

Whipple's disease: easily diagnosed, if considered

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ABSTRACT

Patients present with arthralgia, abdominal pain, diarrhoea and weight loss. The disease is commonly diagnosed by histological examination of small bowel biopsies, especially after staining with periodic acid-Schiff. Because of the rarity of the disease, its diagnosis is not often considered. Therefore the necessary investigations might be omitted. This case report might serve as a reminder for internists or gastroenterologists to consider Whipple's disease in patients with abdominal, articular or other symptoms after having excluded common differentials. We also review the current literature on Whipple's disease. Whipple's disease is an infectious disorder caused by *Tropheryma whipplei*.

KEYWORDS

Abdominal lymphadenopathy, abdominal pain, arthralgia, malabsorption, Whipple's disease

INTRODUCTION

Whipple's disease is a rare systemic infectious disorder caused by the *Tropheryma whipplei*, an intracellular gram-positive bacillus.¹ Patients present with arthralgia, abdominal pain, diarrhoea and weight loss.^{2,3} The disease is commonly diagnosed by histological examination of small bowel biopsies, especially after staining with periodic acid-Schiff (PAS). Because of the rarity of the disease, it is often not considered in the differential diagnosis. Therefore the necessary investigations might be omitted. This case report might serve as a reminder for internists, gastroenterologists and rheumatologists to consider Whipple's disease in patients with abdominal, articular or other symptoms after having excluded common differentials. We also review the current literature on Whipple's disease.

CASE REPORT

A 68-year-old male was admitted to our hospital for analysis of multiple enlarged lymphomas seen on abdominal computerised tomography (CT). For five months he had suffered from severe tiredness, loss of appetite, and had a weight loss of 10 kg. He also mentioned nausea without vomiting, diffuse abdominal pain and fatty, nonbloody diarrhoea for seven weeks. Occasionally he had fever and chills. His medical history included a gastric ulcer ten years ago, migrating arthralgia diagnosed as polymyalgia rheumatica and a 45 pack-year history of smoking. He seldom used alcohol. He was taking prednisone (5 mg daily), frusemide, pantoprazole and pyridinyl bisphosphonate. His family history revealed no malignancies. Physical examination showed a cachectic, fatigued male with a height of 1.75 meter and a weight of 46 kg. His blood pressure was 115/65 mmHg, pulse rate 72 beats/min and body temperature 37.7°C. His skin was dry and pale. There were no enlarged palpable lymph nodes in the neck, supraclavicular, axillar or inguinal. Auscultation of lungs and heart was normal. Palpation of the abdomen revealed no abnormalities, in particular no palpable mass. All peripheral pulses were palpable. No signs of arthritis. Neurological examination was normal.

Laboratory investigation showed a normocytic anaemia with reduced serum iron, and normal levels of transferrin and ferritin. Also elevated C-reactive protein, mild hyponatraemia and hypokalaemia were found. Furthermore, the patient had hypoalbuminaemia and a decreased total protein level. Electrolytes, renal function and liver tests were within the normal limits. Faecal fat analysis demonstrated steatorrhoea: 69 g/24 h stools. Chest X-ray showed mild signs of emphysema but no other abnormalities. Abdominal CT did not show any masses except enlarged lymph nodes in the para-aortal region and in the peritoneal fat (*figure 1A*). Gastroduodenoscopy revealed signs of gastritis but no primary tumour. During

diagnostic laparoscopy multiple enlarged mesenteric nodes were detected, besides a thickened peritoneum. Gastric antral biopsy showed intestinal metaplasia with atrophy but without signs of infection. Examination of the endoscopic duodenal biopsies and of the laparoscopic biopsies from peritoneum and abdominal lymph nodes all showed the same aspect of numerous macrophages, laden with intracellular PAS-positive material (*figure 2A and B*). There were no signs of malignancy or mycobacterial infection. Because of these findings the diagnosis Whipple's disease was assumed. Therapy with parenteral ceftriaxone was initiated for two weeks. Twenty-two days after admission the patient was discharged with a mildly improved clinical status.

During 2.5 months of treatment with co-trimoxazole the patient's condition improved dramatically. He had gained 5.5 kg, and his appetite returned. The abdominal pain

had vanished and he had normal daily stools, without any diarrhoea. There was no articular pain either. Laboratory tests showed an increased haemoglobin (from 6.0 to 7.7 mmol/l) and iron level (from 2.7 to 8.7 mol/l). The albumin and total protein level had returned to normal (from 25.2 to 40.4 g/l and from 51 to 73 g/l respectively). After six months he had gained another 10 kg. The abdominal CT scan showed a sizable reduction of the para-aortal lymphomas (*figure 1B*). Additionally, there was a reduction of the intraperitoneal lymphomas.

