Peripheral nerve granuloma in a patient with tuberculosis

R W Orrell, R H M King, J V Bowler, L Ginsberg

The cause of peripheral neuropathy associated with tuberculosis is controversial. Possibilities include an immune mediated neuropathy, direct invasion of nerves, vasculitic neuropathy, compressive neuropathy, a meningitic reaction, and the toxic effects of antituberculous chemotherapy. This report describes the unusual finding of granulomas in the peripheral nerve of a patient with tuberculosis. The pathological findings were of a delayed hypersensitivity reaction, but with no more specific indications of the mechanism of the neuropathy.

Neuropathy may occur in patients with tuberculosis for a number of different reasons. It was originally attributed to alcohol and malnutrition, and more recently has been related to the neuropathic effects of medication, and a radiculopathy as a result of tuberculous meningitis. In one patient the nerve roots were reported to have been invaded by bacilli. A vasculitic neuropathy has also been proposed, but with no direct evidence of vasculitic abnormality in the nerve. Tuberculomas have been reported in the optic nerve, but not in peripheral nerve. We now describe a patient with a sensory and motor peripheral neuropathy related to systemic tuberculosis. Granulomata were present in a sural nerve biopsy specimen.

CASE REPORT
A 23 year old man, born in Africa, and recently living in England, developed a sensation of pins and needles in the soles, spreading to the toes. He was finding it increasingly painful to walk. One month later this progressed to weakness at the ankles, with bilateral foot drop, and numbness in the toes. There were no other neurological symptoms. Three months earlier he had noticed a prominent lump in the neck, and experienced occasional night sweats, weight loss, and right sided abdominal pain.

Examination demonstrated an enlarged right cervical lymph node. There was a large, firm, regular mass in the right hypochondrium, extending to the right lower quadrant of the abdomen. Cranial nerve examination was normal. He walked with bilateral foot drop. There was normal muscle bulk in the limbs, with no fasciculations. Tone and power were normal in the upper limbs, with diminished biceps reflexes. In the lower limbs, tone was normal. There was moderate weakness (MRC grade 4) of hip flexion bilaterally, absent (MRC grade 0) dorsiflexion of the foot and extension of the big toe bilaterally, and moderate weakness (MRC grade 4) of foot inversion and eversion bilaterally. Lower limb power was otherwise normal (MRC grade 5). Tendon reflexes were brisk at the knees and normal at the ankles, with absent movement of the big toe on plantar stimulation, but some upward fanning of the other toes. Light touch and pinprick sensation were normal. Vibration sensation was diminished at the toes and ankles. Proprioception was preserved.

Sensory nerve conduction studies were normal in the upper limbs (median nerve sensory amplitude 14 µV on the right and 15 µV on the left), but sensory action potential amplitudes were reduced in the sural nerves (right 1.5 µV, left 3.5 µV, normal >8 µV). There was no response to stimulation of the common peroneal nerves when recording at extensor digitorum brevis, but normal velocity (45 m/s on the right, 53 m/s on the left) when recording at tibialis anterior. There were no motor responses from abductor hallucis on stimulation of the right and left tibial nerves. Electromyography of tibialis anterior and gastrocnemius demonstrated frequent fibrillation potentials and positive sharp waves, with a mild excess of polyphasic motor unit action potentials of normal and increased duration, and of normal amplitude. Right quadriceps femoris demonstrated no spontaneous activity, with a mild excess of polyphasic units of normal duration and amplitude, and full interference pattern. Left mid-lumbar and lower lumbar paraspinal EMG demonstrated increased insertional activity, but otherwise normal appearances. The findings suggested a distal sensory and motor axonal polyneuropathy in the lower limbs.

