Whipple’s Disease and Its Intestinal Mucosal Mimics

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Abstract Recently, a male patient, presented to multiple medical specialties that eventually led to development of diarrhea and weight loss followed by eventual review by a gastroenterologist and a specific diagnosis of Whipple’s disease, a systemic disorder first described more than a century ago, but only recently recognized to be caused by Tropheryma whipplei. In this report, an updated review of this apparently very rare clinical disorder was done, including studies permitting a specific diagnosis of this disorder along with exclusion of other intestinal mucosal disorders that may potentially mimic Whipple’s disease.

Keywords: Whipple’s Disease, Tropheryma whipplei, Periodic Acid Schiff Positive Macrophages, Mycobacterium Avium-Intracellulare. Small Intestinal Malabsorption


1. Case Review

A 59 year old Caucasian male developed intermittent, but increasingly severe and generalized joint pain without swelling or joint redness approximately 3 years earlier. In the past year, however, the joint pains increased in severity to the degree that he was virtually housebound. He was initially diagnosed with a “non-specific inflammatory arthritis” and was treated sequentially with a variety of agents. These included hydroxychloroquine, methotrexate, leflunomide, tocilizumab, and prednisone. There was no clinical response. During the past year, his appetite became limited accompanied by weight loss of 15 kg. An unexplained deep venous thrombosis developed. He also developed diarrhea with 5 to 6 loose watery and non-bloody stools daily. He reported poor memory and a generalized tremor. There was no family history of intestinal or joint symptoms. There was no travel history.

Over the 3 years since the onset of symptoms, he was seen in consultation by 2 rheumatologists, 2 hematologists, a neurologist, an ophthalmologist, and, most recently, a gastroenterologist. Several studies were done revealing a mild anemia, normal white blood cell, elevated C-reactive protein (i.e., 68), normal liver chemistry tests and protein electrophoresis. Serological studies for human immunodeficiency virus (HIV) were negative along with a bone marrow biopsy. Fecal studies were negative for routine bacteria, parasites and Clostridium difficile while imaging studies included normal chest radiographs, echocardiogram, computerized abdominal tomograms, except for splenomegaly. Upper GI endoscopy and colonoscopy were macroscopically normal, but biopsies from the duodenum and terminal ileum showed the presence of easily recognizable “foamy” macrophages were positive on Grocott silver and digested periodic acid Schiff (PAS) staining for Tropheryma whipplei. Acid fast staining for Mycobacterium were negative. Confirmatory PCR testing was positive.

He was subsequently treated with antibiotics and, within 2 weeks, his gastrointestinal and joint symptoms were markedly improved. A one-year course of antimicrobials is anticipated.

2. Introduction

Whipple’s disease, initially described in 1907, as a rare chronic intestinal disease with systemic features caused by Tropheryma whipplei. The causative organism, however, was only identified in 1992 [1] as a unique 1321-base bacterial 16S ribosomal RNA (rRNA) sequence using a frozen endoscopic duodenal biopsy from a patient with Whipple’s disease. This was later confirmed using the same polymerase chain reaction (PCR) method in other tissues from 5 other patients with Whipple’s disease [1]. Actual cultivation of the organism in vitro was only first reported in 2000 [2], almost an entire century after the first clinical description of the disease. Later, genome sequencing and antibiotic sensitivity testing were done [3-6]. A PCR assay was first used for diagnosis in small intestinal biopsies in 1996 [7] with more precise disease monitoring [8].

Whipple’s disease is a systemic disease and, as in our case, may mimic a wide spectrum of disorders in multiple systems. In spite of this widespread involvement, only an estimated 1500 cases have been reported in the literature, and most expert clinicians have never seen even a single case in their entire professional careers, including gastroenterologists [9].

Whipple’s disease usually (but, not exclusively) affects mainly middle-aged Caucasian males leading to weight
loss, arthralgia, diarrhea, steatorrhea and abdominal pain. Unusual presentations may occur with involvement of the heart (particularly valves), lungs and central nervous system (including cognitive decline and dementia). However, in a recent epidemiological evaluation from North America, men and women had similar rates [10]. In addition, children as young as 4 years have been described [11]. Interestingly, a German report showed an increasing proportion of women over the 30 year course of the study suggesting that the true prevalence has been increasing in females or, alternatively, the disease has been historically under-diagnosed in women [12]. In North America, older age over 65 years was associated with increased risk of Whipple’s disease [10]. A number of factors may play a role in this increased risk in the elderly including increased antibiotic exposure and increased immune dysfunction with aging. A more recent study of risk factors in hospitalized inpatients from the United States suggested a mean age over 60 years, disproportionately affecting elderly males with heterogeneous clinical presentations and a high mortality associated with central nervous system involvement [13].

The responsible agent is bacilliform or rod-shaped with different ultrastructural forms involving both cells and extra-cellular spaces [14,15]. Lamina propria “foamy” macrophages in the small intestine (with PAS-positive particles, including duodenum, jejunum, ileum) and lymphatic drainage may be affected, often with obstruction and extensive deposits of extracellular lipids (leading to so-called “intestinal lipodystrophy”). As well, epithelial cells (with reduced microvilli) and immune cells may be involved. Occasionally, liver, esophagus, stomach and colon may be affected [16]. Intestinal symptoms (including diarrhea and weight loss) in Whipple’s disease due to Tropheryma whipplei are not specific. These may occur in other diseases, including Crohn’s disease, celiac disease, amyloidosis and small intestinal lymphoma as well as other infections, particularly in AIDS patients. The clinical features associated with intestinal involvement in atypical mycobacterial infections are notorious for mimicry of clinical and pathological features of Whipple’s disease (so-called pseudo-Whipple’s disease), specifically, Mycobacterium avium-intracellulare [17,18,19,20] or Mycobacterium genavense [21]. As noted elsewhere [16], no particular clinical differences from the infection in these immunosuppressed patients have been detailed to date.

