

Diagnostic problems of leptomeningeal lymphoma

A report of 3 cases

J. GARDINER, A. S. DE GRAAF, R. H. HEWLETT

Summary

Three cases are presented in which occult lympho-reticular malignant tumour spread to the spinal and cranial subarachnoid spaces inducing a problematic neurological illness characterised by poorly localised neuralgic pain, slowly progressive paresis and, in 2 patients, papilloedema with computed tomographic evidence of ventricular dilatation. Despite intensive investigations, diagnosis was only achieved at autopsy. A progressive disturbance of spinal and cranial nerve function should direct the attention of the clinician to the possibility of diffuse meningeal involvement by a malignant or inflammatory process.

S Afr Med J 1987; 71: 457-459.

Robbins and Cotran¹ describe lymphomas as 'rare and unwelcome visitors' to the central nervous system (CNS), while Henry *et al.*² are more specific in attributing less than 1% of all malignant lymphomas to a primary site in the CNS. Secondary malignant lymphomas of the CNS are also uncommon, a fact borne out in two studies by Henneman *et al.*³ in which only 3 out of 29 neoplasms in a low-malignancy group and 3 out of 29 neoplasms in a high-malignancy group had metastases to the CNS. By the time there is metastatic spread to the CNS, there are signs of advanced disease, i.e. constitutional symptoms and evidence of extranodal spread.⁴

Although primary CNS malignant lymphomas tend to remain confined to the parenchyma, intrusion into the subarachnoid space by secondary lymphomas is minimised by the barrier that the subarachnoid membrane offers to contiguous spread; a precept convincingly supported by Marshall *et al.*⁵ in studies on Hodgkin's lymphoma.

It is apparent that diffuse spread to the subarachnoid space is an uncommon form of CNS invasion by malignant lymphoma, which gives rise to a clinical picture of chronic meningitis indistinguishable from meningeal carcinomatosis.⁶ Three such cases that proved to be diagnostic problems until autopsy are reported.

Case reports

Case 1

A 74-year-old woman had developed, 4 months before admission and over a period of 1 month, severe biting pain in both gluteal muscles with radiation to the calves. Progressive paraplegia with urinary and faecal incontinence led to her hospitalisation. No lymphadenopathy or splenomegaly was noted at any stage.

The results of routine investigations, including erythrocyte sedimentation rate, full blood count, electrolyte measurement, liver function tests, and protein electrophoresis and collagen screening, were normal; the lactic dehydrogenase level was mildly elevated, with electromyographic and muscle biopsy findings suggestive of a neuropathic process. Lumbar puncture was unsuccessful, and a cisternal myelogram demonstrated a total obstruction at L2-3. Computed tomography (CT) of the brain was normal.

During her stay in hospital, the patient developed inappropriate antidiuretic hormone secretion, hemifacial weakness and bilateral 10th cranial nerve palsies. Emotional lability progressed to confusion, coma and death 1 month after admission.

At autopsy, a histiocytic lymphoma was found arising in the left iliac fossa with dissemination to the spinal subarachnoid space, cauda equina, cord parenchyma and nerve roots (including the supra-optic nucleus of the hypothalamus). Postmortem cerebrospinal fluid (CSF) cytological examination showed large numbers of abnormal mononuclear cells and lymphocytes (Fig. 1).

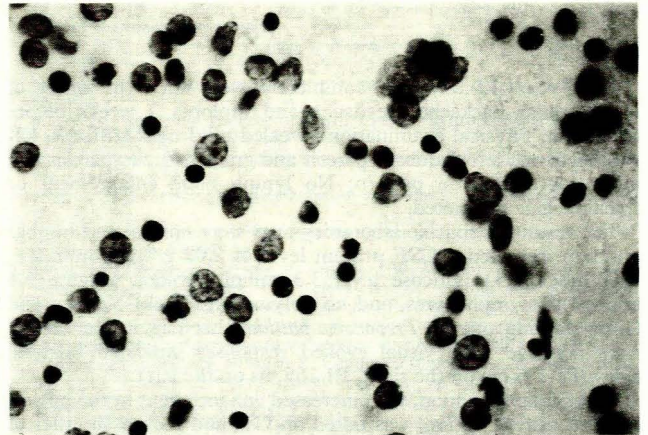


Fig. 1. Case 1 — postmortem CSF cytology. The field is packed with cells some of which are lymphocytes, but the majority have large, irregular nuclei and rather open chromatin (x 400).

