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/μL) 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* infection 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

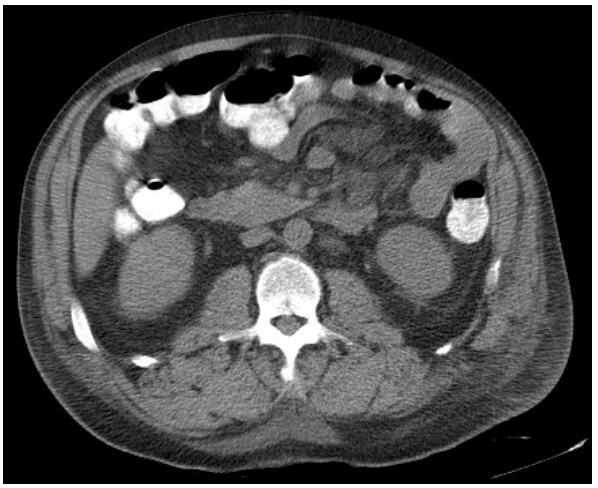

Figure 1. A computed tomography scan of the abdomen revealed mesenteric lymphadenopathy adjacent to unopacified loops of the small bowel.

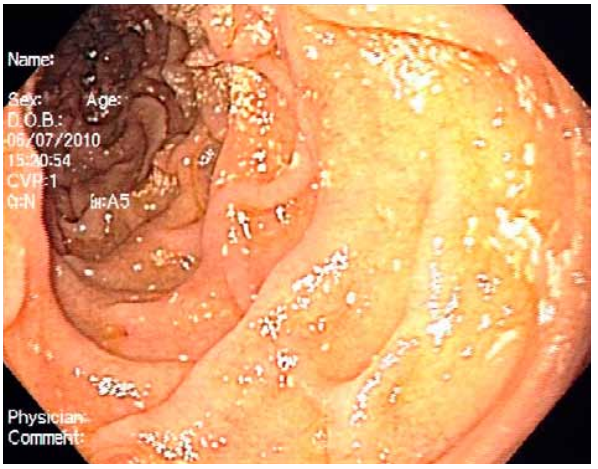

Figure 2. An esophagogastroduodenoscopy revealed prominent folds and white punctate mucosal patches with an overlying yellowish exudate in the second part of the duodenum.

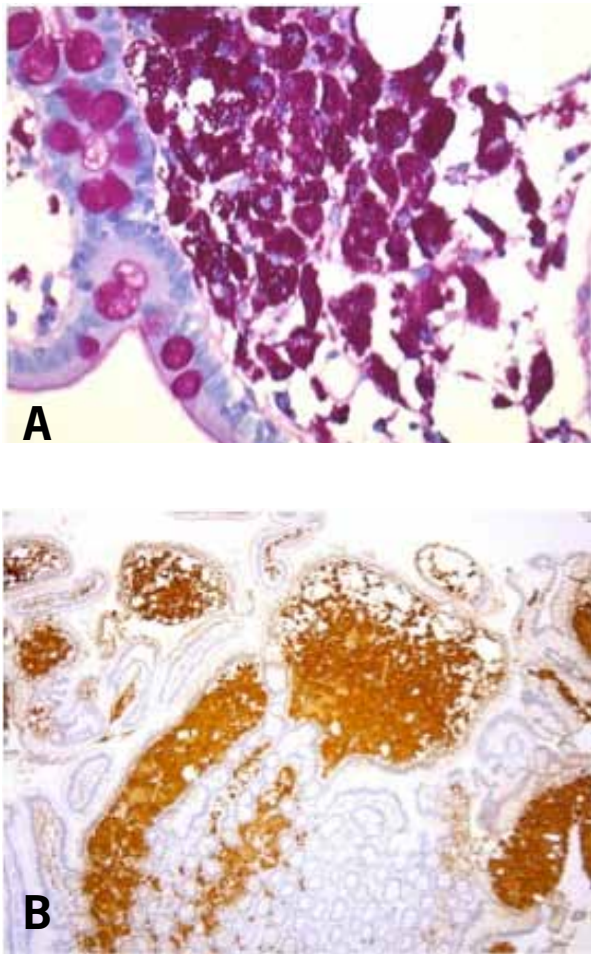

Figure 3. A duodenal biopsy revealed extensive replacement of the lamina propria by sheets of foamy macrophages that were positive for periodic acid-Schiff stain (200× magnification; **A**). *Tropheryma whipplei* immunohistochemistry (polyclonal rabbit antibody, 100× magnification; **B**). Figure 3B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

