Whipple’s Disease
A Case Report

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SUMMARY
A case of Whipple’s disease in which there were some unusual features, although the results of histological investigation were characteristic of the disease, is reported. This is followed by a brief review of the literature concerning this rare condition.


CASE REPORT
A 65-year-old White man, an inspector of mines, was admitted to the H.F. Verwoerd Hospital in September 1977 with a 7-year history of having been unable to conduct his occupation because of severe tiredness. A laparotomy with vagotomy and pyloroplasty was carried out for a duodenal ulcer in 1972, and at operation a moderate hepatosplenomegaly was detected, as well as para-aortic lymphadenopathy.

Biopsy of the liver and lymph nodes showed multiple small non-caseating granulomas. A diagnosis of sarcoidosis was made.

No specific therapy was given and the patient remained well until March 1973, when he had an attack of renal colic. Results of intravenous pyelography done at that time were regarded as normal.

In June 1974 he was admitted to another hospital complaining of weakness and loss of weight; apart from signs of weight loss and anaemia, no abnormal physical features were noted. Further investigations revealed a raised serum urea level, and liver and kidney biopsies were performed. The liver biopsy failed to reveal granulomata and was regarded as normal. However, sections of the kidney showed a severe interstitial nephritis with infiltration of lymphocytes, histiocytes and acute inflammatory cells. The interstitial nephritis was thought to be caused by sarcoidosis, and treatment with steroids was initiated.

On admission to the H.F. Verwoerd Hospital in 1977 his main complaints were tiredness, low-grade intermittent fever with occasional rigors, and a weight loss of 10 kg during the preceding 18 months, his weight having declined to 51 kg.

The patient also complained of myalgia, but not of arthralgia, and except for a single episode of watery diarrhoea 3 weeks before admission, during which time he passed 5-6 watery stools per day, there was no history of diarrhoea or steatorrhoea.

He was a cachectic elderly man, whose blood pressure was 110/60 mmHg, and whose pulse rate was 60/min. Except for ecchymosis, a dry eczema, koilonychia and a 2-cm palpable liver, there were no other obvious physical abnormalities.

The erythrocyte sedimentation rate was 80 mm/1st h (Westergren), the urine was normal and the chest radiograph revealed no abnormality. Results of a purified protein derivative skin test were negative.

Laboratory Investigations
The haemogram showed a normocytic normochromic anaemia with a haemoglobin concentration of 11.2 g/100 ml and a mild neutrophilia. The blood urea level was 8.5 mmol/l (normal 3-7.5 mmol/l), and the creatinine was 180 μmol/l. Serum calcium and magnesium values were very low, i.e. 1.89 mmol/l and 0.70 mmol/l respectively. The protein electrophoretic pattern showed a total protein of 51 g/l (normal 65-85 g/l) with an albumin level of 27 g/l and a gammaglobulin level of 5 g/l. Prothrombin activity was 92%.

Immuno-electrophoresis revealed an IgG of 8.5 g/l, an IgA of 2.2 g/l and an IgM of 0.5 g/l. The results of complement studies were normal, and no immune complexes were noted.

Bone marrow aspirate was normal. The results of rheumatoid factor, antimitochondrial, antismooth muscle and antinuclear antibody tests were all negative.

Microscopical examination of a liver biopsy specimen showed normal architecture, with a slight increase of inflammatory cells in the portal tracts. Some of these cells were polymorphonuclear neutrophils, and this was interpreted as being indicative of a mild cholangitis. A few macrophages with foamy cytoplasm were also present in the portal tracts.

No diagnosis could be made, but because of the low-grade fever with occasional rigors and the previous history of long-term steroid therapy, the patient was temporarily discharged on antituberculous therapy (isoniazid, rifampicin and pyrazinamide), and was followed up as an outpatient.

He was re-admitted in February 1978, having shown no improvement, and having lost a further 2.5 kg in weight, despite an enormous appetite. The only additional finding was a peripheral neuropathy in the legs.

