Lipogranulomatous adenopathy: a characteristic but under-recognized presentation of Whipple's disease

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CASE REPORT

A 50-year-old Caucasian male was admitted with a left popliteal vein thrombosis confirmed on Doppler ultrasound scanning. He was previously well and there was no obvious precipitating cause for his venous thrombosis. Apart from pallor and the swollen left calf there were no abnormal findings on routine examination and he was anticoagulated with heparin followed by warfarin.

Investigations revealed a hypochromic microcytic anaemia (haemoglobin 8.3 g) and a marginally raised serum alkaline phosphatase. Other investigations including a myeloma screen, autoimmune profile and neutrophil cytoplasmic antibodies were negative. An intra-abdominal malignancy was suspected although faecal occult bloods were negative on three occasions and tumour markers (carcinoembryonic antigen (CEA) and CA 19.9) were normal. Upper gastrointestinal endoscopy demonstrated mild gastritis and a normal-looking duodenum only. Computed tomographic (CT) scanning of the abdomen and thorax revealed massive retroperitoneal and retrocrural adenopathy extending down to the small intestinal mesentery (*Figure 1*). The abdominal viscera were otherwise normal and there was no mediastinal lymphadenopathy.

Small bowel lymphoma was suspected and he underwent first a laparoscopic biopsy of the mesenteric lymph nodes and subsequently a laparotomy. There were no abnormal findings apart from the retroperitoneal lymphadenopathy. On both occasions the histological appearances of the lymph nodes were the same: the lymph node architecture was destroyed by large lipid-containing spaces. There was also infiltration by numerous lipid containing macrophages, and occasional multinucleate giant cells (*Figure 2*). No cause for these changes could be recognized clinically or pathologically.

Three months after his initial presentation he developed weight loss, mild diarrhoea, vague abdominal pain and a rash on his legs. A systemic vasculitis was suspected but a skin biopsy showed non-specific changes only. However, 1 week later he died suddenly at home, apparently having been markedly dyspnoeic for the preceding 48 hours.

At postmortem he was found to have a severe constrictive pericarditis, which was felt to be the probable cause of his death. There was no evidence of pulmonary embolism. The liver showed congestive 'nutmeg' changes. There was evidence of a panserositis with inflammation of pericardium, pleura and peritoneum. Bowel histology was not performed because of autolysis. However, the histology of the mesenteric lymph nodes was reviewed and on this occasion stained with periodic acid Schiff. This was taken up by bacilliary organisms in the macrophages found in the lymph nodes. The features were considered diagnostic of Whipple's disease.

DISCUSSION

Whipple's disease is a rare systemic illness which was first described in 1907 (Whipple, 1907). It predominantly affects middle-aged men and almost exclusively occurs in Caucasians. Any organ can be affected by the disease which is caused by a Gram-negative rod-shaped bacillus which has now been named *Tropheryma whippeli*.

The textbook presentation with a malabsorption syndrome is rarely seen. Only 15% of patients have abdominal symptoms before diagnosis, and in one series the most common early presenting feature was found to be arthralgia (Feldman, 1986). Other early features of the disease are non-specific: it should be considered in patients presenting with joint pains, persistent pyrexia or chronic pericarditis. Other presentations include neurological involvement (dementia, ophthalmoplegia or myoclonus) (Feldman, 1986). Confusion with sarcoidosis, collagen vascular diseases or intestinal lymphoma has been reported (Feldman, 1986; Southern et al, 1989). As a consequence diagnosis can be difficult in the early stages of the disease. A high index of suspicion is therefore required if Whipple's disease is to be diagnosed and effectively treated.

At postmortem this patient had macroscopic evidence of a panserositis and the pericardial involvement was sufficiently severe to be judged the cause of death. The inflammatory involvement of more than one serosal surface is a feature of many conditions including connective tissue disorders (particularly systemic lupus erythematosus), tuberculous infection, uraemia, familial Mediterranean fever and Whipple's disease, but the latter may not be considered in the differential diagnosis. Clinically important pleural involvement in patients with Whipple's disease has only occasionally been described (Symmons et al, 1985) but pericardial involvement is probably quite common. In one series (McAllister and Fenoglio, 1975) 15 out of 19 patients had autopsy evidence of pericarditis and 10 had thickening and fibrotic deformities of at least one cardiac valve; surprisingly perhaps, only one patient had evidence of cardiac failure. Periodic acid Schiff (PAS) positive macrophages were identified in all cardiac tissues and confirmed the underlying cause.

