Fellows' Corner

An Interesting Case of Whipple's Disease

by Anastasia C. Waechter and Darren C. Schwartz

CASE PRESENTATION

A 67-year-old Norwegian-American man presented with a history of progressive weight loss and diarrhea. He had lost approximately 50 lbs. during the year prior to presentation and his stool frequency had increased to 6–7 loose, non-bloody bowel movements over the preceding 2 months. The patient reported marked fatigue with dyspnea on exertion, as well as arthralgias involving the hands and knees. While he admitted to anorexia, he denied abdominal pain, nausea, vomiting, fevers, chills, or night sweats.

Past medical history was significant for hypothyroidism and diabetes mellitus type 2. There was no history of prior surgeries or hospitalizations. He was a retired farmer and had a remote history of both alcohol and tobacco use. Family history was negative for celiac sprue, inflammatory bowel disease, and gastrointestinal malignancies.

Physical examination revealed a cachectic white man with temporal and interosseus muscle wasting. Conjunctivae were pale without icterus. Abdomen was scaphoid but otherwise benign, without organomegaly or masses. On neurological examination, he exhibited poor short-term memory. There was evidence of bilateral cranial nerve III palsy with disconjugate gaze. Diffuse hyperreflexia was present with bilateral ankle clonus and plantar extensor responses. Strength was decreased symmetrically in both upper and lower extremities.

Laboratory data demonstrated evidence of iron deficiency anemia, with hemoglobin of 10.7 g/dL, MCV of 84.3 fl, iron of 10 µg/dL, and iron saturation of 6.4%. Vitamin B_{12} was 188 pg/mL (nl 211–911 pg/mL), albumin 2.0 gm/dL , and 25-hydroxy Vitamin D <7.0 ng/mL (nl 10–68 ng/mL). Both the ESR and CRP were elevated at 100 mm/hr and 6.1 mg/dL, respectively. Electrolytes were normal except for evidence of mild hyponatremia. Stool was guaiac positive.

CT scan of the abdomen and pelvis demonstrated extensive mesenteric lymphadenopathy with diffuse small bowel thickening. At upper endoscopy, the second and third portions of the duodenum exhibited diffusely scalloped and friable mucosa with adherent whitish plaques (Figure 1). Colonoscopy was remarkable only for mild sigmoid diverticulosis.

Question 1: What is the clinical diagnosis?
Question 2: What are several means by which the diagnosis can be made?
Question 3: What is the appropriate treatment?
Question 4: What is the classic tetrad seen in this illness?

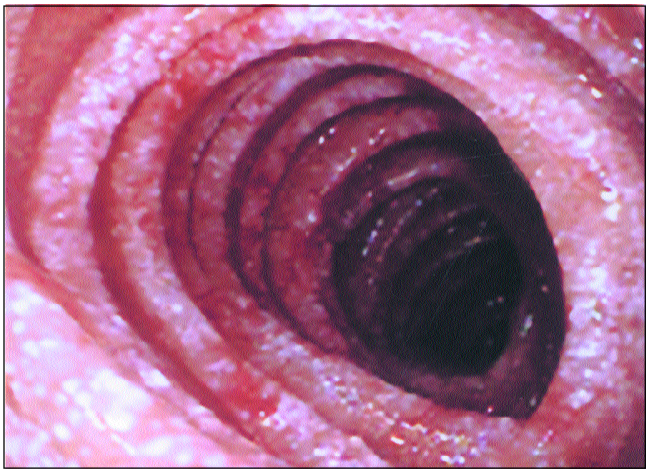

Figure 1. Diffusely scalloped and friable duodenal mucosa with adherent whitish plaques.

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Answers

1. Whipple's Disease
2. Duodenal biopsy with PAS staining and electron microscopy; PCR of affected tissues/body fluids
3. Two weeks of IV ceftriaxone (or penicillin plus streptomycin) followed by 1 year of oral trimethoprim-sulfamethoxazole
4. Diarrhea, weight loss, arthralgias, and abdominal pain

DISCUSSION

Duodenal biopsies revealed marked infiltration of the lamina propria with large foamy macrophages staining PAS positive and acid-fast negative (Figure 2). These findings were consistent with a diagnosis of Whipple's disease. While cerebrospinal fluid could not be obtained for analysis, neurological involvement was presumed secondary to mild dementia and a multitude of characteristic neurologic findings on physical exam. The patient was initially treated with a 2-week course of intravenous ceftriaxone, total parenteral nutrition, and B_{12} supplementation. Despite therapy, he continued to decline neurologically. CT of the head demonstrated multiple infarcts in both cerebral hemispheres and the right occipital lobe. Echocardiography showed likely valvular vegetation, raising the suspicion of cardiac-related Whipple's disease. The patient was eventually discharged on oral trimethoprim-sulfamethoxazole but remained with an expressive aphasia.