Further investigations did not reveal significant alterations. The serum iron concentration was 4.0 μmol/l, and

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the haemoglobin concentration had fallen to 8.1 g/dl with a mean corpuscular volume of 75 fl.

Because of melaena, a gastroscopy was performed, and the results were regarded as normal. At this stage the possibility of a small-bowel malabsorption syndrome was entertained, and a small-bowel biopsy was performed with a Watson capsule.

The duodenal biopsy specimen measured 1.0 × 0.5 cm. The tissue was divided, and one half was examined through a stereo microscope. This revealed thickening of some of the intestinal villi, while others had a club-shaped appearance.

The rest of the biopsy tissue was processed, and histological sections showed the typical changes associated with Whipple's disease. The thickened villi had a dense infiltrate of foamy macrophages which displaced the cell population normally found in the lamina propria (Figs 1 and 2). In places these macrophages were also present in the submucosa. Stains for neutral fat were negative, but with the periodic acid-Schiff (PAS) staining technique, the cells were shown to contain granular PAS-positive material.

Some of the biopsy material was processed for electron microscopical examination, which revealed the presence of cytoplasmic dense bodies in the lysosomes (Fig. 3). These

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**Fig. 1.** Club-shaped appearance, with a dense infiltrate of foamy macrophages (× 220).

**Fig. 2.** Thickened villus with infiltrate of foamy macrophages and polymorphonuclear leucocytes (× 220).

**Fig. 3.** Electron micrograph of a portion of the cytoplasm of a PAS-positive macrophage, demonstrating cytoplasmic dense bodies in the lysosomes (× 36 000).

**Fig. 4.** Electron micrograph of a lysosome demonstrating trilaminar structures (× 270 000).
bodies varied in size and shape, but some appeared rod-shaped, and remnants of a bacterial cell wall in the form of trilaminar structures in the lysosomes could be demonstrated (Fig. 4).

After examination of the duodenal biopsy specimen, a PAS stain was done on the previous liver biopsy specimen. The foam cells stained positively and it was concluded that they represented systemic involvement by Whipple’s disease.

With this diagnosis the following investigations were performed: A xylose absorption test with 25 g xylose revealed a urinary excretion of only 2.8% at 2½ hours. Repeat gastroscopy showed the mucosa of the first part of the duodenum to be partially covered with a granular yellow-white material, an appearance compatible with that described by Volpucelli et al.² A barium meal examination showed a non-homogeneous thickening of the valvulae conniventes with scattered areas of nodularity, very little dilatation and no segmentation or fragmentation. The thickening of the folds in some segments could aptly be described as ‘wild’ (Figs 5 and 6). The serum cholesterol level was 3.9 mmol/l, triglycerides 0.98 mg/100 ml and serum carotene 1.12 µmol/l (normal 0.93 - 3.7 µmol/l).

Fig. 5. Radiograph of barium meal examination showing non-homogeneous thickening of the valvulae conniventes, with scattered areas of nodularity.

Fig. 6. Close-up view of the duodenum to demonstrate the ‘wild’ appearance.

HLA typing showed the following: A locus A1 A2; B locus B7.

Radiographs of the sacro-iliac joints showed sclerosis of the right sacro-iliac joint, but failed to demonstrate any other signs of spondylitis.

Treatment was started with procaine penicillin 600 000 U twice daily intramuscularly for 10 days; streptomycin 1 g intramuscularly daily for 10 days; and prednisone 10 mg per day orally. This was then followed by a maintenance dose of oral tetracyclines 250 mg 4 times daily.

Within 5 days of commencing treatment the patient had gained 1 kg in weight, his fever had disappeared, and he had improved considerably. He is being followed up as an outpatient and when last seen, 4 weeks after commencing treatment, he had gained a further 5 kg in weight.

