

CASE REPORT

An unusual cause of pancytopenia: Whipple's disease

Nay T. Tun, MD^{1*}, Shwetanshu Shukla, MD¹,
Jaykrishnan Krishnakurup, MD¹, Binu Pappachen, MD¹,
Mahesh Krishnamurthy, MD, FACP, FHM¹ and Hayman Salib, MD, FACP²

¹Department of Internal Medicine, School of Medicine, Easton Hospital, Residency Program, Affiliated with Drexel University, Easton, PA, USA; ²Hematology and Oncology Department, School of Medicine, Easton Hospital, Easton, PA, USA

Whipple's disease is a systemic infectious disease caused by the bacteria *Tropheryma whippelii*. The most common clinical manifestations of Whipple's disease are weight loss (92%), hypoalbuminemia and steatorrhea (91%, respectively), diarrhea (72%), arthralgia (67%), and abdominal pain (55%). Neurological signs and symptoms from dementia to oculomasticatory myorhythmia or oculofacioskeletal myorhythmia (pathognomonic of Whipple's disease), lymphadenopathy, and fatigue can also be present. Pancytopenia is a rare and less recognized clinical feature in Whipple's disease patients. We are describing a case where a middle-aged Caucasian male diagnosed with Whipple's disease was found to have pancytopenia. Etiology of pancytopenia is postulated to be due to the invasion of bone marrow by *T. whippelii*. It is important to recognize that bone marrow involvement by the Whipple bacillus is not uncommon. In the presence of lymphadenopathy and pancytopenia, clinicians should think of Whipple's disease as a differential diagnosis apart from lymphoma or other non-specific granulomatous reticuloendothelial disorders.

Keywords: PAS positive macrophages; bone marrow invasion; pancytopenia; *Tropheryma whippelii*

*Correspondence to: Nay T. Tun, Internal Medicine Medical Resident, Easton Hospital, 250 South 21st Street, Easton, PA 18042, USA, Email: eileeney@gmail.com

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Whipple's disease is a rare, multi-systemic chronic infectious disease that preferentially affects middle-aged Caucasian men. Overall annual incidence is reported to be less than 1 per 1,000,000 (1–8). We present a case of a 53-year-old Caucasian male who presented with significant weight loss, chronic diarrhea, generalized arthralgia, as well as cognitive function impairment. Diagnosis of Whipple's disease was confirmed by multiple organs' biopsies showing periodic acid Schiff (PAS) positive, diastase-resistant intracellular large particles and positive polymerase chain reaction (PCR) for Whipple's disease. He was also found to have an unexplained pancytopenia on further studies. On review of the literature, there was no recent evidence or reported case of Whipple's disease causing pancytopenia.

Case presentation

A 53-year-old Caucasian male presented to the emergency department with swelling of bilateral lower extremities for 1-week duration and non-specific left lower abdominal pain for 2 weeks. He also complained of chronic non-bloody, watery diarrhea, significant weight loss, and generalized arthralgia involving bilateral ankle joints,

cervical and lumbo-sacral spines for almost a year. Lower abdominal pain was located on the left side which was non-radiating, non-exertional, and unrelated with food intake, urine, or bowel movement. He denied having any fever, chills, exertional or resting dyspnea, and orthopnea. He denied having any risk factors for immunocompromised state or any recent travel outside of the United States. The patient was worked up in an outside hospital with abdominal lymph node biopsy, revealing chronic lymphadenitis. Upper and lower GI endoscopies were not revealing of the cause of his diarrhea and significant weight loss. Family members also noted impairment of his cognition, with worsening memory and alertness. His medical history included flare-up of rheumatoid arthritis, which was treated with prednisone. The patient was taking ibuprofen as needed for arthralgia. He was found to be drinking water from a well.

On physical examination, the patient appeared to be thin, chronically ill, and pallid with loss of buccal fat and tight skin over his face. He was afebrile, alert, and oriented to his surroundings along with stable vital signs. Shotty lymph nodes were palpated in the supraclavicular, axillary and groin regions. Abdominal examination

revealed the presence of scar from a previous incision in the left lower quadrant but otherwise no organ enlargement or tenderness. Musculoskeletal examination revealed remarkable stiffness on rotation and flexion of his neck and stiffness on bilateral ankles and wrists. There were 3+ pitting edema, extending from the ankles to the knees. The skin of both legs was dry with some excoriations. The rest of the physical examination was unremarkable.

