

## Case report

## Mesenteric lymphadenitis as a presenting feature of Whipple's disease



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## ABSTRACT

Detecting Whipple's disease, a "great imitator", requires a high index of suspicion so that antimicrobial treatment can be initiated in a timely manner; a missed diagnosis can be fatal. Although an uncommon cause, Whipple's disease must be considered in adults with mesenteric lymphadenitis. We report the case of a 39-year-old African American man who presented with chronic joint pain, chronic weight loss, and acute onset epigastric pain. Contrast-enhanced computed tomography of the abdomen and pelvis showed extensive mesenteric lymphadenopathy. A diagnosis of Whipple's disease was made based upon demonstration of PAS-positive macrophages in the mesenteric lymph node and duodenal biopsies. Antimicrobial therapy resulted in weight gain and resolution of abdominal pain and arthralgia at six months follow-up.

Whipple's disease can be fatal without antibacterial therapy and it always needs to be considered in individuals presenting with any combination of abdominal pain, weight loss, and diarrhea in the background of nonspecific arthritis or arthralgia. Whipple's disease must also be considered in adults presenting with mesenteric lymphadenitis. Review of CT scans may be helpful, as Whipple's disease characteristically causes low attenuation mesenteric lymphadenopathy.

## Introduction

Whipple's disease, first described by George H. Whipple over a hundred years ago, is a multisystemic disease caused by the Gram-positive bacterium *Tropheryma whipplei* [1]. Whipple's disease (WD) is a diagnostic challenge because it is a "great imitator" and relatively uncommon, with less than 1000 cases described [2]. All clinicians and pathologists must, therefore, be aware of its features and have a high index of suspicion so that antibacterial treatment can be initiated in a timely manner; a missed diagnosis can be fatal. The classically described quartet of symptoms (arthralgia, diarrhea, weight loss, and abdominal pain) may occur but many other symptoms have been reported [3]. Here we report a case of classical Whipple's disease presenting with mesenteric lymphadenitis.

## Case report

A 39-year-old African American man presented to the Emergency Department (ED) with a one-week history of epigastric pain. He had a seven-year history of chronic arthritis in his hands, feet, and back but was otherwise healthy. He reported experiencing epigastric pain after dining out for his birthday a week prior to presentation. The pain was gnawing, non-radiating, non-positional, and constant, but there were no fevers, chills, nausea, vomiting, or diarrhea. All other individuals

dining with him were asymptomatic. He medicated himself with naproxen but the pain worsened, prompting his visit to the ED.

The patient had emigrated from Cape Verde to the United States 20 years previously. He was a bodybuilder, had noticed recent weight loss as well as a poor appetite and had lost 30lbs in the three months before presentation. He lived with his wife and worked for a printing company, did not smoke tobacco or use illicit drugs, rarely drank alcohol and had no allergies. There was no family history of note. His only outpatient medication was naproxen as needed for arthritis.

On examination he was in extreme pain with a blood pressure of 112/70, pulse 111, respiratory rate 18, and oxygen saturation was 100% breathing room air. Abdominal examination revealed a flat abdomen, normoactive bowel sounds, no bruits, a soft and tender epigastrium, and no rebound tenderness, rigidity, or guarding. Carnett's and Murphy's signs were negative. There were no palpable masses, no hepatosplenomegaly, and no hernias. Rectal examination was normal. There was no palpable lymphadenopathy. There was no active synovitis, palpable swelling, or joint line tenderness on peripheral joint examination. Neurological examination was non-focal. Laboratory results revealed microcytic anemia (Hb 11.9 g/dL; normal 13.5–18 g/dL) and mild leukocytosis (Table 1). Contrast-enhanced computed tomography (CT) of the abdomen and pelvis showed extensive mesenteric lymphadenopathy (Fig. 1). He was admitted to the general medical floor due to his intractable abdominal pain and for further workup.

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**Table 1**  
Laboratory results at the time of presentation.

Test	Result	Reference Range
WBC	11.7 thous/mm <sup>3</sup>	4–10.5 thous/mm <sup>3</sup>
Gran%	81.8%	40–74%
Lymph%	9.7%	17–48%
RBC	4.64 mill/mm <sup>3</sup>	4.7–6.0 mill/mm <sup>3</sup>
Hemoglobin	11.6 g/dL	13.5–18 g/dL
MCV	78.1fl	78–100 fl
MCHC	25.4 pg	27–31 g/dL
Retic%	0.51%	0.7–1.50
Absolute Reticulocyte count	0.0233 mm <sup>3</sup>	0.0301–0.0885 mm <sup>3</sup>
Iron	25 mcg/dL	49–181 mcg/dL
Iron Binding Capacity	256 mcg/dL	261–462 mcg/dL
Ferritin	232 ng/mL	18–464 ng/mL
Folate	6.45 ng/mL	> 2.76 ng/mL
B12	790 pg/mL	239–931 pg/mL
Fecal occult blood	Neg	N/A

