Whipple's Disease Mimicking Common Digestive Disorders

YOUSEF ELFANAGELY, MD; SEHRISH JAMOT, MD; KWAME DAPAAH-AFRIYIE, MD; SEAN FINE, MD

ABSTRACT

Whipple's disease is a rare infectious disease caused by the bacterium *Tropheryma whipplei*. The prevalence of Whipple's disease is 3/1,000,000 in Western populations. It most often causes a malabsorption disorder with weight loss and diarrhea as common presenting symptoms. In one-third of patients, however, there are no gastrointestinal symptoms at presentation; patients instead report a wide variety of non-specific extraintestinal complaints, potentially involving every organ system. We report a case of a 37-year-old man who presented with a 3-month history of non-bloody diarrhea and 15-pound weight loss. He was ultimately diagnosed with biopsy-confirmed Whipple's disease. Despite its rarity, Whipple's disease remains an important clinical entity and should be included on the differential diagnosis for selected patients presenting with an array of non-specific symptoms.

KEYWORDS: Whipple's Disease, pathology, gastroenterology

INTRODUCTION

Whipple's disease was first described in 1907 by Dr. George Hoyt Whipple. The first small bowel biopsy diagnosis of Whipple's disease was made in 1958. Since then, the organism has been identified and cultured, its genome sequenced, and new PCR-based bacterial identification and immunohistochemical (IHC) diagnostic tests developed.[1] Whipple's disease remains a rare disease that mainly affects middle-aged Caucasian men. Recent studies suggest a prevalence of 3/1,000,000.[1]

Due to its rarity and protean manifestations, the average time between the appearance of the first clinical signs and the diagnosis may be as long as 6 years.[2] Patients most often present with joint pains associated with gastrointestinal symptoms such as diarrhea, malabsorption, and weight loss. However, one-third of patients do not present with classic signs and symptoms. Whipple's disease can also present as a wide spectrum of isolated or multi-system involvement of every organ. The diagnosis is made by the presence of Periodic acid-Schiff (PAS)-positive macrophages in the lamina propria of the small bowel or positivity of IHC using antibodies specifically directed against the bacteria. IHC increases the specificity and sensitivity of the diagnosis especially by decreasing false positives due to PAS-positive staining in cases of Mycobacterium infections.[2] (**Timeline**)

CASE REPORT

Our patient is a 37-year-old Caucasian man with a history of microcytic anemia (diagnosed two months prior to presentation) and a 3-month history of diarrhea, weight loss and abdominal bloating admitted to the hematology service for workup of anemia and possible malignancy. Physical exam revealed a thin, pale man with notable findings of conjunctival pallor, dry mucous membranes and diffuse abdominal tenderness to palpation. Complete blood count was notable for WBC count of 10,500 with 89% neutrophils, hemoglobin of 9.6 with an MCV of 69, and platelets of 530,000/mcl. Iron studies were most consistent with mixed iron deficiency anemia and anemia of chronic disease. Human Immunodeficiency Virus (HIV) Antibody/Antigen Combination test was non-reactive. Computed tomography (CT) scan revealed

Timeline.