DISCUSSION

In 1907, a pathologist George Hoyt Whipple described a 36-year-old male with weight loss, polyarthritis, abdominal pain, lymphadenopathy and fatty diarrhoea.⁴ Fatty material

Figure 1A. Axial CT obtained at the midabdomen showing enlarged paraortal lymphomas (arrow)



Figure 1B. Axial CT showing reduction in size of the lymphomas (arrow)

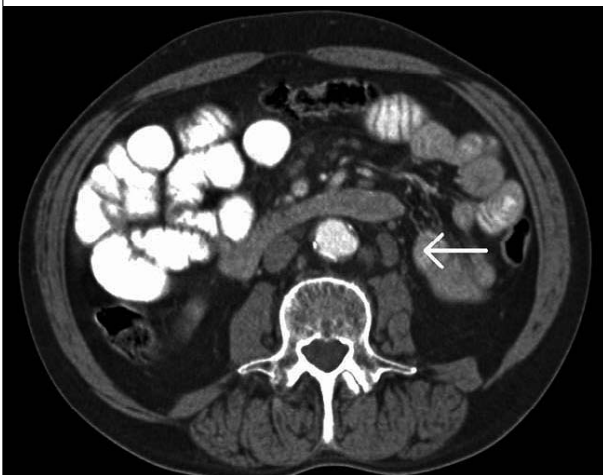


Figure 2A. Photomicrographs of the duodenal biopsy

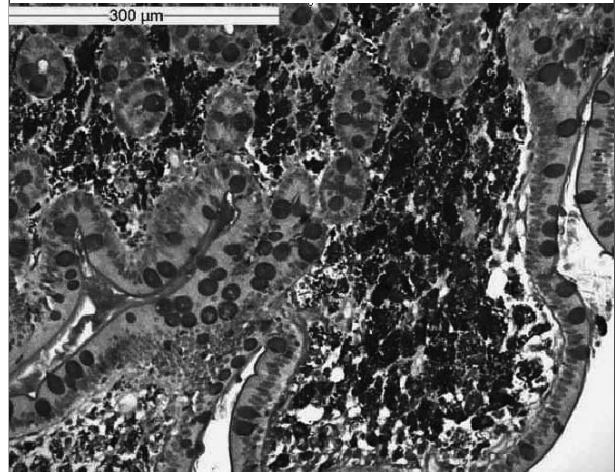
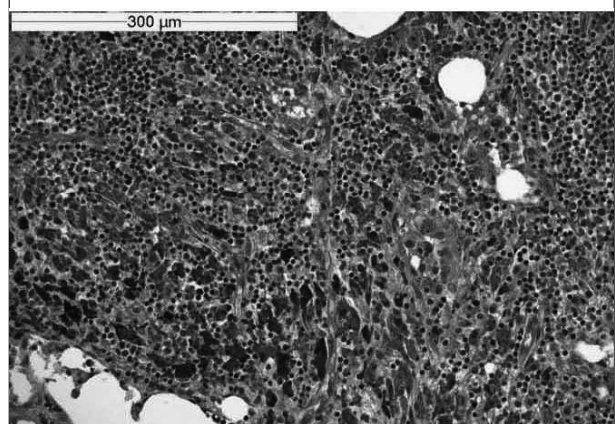


Figure 2B. Photomicrographs of the abdominal lymph node



Within the lamina propria of the duodenal mucosa numerous macrophages laden with periodic acidschiff-positive material are seen. Within the sinuses of the lymph node the same cells are found.

was found in intestinal lymph spaces. An indication for an infectious cause was provided in 1961 by the electronic microscopic detection of bacteria in intestinal macrophages. In 1992 the micro-organism was identified by polymerase chain reaction (PCR) and it was named *Tropheryma whipplei* (Greek, trope: nourishment; eryma: barrier, because of the resulting malabsorption).^{5,6} The first culture of the Whipple bacillus occurred in 2000 and three years later the complete sequence of the genome *Tropheryma whipplei* was characterised.^{5,7,8} Whipple's disease is rare. Between 1907 and 1987 only 696 cases were reported. Of those cases, 55% were reported from Europe and 38% from North America. An annual incidence of 30 cases per year has been mentioned since 1980. No valid estimate of its actual prevalence is available.² Based upon earlier estimations, the prevalence of Whipple's disease in the Netherlands might be nearly 15 to 20 patients over the last 30 years. The disease has been described most frequently in Caucasians and is more common in males than females, with an average age at diagnosis of 49 years. Many of the published cases involved patients from rural areas, most of them with an occupational exposure to soil or animals.²

Pathogenesis

Invasion or uptake of the *Tropheryma whipplei* is spread throughout the body, including the intestinal epithelium, capillary and lymphatic endothelium, synovium, heart, lungs, liver, brains, eyes and skin.

All these sites show a lack of immunological response to the bacillus. This suggests that a host immune deficiency plays a role in the occurrence of the disease.^{2,9} Various immunological deficits were observed in more than just one type of immune cell. The immunological defect is likely to be subtle and specific for *T. whipplei*, since patients are not predisposed to infection with other organisms.^{9,10} In addition, IgG antibodies against *T. whipplei* are detectable in about 70% of healthy individuals. Whipple's disease is rare, but *T. whipplei* is apparently not. An association between Whipple's disease and HLA B-27 has been assumed but not confirmed.⁸ Rare familial cases have been reported, but most studies do not suggest the presence of familial factors.