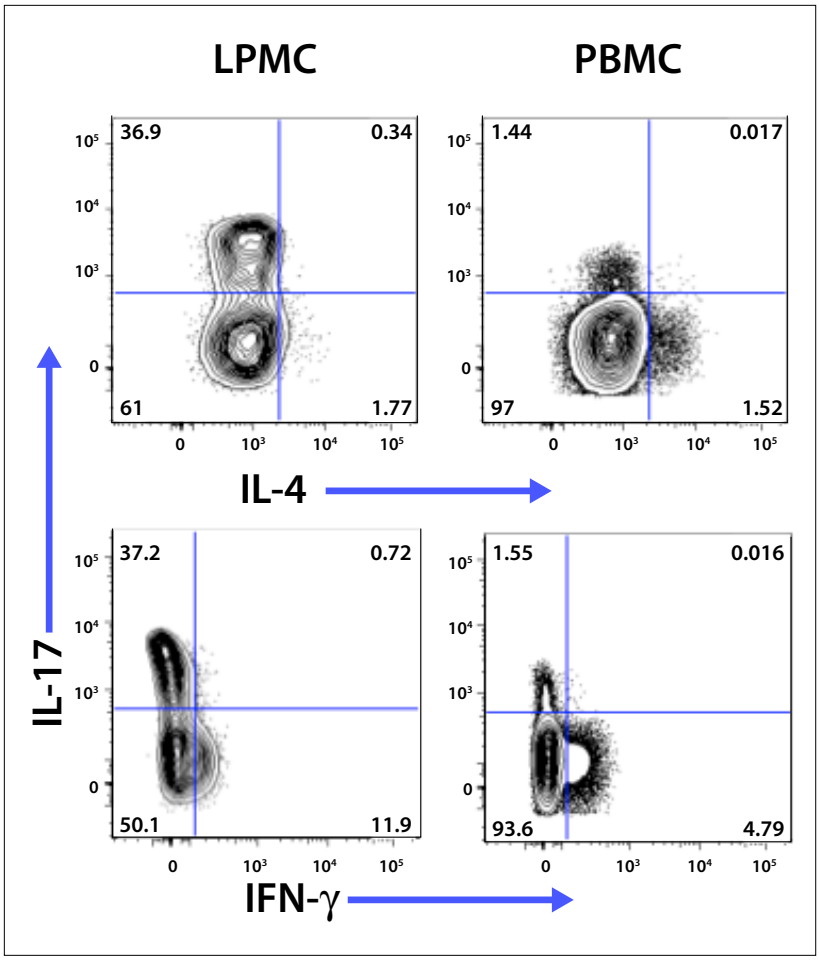

Figure 4. Flow cytometry of lamina propria mononuclear cells (LPMCs) or peripheral blood mononuclear cells (PBMCs) was performed in CD3+/CD4+ cells activated with phorbol myristate acetate/ionomycin for 4 hours. Production of interleukin (IL)-17 is noted on the y-axis, while production of interferon (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 oculofacial-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 extraintestinal 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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caused by *Tropheryma whipplei,* a member of the diverse family of actinomycetes usually found in soil.[2] The disease is most prevalent in individuals in their 40s–60s, with a mean age of 50 years and a male predominance, both of which are characteristics of the Whipple disease patient presented by Longman and colleagues.[1,3] In contrast to this patient, Whipple disease predominantly occurs in whites and has rarely been described in individuals of African descent or other ethnic groups. *T. whipplei* DNA has been found in samples of waste water, in gastric juices and saliva of individuals without Whipple disease, and in fecal samples of asymptomatic healthy donors; these findings suggest that *T. whipplei* may be a ubiquitous environmental or commensal organism.[4-9] Although the mode of transmission is uncertain, these findings are consistent with a common environmental exposure and underlying genetic susceptibility.