Biopsy of the cervical lymph node revealed multiple large granulomas with extensive central caseous necrosis. Scantly acid fast bacilli were identified on Ziehl-Neelsen staining. Culture demonstrated Mycobacterium tuberculosis, resistant to isoniazid. Tuberculin test was not performed. Computed tomography (CT) of the chest demonstrated anterior mediastinal lymphadenopathy, with a 3 cm soft tissue density at the left hilum. CT of the abdomen demonstrated a 10x5x5 cm low density lesion arising from the liver, largely fluid filled, with a thickened wall extending anteriorly over the liver. Magnetic resonance imaging of the brain and spinal cord, with gadolinium, demonstrated no abnormality. Examination of the cerebrospinal fluid was normal, with no cells, no organisms, protein 0.3 g/l, glucose 3.2 mmol/l, blood glucose 5.2 mmol/l. Opening pressure 18 cm of cerebrospinal fluid. There was no growth on culture. Full blood count, urea and electrolytes, and calcium were normal. Liver function tests were normal apart from a raised γ-glutamyltransferase of 117 U/l (normal 9–54 U/l). Erythrocyte sedimentation rate was raised at 69 mm 1st h (normal <20 mm 1st h), and C reactive protein raised at 61 mg/l (normal <7 mg/l). HIV and treponemal serology were negative. Antinuclear antibody titre was <1/1000, and anti-double stranded deoxyribonucleic acid negative. Plasma protein electrophoresis revealed a polyclonal increase in immunoglobulins, with no paraprotein. Thyroxine was normal, but thyroid stimulating hormone raised at 7.3 mU/l (normal 0.3–4.2 mU/l).

Treatment was started before culture and sensitivity results were available, with rifampicin, isoniazid, pyrazinamide, and ethambutol. Within three days of starting treatment there was improvement in the paraesthesias, but gait and weakness remained unchanged. Isoniazid was withdrawn after three weeks when sensitivity results were available, with rifampicin, isoniazid, pyrazinamide, and ethambutol. Within three days of starting treatment there was improvement in the paraesthesias, but gait and weakness remained unchanged. Isoniazid was withdrawn after three weeks when sensitivity results were available. Right sural nerve biopsy was performed to assess the possibility of an inflammatory or vasculitic component to the neuropathy. Light microscopy (fig 1) demonstrated a normal myelinated fibre density within the fascicles, but many myelinated fibres were undergoing acute axonal degeneration, and there were numerous debris containing macrophages (fig 1A). Mild subperineurial oedema was present. Some of the epineurial blood vessels were associated with groups of inflammatory cells, but...
there was no clear evidence of vasculitis. Several non-caseating granulomata were present in the epineurium (fig 1B, C). There were no giant cells. Immunocytochemical staining was negative for B lymphocytes in the endoneurium and epineurium. There was marked staining for CD4 lymphocytes in the epineurium, especially in relation to the granulomata (fig 1D) and also blood vessels (fig 1E), and in patches in the endoneurium. There was significant but less dense staining for CD8 lymphocytes in a similar distribution (fig 1F). An early macrophage marker (CD68) was dense in relation to the granulomata. A late macrophage marker (mac387) was positive in the epineurium, especially in relation to the blood vessels and granulomata, and occasionally in the endoneurium. Bacilli were not demonstrated on Ziehl-Neelsen stain for light microscopy, or by electron microscopy.

After three months of antituberculous medication, there was improvement in power, with weakness of ankle dorsiflexion (MRC grade 4 bilaterally), ankle inversion (MRC grade 4 bilaterally), and eversion (MRC grade 4− on the left). Ankle plantar flexion was normal. There was still marked weakness of extensor hallucis longus (MRC grade 2 bilaterally). He was given prednisolone 40 mg daily, because of continuing concern about an additional inflammatory component to the neuropathy, and the rifampicin, pyrazinamide, and ethambutol were continued. By 12 months, the prednisolone had been reduced and withdrawn. There was full power (MRC grade 5) on the right, and moderate residual weakness (MRC grade 4) on the left.

DISCUSSION

The patient had tuberculosis, affecting the cervical lymph node, and presumably also involving the liver. He had a peripheral neuropathy that preceded chemotherapy for tuberculosis. The peripheral nerve abnormality we describe is consistent with the delayed or type IV hypersensitivity reaction seen with persistent or non-degradable antigens such as tubercle bacilli. Accumulations of macrophages transform into epithelioid cells. An aggregation of epithelioid cells, surrounded by a collar of lymphocytes, is termed a granuloma. The cytokines most directly implicated are interleukin 12, which is produced by macrophages, and interferon gamma, an activator of macrophages.

In the patient we describe, it is not clear how the granulomata relate to the neuropathic symptoms and signs. Possibilities include a compressive or vascular effect, and also cytokine mediated damage.

