

Whipple's Disease

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ABSTRACT

Whipple's disease is a rare chronic multi-systemic infection, caused by Gram-positive bacillus *Tropheryma whipplei*. The infection usually involves the small bowel, but other organs may also be involved. The diagnosis is often challenging and can only be made on histopathological examination. This report describes 2 patients presenting with abdominal pain and weight loss who finally were diagnosed to have Whipple's disease. One of the patients was a renal transplant recipient. To the best of authors' knowledge, no case of Whipple's disease has yet been reported in Pakistan. The diagnosis were made on the basis of histopathological evaluation of duodenal biopsies. The cases underscore the need for diligent histopathological evaluation of the upper gastrointestinal biopsies and a high index of suspicion for an accurate diagnosis of the condition. The approach to the diagnosis and management of the condition is discussed.

Key Words: Whipple's disease. Malabsorption. PAS (periodic acid schiff) stain.

INTRODUCTION

Whipple's disease is a rare chronic, multi-systemic infectious condition chiefly affecting the small intestine and presenting with malabsorption and weight loss. Sometimes other tissues and organs are also involved with protean manifestations. The disease is caused by Gram-positive bacillus *Tropheryma whipplei*.^{1,2} An accurate diagnosis of this disease is often challenging and can only be made on histopathological examination of tissue biopsies. The latter requires a diligent and careful evaluation of the biopsy material and a very high index of suspicion.

To-date, there is no single case of Whipple's disease reported from Pakistan. We herein present two cases, one of whom was a renal transplant recipient and review the relevant literature.

CASE REPORT

Case 1: A 27-year-old female came with history of epigastric pain associated with off and on constipation for last 3 years. There was a weight loss of 3 kilogram (kg) in last 3 months. Past history revealed depression and migraine. There was no history of drug abuse. In addition to the antihelminths, she received antacids and spasmolytics, which temporarily alleviated her symptoms. Clinical examination demonstrated a normal general physical condition with normal body temperature, general physical examination showed no

lymphadenopathy, skin lesion or sign of articular involvement. Abdominal examination revealed mild tenderness in epigastric region with audible gut sounds. Pulmonary, cardiovascular and neurological examinations were unremarkable.

Investigations including complete blood count, urea, creatinine, electrolytes, liver function tests, prothrombin time, international normalized ratio (INR), HIV serology, autoimmune profile (ANA, ASMA, Anti-LKM, AMA), ultrasound of whole abdomen, echocardiography and small bowel enteroclysis were normal.

Upper gastrointestinal endoscopic findings revealed no abnormalities in the esophagus, stomach or first part of the duodenum. Biopsies from antrum and distal duodenum were taken. The tissue samples were immersed in 10% buffered formalin and sent for histopathological examination. The sections from duodenal biopsy showed intact villi, scattered large clusters of foamy macrophages with fine granular eosinophilic cytoplasm and moderate lymphoplasmic cell infiltrate in the lamina propria (Figure 1A).

Alcian blue-Periodic acid Schiff (AB PAS) staining was performed with and without diastase, which revealed foamy macrophages filled with PAS positive and diastase resistant material in the cytoplasm, suggestive for *Tropheryma whipplei* (Figure 1 B). Zeil-Nelson (ZN) and modified ZN staining were negative for acid fast bacilli (AFB). Considering all the data, the patient was questioned about risk factors for *T. whipplei* infection but she denied any unusual exposure to soil. However, there was history of ingestion of large amount of water when she fell accidentally into swimming pool.

For the current symptoms, she was treated with standard treatment consisting of 2 weeks parenteral therapy with Ceftriaxone followed by Sulphamethoxazole 800 mg: Trimethoprim 160 mg/day for 6 months. This treatment

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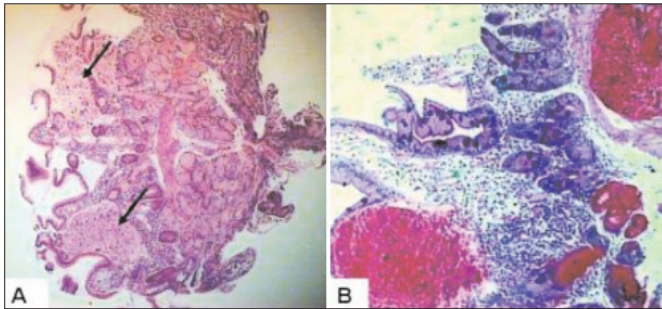


Figure 1: (A) HE staining of duodenal biopsy showing large localized aggregates of foamy macrophages in the lamina propria (arrows). There is also moderate lymphoplasmic cell infiltrate in the lamina propria. (HE, x100). (B) ABPAS-D staining of duodenal biopsy showing large localized aggregates of foamy macrophages filled with PAS positive and diastase resistant material, suggestive of Whipple's disease. (ABPAS-D, x 200).

was followed by relief of her primary symptoms, and weight gain of 5 kg in this duration. Follow-up endoscopy could not be done as patient moved out of the city after marriage.