Case 2

A 19-year-old man presented after 4 weeks of progressive weakness and paraesthesia in the left lower limb, anosmia, headache, poor memory and audiovisual hallucinations. Examination revealed lower motor neuron weakness of the facial muscles bilaterally, abductors of the left shoulder and all muscles of the left lower limb (grade 4/5). Segmental sensory loss (L5-S1) was

Departments of Neurology and Anatomical Pathology (Neuropathology), University of Stellenbosch and Tygerberg Hospital, Parowvallei, CP

J. GARDINER, B.SC. HONS, M.B. CH.B.

A. S. DE GRAAF, M.D.

R. H. HEWLETT, PH.D., M.R.C.PATH.

noted in the left leg. There was no lymphadenopathy or splenomegaly.

The results of routine laboratory investigations and of bone marrow aspirate biopsy were normal. Lumbar puncture showed a total protein level of 0,8 g/l, globulin +, IgG index 0,50, (normal < 0,58), lymphocytes 10 and polymorphs 0. Cyto centrifugation did not demonstrate malignant cells. CT showed slight ventricular dilatation; myelography was not attempted.

During a protracted hospital stay of more than 3 months, weakness and sensory changes in the left lower limb progressed and hallucinations became more frequent. An episode of gastric bleeding prompted gastroscopy, which showed a malignant-looking ulcer, which the histologist was unable to confirm. The patient responded clinically to antacids and H₂-antagonists. At the time of death from bronchopneumonia he weighed 31 kg (61 kg on admission) and papilloedema was apparent in the left eye.

Autopsy revealed a gastric lymphoma with local adenopathy and diffuse infiltration of the meninges and the cranial and spinal nerves, and superficial parenchyma of cord and brain (Fig. 2).

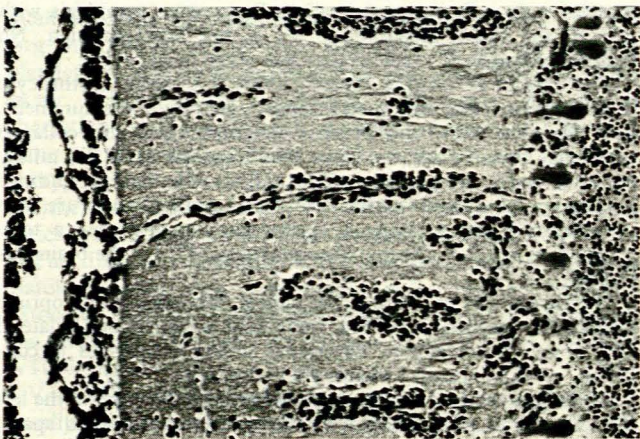


Fig. 2. Case 2 — subarachnoid space and superficial parenchymal invasion by lymphoma cells. Note perivascular spread (arrows) (x 250).

Case 3

A 16-year-old boy was completely well until the onset of interscapular backache, headache and diplopia 2 weeks before admission. Physical examination revealed mild neck stiffness, left papilloedema, left abducens paresis and grade 4/5 paraparesis of a lower motor neuron pattern. No lymph node enlargement or splenomegaly was noted.

The results of routine laboratory tests were normal and lumbar puncture revealed a CSF protein level of 2,08 g/l, globulin 2+, IgG index 3,54, glucose level 3,3 mmol/l (blood glucose 6,4 mmol/l), 5 lymphocytes, and no polymorphs. Ziehl-Neelsen and Gram staining and the *Treponema pallidum* haemagglutination test were negative. The visual evoked responses indicated bilateral delay (P1 135 ms on the right, P1 165 ms on the left).

Ventricular dilatation, with increased enhancement in the pineal-ambient cistern region, was noted on CT, and the possibilities of granuloma or vascular malformation were suggested (Fig. 3, left).

