

Short report

Peripheral neuropathy associated with mycosis fungoides

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SUMMARY A 56 year old man with acute sensory-motor polyneuropathy associated with mycosis fungoides is described. EMG studies showed diffuse signs of muscle denervation. A skin biopsy specimen showed a lymphocyte infiltration in the dermis, composed of mycosis cells characterised by deep invaginations of the nuclear membrane, and small Pautrier's microabscesses in the epidermis. Sural nerve biopsy revealed endoneurial fibrosis, a decreased number of myelinated fibres and acute axonal degeneration.

Mycosis fungoides is a malignant T-cell lymphoma that originates in the skin. There is systemic involvement in 50-70% of the cases. Lymph nodes, lung spleen, liver and kidney are the viscera most commonly involved.^{1,2} Nervous system involvement is rare. Cellular infiltration of leptomeninges and/or cerebral hemispheres is the most common pathological feature.³ We describe a patient with mycosis fungoides and acute sensory-motor polyneuropathy. To our knowledge this clinical association has not been previously described.

Case report

A 56 year old patient developed 7 days after an influenza-like episode an acute progressive weakness of all four limbs, associated with paraesthesias over the hands and feet. A week later he was admitted to the Neurological Department H. S. Raffaele, Milan. General examination was normal, save for multiple, erythematous, partly infiltrated cutaneous plaques, from 2 to 4 cm in diameter, scattered over the back.

Neurological examination showed tetraparesis, predominantly of the lower limbs and distally, without muscle atrophy. The patient could stand with support but could not walk. There was diffuse loss of tendon reflexes. The hypoesthesia presented a glove and stocking distribution; vibration and

joint position were the most compromised sense modalities. ESR was 50 mm after one hour; serum IgA was 543 mg/dl (normal 65-300 mg/ml); complement C4 was 16 mg/dl (normal 40 ± 15 mg/dl). The search for circulating immunocomplexes (¹²⁵I Cl_q BA) was positive. The following laboratory data were normal: blood count, liver tests, thyroid and kidney functions, electrolytes, glucose tolerance test, urinary porphyrin assay, RF latex test; LE test, cryoglobulins, serum vitamin B12 and folate levels.

A study of peripheral blood lymphocyte subpopulations showed an increase of CD4 to 1800/cmm. Total lymphocyte count was 3200/mm³; CD3 60% (normal 75% ± 7); CD4 56% (45% ± 10); CD8 28% (28% ± 9). HIV antibody status was negative. No other metabolic, nutritional or toxic causes of peripheral neuropathy were disclosed. At admission and after 15 days the protein content of cerebrospinal fluid was normal and there were no cells. Motor conduction velocities (MCV) were slightly slowed; Peroneal nerve MCV 35.9 m/s (normal > 44.2 m/s), ulnar nerve MCV 45.8 m/s, (normal > 51.2 m/s), while distal motor latencies were normal. Sensory conduction velocities (SCV) were also slowed: median nerve SCV 43.5 m/s (normal > 51.3 m/s), sural nerve SCV 34.8 m/s (normal > 43.4 m/s). Motor (MAP) and Sensory (SAP) action potential amplitudes were severely decreased: peroneal nerve MAP 0.6mV (normal > 5mV), ulnar nerve MAP 8mV (normal > 10mV), median nerve SAP 1 μV (normal > 18 μV), sural nerve SAP 2 μV (normal > 9 μV). Signs of acute denervation were present in all the muscles examined, more striking in the distal muscles of the legs. The electrophysiological findings were considered to be an expression of acute symmetric axonopathy. By light microscopy, a skin biopsy specimen showed a fairly polymorphous cellular infiltrate, heavier in papillary and subpapillary dermis,

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mainly composed by medium size atypical lymphocytes with hyperchromatic and irregularly shaped nuclei, deeply margined chromatin and a scant rim of cytoplasm; these cells are similar to the so called mycosis fungoides cells. The epidermis shows epidermotropism characterised by the presence of these cells surrounded by a halo scattered through the keratinocytes. In some area we could observe small intraepidermal groups of these cells to form typical "Pautrier's" microabscesses. On electron microscopy, mycosis cells were characterised by a convoluted nuclear contour, cerebriform in aspect with deep invaginations of the nuclear membrane, a thick rim of marginated heterochromatin and scanty cytoplasmic organelles.

A fascicular biopsy specimen of the sural nerve at the ankle was obtained. The specimens were prepared by routine methods for light microscopy, teasing of the fibres and electron microscopy.⁴ The paraffin sections did not show any inflammatory cells or deposits of pathological material. The epon-embedded semithin sections showed a mild degree of endoneurial fibrosis, more marked in the centre of two fascicles. Many fibres were degenerative (fig). In quantitative histometric studies, the total number of myelinated fibres was reduced (1561; normal 5200-9500). The histogram of the size distribution of myelinated fibres did not show the normal bimodal distribution, but was uniformly flat. Fifty teased

fibres were classified morphologically according to Dyck *et al.*⁴ 54% of them had linear rows of myelin ovoids at same stage of degeneration (condition E); 6% had excessive variability of myelin thickness between internodes (condition D); and 40% were normal (condition A). Electron microscopy confirmed a primary disorder of the axon, showing abnormal organelles, disintegration of microtubules and neurofilaments and vacuolisation of axoplasm. All attempts to detect visceral involvement of mycosis fungoides were negative, including bone marrow biopsy.

