

SHORT REPORT

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Vasculitic neuropathy in a patient with inactive treated lepromatous leprosy

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Abstract

A 46 year old Asian male with previously treated lepromatous leprosy developed a stepwise multifocal sensory disturbance 25 years later. Neurophysiology demonstrated marked deterioration from previous studies. Sural nerve biopsy disclosed a vasculitic process superimposed on inactive lepromatous leprosy. Immunocytochemical stains for mycobacterial antigen showed deposits within nerve and vessel walls. A delayed vasculitic neuropathy precipitated by persisting mycobacterial antigen is proposed.

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Leprosy is the cause of the world's commonest treatable neuropathy, leading in many cases to severe sensory loss and motor paralysis affecting eyes, hands, or feet. A recent report by the World Health Organisation gives an estimate of 1.15 million cases worldwide.¹ The number registered for treatment is 888 340.

Between 1 and 2 million people have obvious (visible) disabilities and deformities due to this disease.² Despite numerous publications and reviews of the neuropathology and immunology of leprosy,^{3,6} including the changes which occur in nerves during the course of adverse immunological reactions due to either cell mediated or humoral mechanisms, the exact pathophysiology is incompletely understood.

Ridley and Job⁷ have drawn attention to the tolerance of the Schwann cell for limited growth of *Mycobacterium leprae* and to various properties which make it an ideal site for the sequestration of antigen—its status as a “non-professional” phagocyte, not well adapted for antigen presentation, the fact that it is bounded by a basal lamina, and its long lifespan, far exceeding that of the macrophage. Ridley and Job have described the most important anatomical and immunological factors accounting for nerve damage at certain specified sites,⁶ while at the same time emphasising that the extent of involvement, the histopathological changes, and the mechanism of nerve damage depend crucially on classification in a range of disease from high resistant tuberculoid to low resistant lepromatous leprosy.⁸

We describe a subacute vasculitic neuropathy in a patient with previous lepromatous leprosy that developed 10 years after successful completion of antileprosy therapy.

Case report

A 46 year old Asian male was referred for neurological assessment with a stepwise, painless, multifocal sensory disturbance of 2 months duration.

Twenty five years previously he had presented with cutaneous lesions of lepromatous leprosy and slight numbness of the feet.

He was treated with daily rifampicin (600 mg) and dapsone (100 mg) for 18 months, being one of the first patients in the United Kingdom to receive rifampicin for the treatment of this disease. On completion of

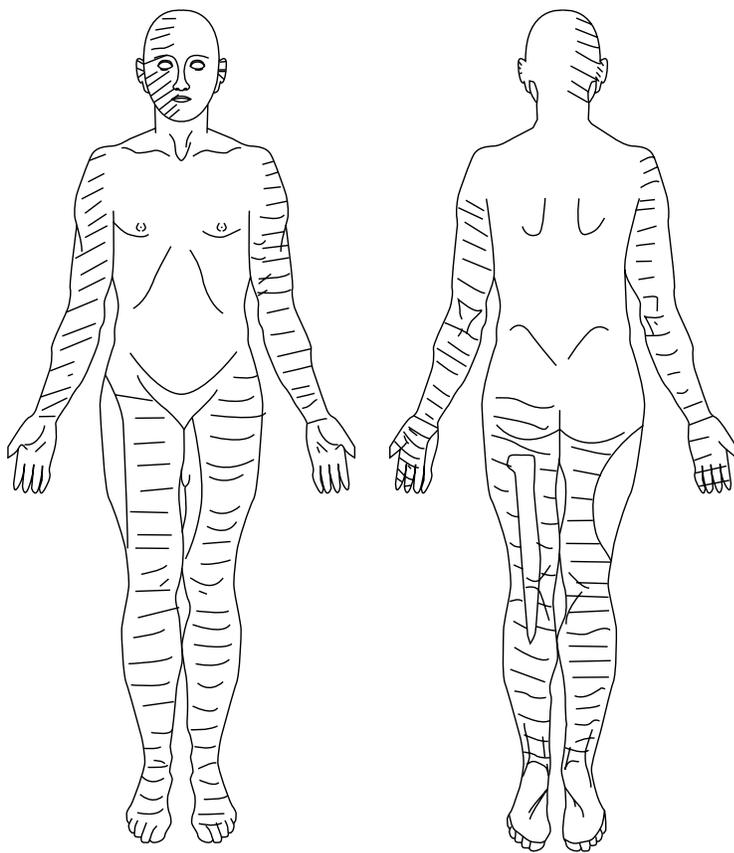


Figure 1 Widespread confluent sensory disturbance to pin prick with sparing of the individual cutaneous nerve territories including left posterior cutaneous and right lateral cutaneous nerve of thigh, plantar nerves, and branches of both median and left ulnar nerves.