The clinical manifestations of Whipple's disease are characterised by two stages, a prodromal stage and a steady-state stage. The prodromal stage is marked by various symptoms along with arthralgia and arthritis. It can last for six to ten years before the steady-state stage sets in. The steady-state stage is characterised by diarrhoea, weight loss and other manifestations, since many organs can be involved (*table 1*).⁵ Approximately 15% of patients do not have the classic signs and symptoms of the disease so the diagnosis can be challenging. In every patient with

Table 1. Clinical manifestations of Whipple's disease

Classical manifestations

- Migratory arthralgia or arthritis
- Diarrhoea
- Weight loss
- Malabsorption
- Abdominal pain
- Lymphadenopathy
- Mild fever

Other manifestations

- Hyperpigmentation of the skin
- Endocarditis, pericarditis, myocarditis
- Cerebellar ataxia, myoclonus, hemiparesis, dementia, epilepsy, oculomasticatory myorhythmia (continuous rhythmic movements of eye convergence with concurrent contractions of the masticatory muscles; pathognomonic for Whipple's disease but rare)
- Supranuclear ophtalmoplegia
- Hepatosplenomegaly
- Hepatitis
- Uveitis
- Retinitis
- Keratitis
- Skeletal muscle myalgia
- Pleural effusion

intermittent episodes of unexplained arthritis, especially when accompanied with diarrhoea, the diagnosis should be considered.

Clinical diagnosis

Several nonspecific laboratory abnormalities can be found, suggesting inflammation (anaemia, leucocytosis, thrombocytosis, elevated levels of acute phase proteins) or malabsorption. At upper gastrointestinal endoscopy the macroscopic aspect is aspecific; biopsies should be taken from duodenum and jejunum. At histological examination villous atrophy and epitheloid-cell granulomas may be present, but the PAS staining of the biopsies is usually diagnostic. The intestinal tissue is characterised by extensive PAS-positive material in macrophages in the lamina propria. Additionally, PCR techniques should be performed to detect *T. whipplei* in the small bowel, blood and other affected tissues or body fluids.^{5,11} Testing of cerebrospinal fluid (CSF) in Whipple's disease yields a high rate of positive results, even in patients without neurological symptoms.¹² Because the presence of neurological Whipple's disease can have important implications for therapy and prognosis, PCR should be used to investigate the CSF of all patients with Whipple's disease. Culture of *T. whipplei* can be achieved, but is not generally available.¹³ Whipple's disease has a wide variety of clinical manifestations. Therefore, the differential diagnosis includes many diseases including malabsorption with small-intestine

involvement, such as coeliac disease, Crohn's disease, sarcoidosis, abdominal lymphoma and HIV enteropathy. Other diseases to be considered are inflammatory rheumatic diseases, connective tissue diseases, bacterial endocarditis and cerebrovascular diseases.⁵

Treatment

Without treatment, Whipple's disease may be fatal. Tetracycline was the treatment of choice for many years but the frequency of relapse was high. Nowadays, the recommended treatment for Whipple's disease consists of an initial course of parenteral ceftriaxone (2 g daily) followed by oral co-trimoxazole (trimethoprim plus sulphamethoxazole, 960 mg twice per day) for one to two years.^{1-5,13,14} However, current recommendations are not based on clinical trials. Treatment failures and relapses have been documented, therefore alternative therapy is suggested. In patients without neurological involvement, doxycycline (100 mg twice per day) in combination with hydroxychloroquine (600 mg per day) without induction therapy is proposed.^{5,11} Therapy with sulphadiazine is suggested in patients with neurological involvement or a positive *T. whipplei* PCR assay on CSF.^{11,15} In patients with relapsing disease, additional supportive therapy with Th1 cytokines, such as interferon γ , could be useful. Furthermore, additional treatment with corticosteroids can be beneficial in patients with severe neurological manifestations and in patients with long-lasting fever. The prognosis for patients with neurological signs remains poor. More than 25% of such patients die within four years.¹⁶ Clinical improvement of extraneurological symptoms occurs often within seven to 21 days, and most patients recover completely.¹¹ The clinical picture of the patient discussed in this case report is a good example of classical Whipple's disease. The patient showed all the classical manifestations of the disease such as abdominal pain, along with malabsorption, diarrhoea, lymphadenopathy and mild fever. Moreover, he had had a typical prodromal stage consisting of migratory arthralgia for several years. The rheumatologist had diagnosed the arthralgia as polymyalgia rheumatica, but because of the poor response to prednisone, he questioned the diagnosis. Afterwards it became clear that this arthralgia was a manifestation of Whipple's disease. The description of this case might help in recognising classical Whipple's disease. Obviously, the less classical manifestations, such as cardiac or neurological symptoms, discussed in many other case reports must not be neglected. However, more than 85% of patients with Whipple's disease have the classic signs and symptoms of the disease.

CONCLUSION

Whipple's disease has a variety of clinical manifestations. For clinical practice, Whipple's disease should be considered in any patient with migrating arthralgies, diarrhoea, fever, malabsorption, weight loss, abdominal pain and lymphadenopathy. If the diagnosis is considered, this condition can be readily diagnosed and treated.

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