Although symptoms may not be apparent, the small intestine is involved in most cases; thus endo-

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scopic intestinal biopsy is the investigation of choice once the diagnosis is suspected. The microscopic appearances are those of villous atrophy, dilated lacteals and oedema. Staining with PAS reveals the lamina propria to contain macrophages which contain bacillary organisms. Electron microscopy may confirm the characteristic trilamellar membrane of Whipple's bacilli but this investigation was not available in this case. Increasingly polymerase chain reaction techniques are used to confirm the presence of *T. whippeli* (Relman et al, 1992) and have classified the bacterium as actinomycetes but the organism has not yet been successfully cultured.

Whipple's disease was referred to in the older literature (Puite and Teslik, 1955) as lipogranulomatosis — a reference to the conspicuous presence of fat and granulomata in mesenteric nodes — but is often omitted from the initial differential diagnosis of lymph node granulomata in favour of commoner conditions such as sarcoidosis or tuberculosis. Unfortunately even if Whipple's disease is considered the diagnosis may be delayed as these granulomata do not invariably show PAS positivity (Wilcox et al, 1987). Mesenteric lymph nodes are enlarged and will often contain fat-filled vacuoles and spaces which destroy the normal architecture of the node (Dobbins, 1987).

In approximately 10% of cases granulomatous changes can be seen along with numerous fat-filled 'foamy' macrophages, similar to those found in this patient. The granulomata are probably a response to the bacterium but the cause of the lipid accumulation is less clear: large lipid droplets can be identified in the lamina propria possibly because of lymphatic obstruction to the intestine. This histological pattern is only seen with a few other conditions — most commonly following radiological investigation (e.g. in the gall bladder) or following ingestion of mineral oil. Infiltration of the lamina propria by foamy PAS positive macrophages is virtually diagnostic of Whipple's disease but similar appearances are occasionally seen with atypical mycobacterial infection in the severely immunosuppressed (Gillin et al, 1983).

Once the diagnosis is made prolonged treatment with antibiotics is mandatory. There are no controlled trials in this area but trimethoprim-sulphamethoxazole appears to be superior to tetracycline in terms of the number of treatment successes and in the management of recurrences (Fuerle and Marth, 1994). Unfortunately central nervous system relapse is relatively common, more resistant to therapy and carries a poor prognosis. Parenteral penicillin and streptomycin followed by 1 year of trimethoprim-sulphamethoxazole has been recommended by some authorities (Keinath et al, 1985).

CONCLUSION

This case is reported in the hope that other clinicians may now recognize this unusual presentation and initiate treatment for this serious but potentially curable condition. HM

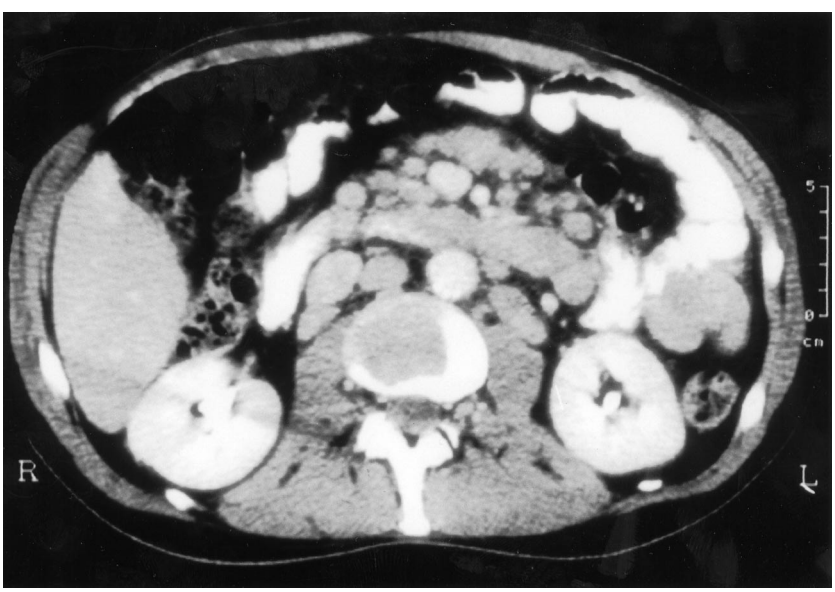

Figure 1. Computed tomography scan of the abdomen (post contrast) demonstrating mesenteric and retroperitoneal lymphadenopathy.

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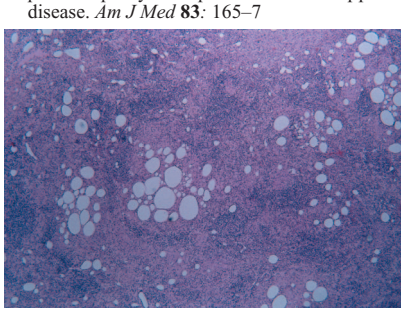

Figure 2. Lymph node demonstrating a lipogranulomatous reaction (haematoxylin and eosin stain, magnification x 40).