Neurophysiological results

	1992		1995			
	Amplitude (μV)	Latency (ms)	Amplitude		Amplitude	
Sensory study:						
Right median ¹	4*	3.1	Absent		Absent	
Right and left ulnar ²	Absent		Absent		Absent	
Left radial ³	7	2.5	Absent		Absent	
Motor study:						
	CMAP (mV)	CV (m/s)	EMG	CMAP	CV	EMG
Right ulnar ⁴	14.5	52	Ax	3.9	52	CPD
Left ulnar	9.0	53	—	1.5	49	CPD
Left median	8.5	49	—	10.3	51	NAD
Normal values ¹⁸ :						
	Amplitude (μV)		Latency (ms)			
1	>10		<3.8			
2	>5		<3.2			
3	>15		<3.3			
	CMAP (mV)		CV (m/s)			
4	>5		>51			

*Low amplitude reflecting previous nerve damage: see text.

SAP=sensory action potential (μV); CMAP=compound muscle action potential (mV); CV=conduction velocity (m/s); EMG=needle electromyography; Ax=mild active axonal damage; CPD=chronic partial denervation with reinnervation; NAD=No abnormality detected.

treatment there were no clinical signs of disease activity. Skin smears from multiple sites were negative for acid fast bacilli and fresh tissue biopsies of skin, nerve, and muscle failed to produce growth of bacilli in the mouse foot pad model (Dr RJW Rees, Laboratory for Leprosy and Mycobacterial Research, National Institute for Medical Research, London). He continued dapsone, 50–100 mg daily for the next 15 years and received intermittent courses of prednisolone and thalidomide for recurrent erythema nodosum leprosum, including orchitis and arthralgia. All antileprosy treatment had ceased 10 years before presentation.

In 1991 he had presented with sensory symptoms consistent with mild bilateral ulnar neuropathies, localised to the elbows, but had been otherwise well. No other neurological

abnormalities had been noted at this time and a compressive aetiology was presumed.

Examination showed no evidence of active leprosy. Neurological abnormalities included a tear shaped pupil (secondary to previous uveitis), peripheral diminution of pin prick sensation, sparing discrete peripheral nerve territories (left posterior cutaneous nerve of thigh, right lateral cutaneous nerve of thigh, plantar nerves, branches of both median and left ulnar nerves (fig 1), and reduced distal vibration sense with mild upper limb pseudoathetosis. No weakness was demonstrable and tendon reflexes were normal with flexor plantar responses.

The erythrocyte sedimentation rate was persistently raised (60–70 mm/h). Haematology, biochemistry, B12, immunoglobulins, antinuclear antibody, antinuclear cytoplasmic antibody, C3 and C4 complement concentrations, cryoglobulins, *Treponema pallidum* haemagglutinin assay, hepatitis B surface antigen, *Borrelia burgdorferi* titres, urinalysis, urinary sediment microscopy were unremarkable. Cerebrospinal fluid was acellular with an increased protein (0.81g/l). Serum immunoelectrophoresis showed a raised $\alpha 2$ fraction. Magnetic resonance imaging of the brain and lumbosacral spine was normal. No enhancement after gadolinium administration was seen. Chest radiography was unremarkable.