Case 2: A 37-year-old male, diagnosed as end-stage renal disease (ESRD) in 2005 and sustained on renal replacement therapy for 4 years, underwent renal transplant in 2009. He was on standard triple drug immunosuppressive medications (prednisolone, azathioprine, cyclosporine). He remained asymptomatic for one year after kidney transplantation, when he was admitted with symptoms of persistent large volume diarrhea with a frequency of 5 - 6 times a day associated with significant weight loss of 4 kg in 1 month. There was no history of drug abuse. General physical examination was unremarkable. However, on abdominal examination, there was mild tenderness in epigastric region. Gut sounds were audible. Pulmonary, cardiovascular and neurological examinations were unremarkable.

Investigations related to malabsorption, including laboratory and radiological studies were normal.

Upper gastrointestinal endoscopic findings revealed no abnormalities in the esophagus, stomach or first part of the duodenum. Biopsies from antrum and distal duodenum were taken and sent for histopathological evaluation. The results of the later were similar to those described above for case 1. ZN and modified ZN staining was negative for AFB. He was diagnosed as a case of Whipple's disease, which was treated as mentioned in previous case. There was improvement in diarrhea and weight gain.

Repeat endoscopy was performed after 8 months and duodenal biopsy revealed no signs of Whipple's disease.

DISCUSSION

In 1907 George Whipple, during autopsy studies of lymph nodes, found foamy macrophages and large number of argyrophilic rod-shaped structures, positive for Periodic Acid Schiff (PAS) later proven to be as of

bacterial origin.^{1,2} Nowadays the diagnosis of Whipple's disease is dependent on the amplification of 16s rRNA of the bacterium isolated from duodenal biopsy.³ Currently, the rRNA PCR technique is used for diagnosing Whipple's disease.

The bacillus is present in sewage water and in the soil.^{4,5} Neither of these patients had any history of contact with soil. There is an underlying genetic predisposition such as defects in the cell-mediated immune responses which predispose to the typical form of the disease. In first patient, endoscopy of the mother revealed normal histology. Whipple's disease is characterized by diarrhea, malabsorption, abdominal pain, weight loss, arthritis or arthralgia, fever, lymphadenopathy, and neurological signs, i.e. headache, cognitive dysfunctions and disturbances of the ocular movement. CNS involvement is the most serious manifestation of the disease and occurs in up to 43% of cases.⁶ In these patients although patients had abdominal pain associated with significant weight loss, patient 1 had depression and migraine while second had no neurological or ocular involvement.

The bacillus has an increased affinity for macrophages and monocytes. In predisposed individuals, the persistence of high intracellular bacterial burden points toward an impairment of the host immune response, possibly secondary to the infection itself i.e. alterations in the immune control.^{7,8} Considering the treatment of this disease, there are a number of options available as shown in recent randomized trial. Induction treatment with intravenous ceftriaxone or meropenem for 2 weeks followed by 12 months treatment with oral Sulphamethoxazole 800 mg: Trimethoprim 160 mg/day.^{9,10} Recovery is usually complete, but sometimes the neurologic lesions are irreversible. Our patients were also treated in the standard way and responded to treatment. The immune reconstitution inflammatory syndrome is a severe complication arising during the treatment in 10% of patients. It manifests as fever and sterile inflammation affecting the joints or the small bowel and requiring corticosteroids. Severe CNS disease is another classical indication for intravenous steroids. Regular check-ups are indicated, at first monthly, then every 6 months in the first year, then yearly for at least 2 - 3 years, in order to promptly identify those with relapsing disease or those with neurologic sequelae.

Proof of cure is based on clinical grounds (usually the diarrhea and malabsorption improve in weeks), on PCR (which quickly becomes negative after efficient therapy) and on repeated endoscopy with biopsies (with the endoscopic changes disappearing in weeks but the histological aspect may persist for several years).

These patients presented with abdominal pain with significant weight loss along with PAS-positive material inside the macrophages from duodenal biopsies. We

could not perform 16s rRNA PCR for *Tropheryma whipplei*. However, both patients responded very well to the treatment and there were improvement in symptoms and weight gain.

Whipple's disease is rare, but should be considered in the differential diagnosis of un-explained abdominal pain and weight loss of gastrointestinal origin.

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