

A Rare Intestinal Infection with Systemic Effects

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Case Report

A 53-year-old black man presented to our medical center with a new-onset seizure. He had been feeling well until the day he was admitted, when he felt shortness of breath and lightheadedness during a period of exertion. A family member contacted emergency medical services. During transport, the patient developed tonic-clonic-like seizure activity, and right eye gaze deviation was noted during an examination in the emergency room. The patient was intubated for airway protection and given fosphenytoin as well as empiric antibiotics for treatment of suspected meningitis. During transfer to a neurologic intensive care unit, persistent hypotension was noted, and the patient responded to phenylephrine.

The patient's medical history was notable for a right middle cerebral artery stroke that had occurred 6 months earlier and had been diagnosed at another institution. At that time, his transthoracic echocardiogram was notable for left ventricle thrombus, for which he was maintained on warfarin sodium (Coumadin, Bristol-Myers Squibb). Also of note, he had a 10-year history of arthralgias. He had been diagnosed with seronegative arthritis that was intermittently managed with steroids. Over a period of several years prior to presentation, the patient experienced progressive hearing loss (predominantly affecting his left ear), and progressive cognitive impairment was noted by his family

members. He had no recent illnesses or changes in his medical regimen, and he denied any recent travel. His family history was notable for a sister who died from pancreatic cancer at an early age.

The patient's complete blood count revealed leukocytosis (19,400 cells/ μ L) and normocytic anemia (with hematocrits measuring 26.2%). His blood urea nitrogen/creatinine ratio was elevated (40/1.6) but rapidly improved with hydration. Following hydration, his total serum protein level was 4.6 mg/dL, and his albumin level was 2.3 mg/dL. The patient's blood and urine cultures were unrevealing. Analysis of his cerebrospinal fluid (CSF) revealed normal glucose and total protein levels and no pleocytosis. An electroencephalogram showed diffuse slowing, with no evidence of epileptiform activity. His subsequent neurologic examination did not reveal any focal abnormalities. His blood pressure subsequently stabilized. The patient was weaned off of vasopressors within 24 hours, and he was extubated within 36 hours. A magnetic resonance image of the brain did not reveal any acute processes. A chest radiograph revealed a possible right lower lobe infiltrate, and the patient was discharged to the hospital floor for continued treatment of pneumonia.

While being transferred, the patient complained of abdominal pain. Six months prior to presentation, he had complained of alternating constipation and diarrhea associated with significant bloating. Ten days after admission, he developed mild transaminitis (an alanine aminotransferase level of 94 U/L and an aspartate aminotransferase level of 102 U/L), with a normal alkaline phosphatase level and a transiently elevated lipase level (349 U/L). Abdominal ultra-

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sonography revealed sludge without cholelithiasis, and a hepatobiliary iminodiacetic acid scan was negative. A computed tomography scan of his abdomen and pelvis revealed duodenal and jejunal thickening with associated mesenteric lymph node enlargement (Figure 1). His pancreas appeared normal. An esophagogastroduodenoscopy revealed prominent folds and white punctate mucosal patches with an overlying yellowish exudate in the second part of the duodenum (Figure 2). Pathology revealed extensive replacement of the lamina propria by sheets of foamy macrophages that were positive for periodic acid-Schiff (PAS) stain (Figure 3A). Immunohistochemistry for *Tropheryma whipplei* infec-

tion was positive, which was consistent with Whipple disease (WD; Figure 3B). Polymerase chain reaction (PCR) analysis of the CSF was similarly positive for *T. whipplei* infection. A transesophageal echocardiogram revealed a vegetation on the anterior leaflet of the mitral valve, which prolapsed into the left ventricle.

The patient was treated with intravenous ceftriaxone for 4 weeks followed by oral trimethoprim/sulfamethoxazole for 1 year. Due to his central nervous system (CNS) involvement and history of immunosuppressive therapy for arthritis, treatment with steroids was started to decrease the risk of immune reconstitution inflammatory syndrome (IRIS). A repeat endoscopy performed

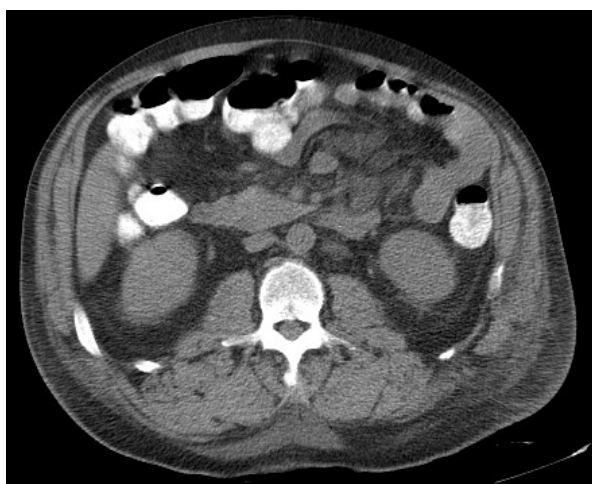


Figure 1. A computed tomography scan of the abdomen revealed mesenteric lymphadenopathy adjacent to unopacified loops of the small bowel.



