A Man with Chronic Leg Edema, Purpuric Skin Lesions, and Abdominal Lymphadenopathy

(See pages 519–20 for Photo Quiz)

Figure 1. Non-thrombocytopenic, purpuric skin lesions on the patient’s arms (arrows)

Diagnosis: Whipple’s disease.

The laparoscopic lymph node biopsy demonstrated the classic findings of Whipple’s disease: large dilated lymphatic ducts, clusters of polymorphonuclear leukocytes and lymphocytes, and rare granulomas and macrophages filled with periodic acid–Schiff–positive, rod-shaped organisms consistent with *Tropheryma whipplei* (figure 1). PCR of a peripheral blood sample was positive for *T. whipplei* 16S rRNA. The patient was treated with intravenous penicillin G and streptomycin for 14 days, followed by oral trimethoprim-sulfamethoxazole double-strength tablets twice per day, and demonstrated complete resolution of all signs and symptoms within 1–3 months.

Whipple’s disease was described in 1907 by Dr. George Whipple on the basis of an autopsy performed on a 36-year-old medical missionary with a 5-year history of arthritis, fever, cough, weight loss, and diarrhea [1]. Evidence for an infectious cause of Whipple’s disease was provided in 1961 by electron microscope pictures of bacillary bodies within macrophages [2]. *T. whipplei*, which was isolated only recently, appears to be related to soil actinomycetes, according to the findings of 16S RNA sequencing [2].

Major features of Whipple’s disease include weight loss, arthropathy, diarrhea, and abdominal pain, which are present in 60%–90% of patients [2]. With the availability of PCR for identification of *T. whipplei* in peripheral blood and tissues, more cases with atypical features and without diarrhea or evidence of malabsorption have been reported [2–4]. Less common symptoms are peripheral edema (in 30% of patients), cough (in 15%), and hyperpigmentation (in 35%). Pulmonary hypertension and non-thrombocytopenic skin purpura (figure 1) are rare. For our patient, a skin biopsy was not diagnostic, but the pigmentation and skin lesions quickly resolved with antimicrobial therapy. Other atypical manifestations of Whipple’s disease include eye disease (papilledema, retinitis, and
uveitis); cardiovascular disease (myocardopathy, congestive failure, shortness of breath, and hypotension); and neurologic disease (cognitive dysfunction, hemiparesis, dementia, seizures, and peripheral neuropathy) [2, 3].

The finding of nonenhancing, homogeneous, hypodense lymph nodes with a density of −2.09 Hounsefield units (i.e., less than that of water) on a CT scan (figure 2) was an important clue to the diagnosis of Whipple’s disease prior to the lymph node biopsy [3]. This finding is related to the high concentration of fat in the lymph nodes (figure 3), compared with patients who have lymphadenopathy due to metastatic cancer, lymphoma, or granulomatous diseases.

![Abdominal CT scan demonstrating diffuse, nonenhancing, hypodense lymph nodes (arrows) with a density of −2.09 Hounsefield units (i.e., less than that of water).](image)

Figure 2. Abdominal CT scan demonstrating diffuse, nonenhancing, hypodense lymph nodes (arrows) with a density of −2.09 Hounsefield units (i.e., less than that of water). This finding is related to the high concentration of fat in the lymph nodes, compared with patients who have lymphadenopathy due to metastatic cancer, lymphoma, or granulomatous diseases.

![Histological section of an abdominal lymph node biopsy specimen demonstrating large, dilated lymphatic ducts (A), lymphocytic and neutrophilic infiltrates (B), and macrophages filled with periodic acid–Schiff–positive Tropheryma whipplei organisms (C).](image)

Figure 3. Histological section of an abdominal lymph node biopsy specimen demonstrating large, dilated lymphatic ducts (A), lymphocytic and neutrophilic infiltrates (B), and macrophages filled with periodic acid–Schiff–positive Tropheryma whipplei organisms (C).
Pitfalls for the diagnosis of Whipple’s disease include an atypical presentation, waxing and waning symptoms, and the impact of antibiotic therapy. Of the 28 patients with Whipple’s disease described by Fleming et al. [3], only 39% had diarrhea, 25% had weight loss, 18% had fever, and 11% had arthritis or arthralgia at the time of initial examination. However, there was a history of these symptoms from months to years in 75% of patients with diarrhea, 89% of those with weight loss, 54% of those with fever, and 82% of those with arthritis or arthralgia. The natural history and clinical manifestations of Whipple’s disease may also be altered by antibiotic treatment with penicillin, doxycycline, macrolides, and trimethoprim-sulfamethoxazole.

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