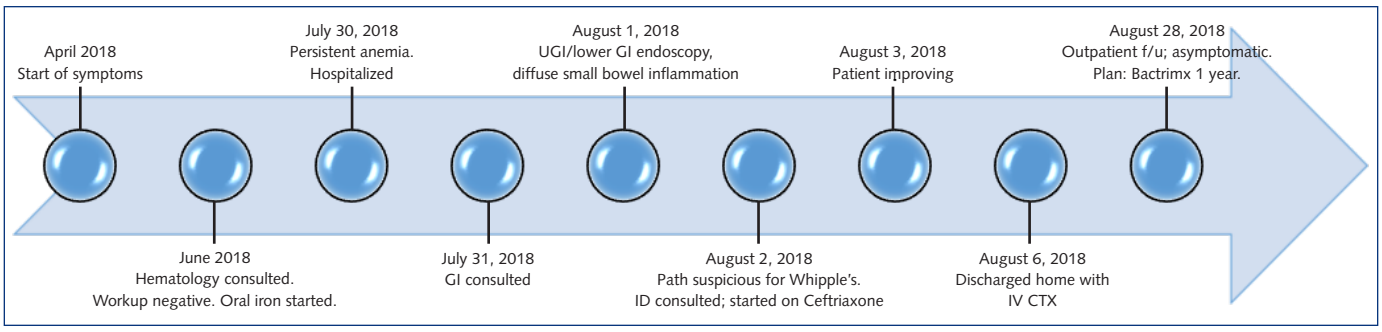


Image A. Computed tomography (CT) scan
Numerous low attenuating, enlarged mesenteric and retroperitoneal lymph nodes (black arrows)

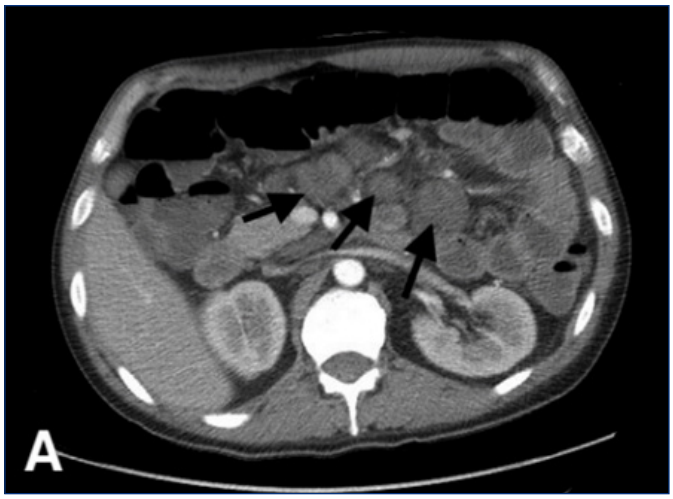
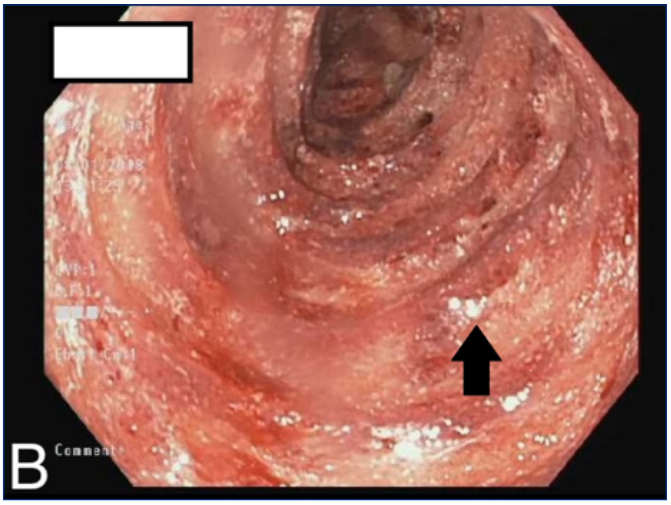


Image B. Esophagogastroduodenoscopy
Diffuse severe mucosal changes characterized by congestion, erythema, friability (with spontaneous bleeding) and inflammation in the first portion of the duodenum (black arrow)

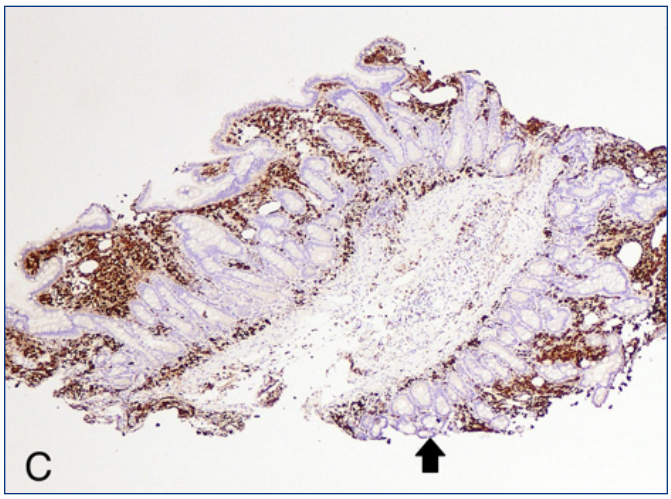


numerous low attenuating, enlarged mesenteric and retroperitoneal lymph nodes (**Image A**).

