopsy-based diagnosis of inflammatory bowel disease, there are overlapping histopathology findings in Crohn's disease (non-caseating granulomatous inflammation) and Whipple's disease (histiocytic/granulomatous infection). PAS stains on biopsy specimens are simple and inexpensive, but they must be specifically requested in most hospitals on biopsy specimens to exclude the presence of histiocytic or granulomatous inflammation to rule out Whipple's disease. Patients presenting with abdominal pain/diarrhea syndromes in their fourth to sixth decades should have PAS stains performed on anti-TNF therapies.

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