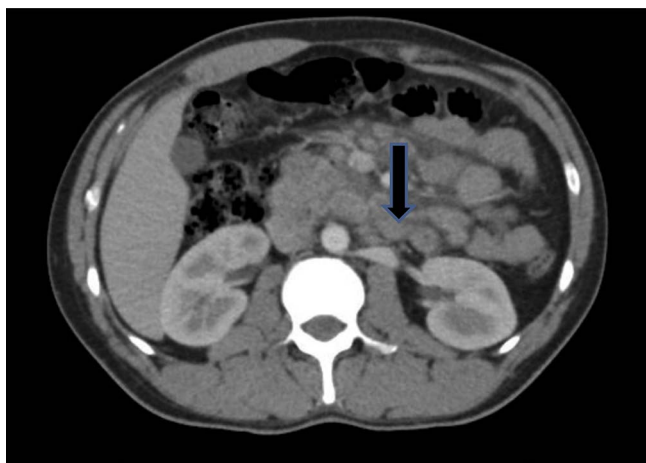


Fig. 1. CT of the abdomen demonstrating mesenteric lymphadenopathy (arrow).

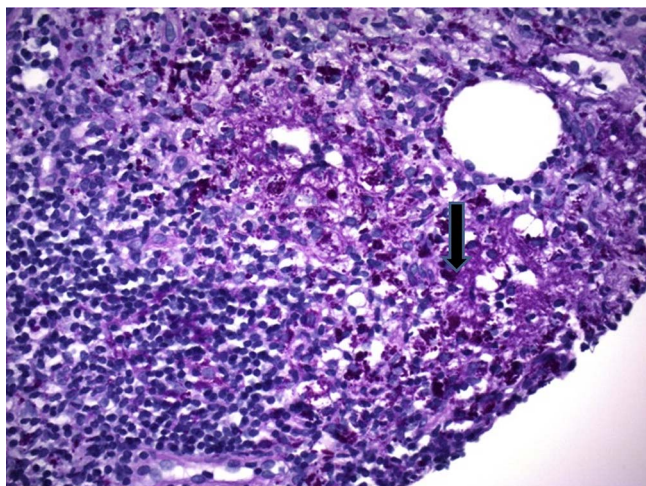


Fig. 2. Mesenteric lymph node biopsy (PAS stain,  $\times 10$  objective) with numerous macrophages containing PAS-positive granules (arrow).

At that point, the differential diagnosis for this relatively young man with chronic joint pain, chronic weight loss, recent onset epigastric pain, and microcytic anemia included primary GI lymphoma, gastroduodenal tuberculosis (TB), and peptic ulcer disease. He was treated with morphine, pantoprazole, and intravenous fluids, and kept nothing by mouth for an esophagogastroduodenoscopy (EGD) the following day. The EGD performed on admission day two was macroscopically normal; gastric and duodenal biopsies were taken. He resumed eating and the

abdominal pain was controlled with acetaminophen. On admission day three, he underwent ultrasound-guided mesenteric lymph node biopsy. The same day, histopathological examination of the duodenal biopsy revealed Periodic Acid-Schiff (PAS)-positive macrophages. Whipple's disease was diagnosed, and the mesenteric lymph node biopsy was subsequently found to be congruent with a diagnosis of Whipple's disease, revealing PAS-positive macrophages (Fig. 2).

The patient received ceftriaxone (2 g i.v.) for two weeks and was prescribed trimethoprim-sulfamethoxazole (160 mg trimethoprim/800 mg sulfamethoxazole) for one year. At six months follow-up, abdominal pain and arthralgia had resolved.

## Discussion

The exact prevalence of Whipple's disease (WD) is unknown but it is uncommon [4]. For an excellent overview of published case reports, see the recent summary by Maresi et al. [2]. Here we report a case of classic Whipple's disease presenting with mesenteric lymphadenitis. The patient was likely to have had the disease for several years, the first manifestation being arthralgia that had been treated as arthritis by his primary care physician, who had perhaps understandably missed the diagnosis given the absence of any other symptoms (i.e., abdominal pain and weight loss). By the time of presentation to our hospital, he had developed anorexia, weight loss, and abdominal pain, most likely due to mesenteric adenitis. The presence of iron deficiency anemia supported the diagnosis of Whipple's disease, and the diagnosis was confirmed by PAS-positive macrophages in the duodenal biopsy and mesenteric lymph nodes.

