with antiretroviral therapy. A weak humoral response, perhaps due to bacterial glycosylation in patients with chronic disease, appears to differentiate persons who clear the bacillus from asymptomatic carriers. In the initiation of chronic infection, the relative importance of the host's genetic background versus the modulation of the host response by *T. whipplei* is unknown.

T. whipplei has a tropism for myeloid cells, which it invades and in which it can avoid being killed. Infiltration of infected tissue by large numbers of foamy macrophages is a characteristic finding. In the intestine, villi are flat and wide with dilated lacteals. Involvement of lymphatic or hepatic tissue may manifest as noncaseating granulomas that can mimic sarcoid.

CLINICAL MANIFESTATIONS

Asymptomatic Colonization/Carriage Studies using primarily PCR have detected *T. whipplei* sequence in stool, saliva, duodenal tissue, and (rarely) blood in the absence of symptoms. Although prevalence rates are still being defined, in Western European countries, detection in saliva (0.2%) is less common than that in stool (1–11%) and appears to occur only with concomitant fecal carriage. The prevalence of fecal carriage is elevated in individuals with exposure to waste water or sewage (12–26%). However, in rural Senegal, 44% of children age 2–10 had *T. whipplei* detected in fecal samples. The duration of carriage at these sites is still being examined but can be at least 1 year. It is not known how often the carrier state is associated with acute infection, but evolution into chronic disease is uncommon. Bacterial loads are lighter in asymptomatic carriage than in active disease.

Acute Infection *T. whipplei* has been implicated as a cause of acute gastroenteritis in children. It was also detected via PCR in the blood of 6.4% of febrile patients (primarily children) from two villages in Senegal, often with concomitant cough and rhinorrhea. Further, *T. whipplei* has been implicated as a cause of acute pneumonia in the United States and France. These data suggest that primary acquisition can result in symptomatic pulmonary or intestinal infection, which may be more common than has been thought, and only rarely results in chronic disease.

Chronic Infection • *"CLASSIC" WHIPPLE'S DISEASE* So-called classic Whipple's disease was the initial clinical syndrome recognized, with consequent identification of *T. whipplei*. This chronic infection is defined by involvement of the duodenum and/or jejunum that develops over years. In most individuals, the initial phase of disease manifests primarily as intermittent, occasionally chronic and destructive migratory oligo- or polyarthralgias/seronegative arthritis. Spondylitis, sacroiliitis, and prosthetic hip infection also have been described. This initial stage is often confused with a variety of rheumatologic disorders and, on average, lasts 6–8 years before gastrointestinal symptoms commence. Treatment of presumed inflammatory arthritis with immunosuppressive agents (e.g., glucocorticoids, tumor necrosis factor α antagonists) can accelerate progression of the disease process. Alternatively, antimicrobial therapy used for another indication may reduce symptoms. In fact, the modulation of symptoms in these settings should prompt consideration of Whipple's disease. The intestinal symptoms that develop in the majority of cases are characterized by diarrhea with accompanying weight loss and may be associated with fever and abdominal pain. Diagnostic misdirection can be caused by co-infection with *Giardia lamblia*, which is occasionally identified. Occult gastrointestinal blood loss, hepatosplenomegaly, and ascites are less common. Anemia and hypereosinophilia may be detected. Rheumatoid factor and antinuclear antibody tests are usually negative. The most common finding on abdominal CT is mesenteric and/or retroperitoneal lymphadenopathy. The endoscopic or video capsule observation of pale, yellow, or shaggy mucosa with erythema or ulceration past the first portion of the duodenum suggests Whipple's disease (Fig. 200-5). In addition to rheumatologic and proximal intestinal disease, neurologic (6–63%), cardiac (17–55%), pulmonary (10–40%), lymphatic (10%), ocular (5–10%), dermal (1–5%), and (in rare instances) other sites are variably involved in classic Whipple's disease.

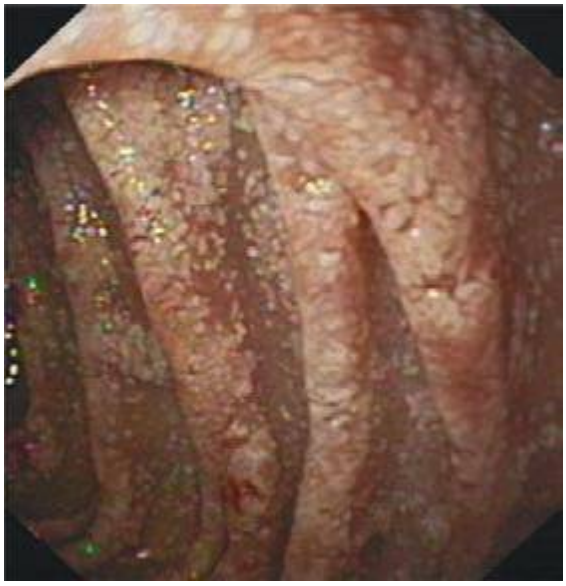

FIGURE 200-5 Endoscopic view of the jejunal mucosa demonstrating a thickened, granular mucosa and "white spots" due to dilated lacteals. *(Reprinted with permission from J Bureš et al: Whipple's disease: Our own experience and review of the literature. Gastroenterol Res Pract , 2013. http://dx.doi.org/10.1155/2013/478349.)*

Neurologic disease Asymptomatic neurologic involvement in Whipple's disease has been documented by PCR-based detection in cerebrospinal fluid (CSF). A variety of neurologic manifestations have been reported, the most common of which are cognitive changes progressing to dementia; personality, mood, and sleep-cycle disorders; hypothalamic involvement; and supranuclear ophthalmoplegia. In addition to the latter, neuro-ophthalmologic manifestations of Whipple's disease include supranuclear gaze palsy, oculomasticatory and oculofacial myorhythmia (highly suggestive of Whipple's), nystagmus, and retrobulbar neuritis. Focal neurologic presentations (dependent on lesion location), seizures, ataxia, meningitis, encephalitis, hydrocephalus, myelopathy, and distal polyneuropathy also have been described. Neurologic sequelae occur with CNS disease, and the mortality risk is significant.

MRI results may be normal. Identified lesions (solitary or multifocal) are usually T2 and fluid-attenuated inversion recovery (FLAIR) hyperintense and may enhance with gadolinium. Findings are myriad and not diagnostic, but the limbic system is commonly involved. FDG-PET may reveal increased uptake. CSF analysis may be abnormal; leukocytosis (generally lymphocyte-predominant) and an elevated protein concentration are common. A low CSF glucose level has been reported.

Cardiac disease Endocarditis, which is increasingly recognized in Whipple's disease, presents as culture-negative infection and/or congestive heart failure; hypotension occurs rarely. Embolic events or various arrhythmias may also be noted. Fever is often absent, and Duke clinical criteria are rarely met. Vegetations are identified by echocardiography in 50–75% of cases. All valves, alone or in combination, can be affected; most commonly involved are the aortic and mitral valves. Preexisting valvular disease is found in only a minority of cases, although infection of bioprosthetic valves has been described. Mural, myocardial, or pericardial disease also occurs alone or in combination with valvular involvement. Constrictive pericarditis develops infrequently.

Pulmonary disease Some combination of interstitial disease, nodules, parenchymal infiltrate, and pleural effusion is observed. The clinical significance of *T. whipplei* dominating sequence reads in BALF from HIV-infected individuals is unresolved.

Lymphatic disease Mesenteric and retroperitoneal lymphadenopathy are common with intestinal disease, and mediastinal adenopathy may