The patient's complete blood count showed hemoglobin of 9.2 g/dL, white cell count of $3.7 \times 10^9/L$ and platelets of $98 \times 10^9/L$. Complete metabolic panel revealed mild hypokalemia and hypoalbuminemia (albumin 2 g/dL). CT scan of the abdomen and pelvis revealed that the patient had diffuse multifocal mesenteric, retroperitoneal, and inguinal lymphadenopathy. Stool studies showed the presence of occult blood but were negative for ova and parasites. Clostridium difficile toxin in the stool was negative. HLA-B27 was negative.

The patient underwent a colonoscopy and esophago-gastro-duodenoscopy. Multiple biopsies were taken from the duodenum and the terminal ileum which showed diastase resistant, PAS stain positive intracellular organism, consistent with Whipple's disease. Terminal ileum biopsy showed flattening of villi and numerous histiocytes within lamina propria with PAS-positive, diastase resistant intracellular inclusions (Fig. 1) and duodenal biopsy showed PAS-positive, diastase resistant intracellular inclusions (Fig. 2). On day three of the admission, his white blood cell count was $1.5 \times 10^9/L$ (41% segmented neutrophils, 35% bands, 17% lymphocytes, 6% monocytes), hemoglobin was 8.9 g/dL and platelet count was $54 \times 10^9/L$. Mean corpuscular volume (MCV) was 80.9 fl; mean corpuscular hemoglobin was 25.4 pg. To diagnose the cause of his pancytopenia and cognitive changes, he underwent a bone marrow biopsy and lumbar puncture. Bone marrow biopsy showed PAS positive diastase resistant intracellular bacilli (Fig. 3), while lumbar puncture was non-diagnostic. The patient also underwent transesophageal echocardiogram which ruled out any vegetations and, thus, endocarditis. The patient was started on intravenous ceftriaxone along with oral trimethoprim-sulfamethaxazole after obtaining advice from the infectious disease specialist.

The patient's condition started improving in terms of resolution of diarrhea, weight gain as well as pancytopenia. He was discharged home on intravenous ceftriaxone with a total duration of 28 days on a peripherally inserted central catheter and the therapeutic regimen continuation was based on clinical response. Oral trimethoprim-sulfamethaxazole was continued for 1 year. The patient was followed up closely in the office periodically. He reported improvement in cognitive function. Further periodic complete blood count on follow-up revealed no recurrence of pancytopenia.

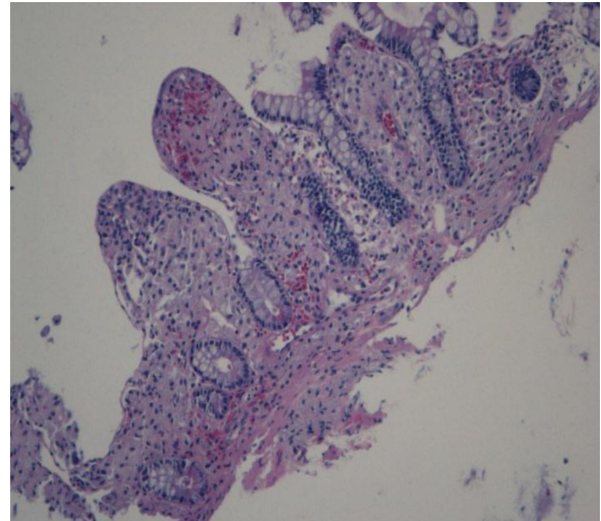


Fig. 1. Terminal ileum biopsy showing flattening of villi and numerous histiocytes within lamina propria with PAS-positive, diastase resistant intracellular inclusions.

Discussion

George Hoyt Whipple described Whipple's disease in 1907 where he named the disease as 'intestinal lipodystrophy' (9). However, the ability to identify and confirm the causal organism by genomic sequencing with 16S ribosomal RNA (rRNA) was accomplished in 1992 (9). Molecular amplification of the 16S rRNA of Tropheryma Whipplei by PCR and cell culture of the organism (10) greatly improved our knowledge of Whipple's disease (11). It has made tremendous improvements in enabling the clinicians to make the diagnosis in patients who do not have gastrointestinal symptoms (12). Initially, the organism was named Tropheryma Whipplei (Greek Trophi: food; Eryma: barrier, because of the resulting malabsorption) (9). The name was officially corrected to Tropheryma Whipplei in 2001 (13).

