Whipple Disease
A Case Report and Review of the Literature

MAJ Jeannie Muir-Padilla, MC, USA; COL Jerome B. Myers, MC, USA

Whipple disease is a chronic, relapsing, and multisystem disease. It presents a diagnostic challenge for both clinicians and pathologists. Recent advances in isolation and culture have identified the organism responsible for the disease to be a member of the order Actinomycetes designated *Tropheryma whipplei*. Several immune system changes have been noted in patients with Whipple disease, but whether these are primary or secondary is as yet undetermined. Long-term antibiotic therapy is required, and relapses are common, especially with central nervous system involvement.

(Arch Pathol Lab Med. 2005;129:933–936)

REPORT OF A CASE

A 62-year-old woman presented to her primary care physician complaining of worsening shortness of breath. The patient’s past medical history included restrictive cardiomyopathy of unknown etiology, sick sinus syndrome with pacemaker placement, congestive heart failure, arthritis, hepatomegaly, spontaneous bacterial peritonitis, intermittent diarrhea, and hypothyroidism. Physical examination revealed a febrile woman with mild venous jugular distension, bilateral diffuse crackles in the lower and mid lung fields, and a distended abdomen with guarding and a positive fluid wave.

Examination of the peritoneal fluid revealed 4+ neutrophils with no bacteria. The patient was treated with furosemide for her diagnosis of congestive heart failure and appropriate antibiotic therapy for spontaneous bacterial peritonitis. She was discharged on hospital day 8 after showing improvement in her oxygenation status. Four days after discharge from the hospital, the patient again complained of difficulty breathing. Emergency medical personnel were summoned, and the patient was found apneic and pulseless with perioral cyanosis. Based on the previously documented wishes of the patient, resuscitative measures were not undertaken, and the patient was pronounced dead.

PATHOLOGIC FINDINGS

An autopsy was performed. External examination showed musculoskeletal changes consistent with rheumatoid arthritis. Gross examination of the abdominal and hilar lymph nodes revealed poorly formed granulomas and individual histiocytes with intracellular rod-shaped organisms. Periodic acid–Schiff (PAS) both with (Figure 3) and without diastase digestion showed intracellular PAS-positive rod-shaped organisms. Electron microscopy revealed organisms consistent with *Tropheryma whipplei* (Figure 4). The patient’s death was attributed to Whipple disease (WD) with resultant constrictive pericarditis and pulmonary fibrosis.

COMMENT

Causative Agent

First described in 1907 by G. H. Whipple as intestinal lipodystrophy because of the appearance of the organism-laden macrophages in tissue, this disease has since been linked to the causative organism by Wilson et al1 in 1991. This group used a broad range of primers to amplify and sequence a portion of the 16S ribosomal RNA. Previously thought to be a Corynebacterium, it was identified as belonging to the order Actinomycetes and named *Tropheryma whipplei*.2,3

This gram-positive organism has a trilamellar membrane resembling that of gram-negative bacteria. *Tropheryma whipplei* organisms are PAS positive and diastase resistant and do not stain with acid-fast bacillus stain (Ziehl-Neelsen or Fite methods).2 This can be useful when the differential diagnosis includes the organism *Mycobacterium*...
**Epidemiology**

The incidence of WD is low, with fewer than 1000 cases reported in the medical literature. Eighty percent of those affected are white men, with a mean age of 50 years.

The causative agent, *T. whippelii*, has no documented mode of transmission, nor has infection of laboratory animals been successful. A recent study found immunoglobulin (Ig) G antibodies directed against the bacillus in 9 of...
9 patients with WD as well as in 30 of 40 control subjects. However, the specificity of IgM antibodies is greater, with 7 of 9 patients with WD testing positive and only 3 of 40 controls testing positive when a cutoff value of 1:50 was used. This may indicate that this is a ubiquitous organism that causes disease only when the host has an inherent susceptibility or when there is a unique route of exposure; alternately, it may indicate that there are differences in virulence between strains of the organism.

Pathogenesis and Immunology

The exact mechanism for acquiring the Whipple bacillus remains unknown. Some predisposing factors with regard to immune system function have been elucidated. These raise the question of some type of primary or secondary immune suppression or perhaps displacement of the normal constituents of the immune system.

Although B-cell function does not appear to be inhibited in patients with WD, several studies have shown that the number of lymphocytes and IgA plasma cells in the lamina propria of the small bowel are decreased in WD. After appropriate antibiotic therapy, the number of these IgA plasma cells has been shown to increase.

Patients with WD have been shown to have cutaneous anergy, decreased monocyte phagocytosis, and decreased ability to degrade the organism. These patients exhibit decreased CD11b expression. CD11b belongs to the integrin receptor family and is critical in cellular adhesion reactions of leukocytes. It is expressed by more than 90% of normal peripheral monocytes. Also noted in patients with WD is decreased interleukin 12 production by monocytes and decreased interferon-γ levels when compared with normal controls. This may mean that a defect in the circulating monocytes leads to a decrease in interferon-γ production in T cells. Low serum concentrations of IgG2, which are interferon-γ dependent, may result.