Figure 2. An esophagogastroduodenoscopy revealed prominent folds and white punctate mucosal patches with an overlying yellowish exudate in the second part of the duodenum.

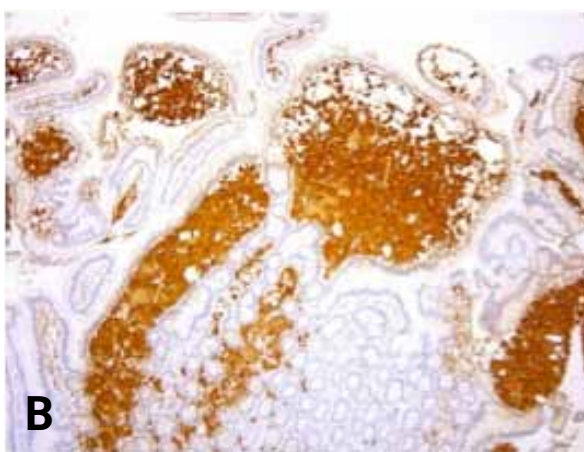
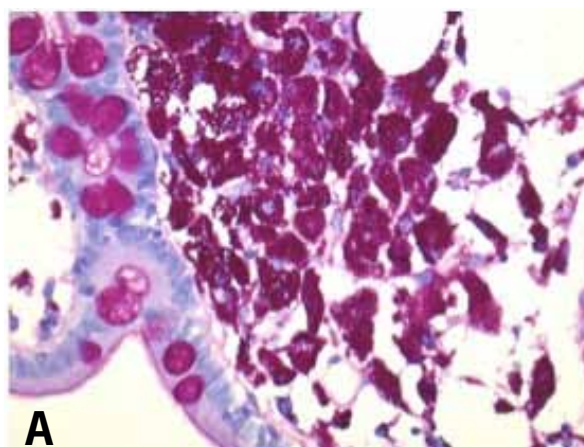


Figure 3. A duodenal biopsy revealed extensive replacement of the lamina propria by sheets of foamy macrophages that were positive for periodic acid-Schiff stain (200× magnification; A). *Tropheryma whipplei* immunohistochemistry (polyclonal rabbit antibody, 100× magnification; B). Figure 3B courtesy of Dr. Christina A. Arnold, Johns Hopkins University, Baltimore, Maryland.

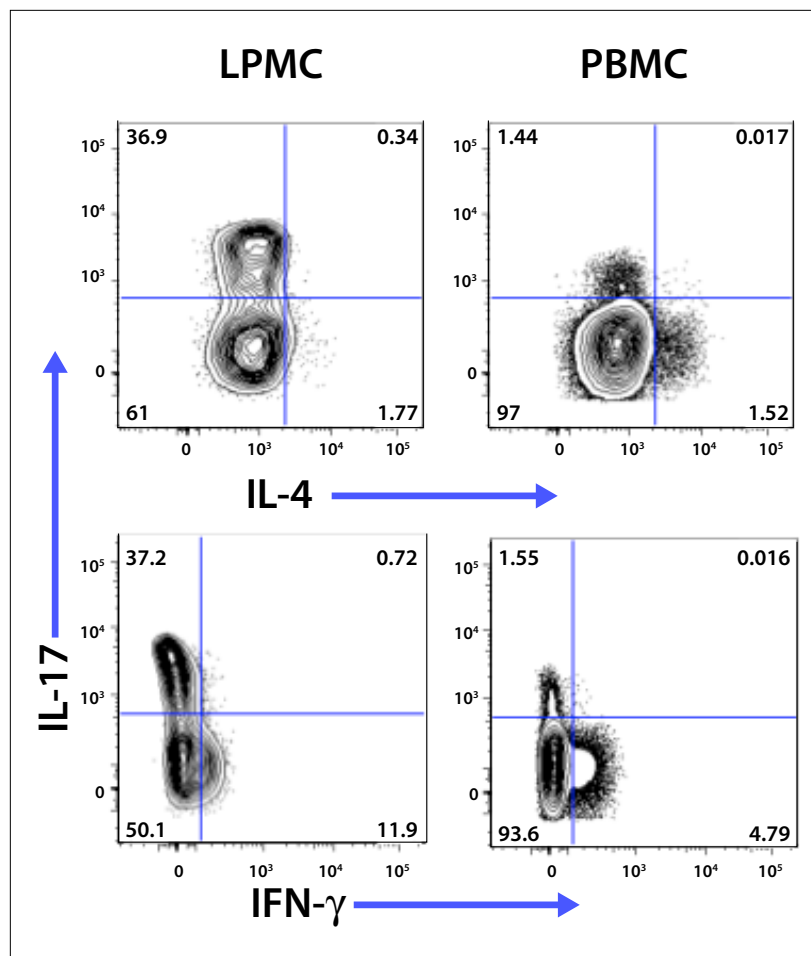


Figure 4. Flow cytometry of lamina propria mononuclear cells (LPMCs) or peripheral blood mononuclear cells (PBMCs) was performed in CD3+/CD4+ cells activated with phorbol myristate acetate/ionomycin for 4 hours. Production of interleukin (IL)-17 is noted on the y-axis, while production of interferon (IFN)-γ or IL-4 is noted on the x-axis. The percentage of cells positive for each respective marker is indicated.