His hospital course was complicated by rectal bleeding requiring transfusion of 4 units PRBCs and iron infusions. UGI endoscopy and colonoscopy revealed severe duodenal and ileal inflammation and friability (**Image B)** with biopsy showing villous blunting, dilated lymphatics, foamy macrophages that were periodic acid-Schiff (PAS) positive and acid-fast bacilli (AFB) negative (**Image C**).

Pathology results were consistent with Whipple's disease. Infectious disease was consulted and recommended starting ceftriaxone 2g daily for 2 weeks, then 1 year of Sulfametoxazole/Trimethoprim 800-160 mg tablet every 12 hours with

Image C. Biopsy from the first portion of the duodenum
Villous blunting, accumulation of foamy macrophages in the lamina propria (arrow); prominent dilated lymphatic spaces



weekly labs. He reported improvement in symptoms shortly after starting antibiotics; at discharge, his diarrhea had resolved and he was eating a normal diet. Confirmatory testing for *Tropheryma whipplei* by polymerase chain reaction (PCR) was sent to an outside lab and returned positive. The patient was seen a few weeks after discharge at an outpatient clinic. He reported compliance with the antibiotic regimen and resolution of his symptoms; his weight was stable and diarrhea had resolved.

DISCUSSION

Whipple's disease is a rare systemic, chronic infection that may present initially with rheumatologic manifestations that precede gastrointestinal symptoms. The typical patient is a middle-aged white man, but as our case indicates, it can occur at all ages, although pediatric cases are very uncommon.[3] Although not seen in our patient, immunodeficiency is commonly associated with Whipple's disease. Immunosuppressive therapy, such as treatment with corticosteroids or tumor necrosis factor antagonists, can precede presentation of symptoms.[4]

The classic tetrad seen in a minority of patients is fever, diarrhea, abdominal pain, and arthralgias.[5] The majority of patients present with heterogeneous clinical complaints.[6] Symptoms can vary widely and involve only one organ or multiple organ systems such as the heart, brain, eyes, lungs, and skin.[7] For example, neurologic symptoms secondary to Whipple's disease are wide-ranging and include confusion, memory impairment, encephalopathy, ataxia, vertigo, diplopia, proximal muscle weakness, seizures, and paresthesia.[1] Our patient was initially admitted for evaluation of a possible malignancy because of his weight loss, anemia, and diffuse intraabdominal lymph node enlargement on imaging.

His initial presentation and reason for admission highlight the non-specific symptoms in Whipple's disease.

This diagnosis is commonly missed or delayed. In one large cases series reported in 2020, the median time from symptoms to diagnosis was 3 years.[6] Firstly, given its rarity, the index of suspicion for Whipple's disease may be low. Secondly, with a wide array of non-specific symptoms, Whipple's disease can mimic more common neoplastic, infectious, or inflammatory disorders. Thirdly, relapse can occur even years after treatment, with a different presentation and thus, not linked by patient or physician to prior Whipple's disease. Our patient was ultimately diagnosed on duodenal biopsy obtained during upper endoscopy.

Accurate diagnosis is important. Without treatment, the disease is fatal. Current treatment recommendations are antibiotic therapy capable of crossing the blood-brain barrier, given the possibility for neurologic manifestations.[8] Patients are often initially treated with intravenous antibiotics (ceftriaxone or penicillin G) for 2 weeks before transitioning to oral administration of Trimethoprim-Sulfamethoxazole for 1 to 2 years.

CONCLUSION

We report a rare case of Whipple's disease. Our patient demonstrates the importance of considering this rare disease in selected patients presenting with a wide array of non-specific symptoms. Timely diagnosis and initiation of appropriate treatment greatly improves prognosis in a potentially fatal disease.

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Disclosures

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