DISCUSSION

Whipple’s disease is a rare disorder classically characterized by fever, lymphadenopathy, malabsorption, progressive weight loss, anaemia, joint symptoms, serositis and increased skin pigmentation. It would appear that any organ in the body may be affected.

In a review of 19 patients by Maizel et al.² at the Duke University Medical Center, the 4 most frequent symptoms were said to be weight loss (100%); diarrhoea (72%); arthralgia (90%); and abdominal pain (72%).

Our patient had only lost weight and had had a single brief episode of diarrhoea, and even after the diagnosis was confirmed, no history of the other symptoms was obtained.

Some patients may in fact be constipated, as is the occasional patient with coeliac sprue,³ but usually the patient with Whipple’s disease passes 5 - 10 large, watery, malodorous stools per day. Occasionally a grossly bloody diarrhoea results from small-bowel ulceration or ulceration of the rectosigmoid: compounded by hypoprothrombinemia caused by defective vitamin K absorption. However, occult gastro-intestinal bleeding is more common.
Arthralgia may precede the more familiar gastrointestinal manifestations by a few years. De Luca et al. recently reported a patient in whom the joint manifestations had preceded the other symptoms by 20 years, the patient having been thought to have palindromic rheumatism. Classic arthralgias are migratory, and involve most joints, which may be swollen and inflamed, with some limitation of movement, although chronic joint deformity is unusual.

A few patients who had spondylitis were men with peripheral arthritis, but true ankylosing spondylitis had been reported in only 6 cases by 1965.

Abdominal pain is common, usually nonspecific, and often epigastric in location, and tends to be worse after meals. It may in part be caused by retroperitoneal lymphadenopathy which can be quite marked, and may even cause inferior vena cava obstruction. Another possible explanation for pain is an arteritis which has been found to involve particularly the small coronary and hepatic arteries, and less often the splenic, renal and pulmonary arteries.

Two other fairly common symptoms, which our patient had, were fever and peripheral neuropathy. Fifty-five per cent of the patients in the Duke series had low-grade fever, although fever spikes have been reported. Our patient had a number of fever spikes of 39°C during hospitalization. The peripheral neuropathy was possibly caused by malabsorption, although our patient only developed this after having taken INH. A multitude of neurological symptoms and signs as presenting manifestations have been described. These range from personality changes, dementia, memory deficits, myoclonus, ophthalmoplegia, ataxia, and seizure-like disorders, all of which may appear for the first time in a patient after inadequate treatment, although full antibiotic therapy tends to stabilize the neurological disease, or may cause some improvement.

**Physical Findings**

Signs of weight loss are the most common, although other evidence of multisystem involvement may be present. Hypotension, peripheral oedema, glossitis, increased muscular irritability, and even frank tetany are related to the loss of fluids and electrolytes, and the malabsorption of vitamins.

The lymphadenopathy and splenomegaly are caused by infiltration with PAS-positive macrophages, and non-caseating granulomas may be found in the lymph nodes. The lymphadenopathy responds dramatically to antibiotic therapy.

Cardiac involvement in Whipple’s disease is more common than previously reported. Although initially reported in 1952 by Upton, previous authors had described cardiac valvular deformity and pericarditis in Whipple’s disease which was usually ascribed to coexistent rheumatic disease. In McAllister and Fenoglio’s series of 19 patients, 58% had clinically detectable cardiac lesions and 79% had gross cardiac lesions at autopsy. Patients may present with pericarditis, myocarditis or endocarditis. Clinically pericardial friction rubs, cardiac murmurs and, in addition, electrocardiographic changes may be noted.

Histological examination may show PAS-positive macrophages in the pericardium, endocardium and myocardium. The valvular lesions result in the development of dense fibrous tissue, with few macrophages containing PAS-positive cytoplasmic particles.

Kent et al. have noted aortic and mitral valve lesions in one patient. Both James and Haubrich and McAllister and Fenoglio noted tricuspid valve involvement, and James and Haubrich have gone so far as to suggest that in some cases chronic rheumatic valvulitis or cardiomyopathy may be the long-term residuum of burnt-out Whipple’s disease.

