

# Whipple's Disease

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## Abstract

A 74 year old male patient with weight loss, diarrhoea, loss of appetite, anemia, thrombocytopenia and culture negative endocarditis was diagnosed to have Whipple's disease. We are reporting this case, as it is a rare disease with fewer than 1000 validated cases reported in literature.

## Introduction

Intestinal lipodystrophy, now referred to as Whipple's disease was first recognised as a disorder in 1907 by the great American pathologist, George Whipple. It is a multisystem infectious disorder presenting as cardiomyopathy, malabsorption, pleuritis, various CNS manifestations, weight loss and arthralgias. The diagnosis is based on demonstration of periodic acid Schiff positive (PAS) inclusions in infected tissues.

## Case History

A 74 year old male, resident of Mumbai, was on a visit to the United States in October 2003. He had loose stools, melena, loss of appetite and weight loss of more than 10 kgs in 3 months. He had deep vein thrombosis in right leg while in U.S. 3 months ago and was given anticoagulants. He returned to India in December 2003. The significant past illness was inferior wall myocardial infarction few years ago for which he was on aspirin. He had no Diabetes mellitus and tested negative for HIV. He was cachectic, pale on admission, was detected to have microcytic hypochromic anemia with thrombocytopenia, raised CRP, occult blood positive in stools. 2D Echo showed an ejection fraction of 48%, RWMA was present, X ray chest, ultrasound abdomen were normal. Upper GI endoscopy revealed duodenitis and colonoscopy showed prominent villous pattern. Histopathology from terminal ileum revealed hyperplastic lymphoid tissue with few epithelioid granulomas. He was empirically started on anti tuberculous treatment (Isoniazid, Rifampicin, Ethambutol,

Pyrazinamide). He was symptomatically better and had weight gain.

He was readmitted 3 months later with loose motions, diminished appetite and further weight loss and low grade intermittent fever. He was detected to be anemic, icteric. Repeat colonoscopy was done. Biopsy of terminal ileum showed blunted villi with sheets of large macrophages with foamy cytoplasm in lamina propria intensely PAS positive bacilli were seen in macrophages, no granulomas, no acid fast bacilli seen. The above histological picture was suggestive of Whipple's disease. Similar PAS positive material and foamy macrophages were identified on review of previous slides. He developed right hemiparesis during this admission. MRI brain revealed a left thalamic infarct. 2D echo showed a ejection fraction of 35% and a large 1.4 X 1.8 cm mass attached to aortic leaflets ? vegetation / ? mass / ? fungal vegetation. Three blood cultures and one fungal culture were negative. He was treated with ceftriaxone, gentamycin and co-trimoxazole. His clinical course was complicated by heart failure. He was advised aortic valve replacement but he refused surgery and was discharged on ceftriaxone and cotrimoxazole.

We subsequently heard that he succumbed to his illness 4 weeks after discharge.

## Discussion

Whipple's disease is a rare multisystem disorder associated commonly with gastrointestinal involvement. However the clinical features may be diverse – weight loss, lymphadenopathy, seronegative arthritis, endocarditis, neurological manifestations, low grade fever, hyperpigmentation have been described.<sup>1</sup>

In 1907 George Whipple in autopsy studies demonstrated foamy macrophages and large numbers of argyrophilic rod-shaped structures in the lymph nodes. These were later found

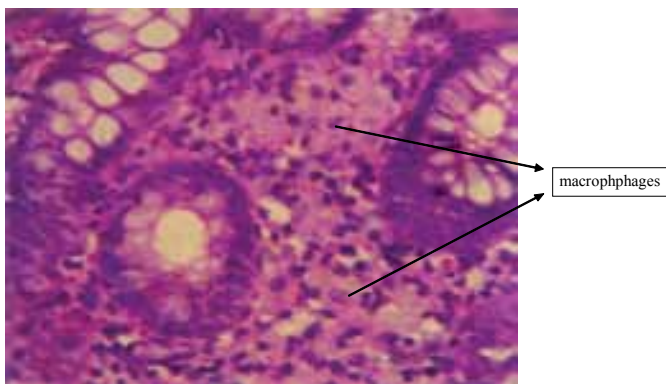


Fig. 1 : Microscopy showing sheets of foamy macrophages in the lamina propria of the small intestine (original magnification X 40, H & E)

