Cerebral involvement in multiple myeloma: case report

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SUMMARY Cerebral myeloma in a 49-year-old white man took the form of diffuse arachnoid infiltration, intracerebral perivascular cuffing, and frank intracerebral invasion.

Involvement of the nervous system, one of the more common complications of multiple myeloma (Clarke, 1954), usually takes the form of 'myelomatous paraplegia' due either to compression of the spinal cord by extradural deposits of myeloma or, more rarely, to a collapsed vertebra (Victor et al., 1958). Intracranial involvement usually presents in one of three forms—cases with single or multiple cranial nerve palsies caused by myeloma deposits in the bone of the base of the skull, cases simulating intracranial space-occupying lesions, and cases with orbital involvement. Unusual presentations include diffuse infiltration of the leptomeninges and invasion of the cerebral parenchyma. This last form is said to be exceedingly rare (Sparling et al., 1947).

We report the case of a middle-aged man who presented with a grand mal convulsion and was found to have multiple myeloma.

Case report

A 49-year-old Caucasian man was admitted to hospital in September 1975 after he had had a grand mal convulsion. Two weeks before he had experienced transient paraesthesia down his left side for a few minutes. On admission his only complaints were of paraesthesia of the tongue and some difficulty in chewing and swallowing associated with nasal regurgitation. During his stay in hospital he began to complain of generalised back pain.

On examination there was no impairment of higher functions and the neurological signs were minimal, with a left palatal palsy and slight left-sided weakness not associated with hyperflexia. Neck stiffness was absent; Kernig's sign negative; pulse 92/min, regular; blood pressure 140/80 mm Hg. There were no cranial bruits or papilloedema.

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A lumbar puncture revealed clear CSF not under pressure containing lymphocytes $35 \times 10^6/l (35 \text{ mm}^3)$. CSF protein was 2·1 g/l (normal 0·15-0·4 g/l) with 0·5 g/l gammaglobin (normal 0·01-0·05 g/l). EEG was normal but a brain scan showed marginally increased uptake of isotope over the left temporo-frontal region. A skull x-ray picture showed no evidence of increased intracranial pressure. However, x-ray examination of the spine showed two wedged thoracic vertebrae, D7 and D8. No osteolytic lesions were seen. The total serum protein was abnormal at 91 g/l (albumin 44 g/l). An M band was present on electrophoresis. ESR (Westergren) 9 mm in one hour. Immuno-electrophoresis showed IgG 33·68 g/l (normal 9·5-16·5 g/l). Urine immuno-electrophoresis showed no light chains. Peripheral blood: Hb 12·9 g/dl, WBC $6·0 \times 10^9/l$ (polymorphs 81%, lymphocytes 16%, monocytes 2%, eosinophils 1%), platelets $300 \times 10^9/l (300\,000/\text{mm}^3)$. The blood film was normal. Bone marrow, examined twice, showed an increase in number of plasma cells with many multinucleate forms. Plasma urea, electrolytes, serum calcium, glucose tolerance test, uric acid, acid phosphatase, sputum cytology, and VDRL were all normal.

TREATMENT AND PROGRESS

Multiple myeloma was diagnosed. The neurological signs and symptoms were thought to be due to vascular disease. Melphelan 5 mg with prednisone 40 mg were given daily for one week. This regimen was repeated at six-weekly intervals. Phenobarbitone 30 mg was given twice daily as prophylaxis against convulsions.

The patient remained well for 11 months but there was no reduction in the levels of IgG. A year after initial admission he was readmitted after a series of grand mal convulsions. His temperature was normal, there was slight meningism, and concious-
ness was much impaired. The pupils were equal and reactive and there was no papilloedema. Response to painful stimuli was present on the right side but sensory inattention was total on the left. Tone was normal but there was generalised hyperflexia with extensor plantar responses. Lumbar puncture revealed clear CSF not under pressure. CSF: plasma cells $250 \times 10^6/l$ ($250/mm^3$) (Fig. 1); protein $19.0$ g/l (normal $0.15-0.4$ g/l); sugar $6.9$ mmol/l (normal $2.2-4.4$ mmol/l). Peripheral blood: Hb $11.5$ g/dl, WBC $13.4 \times 10^9/l$ ($13,400/mm^3$); (polymorphs $35\%$, lymphocytes $45\%$, plasma cells $20\%$), platelets $400 \times 10^9/l$ ($400,000/mm^3$). Four days later: WBC $50 \times 10^9/l$ ($50,000/mm^3$) (80% were immature plasma cells).

Plasma cell leukaemia with meningeal and probable cerebral involvement was diagnosed. Treatment consisted of daily intrathecal methotrexate $7.5$ mg/m$^2$ and cranial irradiation. The patient died two weeks later, when the plasma cells in peripheral blood numbered $90 \times 10^9/l$ ($90,000/mm^3$).