A significant number of patients have died suddenly, and Whipple’s own patient died unexpectedly. The cause is unknown, but abnormalities in the conduction tissue secondary to a small-vessel arteritis may be the underlying factor.

Abdominal distension is a relatively common late manifestation, and is possibly due to mesenteric adenopathy.

**Haematological Findings**

Anaemia occurs in about 90% of patients. It tends to be normocytic normochromic or, in the later stages of the disease, microcytic hypochromic, owing to iron deficiency. The white blood count is either normal or slightly elevated. In the Duke series there was eosinophilia present in 3 of 19 cases.

**Biochemistry**

Hypo-albuminaemia, as might be expected, is common, and is due to malabsorption and a protein-losing enteropathy. One patient described by Cochran et al. had low IgM levels. Cochran et al. were also able to find 6 instances of similar changes in the literature, although Martin et al. reported a patient who had elevated IgG, IgA and IgM and complement levels in the active disease state, and in whom these values returned to normal after antibiotic therapy. Other biochemical abnormalities include hypocalcaemia, hypokalaemia, low serum cholesterol, carotene and prothrombin levels. The hypocalcaemia may be associated with tetany and the hypokalaemia may be severe enough and of sufficiently long duration to cause a hypo­kalaeic nephropathy.

**Intestinal Absorption Studies**

The most important finding is an increase of faecal fat in 90% of patients. Although D-xylene absorption is usually severely impaired, that of vitamin B12 is usually normal.

**Endoscopic Findings**

Volpucelli et al. were the first to describe the appearance of the duodenum in Whipple’s disease during endoscopic examination. They described the duodenal mucosa as being partially covered with yellow-white material consisting of
enlarged villi, and this was interspersed with a normal-looking mucosa, such as was seen in this patient. Histological examination of these enlarged white villi shows that they contain a heavy accumulation of lipid and PAS-positive macrophages. This condition reverts to normal after institution of appropriate antibiotic therapy. Waldenström's macroglobulinaemia and intestinal lymphoma may appear similar on endoscopy.

**Radiographic Findings**

Clemett and Marshak feel that the single most prominent finding in Whipple's disease is the alteration in the appearance of the valvulae conniventes, being thickened and nodular. The mucosal folds are redundant and lack a homogeneous configuration. These are most severe in the duodenum and jejunum, but the ileum may also be involved. The thickening has been explained by the extensive infiltration of the mucosa and submucosa by macrophages containing PAS-positive material, with interstitial oedema and lymphatic distension. Phillips and Carlson were impressed by the slight dilatation of the small bowel, for 7 of their 8 patients had a jejunal width of 25 mm or more. Some patients show segmentation and flocculation of the barium column owing to increased secretions. However, the barium meal findings are not diagnostic of Whipple's disease and the differential diagnosis can include the other conditions that produce thickening of the valvulae conniventes, for example intestinal lymphangiectasis, lymphoma, amyloidosis, giardiasis and systemic mastocytosis.

The other features revealed by radiography pertain to the polyserositis, and include pleural and pericardial effusions.

**Pathology**

The macroscopical appearance is of roughened, dull grey peritoneal surfaces with fibrous adhesions. The small intestine is thickened and slightly rigid. The mesentery is thickened, with marked enlargement of mesenteric, periaortie and iliac lymph nodes. The intestinal mucosa is often discoloured and interspersed with yellow flecks, and there may be splenomegaly. There may also be pleural adhesions and endocarditis, as described above.

Light microscopy shows the villi to be typically club-shaped and to contain the characteristic PAS-positive macrophages with sickle-form particles. The lamina propria may also contain an accumulation of polymorphonuclear leucocytes, and there is a marked decrease in the normal cellular elements in the lamina such as plasma cells, lymphocytes and eosinophils, which have been largely replaced by macrophages. The mucosal and submucosal lymphatics are dilated and filled with fat. There are also fat droplets in the extracellular spaces of the lamina.

