Case report

Whipple's disease diagnosed at hip arthroplasty

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SUMMARY A patient is reported with a six-year history of seronegative inflammatory arthritis, lymphadenopathy, and a rash. Many investigations, including repeat jejunal and synovial needle biopsies, failed to establish the diagnosis. Eventually right hip destruction led to arthroplasty. Synovial membrane obtained at operation was examined by electron microscopy and organisms were found with the morphological characteristics of those in patients where the diagnosis was firmly established as Whipple's disease. We propose that Whipple's disease should be seriously considered as a rare but distinct and treatable possibility in the differential diagnosis of seronegative inflammatory arthritis.

Whipple's disease¹ is a rare disease in which the presenting features are protean but the commonest symptoms are abdominal discomfort and diarrhoea. If untreated the gastrointestinal symptoms are accompanied by weight loss, lymphadenopathy, anaemia, fever and respiratory symptoms, purpura (30%), and arthritis (60%). The arthritis often precedes the gastrointestinal symptoms, sometimes by many years. It occurs predominantly in males (M : F, 4 : 1) aged 30–60 years. A raised ESR, leucocytosis, anaemia, hypoalbuminaemia, and hyperglobulinaemia are common features.

This chronic inflammatory condition is associated with the presence of rod-shaped organisms which have been identified in several organs including the jejunum and lymph nodes.^{2–3} Clancy *et al.*⁴ reported they had isolated the aetiological agent from a lymph node – a cell-wall-deficient α -haemolytic streptococcus. Hawkins *et al.*⁵ found bacteria in the synovium with similar morphological characteristics on electron microscopy to those in other organs.

This present report describes a young man with a seronegative inflammatory arthritis in whom the diagnosis of Whipple's disease had been considered for many years despite the absence of gastrointestinal symptoms but no organisms had been

found until the time of hip arthroplasty. Electron microscopy showed structures with an appearance similar to those seen in our previously reported case.⁵

Case report

A 34-year-old man presented in 1976 with a four-year history of pain and swelling of his knees, wrists, and ankles, initially accompanied by sweating, but no other symptoms. He gave a history of dislocating his right hip in a road traffic accident when he was 18 years. There was no family history of arthritis or personal history of allergy. Examination showed active synovitis of wrists, ankles, and knees, which also had large effusions. Axillary lymph nodes were enlarged. Haemoglobin was 16.3 g/dl, erythrocyte sedimentation rate 50 mm/h, white cell count $7.7 \times 10^9/l$. The biochemical profile was normal apart from increased globulins and diffuse hypergamma-globulinaemia (IgG 26.8 g/l, IgA 3.82 g/l, IgM 3.51 g/l). Rheumatoid factor and latex tests were negative, as also were the syphilis screening tests. He did not possess the HLA-B27 antigen. X-rays of his joints did not show an erosive arthritis, and his chest X-ray was normal. Inflammatory fluid was aspirated from his knees, which were injected with intra-articular steroids. A working diagnosis of seronegative inflammatory polyarthritis was made. During the next four years he was treated with a variety of non-steroidal anti-inflammatory drugs, as well as

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gold, penicillamine, and dapsone, none of which helped him. Recurrent large effusions of his knees required intra-articular steroids on many occasions. Chemical synovectomy of the knees was also carried out with $^{90}\text{yttrium}$.

In 1980 he developed a diffuse non-irritating maculopapular erythematous rash over most of his body. It fluctuated but was aggravated by heat. It was accompanied by lymphadenopathy and splenomegaly. Biopsy of an inguinal node showed reactive changes, and skin biopsy showed minimal inflammatory change.

Whipple's disease was suggested and jejunal biopsy was carried out. No microscopic evidence of mucosal change was seen by light microscopy, and no PAS-staining macrophages were seen. Electron microscopy showed large numbers of myelin figures in the lamina propria of the jejunum but no rod-shaped organisms (Fig. 1). Synovial needle biopsy of the knee showed marked fibrosis and no evidence of cellular modifications characteristic of Whipple's disease.

In 1981 he complained of pain in the right hip and developed avascular necrosis of the femoral head. Synovial membrane obtained at the subsequent hip

replacement showed marked synovial cell proliferation, lymphoid proliferation with the formation of follicles, and infiltration by plasma cells. Electron microscopy showed a rod-shaped organism with the characteristics of the organisms previously seen in established Whipple's disease (Fig. 2). At this time his rash also flared up, effusion of his right knee recurred, and axillary lymph nodes were again swollen. He was treated with erythromycin, and on review one month later his knee had improved and the rash faded.

He then emigrated to Australia, so further follow-up was not possible until his return to Britain a year later. He stopped therapy with erythromycin after five months and now had another flare-up of his joints. Repeat synovial biopsy of his knee showed foci of mononuclear cells staining with PAS-reactive material. Electron microscopy showed many heterophagic vacuoles containing bacterial cell wall remnants. This added further support to the diagnosis of Whipple's disease.