In experimental studies, using intravenous injection of a variety of strains of mycobacteria in mice, granulomata developed in the peripheral nerves. Nodules within the peripheral nerves consisted principally of macrophages, with no epithelioid cells or necrosis. In these experimental studies, it was suggested that the neuropathy was caused by compressive effects of the nodules. More typical tuberculous granulomata with destructive features were present in other organs. The origin of the neural granulomata, probably from macrophages or...
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Schwann cells, was difficult to define. The nodules appeared later in peripheral nerves (15 days) than in lungs (two days), and were present in peripheral nerves only when using virulent strains.

Infection with the related bacillus, Mycobacterium leprae, is one of the most common causes of neuropathy in the world. This may present as lepromatous leprosy (with infiltration of the nerve by bacteria and inflammatory cells, and fibroblast proliferation, causing fusiform enlargement of nerves); tuberculosis leprosy (where nerve enlargement occurs as a result of the inflammatory response rather than bacterial infiltration); and an acute neuritis. There is also a broad range of borderline or intermediate forms, which combine features of the lepromatos and tuberculous forms. The pathological features we describe most closely resemble tuberculoid leprosy, with granuloma formation. In leprosy, the entire endoneurium may be replaced by a single granuloma, and caseation may occur. Organisms may not be detectable. The primary process is axonal damage, often multifocal, and probably secondary to the inflammatory response.” Intrafascicular ischaemia attributable to increased endoneurial pressure may be important. In lepromatous leprosy, there is evidence to suggest hemogenous spread of the bacilli, with entry into the nerve through the endoneurial capillaries. The organism is relatively insensitive to the immune system within the nerve. The Schwann cell is probably primarily infected, and the organism spreads within the nerve. Macrophages may also carry the organism, by travelling in the subperineurial space.

In tuberculoid leprosy, where no organisms are detectable, other granulomatous conditions, including sarcoidosis may be considered. Peripheral neuropathy is a rare manifestation of sarcoidosis. Epineurial non-caseating granulomas may be found. Sarcoidosis and tuberculosis may occasionally coexist, for example tuberculosis may develop after corticosteroid treatment for sarcoidosis, or tuberculosis may masquerade as sarcoidosis. The temporal relation and response to treatment make additional sarcoidosis unlikely in this patient. Mycobacterium avium-intracellulare has been implicated in neuropathy in patients with HIV.

In patients with tuberculosis, neuropathy attributable to direct peripheral nerve infiltration has not been previously recognised. In a patient with tuberculosis, neuropathy occurs as a complication of meningitis, causing spinal nerve root and cranial neuropathies (especially cranial nerves II, III, VI, VII, and VIII). Cranial nerve involvement may result from longstanding increased intracranial pressure, and direct effects of the tuberculoid exudates on the nerve. Arteritis of the nerve root, within exudates, has been described. Isolated tuberculomas in the optic nerve have been reported. Local pressure in the nasopharynx (cranial nerves IX, X, and XI palsies), in the middle ear and mastoid (cranial nerve VII palsy and hemifacial spasm), and chest (recurrent laryngeal nerve palsy), have all been observed. Carpal tunnel syndrome may result from tuberculosis tenosynovitis in the hand. The association of tuberculosis with Guillain-Barré syndrome is uncertain, although patients have been reported with both conditions coexisting. This may be a chance association.

The most important consideration in a patient with tuberculosis is probably the potential neurotoxic effects of antituberculous medication. Isoniazid combines with pyridoxine (vitamin B6), causing a pyridoxine (vitamin B6) deficiency neuropathy. The peripheral neuropathy is initially sensory, and later motor, with features of axonal degeneration. This should be prevented by coadministration of pyridoxine. Excess pyridoxine itself may cause a reversible sensory neuropathy. Neuropathies are also observed with ethambutol and streptomycin. Ethambutol more commonly produces a retrolubar toxic neuropathy, but may also occasionally cause a reversible distal sensory peripheral neuropathy, with late motor involvement, and axonal features. Streptomycin is vestibulotoxic, but does not cause peripheral neuropathy.

In the patient we describe, there was definite evidence that the neuropathy preceded treatment. We suggest that the granuloma disrupted the endoneurial blood supply, producing the acute Wallerian-type degeneration observed. It should not be assumed that neuropathy in patients with tuberculosis is iatrogenic, and the possibility of a primary effect on the nerves should be considered.
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