Short report

Brain biopsy in the diagnosis of cerebral mycosis fungoides

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SUMMARY A case of cerebral mycosis fungoides co-existing with progressive multifocal leucoencephalopathy presented with dementia. Brain biopsy established the diagnosis of mycosis fungoides after cerebrospinal fluid examinations and computerised tomographic scanning of the brain produced non-specific abnormalities.

Mycosis fungoides is a cutaneous lymphoma with characteristic histological and cytological features.¹ Visceral infiltration is a common necropsy finding and although the nervous system usually is spared,¹⁻⁵ metastatic involvement of many parts of the nervous system and various non-metastatic neurological complications have been described (table). Cytological examination of the CSF has been helpful in

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establishing the diagnosis of meningeal mycosis fungoides in a few patients,⁶⁻⁸ but in others the CSF has been normal although meningeal and parenchymal infiltration was found at subsequent necropsy. As mycosis fungoides is potentially treatable with radiotherapy or chemotherapy or both, other techniques are needed to establish the diagnosis. This case report describes the use of CT scan and brain biopsy, neither of which have previously been reported, and the unexpected occurrence of both progressive multifocal leucoencephalopathy (PML) and cerebral infiltration with mycosis fungoides.

Table Neurological complications of mycosis fungoides*

Metastatic	References
Eye	8, 18, 19
Cranial nerve	11, 12, 13, 18, 19
Peripheral nerve	11
Spinal ganglia, roots	22
Cerebral parenchyma	1, 4, 6, 10, 14, 18, 19
Meninges	1, 2, 6-8, 9, 12, 18, 19
Ventricles, choroid plexus	4
Pituitary	4
Non-Metastatic	
Infection	
Viral (progressive multifocal leucoencephalopathy)	20
Fungal (cryptococcus)	
Bacterial (<i>Listeria m</i>)	
Protozoal (<i>Toxoplasma</i>)	
Vascular	
Nutritional, metabolic (central pontine myelinolysis)	19
Iatrogenic (radiotherapy, chemotherapy, diagnostic or surgical procedures)	14-17
Idiopathic (demyelination)	
Paraneoplastic	
Dermatomyositis	23
Myelopathy, neuromyopathy	24, 25

*Complications without references are known complications of lymphomas not yet described in mycosis fungoides.²¹

Case report

A 62-year-old engine driver was admitted to a dermatology department in March 1980 with a 4 year history of discoid and annular lesions of parapsoriasis on the back, the flank and the legs, and with an itchy raised, scaly fissured lesion on the dorsum of the right hand for 6 months. Biopsy showed features consistent with mycosis fungoides and treatment was started with superficial radiotherapy and cyclophosphamide 50 mg twice daily. Four months previously he had developed a right anterior uveitis, treated with topical atropine and betamethasone. Two weeks before admission he developed slight confusion and disorientation, expressive dysphasia, and a mild left hemiparesis. An isotope scan showed increased activity superficially in the left frontal region, and the right posterior parietal region. The illness was attributed to a stroke, and he was discharged home. He became increasingly confused over the next 3 weeks and was admitted to the Department of Neurology in April 1980. On examination he was obese, with cutaneous features of mycosis fungoides and parapsoriasis. He was disorientated in time and place, could not give a history, read, calculate, dress or recall short or long-term items. His speech was incomprehensible except for profanities, and he responded to simple commands only. The optic fundi were normal, and the pupils dilated and unreactive (owing to atropine). The cranial nerves were intact. Power was minimally less on the left than the right. Muscle tone was normal, tendon reflexes brisk and symmetrical, and the plantar responses extensor bilaterally. Bilateral grasp

reflexes were present. The gait was broad-based and shuffling. Movements of the hands were clumsy. He perceived pin-prick but other modalities of sensation could not be reliably assessed.

After admission he developed a right facial palsy, dysphagia, and the confusion increased. Full blood count, ESR, serum electrolytes, liver function tests, chest and skull radiographs, and an ECG were normal. TPHA and FTA-ABS were negative. An EEG showed diffuse slow-wave activity, more marked over the left hemisphere. A CT scan showed, after contrast injection, enhancement in the left periventricular region (fig 1). At lumbar puncture the opening pressure was 10 cm H₂O. The CSF protein concentration was 453 (normal less than 400) mg/l, IgG 83 mg/l, and the glucose was 4.1 mM/l. There were 57 erythrocytes and 8 white cells/mm³ of CSF (70% lymphocytes, 30% polymorphs). Centrifuged deposits showed several large and small lymphoid cells but no pleomorphic histiocytic cells. Bacteriological examination and culture was negative. At a repeat examination a week later the CSF protein concentration was 529 mg/l, the IgG 157 mg/l, and cytological examination again showed lymphoid cells only.

