Whipple's Disease

Sergio Schwartzman, MD[a,*], Monica Schwartzman, BA[b]

KEYWORDS

• Whipple's disease • *Tropheryma whipplei* • Inflammatory arthropathy
• Nervous system disease

KEY POINTS

- Whipple's disease is caused by the bacillus *Tropheryma whipplei*.
- The diagnosis is confirmed by tissue sampling with periodic acid-Schiff staining and/or polymerase chain reaction.
- The clinical manifestations most frequently manifest in the gastrointestinal, musculoskeletal, neurologic, cardiac, and ophthalmic organs, but can affect any site.
- Successful therapy with appropriate antibiotics is potentially curable, but recurrences may occur.

Although it is hypothesized that many rheumatic diseases may be initiated and perhaps maintained by an infectious agent, causative organisms have been rarely delineated as being causative in this group of illnesses. Whipple's disease, an illness caused by *Tropheryma whipplei* and characterized by multivariate clinical manifestations including an inflammatory arthropathy, is one such disease. In the description of the first case of Whipple's disease[1] in a physician who had contracted this disease, by the pathologist George Whipple's, the illness was characterized as an "intestinal lipodystrophy" and, although the focus was on the pathologic manifestations, an infectious cause was in fact considered, as Whipple's noted "a bacillus belonging to the colonic group" in the submucosal layer of the intestine.

Over the last century the etiology of Whipple's disease has been established, and the causative organism has been identified and characterized. However, many questions remain, as it is unknown as to why the clinical spectrum of the disease is so varied and why only a certain number of exposed patients develop the clinical illness. This article reviews the microbiology, pathophysiology, epidemiology, clinical manifestations, diagnostic testing, and treatment of Whipple's disease.

MICROBIOLOGY

George Hoyt Whipple's was the first to consider an infectious cause based on the pathology, which demonstrated a bacillus.[1] However, he was unsure as to whether this

[a] Hospital for Special Surgery, Weill Cornell Medical College, New York, NY, USA; [b] Icahn School of Medicine, Mount Sinai Hospital, New York, NY, USA
* Corresponding author.
E-mail address: SchwartzmanS@HSS.EDU

Rheum Dis Clin N Am 39 (2013) 313–321
http://dx.doi.org/10.1016/j.rdc.2013.03.005 **rheumatic.theclinics.com**
0889-857X/13/$ – see front matter

organism was in fact pathologic or part of the intestinal flora, and did not directly attribute the illness to an infectious cause. It was not until 1949, when the periodic acid-Schiff (PAS) stain revealed that foamy macrophages contained a glycoprotein material and not lipids, that an infectious cause was more concretely suspected.[2] In 1961, Chears and Ashworth[3] definitively identified macrophage-engulfed bacteria on electron microscopy. The PAS-positive bacilli with a classic trilamellar plasma membrane were hypothesized to be causative. The infectious nature of the disease has now been definitively confirmed using cell culture[4] and polymerase chain reaction (PCR) assays.[5,6]

PATHOPHYSIOLOGY

Although there is clearly a direct infectious component to Whipple's disease and, indeed, PCR can identify the characteristic unique bacterial 16S ribosomal RNA in affected tissues, there may be other potential etiologic factors that play a role in the phenotypic expression of this disease. Indeed there are 2 clinical stages of Whipple's disease, separated by a prolonged period of time. The initial manifestations are undoubtedly infectious and are characterized by fever, fatigue, arthralgias, or arthritis, whereas the later manifestation, which includes diarrhea, weight loss, musculoskeletal symptoms, hepatic, cardiac, pulmonary, neurologic, and ophthalmic manifestations, may have an autoimmune component superimposed on an underlying infectious process.

Several autoimmune and genetic abnormalities have been hypothesized to be potentially present in patients with Whipple's disease, with the predominant hypothesis being that immune abnormalities result in an increased risk of developing an infectious process such as Whipple's disease. It is well known that the majority of people exposed to *Tropheryma whipplei* do not develop this illness. In a study of the prevalence of the organism in saliva and duodenal biopsies and/or gastric juice of asymptomatic healthy carriers, there was evidence of the organism.[7] Between 1.5% and 7% of the general population may be asymptomatic carriers of the organism.[8] *T whipplei* is a ubiquitous commensal bacterium.

Autoimmune abnormalities have been described in patients with Whipple's disease. Circulating monocytes of patients with active Whipple's disease are endogenously stimulated to express prothrombinase activity.[9,10] A significantly reduced number of mononuclear cells express the complement receptor 3α chain (CD11b). T cells in acute Whipple's disease are activated and exhibit a low CD4/CD8 ratio.[11] Interleukin-16 is a critical cytokine in the pathogenesis of Whipple's disease in that the expression of this cytokine is crucial for the replication of *T whipplei* in a monocyte/macrophage model, and blocking of this cytokine can result in bacterial clearance.[12] An immune reconstitution syndrome characterized by fever and arthritis/arthralgias has also been described in a minority of patients after antibiotic therapy is instituted.[13] A genetic association with human leukocyte antigen (HLA) B27 has also been hypothesized, though not universally accepted.[14]

It is likely that the immunologic abnormalities in patients with Whipple's disease predispose to the expression of an infectious illness. However, there may be a "reactive" autoimmune type response in the correct genetic host that is responsible for some of the clinical manifestations of this illness.

EPIDEMIOLOGY

Whipple's disease is a rare condition, and little is known about its epidemiology. There is no universally accepted incidence rate,[15] but there have been estimates of a