There are very few reported case of Whipple's disease presenting with mesenteric lymphadenitis [5–9]. However, in a retrospective study from a Whipple's disease referral center in France, the prevalence of mesenteric lymphadenopathy in Whipple's disease was reported to be 17% [10]. The finding of mesenteric lymphadenitis on CT in our patient concerned us because it is uncommon in adults (albeit with unknown exact prevalence) and can be associated with serious disease.

Causes of mesenteric lymphadenopathy include, but are not limited to, inflammation, malignancy, and infection [11]. Inflammatory causes of mesenteric lymphadenopathy include appendicitis, cholecystitis, and diverticulitis [11], none of which were consistent with our patient's presentation. Malignancy (particularly primary GI lymphoma, the commonest malignancy-related cause of mesenteric lymphadenopathy [11]) was a major consideration in our patient in the context of anemia and weight loss and heavily influenced our decision to evaluate him with upper gastrointestinal endoscopy. Other malignancy-related causes of mesenteric lymphadenopathy include bladder carcinoma, malignant melanoma, leukemia, Kaposi sarcoma, and sarcomas arising from abdominal structures [11]. Finally, we considered infection-related mesenteric lymphadenopathy, especially common viral gastroenteritis, but again the presentation was inconsistent with this diagnosis. Yersiniosis, HIV, tuberculosis, and Whipple's disease are also known to cause mesenteric lymphadenopathy [11]. Enlarged mesenteric lymph nodes caused by TB and Whipple's disease are characteristically low attenuating on CT with IV contrast, which can be useful in distinguishing these entities from other infectious, inflammatory, and malignant causes of mesenteric lymphadenopathy [11]. In hindsight given this knowledge, in addition to the history of arthritis and weight loss in our case, should have made our suspicion of Whipple's disease much higher.

There is no published consensus on how best to investigate adults presenting with mesenteric lymphadenitis. In general, inflammatory causes do not pose a diagnostic dilemma, malignancy needs to be considered based on risk factors, and, if lymphoma is of significant concern, lymph node biopsy should be considered. Infection-related mesenteric lymphadenopathy does not warrant extensive workup especially if the presentation is consistent with viral gastroenteritis. HIV can easily be evaluated with a 4th generation test and, if the diagnosis

remains uncertain, abdominal CT with contrast may be useful, particularly if it demonstrates low attenuation lymph nodes consistent with TB, celiac disease, or Whipple's disease.

When Whipple's disease is suspected, small bowel endoscopy is the most promising diagnostic procedure for patients with gastrointestinal symptoms and/or suspected extraintestinal manifestations of Whipple's disease. Small bowel biopsies should be obtained for *T. whipplei* testing even if the mucosa appears macroscopically normal, as in our case, since a macroscopically normal bowel does not exclude the diagnosis. In cases with negative small bowel biopsies, biopsies from other areas of involvement should be obtained for histological analysis. In this case, lymph node biopsies were obtained due to the high index of suspicion for GI lymphoma but they also revealed characteristic features of Whipple's disease that would have been useful had the small intestinal biopsies been negative.

Whipple's disease can be fatal without treatment with antibacterials, and guidelines recommend initial management with an intravenous antibiotic therapy for two weeks to achieve good blood-brain barrier penetration followed by oral treatment for a year. There is, however, little high-quality evidence to support a particular regimen for Whipple's disease, with data mainly coming from observational studies [12]. However, in a recent randomized controlled trial [12], forty patients with Whipple's disease were treated with either ceftriaxone or meropenem for two weeks followed by twelve months of trimethoprim-sulfamethoxazole (TMP-SMX). All patients achieved remission (determined by clinical, histological, and laboratory data) and maintained remission over a three-year follow-up period except for two patients who died from unrelated causes. A follow up open label non-randomized study by the same investigators enrolled thirty patients with WD to evaluate the efficacy of treatment with two weeks of ceftriaxone daily followed by oral TMP-SMX twice daily for three months [13]. The primary endpoint was treatment efficacy compared with the previous study. The study showed that twelve months of treatment with TMP-SMX was not superior to three months of treatment, as indicated by clinical, laboratory and histological data. Although this study suggests short-course TMP-SMX is as effective as a year of therapy, it was a small non-randomized study and further studies are needed to establish the efficacy of this approach. Therefore, we treated our patient according to established guidelines with two weeks of ceftriaxone

followed by TMP-SMX with intention to treat for a year. He had responded well to therapy at six months follow-up, however, suggesting that the short-course approach was probably effective in this case.

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