Two weeks after admission, a wedge biopsy was taken

Fig 1 CT scan with contrast enhancement showing abnormality in the left periventricular region.

Fig 2 Brain biopsy. An infiltrate consisting mainly of polymorphic mycosis cells occupies a Virchow-Robin space in deep cerebral white matter. H and E $\times$ 250.

from the left frontal cortex and underlying white matter and needle biopsies were taken in deeper tissue. The cortex was normal, but the deeper cores contained white matter and some fragments of caudate nucleus with striking perivascular and intravascular infiltration by a polymorphous collection of mitotically-active histiocytes, lymphocytes and smaller numbers of other inflammatory cells (fig 2). There was oedema and astrocytosis but no demyelination. These appearances were considered to be in keeping with cerebral mycosis fungoides. Two days after the biopsy a repeat CT scan showed an area of enhancement in the left thalamus and hypothalamus, and air at the biopsy site. Intravenous infusion of carmustine (BCNU), 200 mg/m² (400 mg) over 2 hours was given and radiotherapy was planned. He continued to deteriorate into deep coma and developed Cheyne-Stokes respiration and bilateral basal crepitations. Despite antibiotic therapy and intensive care he died on the third day after the biopsy.

At necropsy there were changes of broncopneumonia, the skin changes of mycosis fungoides, but no visceral involvement apart from the central nervous system. Macroscopic examination of the fixed brain revealed foci of opaque yellow necrosis 5-12 mm in diameter in the left anterior hypothalamus, right mid-parietal cortex, right middle frontal gyrus, both hippocampal gyri and white matter, and the right posterior parietal white matter. The cerebellum showed multiple small (2-3 mm) grey punctate areas of white matter, but the spinal cord was macroscopically normal. Histologically, these changes were seen to be those of progressive multifocal leucoencephalopathy. Foci of coagulative necrosis were surrounded by variable demyelination and other smaller areas of demyelination without necrosis were also present. The white matter was oedematous and showed striking astrocytic hyperplasia with many giant and bizarre binucleate and multinucleate forms. Occasional eosinophilic inclusions were seen in glial nuclei. In addition, there was infiltration of many of the Virchow-Robin spaces and parts of the subarachnoid space by mycosis fungoides cells similar to those found in the brain biopsy.

Discussion

The neurological complications of mycosis fungoides are summarised in the table based on the reports of 14 cases.⁶⁻¹⁹ The average duration of preceding skin involvement was 7.5 years with a range of 8.5 months to 30 years. Neurological features indicate a poor prognosis for the time from the onset of neurological symptoms to death ranged from six weeks to eight months. In our case the time interval was nine weeks. As in our case, the mycosis infiltrate typically involves the Virchow-Robin perivascular spaces.^{7-12 15-19} Occasionally, the infiltrates spread to the cerebral parenchyma diffusely,^{6 14 19} form nodules^{10 18 19} or infiltrate nerves.^{8 11 13 18 19}

The dominant disorder revealed by histology was progressive multifocal leucoencephalopathy. This has been previously described in a patient with

generalised mycosis fungoides²⁰ without cerebral infiltration with mycosis fungoides. Our case also differs in having limited skin infiltration and no evidence of diffuse reticuloendothelial involvement. Progressive multifocal leucoencephalopathy is usually associated with impaired immunological mechanisms such as occurs with reticuloses or cytotoxic therapy. In our case, neurological features preceded treatment with a modest dose of cyclophosphamide at 25 mg twice daily for one month before his death. The precise relationship of the cutaneous lymphoma, impaired immunity, cerebral infiltration and progressive multifocal leucoencephalopathy is unclear. We speculate that the altered immune mechanisms associated with mycosis fungoides may have allowed an opportunistic viral infection associated with progressive multifocal leucoencephalopathy to develop. There was no evidence of polyoma virus. The encephalopathy may have facilitated the infiltration of perivascular tissues with neoplastic cells of mycosis fungoides. It is likely that the spread of mycosis fungoides was haematogenous, although direct spread from overlying scalp to the brain has been reported.¹⁰ Thus the mechanisms of spread appear to be similar to those postulated for other lymphomas,²¹ albeit less commonly.

Although abnormal, the CT scan was not diagnostic of either leucoencephalopathy or cerebral mycosis fungoides but was helpful as a guide to the site of the biopsy. We suggest that a brain biopsy should be done in patients with mycosis fungoides who develop unexplained neurological abnormalities with localising CT scan abnormalities and CSF changes which are not diagnostic. Some improvement with radiotherapy and chemotherapy in patients with meningeal mycosis fungoides has been reported,^{7 8} but the survival was less than 8 months after the onset of neurological symptoms. A brain biopsy may allow earlier diagnosis and therapy and so improve the prognosis.

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