6 months later demonstrated resolution of endoscopic findings and near-complete disappearance of PAS-positive macrophages. Peripheral blood mononuclear cells were purified via discontinuous Ficoll-Hypaque gradient, and lamina propria mononuclear cells were isolated via collagenase digestion followed by discontinuous Percoll gradient in order to evaluate cytokine production by CD4+ T cells. To assess T-helper (Th)1, Th2, and Th17 cells, flow cytometry was used to measure production of interferon-γ, interleukin (IL)-4, and IL-17, respectively, in CD3+/CD4+ mononuclear cells (Figure 4). Th17 cells predominate in the lamina propria, with 36.9% of CD4+ T cells producing IL-17; in comparison, 11.9% and 1.8% of CD4+ T cells were Th1 and Th2 cells, respectively.

Discussion

WD is caused by the rod-shaped bacteria *T. whipplei*. Phylogenetic analysis of bacterial ribosomal RNA

characterizes *T. whipplei* as an actinomycete.¹ The classic clinical manifestations of WD described by George Whipple in 1907 include diarrhea, weight loss, abdominal pain, and arthropathy.² Late-onset WD is rare, but exposure to the bacteria may be underestimated. Detection of *T. whipplei* bacterium via PCR has been reported in 1.5–11% of fecal samples from asymptomatic healthy donors, suggesting that there may be an underlying genetic predisposition to the condition in affected individuals.³ Although WD is generally regarded to be a gastrointestinal disease, joint manifestations typically precede gastrointestinal manifestations by several years in up to 63% of affected individuals.⁴ In this patient, the onset of arthralgias preceded intestinal symptoms by 9 years. Joint complaints may improve with the onset of gastrointestinal symptoms. Cardiac involvement has also been described, usually affecting the mitral and/or aortic valves.⁵ Whipple endocarditis is culture-negative and is generally diagnosed via valvular histology, culture, or PCR. Biomarkers of WD (including IL-16) have been

reported, but evidence of valvular vegetation in the setting of systemic WD (PCR-positive CSF) supports the diagnosis of Whipple endocarditis in this patient.⁶ In addition, neurologic symptoms occur in 15–20% of WD patients and typically include cognitive changes, as seen in this patient. Pathognomonic findings include oculomasticatory or orofacial-skeletal myorhythmia, which generally occur with supranuclear vertical gaze palsy.⁷ Cranial nerve findings (including hearing loss and visual changes) have also been described.⁸ Rarely, WD may manifest as stroke-like symptoms secondary to vasculitis.

Treatment with antibiotics can be complicated by a Jarisch-Herxheimer response, which may have accounted for the profound hypotension initially seen in this patient.⁹ IRIS may occur during the first few weeks of antibiotic treatment, particularly in patients with CNS disease or a history of immunosuppressive therapy for presumed rheumatic disease.¹⁰ Corticosteroids may be helpful as prophylaxis for IRIS.

Several studies have investigated the immune pathogenesis of WD. Immunoglobulin (Ig)A plasma cells have reportedly been a target of *T. whipplei* infection and may account for the decreased levels of mucosal IgA.¹¹ *T. whipplei* similarly infects macrophages in the lamina propria, which may stimulate alternatively activated macrophages and may favor Th2 polarization.¹² Additionally, infection of monocytes impairs IL-12 production and subsequent Th1 polarization.¹³ Consistent with these results, *T. whipplei*-specific Th1 responses are reduced in infected individuals.¹⁴ Analysis of the CD4+ T compartment in this patient suggests that IL-17-producing CD4+ T cells (Th17) predominate in the lamina propria compared to the peripheral blood (Figure 4). Th17 responses play an important role in the intestinal immune response to microbes. Dysregulation of this immune response has been associated with inflammatory bowel disease as well as systemic manifestations of autoimmunity (including arthritis and multiple sclerosis).^{15,16} Further analysis of the role of Th17 in the pathogenesis of intestinal and extra-intestinal manifestations of WD is warranted.

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Review

Connecting the Dots: The Many Systemic Manifestations of Whipple Disease

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Longman and colleagues present a case of Whipple disease with many extraintestinal manifestations, which emphasizes the importance of recognizing the varied clinical presentations and systemic nature of this disease.¹ Whipple disease is a rare, chronic, multisystemic bacterial infection

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