Neurophysiological examination demonstrated absence of all sensory nerve action potentials (SAPs) examined, representing a clear deterioration from an earlier examination. Compound muscle action potential (CMAP) amplitudes from ulnar innervated muscles were markedly reduced from the previous study, although median nerve CMAP

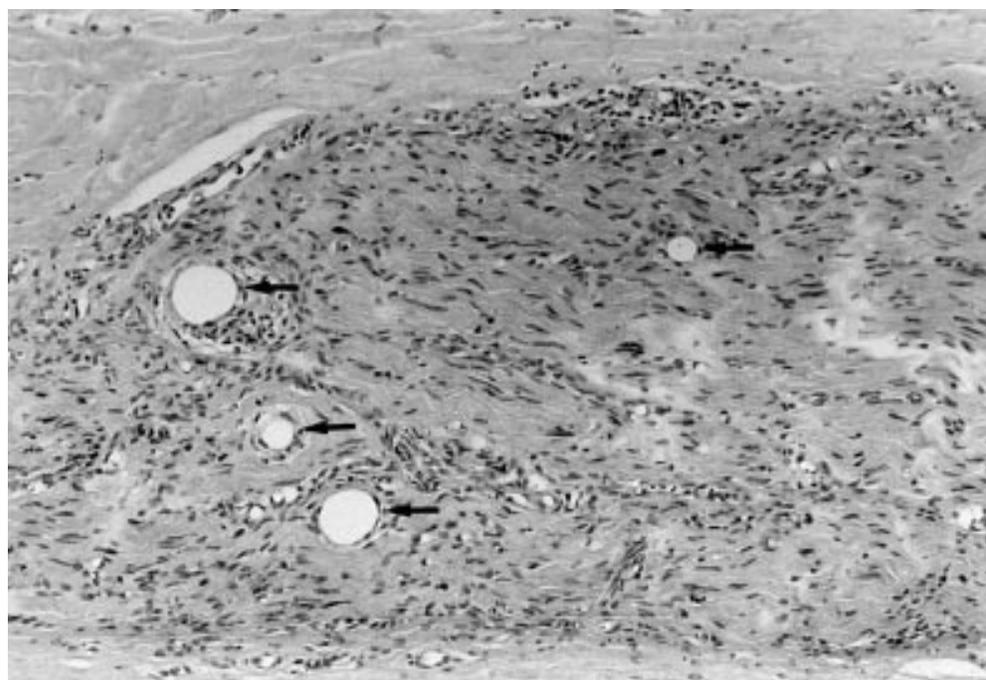


Figure 2 Low power photomicrograph of a nerve fascicle showing disruption of the intrafascicular architecture with a variable inflammatory infiltrate. Four intraendoneurial vacuoles (arrowed) are present in this section. Haematoxylin and eosin, originally $\times 10$

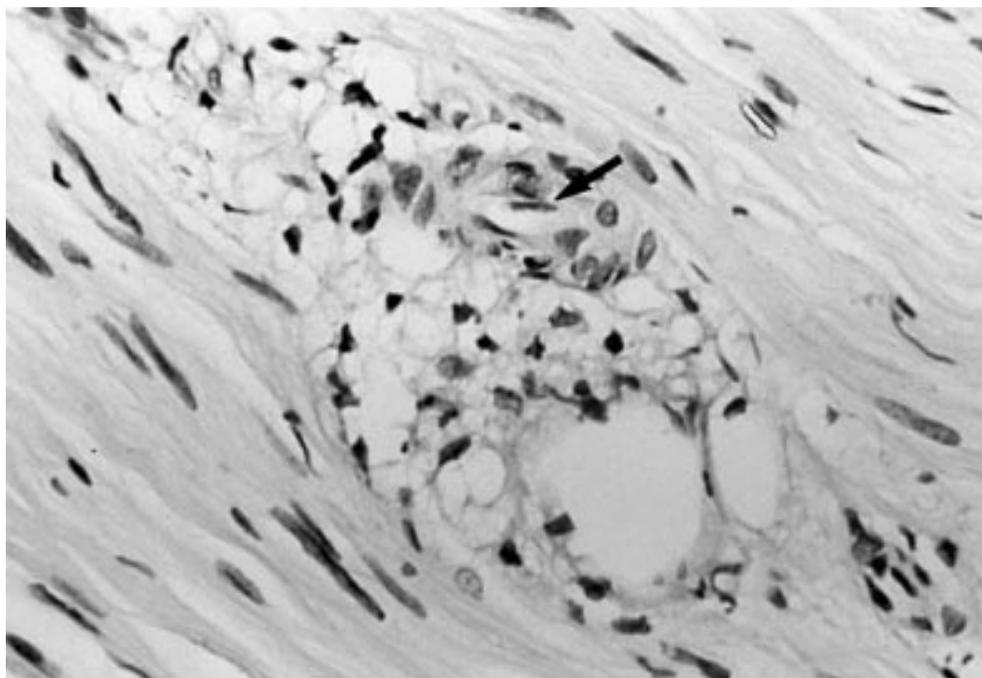


Figure 3 High power view of one of the intraendoneurial vacuoles showing a prominent perivacuolar collection of foamy macrophages. There is hypertrophy of the small endoneurial blood vessel (arrowed) adjacent to the vacuole. Haematoxylin and eosin originally $\times 25$.

amplitudes showed no such decline. Moreover, chronic partial denervation with reinnervation was found on needle electromyography (EMG) of ulnar innervated muscles suggesting a longstanding compensated motor axonopathy. Motor nerve conduction velocities were preserved (table).