Discussion

Our patient had a seronegative inflammatory arthri-

Fig. 1 Electron micrograph of the jejunal biopsy showing large numbers of myelin figures (arrows) which are usually composed of lipid bilayers. Some of the myelin figures appear like bacteria but do not enclose a distinct cytoplasm region differing from the surrounding cell cytoplasm. Scale line = $0.3\ \mu\text{m}$.

Fig. 2 Electron micrograph of the synovial membrane from the right hip arthroplasty showing rather poorly preserved bacteria with electron dense cytoplasm and multilamellar inner and outer bacterial cell walls. Scale line = 0.3 μ m.

tis with a rash lymphadenopathy, splenomegaly, and initially a fever. ESR was raised, with hypergamma-globulinaemia. He denied any diarrhoea or abdominal discomfort, and no evidence was found of intestinal malabsorption. Jejunal biopsy, although not showing the typical features of Whipple's disease, revealed on electron microscopy large numbers of myelin figures. These rarely occur in normal tissue but have previously been reported in association with bacteria in rectal mucosa;⁶ similar findings have not been reported in the synovium. Myelin figures may also be associated with active cell membrane degeneration in the absence of bacteria. Needle biopsy of the synovium of the knee showed fibrosis – presumably the result of recent medical synovectomy with ⁹⁰yttrium. The subsequent flare up of the right hip was most likely a delayed feature associated with the preceding systemic illness, and biopsy of the synovial membrane at the time of hip arthroplasty showed bacteria with the electron-dense cytoplasm and laminated cell walls characteristic of the organisms seen in Whipple's disease. These organisms differ both by their size and structure from other organisms which may

lodge in a previously injured joint or organisms reaching the joint from other possible foci of infection in the body.

The diagnosis of Whipple's disease is seldom considered in patients with atypical symptoms, particularly in those without diarrhoea. The frequency of joint involvement in patients with the intestinal component of the disease often places it in the realm of the rheumatologist. The disease complex of arthritis plus systemic features may suggest a connective tissue disease, adult Still's disease, or even seronegative rheumatoid disease. Rheumatoid arthritis itself is usually excluded by the infrequency of deformities. Spondylitis and sacroileitis have been reported in Whipple's arthritis,^{7,8} and an association with HLA-B₂₇ is implicated. However, this patient was B₂₇ negative, with no deformities, spondylitis or sacroileitis. The occurrence of a severe but remitting polyarthritis over a period of months or years without severe deformity is the picture most frequently seen in Whipple's disease, as in this patient. The arthritis can occur well ahead of gastrointestinal symptoms, which indeed may never develop.^{8,9}

We suggest that the diagnosis of Whipple's disease should be seriously considered in patients with seronegative inflammatory arthropathies, particularly as it is readily treatable. Cases may be being missed because of the considerable difficulties in establishing the diagnosis even when it is considered, as emphasised by this case.

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References

- 1 Whipple G H. A hitherto undescribed disease characterised anatomically by fat and fatty acids in the intestinal and mesenteric lymphatic tissue. *Johns Hopkins Med J* 1907; **18**: 382-91.
- 2 Morningstar W A. Whipple's disease. An example of the value in diagnosis, follow-up and correlation of a pathological process. *Hum Pathol* 1975; **6**: 443-54.
- 3 Maizel H, Rufin J M, Dobbins W O. Whipple's disease. A review of 19 patients from one hospital and a review of the literature since 1950. *Medicine* 1970; **49**: 175-205.
- 4 Clancy R L, Tomkins W A F, Muckle T J, *et al*. Isolation and characterisation of an aetiological agent in Whipple's disease. *Br Med J* 1975; **iii**: 568-70.
- 5 Hawkins C F, Farr M, Morris C J, Hoare A M, Williamson N. Detection by electron microscope of rod-shaped organisms in synovial membrane from a patient with the arthritis of Whipple's disease. *Ann Rheum Dis* 1976; **35**: 502-9.
- 6 Te Yong Lou, Teplitz C. Malakoplakia: pathogenesis and ultrastructural morphogenesis. *Hum Pathol* 1974; **5**: 191-207.
- 7 Russo F R. Whipple's disease. Review of the literature and a report of 2 cases. *Arch Intern Med* 1952; **89**: 00-14.
- 8 Kelly J J, Weisiger B B. The arthritis of Whipple's disease. *Arthritis Rheum* 1963; **6**: 615-32.
- 9 Delcambre B, Luez J, Leonardelli J, Paris J C, Mairesse M, d'Eshougues J R. Les manifestations articulaires de la maladie de Whipple. A propos d'un cas avec étude histologique de la synoviale. *Sem Hop Paris* 1974; **50**: 847-54.