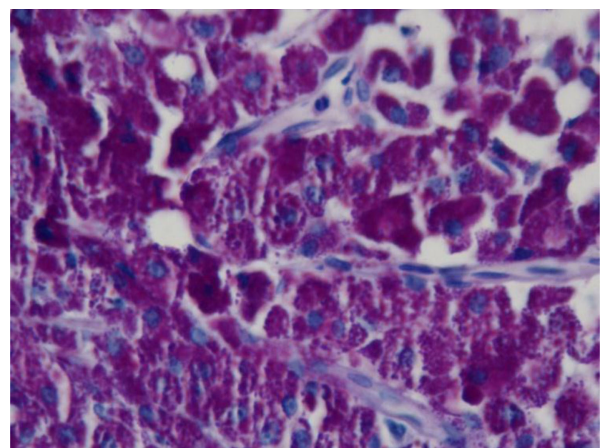


Fig. 2. Duodenal biopsy with PAS staining showing PAS-positive, diastase resistant intracellular inclusions.

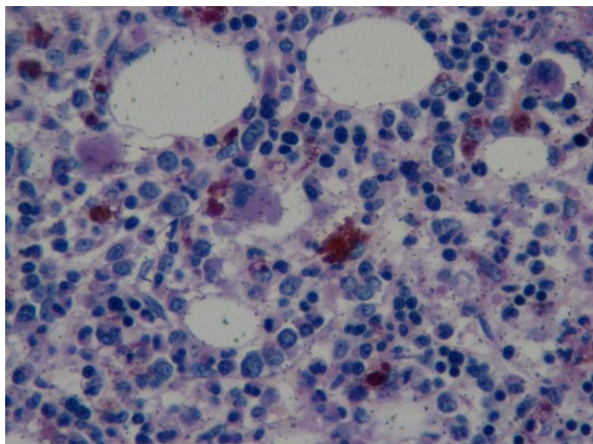


Fig. 3. Bone marrow biopsy with PAS-positive diastase resistant intracellular bacilli.

Whipple's disease is a rare infectious disease mostly characterized by intestinal malabsorption with weight loss. Clinical manifestations can be variable as this disease affects multiple organs. Primarily, Whipple's disease affects the gastrointestinal tract. The disease commonly affects the lamina propria of the small intestine and its lymphatic drainage. Extra intestinal manifestations include arthralgia, weight loss, lymphadenopathy, ascites, fever, splenomegaly and nervous system involvement including dementia, ataxia and myoclonus. Cardiac involvement is rare; however, culture negative endocarditis and congestive heart failure have been reported.

Bone marrow involvement in Whipple's disease is common but often overlooked. Bone marrow involvement could lead to anemia, thrombocytopenia and leucopenia. Bone marrow biopsy showing PAS-positive diastase resistant inclusions within the histiocytes gives a clue to the diagnosis of Whipple's disease in patients presenting with a lymphoma-like syndrome with lymphadenopathy and pancytopenia. Invasion of bone marrow by Whipple's disease could be confirmed with PCR testing of amplification of 16s portion of rRNA of *Tropheryma whipplei* followed by finding PAS stain positive diastase-resistant bacillary particles or identifying the bacterial organism by electron microscopy from tissue biopsy.

Sieracki and Fine described focal bone marrow involvement at autopsy in two out of five patients, finding PAS-positive macrophages containing 'sickle-form particles' (14, 15). A similar finding was described in a 3-month-old child (15, 16) and in a 75-year-old woman at post mortem (15, 17). In 1963, Enzinger and Helwig showed PAS positive macrophages in bone marrow aspiration in four out of 15 cases (15, 18). Remadi et al. described some PAS-positive macrophages as well as reactive hyperplasia being found retrospectively in bone marrow smears of a 58-year-old woman at autopsy (15, 19). Pron et al. (15, 20) presented eight cases in which three patients had

undergone bone marrow biopsies. Two out of three patients showed PAS-positive macrophages and a positive PCR and, in the remaining sample, very rare amounts of PAS-positive macrophages but the PCR test was negative. Walter et al. described one patient with markedly increased megakaryopoiesis with hyper-fragmented forms along with PAS-positive inclusions within the cells. Splenectomy performed in the same patient suggested the presence of non-caseating granulomas in the white pulp along with few foamy macrophages containing diastase resistant, PAS-positive inclusions (15).

Granuloma formation has been observed on repeated occasions. Wilcox et al. described PAS-negative non-caseating granuloma in a bone marrow biopsy of a 58-year-old man who had confirmed diagnosis of Whipple's disease on duodenal biopsy with verification using Electron microscope (21). Jarolim et al. described non-caseating granuloma with PAS-positive bacillary bodies (6).

Conclusion

After reviewing all of the studies described above, bone marrow involvement in Whipple's disease is a rare but not very uncommon clinical entity. It is important to recognize pancytopenia in Whipple's disease as knowledge of this information can prevent further unnecessary investigations, searching for other lymphoproliferative disorders especially in the presence of lymphadenopathy. In addition, pancytopenia can be resolved in Whipple's disease as in this case by treating with systemic antibiotics.