**Necropsy**

There was a thoracic kyphosis due to collapse of several mid-thoracic vertebrae. This was the only relevant finding outside the cranium. The skull and dural membranes were normal and there were no localised deposits of myeloma. The brain weighed 1480 g. The leptomeninges were opaque over the cerebral hemispheres, especially over the right frontoparietal region, where the membranes were grey-white in colour, thickened up to 5 mm in width, and somewhat gelatinous (Fig. 2). This tissue also occupied the sulci over the right frontoparietal region and in some areas merged into the cerebral cortex. There was an area of recent haemorrhage in the right caudate nucleus $10$ mm in diameter (Fig. 3) and in the white matter of the right parietal region was a poorly defined area of softening of about $30$ mm in greatest diameter. There was moderate non-occlusive atherosclerosis of the main cerebral vessels. Both optic nerves were thicker than normal and measured up to $7$ mm in diameter. The bone

Fig. 1  *Plasma cells in CSF. (x 460)*

Fig. 2  *Thickening of leptomeninges over right frontoparietal region.*

Fig. 3  *Haemorrhage into right caudate nucleus. Malignant tissue in sulci of parietal region.*
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Fig. 4 Plasma cells distending the subarachnoid space. (× 45)

Fig. 5 High-power field of plasma cell infiltrate in the cerebral parenchyma showing multinucleate cells. (× 550)
Fig. 6 Perivascular cuffing by malignant plasma cells. (× 47.5)

Fig. 7 Frank invasion of cerebral parenchyma. (× 47.5)
marrow of the sternum was red and rather soft in consistency.

**HISTORY**

The subarachnoid space, particularly over the right frontoparietal region, was distended with pyroninophilic plasma cells (Fig. 4). Some were pleomorphic and had large hyperchromatic nuclei. There were occasional multinucleated cells. Mitoses were infrequent (Fig. 5). The plasma cell infiltration surrounded blood vessels, passing into the cerebral cortex along the Virchow-Robin spaces (Fig. 6). The malignant plasma cell infiltration extended into the cerebral white matter in the deeper parts of the right parietal region. The cells were poorly differentiated in this area and there was necrosis of the affected cerebral parenchyma (Fig. 7). There was also parenchymal plasma cell infiltration of the right caudate nucleus associated with focal recent haemorrhage and necrosis. The optic nerves showed perivascular aggregates of plasma cells, which accounted for their swollen appearance. The dura mater was not involved.

Bone samples from the ribs and the iliac crest showed a cellular marrow with a predominance of plasma cells, some of which were pleomorphic. The spleen also showed an increase in the numbers of plasma cells within the sinusoids.

**Discussion**

Malignant infiltration of the leptomeninges is well recognised in leukaemic patients and is seen in up to 30% of cases of all acute leukaemia. This infiltration most often occurs in acute lymphocytic leukaemia in children who have not been treated with cranial irradiation. Meningeal leukaemia gives rise to a diverse clinical syndrome resulting from raised intracranial pressure, the principal manifestations being nausea and vomiting, headache, lethargy, convulsions, papilloedema, and cranial nerve palsies (Shaw et al., 1960). There may be perivascular infiltration into the brain in up to 52% of cases of meningeal leukaemia (Moore et al., 1960). In contrast, infiltration of the leptomeninges in multiple myeloma seems to be rare. We could find only two reported cases (Afifi, 1974; Maldonado et al., 1970).

The neurological findings in our case parallel many of the clinical and pathological features seen in acute leukaemia with central nervous system involvement. In view of the original mode of presentation it seems likely that there was some central nervous system involvement from the outset and that this did not develop late in the disease simply as a result of the plasma cell leukaemia. It may even be that the subarachnoid space was the primary site of the myeloma. Meningeal myeloma is presumed to develop as a result of neoplastic proliferation into myeloma cells of the totipotent mesenchymal cells accompanying the pial blood vessels. This mechanism may be held responsible for the development of both isolated meningeal myeloma and meningeal lesions complicating systemic myelomatosis (Afifi, 1974). Cerebral myeloma occurring early in the disease is extremely rare. There are few reports of similar cases (Sparling et al., 1947).

Extraosseous spread of multiple myeloma occurs overall in about 70% of cases. The longer the illness the greater the chance of distant extraskeletal lesions developing (Pasmantier and Azar, 1969). The commonest sites of spread are the spleen, liver, lymph nodes, and kidneys. In 57 cases reviewed by Pasmantier and Azar (1969) there were no cases of intracranial or central nervous system involvement, and in 110 cases reviewed by Maldonado et al. (1970) there was only one case of meningeal involvement. Five individually recorded cases of solitary intracranial plasmacytomas have been reported (Clarke, 1954; Medoc et al., 1961; Weiner et al., 1966; Moossy and Wilson, 1967; Gravanis and Someren, 1969).

Treatment of central nervous system myeloma is most unrewarding, especially when diffuse meningeal involvement and plasma cell leukaemia coexist. The short-term improvement after central nervous system irradiation and intrathecal cytotoxic agents seen in acute lymphatic leukaemia is not achieved in myeloma. Whether cranial irradiation and intrathecal methotrexate when the tumour mass was small would have resulted in improvement in our case is a matter for speculation.

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