Radiographs of the spinal column showed a slight thoracic scoliosis but were otherwise normal, as was the marrow biopsy, while two attempts at myelography were unsuccessful.

In hospital, a sensory level developed at T5-6, the right lower limb weakness became worse, and proprioceptive function decreased in both legs. Two weeks after admission he developed rhinorrhoea and papilloedema on the right. Repeat CT showed soft-tissue densities in the left ethmoidal sinus.

The results of a second lumbar puncture were: total protein level 24,2 g/l, globulin 3+, glucose 2,1 mmol/l (blood glucose 5,5 mmol/l), 125 lymphocytes, no polymorphs.

The patient died 3 weeks after admission, following a sudden deterioration in his level of consciousness.

At autopsy, a lymphoma involving the leptomeninges diffusely

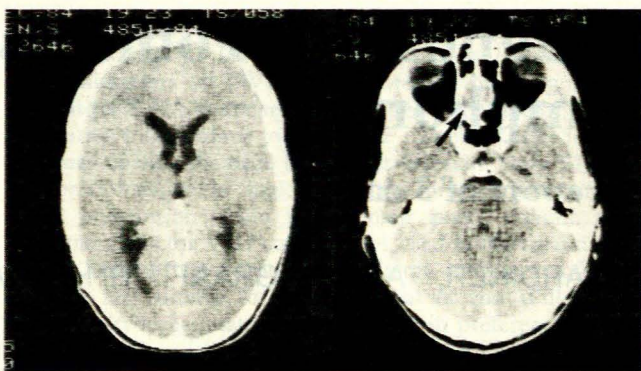


Fig. 3. Case 3 — (left) enhancing lesion of the pineal-superior vermis region; the ventricles are mildly dilated; (right) isodense tissue in ethmoid sinus region (arrow) and fullness of posterior fossa structures (right).



Fig. 4. Case 3 — thoracic cord and nerve roots embedded in tumor, with nodules on the cauda equina.

but most severely over the cerebellum and spinal cord was found; it was apparently primary to the CNS, possibly originating in the spinal cord (Fig. 4).

Discussion

The principal manifestations of headache, backache, radicular pain, cranial nerve palsies and dementia described by Adams and Victor⁷ in carcinomatous meningitis were present in our cases, and it would have been clinically impossible to distinguish between carcinomatous and lymphomatous meningitis. Subacute and progressive spinal and cranial nerve involvement was the most prominent feature in our cases, a point obscured by the degree of pain and weakness of the lower limbs experienced by the first patient. Severe neck stiffness, fever, photophobia, nausea and vomiting so characteristic of acute infective meningitis were uniformly absent, requiring the exclusion of chronic infective meningitides such as tuberculosis, meningovascular syphilis and cryptococcosis.⁶ Similar symptoms may result from cysticercosis of the leptomeninges⁸ and (exceptionally) of the cauda equina.⁹ The neurological complications of vasculitis,¹⁰ sarcoidosis¹¹ and systemic lupus erythematosus¹² may involve both the central and peripheral nervous systems, but were confidently excluded by clinical, radiological and laboratory examinations. Lymphocytic meningoradiculitis (Bannwarth's syndrome)¹³ was thought to

be an unlikely diagnosis because of the absence of both an antecedent tick bite and an erythematous skin rash.

Although the brain and spinal cord have no lymphatic drainage, primary lymphomas, i.e. histiocytic sarcoma or reticulum cell sarcoma, may arise from microglia and this in fact was the pathological diagnosis in case 3. Contiguous spread from extraneural organs is facilitated by the extradural space and its venous plexus: in cases 1 and 2, with primaries in the iliac lymph nodes and stomach respectively, spread probably occurred in this manner.

Only in patient 3 did CT direct our attention to leptomeningeal disease, and even then its full significance was only appreciated retrospectively. The pontine cistern could not be visualised and the brainstem and cerebellum gave an impression of fullness within the posterior fossa while the contrast scan showed enhancement of the pineal gland region and the superior surface of the cerebellum (Fig. 3, right).