HISTOPATHOLOGY

Sural nerve biopsy showed severe axonal loss and endoneurial fibrosis (fig 2). There was focal endoneurial vascular hypertrophy and a moderate variable lymphoplasmacytic infiltrate. Scattered through nerve fascicles were vacuoles surrounded by collections of foamy macrophages (fig 3). Rare multinucleate giant cells were seen in this infiltrate. In the epineu-

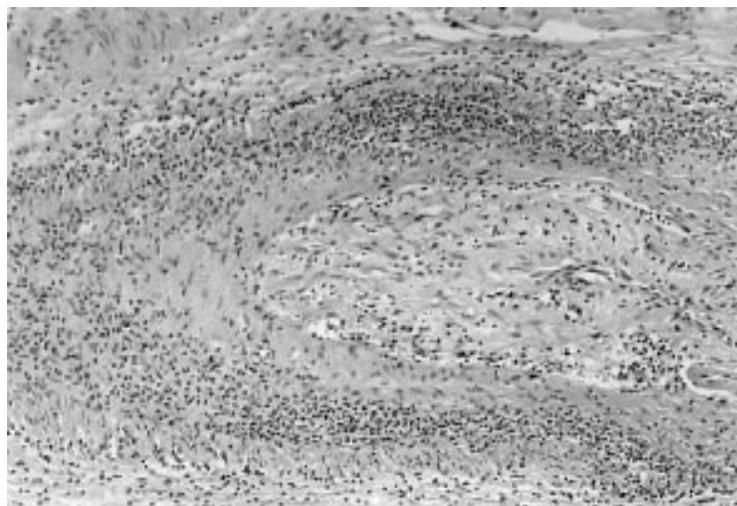


Figure 4 An epineurial artery with a prominent medial and adventitial inflammatory infiltrate. The inner media and intima are relatively uninvolved by the inflammatory reaction but there is pronounced intimal thickening. Haematoxylin and eosin originally $\times 10$.

rial blood vessels there was a marked focal lymphoplasmacytic arteritis with the inflammatory infiltrate concentrated in the outer media and adventitia (fig 4). Although the affected arteries in this patient did not display the features of a typical leukocytoclastic arteritis with fibrinoid necrosis and/or multinucleate giant cells the changes merit the diagnosis of arteritis in the general sense of an inflammatory condition of arteries because of the marked infiltration of the arterial wall by inflammatory cells. In one artery there was a suggestion of granuloma formation, but no giant cells were present. In the affected arteries there was asymmetric intimal thickening but no unequivocal evidence of vascular occlusion. Stains for mycobacteria showed no evidence of the presence of mycobacterium leprae or other mycobacteria in the tissue.

Immunocytochemical stains for mycobacterial antigen (DAKO anti-BCG) showed the presence of antigen within smooth muscle cells in the media of arterial walls (fig 5) and also in scattered cells within the endoneurium. This technique is the standard method of identifying mycobacterium leprae antigen in tissue⁹. No immunocytochemical reactivity to mycobacterium antigen is present in normal nerve.

MANAGEMENT

Treatment was commenced with high dose steroids, tapering to alternate day therapy titrated in response to clinical state and inflammatory markers.

Disability improved subjectively and objectively as assessed by timed walks. No further sensory symptoms developed.