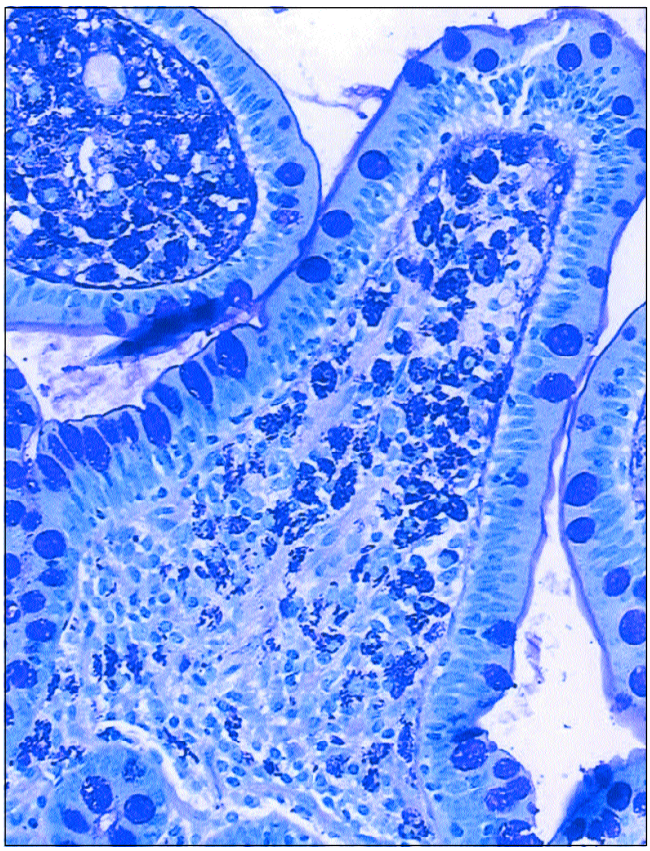

Figure 2. Endoscopic biopsy with marked infiltration of the lamina propria with macrophages staining PAS positive.

Whipple's disease is a rare systemic disorder caused by infection with the bacterium *Tropheryma whipplei*. It has been described most in people of European descent and those with frequent exposure to soil, such as farmers. Prevalence is 8 times greater in males than females, with a mean age at diagnosis of 50. The scant lymphocytic and plasma cell infiltrate seen on duodenal biopsy in Whipple's disease has led to the theory that affected patients have a subtle defect in cellular immunity involving activation and interaction of T cells in response to this specific bacterium.

The clinical manifestations of Whipple's disease are highly variable. Extraintestinal symptoms are common and may precede gastrointestinal complaints by many years. The disease usually begins insidiously with an intermittent and migratory arthropathy. Cardiac involvement may cause congestive heart failure, valvular lesions, or pericarditis. Pulmonary involvement can lead to chronic cough or pleuritic chest pain. The most common CNS symptoms are dementia, gaze paralysis, and myoclonus. However, as in this case, most patients are not diagnosed until they develop gastrointestinal symptoms, including diarrhea with or without steatorrhea, abdominal bloating, and weight loss.

Whipple's disease should be considered in all patients with diarrhea, weight loss, arthralgias, and abdominal pain. Endoscopic biopsy of the small intestine is the diagnostic test of choice. The presence of PAS-positive macrophages containing gram-positive, acid-fast negative bacilli throughout the lamina propria accompanied by dilated lacteals is characteristic but not pathognomonic of Whipple's disease. Electron microscopy may be performed to verify the presence of the characteristic bacillus. PCR of duodenal, cardiac, CSF, and synovial fluid may be a useful adjunct

and is becoming more widely available. Culture of *T. whipplei* has proven difficult given its prolonged incubation time and is currently available for research purposes only in highly specialized laboratories.

A prompt and accurate diagnosis is essential, as untreated Whipple's disease can be fatal. The current recommended treatment is based on empiricism and retrospective analyses. Because of the high frequency of neurological involvement, a two-week course of parenteral therapy with an agent with good penetration of the blood-brain barrier, such as ceftriaxone (or penicillin plus streptomycin) is endorsed by most. This should be followed by long-term therapy (1 year) with oral trimethoprim-sulfamethoxazole. Repeat duodenal biopsies with electron microscopy may be performed to ensure clearance of the bacteria. Those with CNS involvement are more likely to relapse; therefore CSF analysis should be considered every 6 months until the bacterial material is undetectable. An alternative antibiotic regimen should be pursued in rare cases in which the bacterium persists. The first prospective controlled trial in Whipple's disease is currently underway in Europe to help determine the best choice and duration of antibiotic therapy *(www.whipplesdisease.info)*. Patients with severe malnutrition should also receive appropriate supplementation of specific nutritional deficiencies, parenterally if necessary. ■

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