Sensory symptoms and weakness developed acutely over two weeks and during that time widespread muscular atrophy became evident. The atrophy was predominantly distal in the lower limbs. A stable period of 2 weeks was followed by a partial recovery phase, so that 2 months after the onset of the symptomatology the patient was able to walk short distances without assistance. A clinical follow up 2 months later showed no further improvement of strength and sensory deficit. At the same time an electrophysiological re-examination disclosed that none of the nerve conduction parameters had changed. Electromyography showed persistence of diffuse fibrillation and initial signs of collateral reinnervation in all the muscles tested. As far as it concerns the cutaneous lesions a spontaneous reduction of their number and diameter was noted.

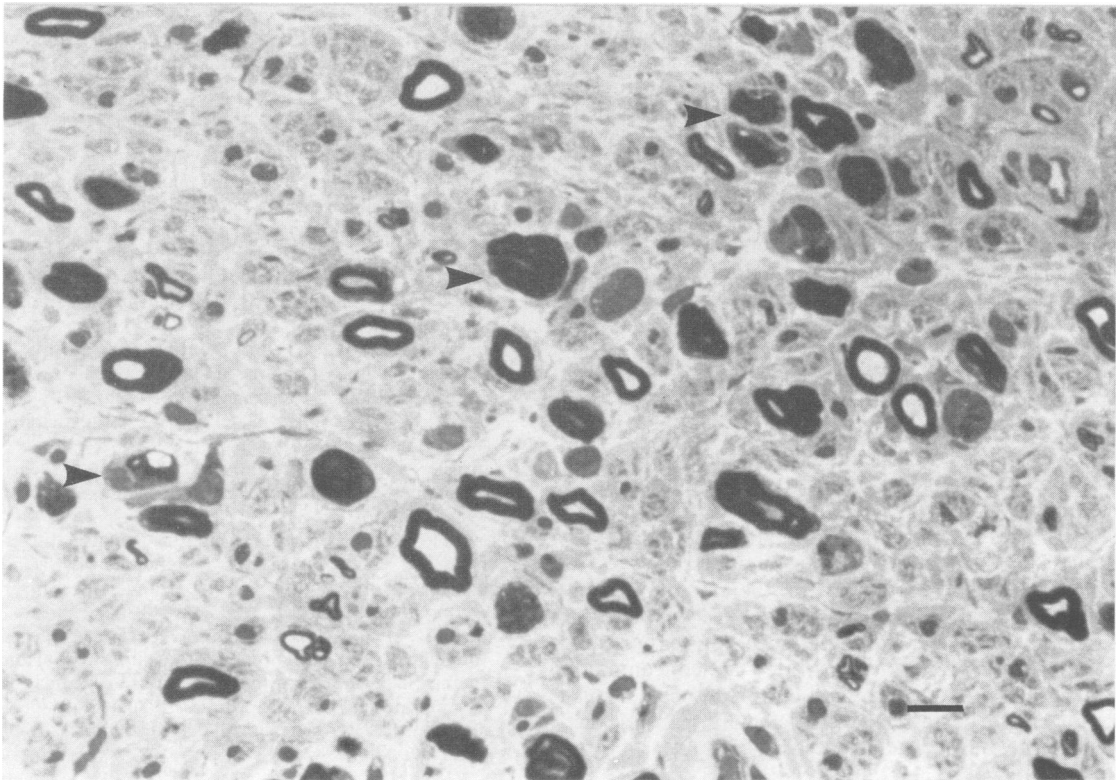


Fig Transverse section of sural nerve. Marked loss of myelinated fibres and remarkable endoneurial fibrosis. Some degenerating fibres (►) are present. Epon-embedded, semithin section. Toluidine blue. BAR = 10 μ m.

Discussion

Nervous system involvement in mycosis fungoides is uncommon.³ It has been noted in up to 10–15% of the largest reported series.¹ Meningeal infiltration was the most frequent pathological feature. A review of 33 necropsy cases of mycosis fungoides of the central nervous system, individually described in the literature, revealed meningeal involvement in 20 cases.³ Meningeal infiltration can be detected by the presence of Sézary cells in CSF.^{5–7} Other possible locations of nervous system infiltration by mycosis fungoides cells are cerebrum, brainstem, spinal cord, choroid plexus and peripheral nerves.^{1,3,8,9} In our case, clinical, neurophysiological and CSF studies excluded central nervous system, meningeal or root involvement. Our patient fulfilled the clinical criteria for the diagnosis of acute Guillain-Barré polyneuropathy.¹⁰ However, neurophysiological and morphological studies indicated that the primary pathology was axonal degeneration. This case is similar to those described by Feasby *et al.*¹¹ They concluded that the evidence of severe axonal degeneration and the very poor recovery of their cases set them apart from the usual cases of Guillain-Barré polyneuropathy and that they represent a separate clinicopathological entity of acute axonal neuropathy. Axonal degeneration has not been previously observed in acute peripheral neuropathy associated with lymphomas in which segmental demyelination is the main pathological mechanism of nerve damage.¹² In our patient we found no Sézary cells in the nerve. This does not mean that these cells might not be present elsewhere since their distribution is patchy, as it is in the skin. Clinical examination and neurophysiological results are otherwise suggestive of diffuse polyneuropathy and are against direct damage of peripheral nerve by neoplastic cell infiltration. The clinical course of the neuropathy and of the skin lesions, characterised by a rapid progression and a fairly rapid partial recovery, suggests a strict relationship between the two phenomena. The aetiopathogenesis of mycosis fungoides is not yet clear. Some authors regard it as a primary neoplastic transformation of T lymphocytes,^{13,14} and others as a lymphocyte reaction to a chronic toxic stimulus acting on the dermal cells of Langerhans.^{15,16} In our patient the immunological data, particularly the increase of the T4 lymphocyte subpopulation and the presence of circulating immunocomplexes, demonstrate a concomitant derangement of the immunological reactivity. If this derangement has a pathogenetic role in causing the neuropathy has to be elucidated.

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