Conflict of interest and funding

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References

1. Dobbins WI. Whipple's disease. Springfield, IL: Charles C Thomas; 1987.
2. Maizel H, Ruffi JM, Dobbins WO. Whipple's disease: A review of 19 patients from one hospital and a review of the literature since 1950. *Medicine (Baltimore)* 1970; 49: 175–205.
3. Durand DV, Lecomte C, Cathebras P, Rousset H, Godeau P. Whipple disease. Clinical review of 52 cases. The SNFMI Research Group on Whipple Disease. *Societe Nationale Francaise de Medecine Interne. Medicine (Baltimore)* 1997; 76: 170–84.
4. Fleming JL, Wiesner RH, Shorter RG. Whipple's disease: Clinical, biochemical, and histopathologic features and assessment of treatment in 29 patients. *Mayo Clin Proc* 1988; 63: 539–51.
5. Messori A, Di Bella P, Polonara G, Logullo F, Pauri P, Haghhighipour R, et al. An unusual spinal presentation of Whipple disease. *AJNR Am J Neuroradiol* 2001; 22: 1004–8.
6. Jarolim D, Parker G, Sheehan W. Bone marrow involvement by Whipple bacillus. *J Infect Dis* 1991; 163: 1169–70.
7. Desnues B, Ihrig M, Raoult D, Mege J. Whipple's disease: A macrophage disease. *Clin Vaccine Immunol* 2006; 13(2): 170–8.

8. In: Warrel D, Cox T, Firth J, Benz Jr E. eds. Oxford textbook of medicine. 4th ed. Oxford University Press. Feb 2004 ISBN 0198529988.
9. Relman D, Schmidt T, MacDermott R, Falkow S. Identification of the uncultured bacillus of Whipple's disease. *N Engl J Med* 1992; 327(5): 293–301.
10. Raoult D, Birg M, La Scola B, Fournier P, Enea M, Lepidi H, et al. Cultivation of the bacillus of Whipple's disease. *N Engl J Med* 2000; 342: 620–5. [Erratum, *N Engl J Med* 2000; 342: 1538.].
11. Fenollar F, Puéchal X, Raoult D. Whipple's disease. *N Engl J Med* 2007; 356: 55–66.
12. Fenollar F, Raoult D. Whipple's disease. *Curr Gastroenterol Rep* 2003; 5: 379–85.
13. La Scola B, Fenollar F, Fournier PE, Altwegg M, Mallet MN, Raoult D. Description of *Tropheryma whippelii* gen. nov., sp. nov., the Whipple's bacillus. *Int J Syst Evol Microbiol* 2001; 51: 1471–9.
14. Sieracki JC, Fine G. Whipple's disease: Observation on systemic involvement. II. Gross and histologic observation. *Arch Pathol* 1959; 67: 81–93.
15. Walter R, Bachmann S, Schaffner A, Rüegg R, Schoedon G. Bone marrow involvement in Whipple's disease: Rarely reported, but really rare? *Br J Haematol* 2001; 112: 677–9.
16. Aust CH, Smith EB. Whipple's disease in a 3-month old infant with involvement of the bone marrow. *Am J Clin Pathol* 1962; 37: 66–74.
17. Rausing A. Bone marrow biopsy in diagnosis of Whipple's disease. *Acta Medica Scandinavica* 1973; 193: 5–8.
18. Enzinger FM, Helwig EB. Whipple's disease – a review of the literature and report of fifteen patients. *Virchows Archiv A Pathol Anat Histopathol* 1963; 336: 238–68.
19. Remadi S, Starobinski M, Wildgren S. Atteinte de la moelle osseuse en cas de maladie de Whipple [Bone-marrow involvement in Whipple's disease]. *Ann Pathol* 1992; 12: 188–92.
20. Pron B, Poyart C, Abachin E, Fest T, Belanger C, Bonnet C, et al. Diagnosis and follow-up of Whipple's disease by amplification of the 16S rRNA gene of *Tropheryma whippelii*. *Eur J Clin Microbiol Infect Dis* 1999; 18: 62–5.
21. Wilcox GM, Tronic BS, Schecter DJ, Arron MJ, Righi DF, Weiner NJ. Periodic acid-Schiff-negative granulomatous lymphadenopathy in patients with Whipple's disease. Localization of the Whipple bacillus to non-caseating granulomas by electron microscopy. *Am J Med* 1987; 83: 165–70.