Electron microscopy shows the typical rod-shaped, slightly sickled organisms present in the phagocytosing macrophages wherein they undergo degeneration and disintegration. However, these Gram-positive bacilli are usually most numerous in the lamina propria of the small intestine. They are 0,25 × 1 – 2,5 μm, and are most abundant beneath the absorptive epithelium. They have a characteristic bacterial wall with a pale central nucleus. It seems likely that some of the PAS-positive glycoprotein within the macrophages may represent the cell walls of degenerated phagocytosed bacilli. After treatment with antibiotics the mucosa of the small intestine gradually reverts to normal with bacilli disappearing from the intracellular spaces within a few days, and 4 - 8 weeks later only degenerating organisms are identifiable within the cytoplasm of the PAS-positive macrophages. The macrophages later decrease in number and are gradually replaced by plasma cells, lymphocytes and eosinophils.

The discovery of PAS-positive macrophages without demonstrable bacilli, especially in the colon, is, however, neither diagnostic of nor specific to this disease, since macrophages containing cytoplasmic PAS-positive glycoprotein may be seen in the normal colonic mucosa and regularly in patients with colonic histicytosis and melanosis coli. Extra-intestinal lesions confirm that Whipple's disease is a systemic condition. PAS-positive macrophages and bacilli have been found in most body tissues.

Sierachi et al. have demonstrated involvement of the following organs in 5 cases at autopsy — the heart, liver, lungs, spleen, pancreas, retroperitoneal tissues, lymph nodes and central nervous system.

Ludwig et al. have described a case of Whipple's disease with sickle-form particle-containing cells (SPC cells) in the vegetations of mitral endocarditis, and expressed the belief that these cells reached the vegetations via the bloodstream.

Hawkins et al. have recently described the identification of rod-shaped organisms in the synovial membrane of a patient with the arthritis of Whipple's disease, and de Groodt-Lasseel and Martin have recently described bacillary bodies in the central nervous system of patients with Whipple's disease.

The cause of Whipple's disease has not been identified with certainty. However, Clancy et al. have isolated a cell wall-deficient form of a haemolytic streptococcus from a monolayer cell culture of a lymph node taken from a patient with Whipple's disease. By means of immunofluorescence studies, Keren et al. have shown a single antigenically definable organism in Whipple's disease. Recently Haemophilus influenzae type E has been cultured from multiple small intestinal specimens. It is of interest that cell-mediated immunity is defective during active Whipple's disease, but whether this anergy is acquired during the disease, as in the cases of tuberculosis and lepromatous leprosy, or before the onset of the disease, is still uncertain. In the case reported by Tytgat et al., which was characterized by a cutaneous anergy, this improved during treatment, possibly indicating the secondary nature of the immunological abnormalities.

**TREATMENT**

Although steroids may bring about a temporary remission of this condition, long-term antibiotic therapy is essential for a possible cure.
Ruffin et al.²³ feel that the treatment of choice should be hospitalization for at least 10-14 days with 1.2 million U procaine penicillin G and 1 g streptomycin given intramuscularly daily. This is followed by oral tetracycline 250 mg 4 times a day for 1 year.

Relapses may occur after inadequate treatment, although the response to a second course of antibiotics still tends to be dramatic.

Knox et al.²¹ described 4 patients who developed neurological symptoms and signs more than 1 year after antibiotic treatment. In these 4 patients generalized systemic relapses occurred, but gastrointestinal symptoms only recurred in 1 patient, and only after his neurological symptoms had already developed. This serves to stress the importance of periodic re-evaluation.

For patients who do not respond to tetracyclines, other antimicrobials may be used. Sulphamethoxazole-trimethoprim combinations may be the treatment of choice. In Whipple's disease is rare and uniformly fatal even if other symptoms and signs are absent.

REFERENCES