Skin anergy and the observation that patients with WD have an increased number of opportunistic infections indicate suppressed immune system function. Many patients with WD have subtle defects in T lymphocytes as demonstrated by decreased response to mitogens and lowered peripheral T-cell lymphocyte counts that recover with antibiotic therapy. Active WD is associated with an increase in CD8 T-cell counts and T-cell populations with activation markers such as CD25 and CD58 in both circulating T cells and those in the lamina propria. B-cell function does not appear to be inhibited in patients with WD.

The incidence of HLA-B27 in patients with WD is 20% to 40%. This may indicate that there are heritable predisposing factors. Secondary immune suppression is supposed, because skin anergy and lymphocyte function improve after antibiotic therapy.

Physical Findings

Whipple disease is a multisystem bacterial infection that presents with a variety of complaints that range from the classic symptoms of weight loss, diarrhea, and abdominal pain to less common presentations such as cardiovascular and neurologic findings.

The most common presentation is diarrhea with weight loss and abdominal pain. Many patients (up to 80%) also have a prohore following recurrent stroke in 1 patient with endocarditis.

Central nervous system (CNS) findings in patients with WD are present in 5% to 40% of patients, and up to 5% of patients have only CNS findings. Dementia, ophthalmoplegia, and myoclonus make up a triad seen in 10% of WD patients. Oculomotor myorhythmia and oculofacial-skeletal myorhythmia are said to be pathognomonic of WD. Other CNS findings include hypothalamic disturbances, including sleep disruptions, hyperphagia, polydypsia, and rarely symptoms mimicking supranuclear palsy. Other CNS findings present in up to 10% of patients with WD include headache, ataxia, deafness, weakness, and dementia.

Some 15% of patients exhibit pleuropulmonary symptoms including cough, pleural effusions, and occasionally a restrictive physiology.

Clinical Pathologic Findings

The changes found in clinical laboratory studies are also quite varied, but they may be useful as ancillary studies in narrowing the diagnosis.

Anemia, present in up to 90% of patients with WD, is believed to be a result of chronic infection. As with many inflammatory conditions, the erythrocyte sedimentation rate is elevated, usually greater than 30 mm/h.

In 1 study, 95% of patients had decreased serum carotene levels, 93% had hypoalbuminemia, and 91% had elevated 24-hour stool fat levels as a result of diarrhea and malabsorption.

Bone marrow involvement by T whipplei may be present in up to 40% of cases, although it is not well documented.

Gross Pathologic Findings

The affected bowel is typically edematous with yellow plaquelike lesions and villiferous mucosa. Affectd lymph nodes appear yellow with a spongy cut surface. Other affected organs, such as lungs and heart, may show plaques and edema.

Central nervous system gross findings include generalized atrophy and scattered granulomas in the gray matter of the cerebral and cerebellar cortex, the periventricular gray matter, and the gray matter around the aqueduct.

Microscopic Pathologic Findings

In most cases, the diagnosis is made by small bowel biopsy; however, the bacillus has been identified in many different tissues as well as in peripheral blood monocytes.

In the small bowel, biopsies show foamy macrophages filling the lamina propria, and these macrophages can be seen in numerous sites. A PAS stain shows PAS-positive globules filling the cytoplasm of the macrophages. Electron microscopy shows the distinctive trilaminar cell wall of T whipplei in phagolysosomes of histiocytes.

Microscopic findings in the CNS include PAS-positive intracellular and extracellular organisms surrounded by reactive astrocytes. The organisms may also violate the
subarachnoid spaces and lead to the death of neurons, vacuolization, and demyelination. 

Polymerase chain reaction is now available to aid in the diagnosis of WD, and this organism has been identified by polymerase chain reaction in many body fluids, including cerebrospinal fluid, aqueous humor, and synovial fluid. Detection in cerebrospinal fluid and peripheral blood is less consistent than in tissue. 

**Treatment**

Numerous antibiotic regimens have been used for the treatment of WD; however, no consensus for therapy has been reached. Regimens include long-term tetracycline (which does not cross the blood-brain barrier in the absence of meningeal inflammation), penicillin and streptomycin, chloramphenicol, and cotrimoxazole. Therapy is typically continued for 1 to 2 years. Those with CNS involvement are at greatest risk for relapse, and some recommend following cerebral spinal fluid with polymerase chain reaction to monitor for recurrence. Some patients have experienced a Jarisch-Herxheimer reaction with initiation of antibiotic therapy. 

**Conclusion**

The case presented here represents an unusual presentation of an uncommon disease. Whipple disease typically affects middle-aged men, who most often present with weight loss and accompanying gastrointestinal symptoms. The female patient presented in this case had multisystem involvement, including a long-standing restrictive cardiomyopathy of uncertain etiology, destructive arthritis, and pulmonary fibrosis. She did not have the classic gastrointestinal involvement seen in most patients with WD. Because the prodrome often associated with WD can present years before the classic gastrointestinal symptoms appear, it is not unusual for patients with WD to go undiagnosed for years, as in this case. Most patients are diagnosed through biopsies of the duodenum, but other sites must be considered if the diagnosis of WD is entertained. Treatment requires long-term antibiotic therapy, preferably with antibiotics that cross the blood-brain barrier, to reduce the risk of recurrence.

**References**