Immune evasion and host interaction are important in the pathogenesis of Whipple disease. Defective macrophage function, impaired T helper (Th)1 cell response, and activation of the Th2 pathway are characteristic of Whipple disease. Longman and colleagues' findings that interleukin-17–producing CD4+ cells predominate in the lamina propria compared to peripheral blood suggests that the Th17 pathway plays a possible role as well.[1] The combination of these findings strongly suggests that underlying defects in monocyte/macrophage function play an important pathophysiologic role in Whipple disease and that defects in host defenses may lead to the inability of the infected individual to eliminate these bacteria.

The clinical manifestations of Whipple disease vary widely and include gastrointestinal and extraintestinal symptoms, reflecting the systemic nature of the infection. Either diarrhea or steatorrhea is the most common presenting complaint; however, this symptom is not invariably present.[3] Other intestinal symptoms include abdominal bloating, cramps, and anorexia. After presenting with a seizure, the patient described by Longman and colleagues reported abdominal pain; he had also experienced other gastrointestinal symptoms, including bloating and diarrhea, during the 6 months prior to presentation.[1] Not surprisingly, these nonspecific symptoms had not previously led to a diagnosis of Whipple disease, as the clinical focus was likely on his cerebrovascular accident (CVA), neurologic symptoms, and cognitive decline. Weight loss is also seen in the majority of patients with Whipple disease. Seronegative arthritis, which is the most common extraintestinal symptom, affects the majority of patients.[3] Arthritis typically develops months to years before the initial diagnosis of Whipple disease. The patient presented by Longman and colleagues demonstrated this classic feature of Whipple disease.[1] Intermittent low-grade fever, fatigue, and generalized weakness are also common, and many other extraintestinal symptoms may occur. Cardiac involvement may be manifested as congestive heart failure, valvular lesions, pericarditis, or endocarditis.[10-18] A transesophageal echocardiogram in the patient presented by Longman and colleagues revealed vegetation on the anterior leaflet of the mitral valve, suggesting cardiac involvement.[1] The combination of polymerase chain reaction (PCR)-positive cerebrospinal fluid (CSF) documenting systemic involvement and the presence of a valvular lesion is consistent with a diagnosis of Whipple endocarditis in this case.

Central nervous system (CNS) involvement is common in Whipple disease; however, symptoms related to CNS Whipple disease may be present in a minority of patients.[19-24] Neurologic symptoms may occur in association with gastrointestinal symptoms or as isolated symptoms. The most common CNS symptoms are dementia, paralysis of gaze, and myoclonus. In the patient presented by Longman and colleagues, progressive cognitive impairment and hearing loss are likely manifestations of CNS involvement.[1] Seizures in the setting of solitary mass lesions or multiple nodular enhancing lesions have also been observed in Whipple disease.[25] However, this patient's magnetic resonance image of the brain was normal.[1] Other potential etiologies for seizure in patients with Whipple disease may include electrolyte disturbance and medication overdose or withdrawal, possibly related to cognitive decline. In addition, there have been reports of stroke-like symptoms related to cerebral vasculitis from hematogenous spread of *T. whipplei* infection as well as recurrent embolic CVA secondary to *T. whipplei* endocarditis.[26,27] One of these mechanisms may have been the underlying etiology of this patient's recent stroke.[1]

Hyperpigmentation and peripheral lymphadenopathy are the most common physical findings and are seen in more than half of patients with Whipple disease. Often, findings related to severe malabsorption such as emaciation, muscle wasting, peripheral edema, and peripheral neuropathy are present. An abdominal examination often reveals mild distention and tenderness, and abdominal fullness or a mass may be evident due to marked enlargement of the mesenteric lymph nodes. Other well-recognized physical findings in patients with Whipple disease include fever, peripheral arthritis, heart murmurs, pleural or pericardial friction rubs, and ocular abnormalities, reflecting the systemic nature of the infection. Potential neurologic findings suggestive of CNS or cranial nerve involvement include dementia, ataxia, muscle weakness, sensory loss, and ophthalmoplegia.