In future, other infectious agents will likely be detected causing a clinical presentation mimicking Whipple’s disease. For example, another organism, Rhodococcus equi was also reported in an AIDS patient with a cavitating pneumonia, intestinal involvement and PAS-positive foamy macrophages containing variably shaped intra-cytoplasmic coccobacilli, histologically resembling the light and electron microscopic features of Whipple’s disease and Mycobacterium infections [22].

Some strains of Tropheryma whipplei are reported to be non-pathogenic while others have suggested that atypical strains of the organism may be responsible for some of the unusual presenting clinical features, including an isolated form of endocarditis [23]. Using PCR, Tropheryma whipplei has also been detected in the environment including sewage, water, fecal material and sewage plant workers without evidence of Whipple’s disease [24,25]. It has been hypothesized that a selective immune defect in host T-cells or host macrophages may result in Whipple’s disease, or alternatively, such immune defects may be secondary to infection by the organism, itself. Environmental detection does raise the issue of contamination, potentially obviating any conclusion on an organism in a specific patient. Interestingly, even the first scientific report [1] of an uncultured bacillus in Whipple’s disease (using a formalin-fixed skin biopsy) in 1992 noted that the patient had underlying bacillary angiomatosis and Mycobacterium avium infection.

3. Clinical and Laboratory Changes

Table 1 lists the percent frequencies of common clinical features in Whipple’s disease [26,27]. Some have suggested an apparent “prodrome” with fever and arthralgia followed by intestinal symptoms, such as diarrhea. Joint pain is often migratory and the rheumatoid factor test is negative. Large joint involvement predominates with resistance to initial anti-rheumatic drug treatment. In some of these, a duodenal biopsy may be negative but PCR testing, electron microscopy or immunohistochemistry of synovial fluid and biopsies may yield a diagnosis. Diarrhea and malabsorption leading to weight loss, a lowered serum carotene and nutrient deficiencies may develop. Anemia and protein-losing enteropathy with resultant hypoalbuninemia, peripheral edema and ascites may occur. Almost a third with Whipple’s disease develop neurological changes, including alterations in cognition with dementia. These may be the initial clinical feature and may occur without any other change. Despite treatment, changes may prove to be irreversible [28,29,30,31]. Altered ocular muscle movement may develop, including progressive supranuclear type of ophthalmoplegia. Also frequent are headache, psychiatric changes, seizure disorders and ataxia. Cerebrospinal fluid infection may be defined by PCR [32]. In the eyes [33], uveitis, retinitis and optic neuritis with papilloedema may occur. The disorder may be recognized as a culture-negative form of endocarditis with diagnosis by valve explantation [23,34].

4. Intestinal Endoscopic and Histopathologic Features

Macroscopic features have been described in some, but not all, cases with endoscopic visualization. Duodenal folds may be thick, erythematous with several yellow to yellow-white plaques [35,36]. These are not specific and may occur in forms of pseudo-Whipple’s disease [20,22]. Duodenal biopsies are important in diagnosis of intestinal involvement [36]. Histological changes can be appreciated with routine hematoxylin-eosin stained sections showing massive infiltration of lamina propria foamy macrophages that contain the organism. Rarely, in some, the infiltrate may be limited to the submucosa. These macrophages are typically PAS stain-positive, but also diastase resistant. It is thought that this staining reaction is related to the inner membrane of the polysaccharide bacterial cell wall.
Ziehl-Nielsen stain (typically used for mycobacteria species) is negative in Whipple’s disease associated with *Tropheryma whippelii*, but positive with Mycobacterial infections. Plasma cells and lymphocytes in the lamina propria may appear to be decreased, especially with significant macrophage infiltration. Small fat collections may be present in the lamina propria (recall, intestinal lipodystrophy) and surface epithelial cells may appear to be vacuolated due to fat accumulation, possibly reflecting lactic acid obstruction and regional lymph node involvement (also showing PAS-positive macrophages). Immunohistochemical staining with specific *Tropheryma whippelii* antibodies may reveal the organism, even in PAS-negative tissues. Post-treatment biopsies may show a reduction in numbers, even disappearance, of bacilli and macrophages, although these may persist for years.

5. Treatment Issues

Prior to antibiotic use, a fatal course was often recorded. Later, tetracycline was used as a form of monotherapy, but recurrence was common. More recently, recommendations were based on use of antibiotics that could cross the blood-brain barrier. Intravenous ceftriaxone for two weeks followed by oral cotrimoxazole for a year was recommended [37]. Resolution occurs, but neurological symptoms may persist. Others have recommended oral trimethoprim-sulfamethoxazole for up to 2 years [38].

Recurrent neurological symptoms in Whipple’s disease has a poor prognosis, and use of gamma-interferon has been suggested [39]. In some of these, persistence of an underlying immunological disorder may be critical to clearing the organism.

Along with increased susceptibility to tuberculosis infections, a special high risk for Whipple’s disease may develop in patients treated with anti-tumor necrosis factor [40,41]. Indeed, a number of Whipple’s disease cases have appeared in patients treated with an ongoing oral or parenteral form of the medication, often in those with rheumatological or gastrointestinal disorders [40,41].

Statement of Competing Interests

The authors declare no conflicts of interest.

References