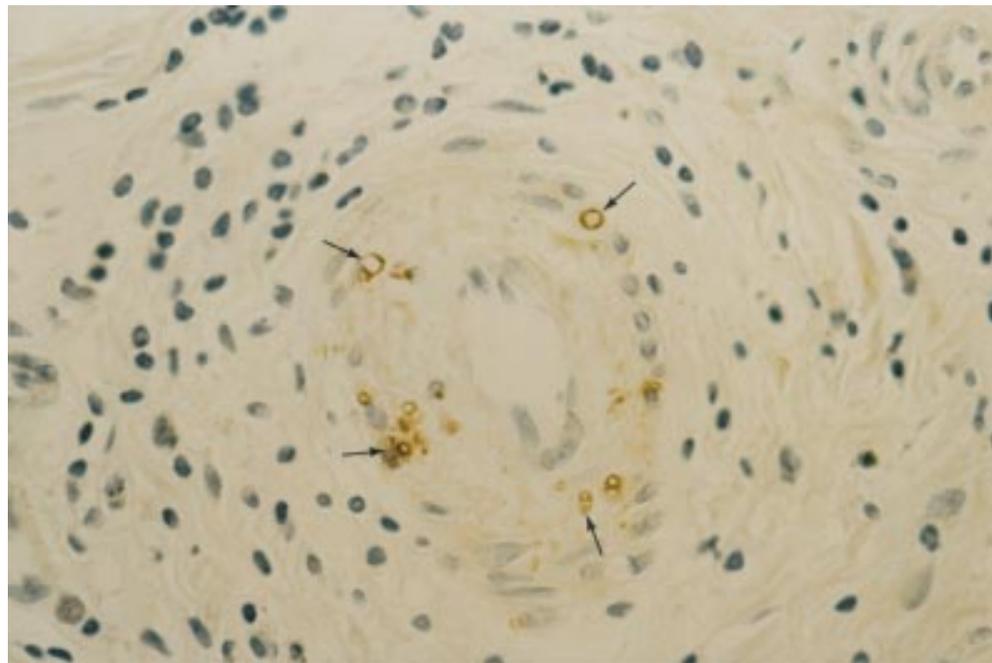


Figure 5 Immunocytochemical staining for BCG antigen showing the presence of antigen within smooth muscle cells in an inflamed portion of epineurial artery. HRP/anti-BCG originally $\times 25$.

Discussion

Recognised associations of vasculitic neuropathy include infection with a variety of organisms including *B burgdorferi*,¹⁰ HIV,¹¹ hepatitis B, systemic inflammatory disorders such as rheumatoid disease,¹¹ systemic lupus erythematosus,¹² polyarteritis nodosa, Churg-Strauss disease, and Wegener's granulomatosis.¹³ Vasculitic neuropathy may also occur as a paraneoplastic entity¹⁴ or in isolation without systemic accompaniment.¹³

Thalidomide neuropathy was excluded in this present case, before nerve biopsy, as this drug was not taken after 1985 and delayed onset of neurological symptoms after such a prolonged latency is unlikely.

Thalidomide may have contributed to the finding of a small median SAP (table) in 1992 but is unlikely to have resulted in further deterioration thereafter. Reduction of SAP amplitude (demonstrated in this case) has been suggested as a reliable indicator of thalidomide neuropathy.¹⁵

The increased CSF protein is of interest given that mycobacterial debris has been demonstrated by BCG antibody staining in postmortem studies of previously treated patients with lepromatous leprosy, both in peripheral nerve, lumbar dorsal root ganglia and posterior spinal roots.¹⁶ The mild increase of CSF protein in our patient may reflect vasculitis of spinal roots.

Vasculitis commonly results from adverse immunological reactions in leprosy, notably erythema nodosum leprosum in lepromatous cases, reaching its greatest intensity in the Lucio phenomenon, a severe form of reaction complicating Lucio leprosy (seen mainly in Mexico and Central America), and characterised by necrosis of subpapillary capillaries with haemorrhage and epidermal infarction.¹⁷

We suggest that this patient's progressive and severe neuropathy resulted from an immuno-

logically mediated vasculitis secondary to persisting *M Leprae* antigen. It is noteworthy that, with the possible exception of the early bilateral ulnar neuropathies with neurophysiologically documented motor axon loss, the vasculitic neuropathy seemed to spare motor nerves, in keeping with the purely sensory nerve involvement in the prior leprosy neuropathy. Although superimposed pressure palsies remain the plausible explanation, it is conceivable that these bilateral ulnar neuropathies may have been part of the leprosy vasculitic process. Vasculitis accompanying persistent mycobacterial antigen in vessel walls after such a prolonged period has not to our knowledge been reported before.

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