Laboratory abnormalities reflective of malabsorption—such as electrolyte disturbances, anemia secondary to chronic disease or iron deficiency, hypoalbuminemia, low serum carotene levels, and prolonged prothrombin

time—are common in patients with Whipple disease. Normocytic anemia and hypoalbuminemia were present in the patient presented by Longman and colleagues.[1] Common radiologic features of Whipple disease include marked thickening of the mucosal folds (predominantly in the proximal small bowel) on a small bowel series, as well as small bowel thickening and massive para-aortic and retroperitoneal adenopathy on an abdominal computed tomography scan. The small bowel thickening and mesenteric lymphadenopathy seen on the computed tomography scan in the case by Longman and colleagues is nonspecific but consistent with Whipple disease, and an endoscopy with a small intestinal biopsy was appropriately pursued.[1] Endoscopy in Whipple disease may reveal a characteristic finding of pale, shaggy, yellow mucosa in the postbulbar duodenum.[28] The endoscopic description of white punctate mucosal patches with overlying yellowish exudate in the second portion of the duodenum in this patient is consistent with Whipple disease.[1]

Diagnosis of Whipple disease is made via a small intestinal mucosal biopsy that reveals infiltration of the lamina propria of the small intestine with large, foamy, periodic acid-Schiff (PAS)-positive macrophages that contain gram-positive, acid-fast–negative bacilli. Immunohistochemical analysis is a sensitive and specific method for diagnosing Whipple disease, and electron microscopy can be performed to verify the presence of the characteristic bacilli. Molecular diagnosis using PCR-based diagnostic tests may be useful for confirming the diagnosis. PAS-positive macrophages and characteristic bacilli have been identified in many extraintestinal tissues, reflecting the systemic nature of the disease. Rarely, diagnosis of Whipple disease is established in the absence of intestinal involvement by identifying the characteristic bacilli in extraintestinal sites. In the patient reported by Longman and colleagues, the diagnosis of Whipple disease was made via small intestinal biopsies that revealed PAS-positive macrophages, and the diagnosis was confirmed via immunohistochemistry.[1] In addition, PCR analysis of the CSF was positive, which is consistent with CNS involvement, as suspected by the patient's clinical presentation.[1]

Treatment of Whipple disease consists of an initial 2-week course of intravenous ceftriaxone or meropenem or parenteral penicillin G and streptomycin, followed by a 1-year course of trimethoprim/sulfamethoxazole, which readily crosses the blood-brain barrier.[29] Jarisch-Herxheimer reactions, which are characterized by fever, rigors, and hypotension, can occur with treatment of Whipple disease. Interestingly, this patient developed hypotension after institution of empiric antibiotic therapy for meningitis.[1] Antibiotic therapy is usually highly effective, with rapid improvement in gastrointestinal and extraintestinal symptoms; however, relapses are fairly common. Relapses of gastrointestinal symptoms and arthritis may occur early or late and may respond favorably to further antibiotic treatment, whereas CNS relapses tend to occur late and respond poorly to additional antibiotic therapy. After 1 year of antibiotic therapy, a repeat small intestinal mucosal biopsy is recommended to document the absence of residual bacilli. A repeat endoscopy in the patient presented by Longman and colleagues revealed resolution of the endoscopic findings and near-complete disappearance of the PAS-positive macrophages.[1] Although PAS-positive macrophages may be present in the lamina propria for many years in patients treated for Whipple disease, the presence of bacilli on electron microscopy suggests inadequate treatment.

Whipple disease is an insidious and elusive disorder that can produce widespread clinical manifestations across multiple organ systems with or without significant gastrointestinal symptoms. The case presented by Longman and colleagues illustrates the chronic and multisystemic nature of the disease, many characteristic and unusual features, and the classic diagnostic findings of Whipple disease.[1] Maintaining a high clinical suspicion for this rare condition with protean manifestations is difficult, but the search for a unifying diagnosis can lead to successful antibiotic treatment. Further investigation into the questions raised by Longman and colleagues regarding the Th17-predominant response may prove to be important in gaining a better understanding of the pathogenesis of Whipple disease.[1]

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