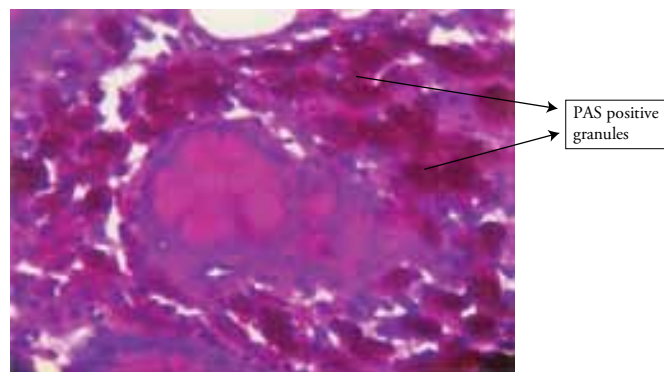


Fig. 2 : Microscopy showing foamy macrophages with PAS positive granules in lamina propria in the small intestine (original magnification X 40, PAS stain)

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to be periodic acid Schiff (PAS) positive. In 1960 - 1961 this PAS positive material in macrophages was thought to be of bacterial origin.<sup>2</sup> In 1991, molecular studies were performed by amplification of 16s rRNA of the bacterium isolated from duodenal biopsy sample of patient with Whipple's disease.<sup>3</sup> This PCR technique is currently used for establishing a diagnosis of Whipple's disease. The bacteria was called *Tropheryma whippelii* (Greek trophe nourishment and eryma barrier, and from Whipple).<sup>1</sup>

The disease is mainly described in Caucasians (middle aged with a male preponderance). Few cases have been described in Hispanic black, Indian, or Asian populations.<sup>4,5</sup> Major clinical features are weight loss, diarrhoea, abdominal pain and arthropathy present in more than two thirds of the patients.<sup>1</sup> On endoscopy, the lesions of Whipple's disease are commonly described as pale yellow shaggy mucosa alternating with an erythematous, erosive, or mildly friable mucosa in the postbulbar region of the duodenum or in the jejunum.<sup>1</sup> Therefore biopsy samples should be taken from both the proximal and distal duodenum or jejunum. The possibility of a defect in host defence predisposing to Whipple's disease has attracted much interest, there is no evidence from the patients investigated to date for a major immune defect. The diagnosis should be considered in a wide variety of clinical situations, whether or not there is gastrointestinal involvement.<sup>6</sup> Our patient presented with diarrhoea, anorexia, weight loss, Malena was probably secondary to the oral anticoagulants and aspirin. He subsequently had culture negative endocarditis and neurological deficit. The second biopsy of terminal ileum revealed macrophages with foamy cytoplasm and PAS positive bacilli suggestive of Whipple's disease. *T. whippelii* is predominantly an intracellular pathogen and frequently causes fatal neurological disease. Cotrimoxazole is often used as the drug of first choice, because of its ability to penetrate the uninfamed blood-brain barrier. Patients with neurological disease at presentation should be treated aggressively with parenteral antibiotics, such as beta lactams, which penetrate the blood-brain barrier.<sup>1</sup>

#### Recommended Treatment

Two weeks parenteral therapy : Ceftriaxone (or penicillin plus streptomycin)

Long term therapy ( $\geq 1$  year): Trimethoprim-sulfamethoxazole (or tetracycline or minocycline)

If the patients have a good clinical response they can be followed up with duodenal biopsies 6 and 12 months after treatment. Antibiotic treatment can be stopped if no PAS – positive material is identified.<sup>1</sup> It is important to emphasize that although Whipple's disease is rare, physicians should always consider it in their differential diagnosis since its clinical presentation is so variable and it may be lethal if left untreated.

### References

1. Thomas Marth, Didier Raoult. Whipple's Disease. Lancet 2003;361:239-46.
2. Chears WC, Ashworth CT. Electron microscopy study of the intestinal mucosa in Whipple's disease: demonstration of encapsulated bacilliform bodies in the lesion. Gastroenterology 1961;41:129-38.
3. Wilson KH, Blitchington R, Frothingham R, Wilson JA. Phylogeny of the Whipple's disease-associated bacterium. Lancet 1991;338:474-75.
4. Dobbins WO III. Whipple's disease. Springfield, Illinois:Charles Thomas, 1987.
5. Mehta A, Patkar N, Duhan S, Srinivas, Nema S. Indian Journal of Gastroenterology 2005; 24:31.
6. Siraj A Misbah, Aamir Aslam, Christine Costello. Eponym on Whipple's Disease. Lancet 2004; 363:654-56.