Both these features were consistent with the findings of Jaeckle *et al.*,¹⁴ who also emphasised the value of serial CT and reported the occasional findings of enhancing nodules and periventricular oedema. Most authors¹⁴⁻¹⁶ acknowledge the limitations of CT in leptomeningeal malignant disease, in that a normal scan does not rule out the diagnosis, nor can the positive findings of enhancement be distinguished from inflammatory exudates. Our own radiologist reported a polypoid structure in the left ethmoid sinus which was related to the nasal CSF leak and was thought to be tumour (arrow, Fig. 3, right).

The difficulties experienced in performing the lumbar punctures for CSF examination and myelography were in keeping with a process of subarachnoid space obliteration, rather than with poor technique. After failed lumbar approaches in patient 1, successful cisternal myelography demonstrated a total obstruction at L2-3, but the omission of a simultaneous CSF sample for laboratory analysis was unfortunate. In case 2 a decision against myelography was based on the predominance of suprasegmental signs and symptoms together with minimally raised CSF protein levels and lymphocyte counts. Fishman¹⁷ makes the point that up to a quarter of patients will have normal CSF protein concentrations from the first puncture. The explanation offered for the subsequent rise in protein concentration commonly noted with malignant involvement of the CNS is that it results from increased capillary endothelial cell permeability. The frequent association of high protein levels in patients with cord tumour reflects a subarachnoid block in addition to a local increase in vessel permeability. This situation was suspected in patient 3 because of high CSF protein levels and severe interscapular pain. Not unexpectedly, lumbar myelography failed in this case.

Since elevated CSF protein levels are a feature of tumours confined to the parenchyma as well as of diffuse leptomeningeal spread, the CSF glucose value may be helpful in distinguishing between these two conditions: the presence of a low CSF glucose level is reliable evidence of extensive meningeal involvement (hypoglycorrhachia), and increased glucose utilisation is supported by increased lactate levels.¹⁷ A lumbar puncture performed on patient 3 before admission to Tygerberg Hospital showed a CSF glucose level of 0,82 mmol/l (blood glucose 6,6 mmol/l). Repeat lumbar punctures, however, failed to confirm this discrepancy. Lymphocytes dominated CSF cell counts and ranged from 5 to 125/mm³. Routine CSF investigations are performed by technical staff who are trained

to distinguish normal cell types only, so that if malignant disease is suspected the services of a cytologist are required, who in turn needs both a fresh and large sample of CSF. A single lumbar puncture yields less than 50% success in carcinomatous meningitis,¹⁷ and serial taps of up to 6 or more may be needed for diagnosis. The cytologist may use either cytocentrifugation or filtration to concentrate the cells, the latter method being less liable to damage to cell morphology. Our failure to make diagnoses from the CSF is a direct result of incorrect use of a cytological method. The use of diagnostic cytology in such cases should not be underestimated, Balhuizen *et al.*¹⁸ having found it positive in 29 out of 39 patients with leptomeningeal carcinomatosis, which reflects a 75% success rate! Because CSF cytology and bone marrow aspirates were either negative or not done in our patients, we are unable to contribute to the correlation made by Bunn *et al.*¹⁹ that patients with bone marrow involvement are at high risk for the development of leptomeningeal lymphoma.

In conclusion, we feel that the justification for this case study lies in emphasising the clinicopathological concept of diffuse, axial or 'top-to-bottom' spread of leptomeningeal malignancy, and the diagnostic importance of serial CSF cytology.

We are grateful to Mrs A. Allen for secretarial help.

REFERENCES

- Robbins SL, Cotran RS. *Pathologic Basis of Disease*. Philadelphia: WB Saunders, 1979: 1575.
- Henry JM, Heffner RR jun, Dillard SH, Earle KM, Davis RL. Primary malignant lymphomas of the central nervous system. *Cancer* 1974; **34**: 1293-1302.
- Henneman HH, Rauff K, Weiss A. CNS involvement in non-Hodgkin lymphoma: clinical aspects and therapy. *Munch Med Wochenschr* 1981; **123**: 51-52.
- Herman TS, Hammond N, Jones SE, Butler JJ, Byrne GE, Kelvey EM. Involvement of the central nervous system by non-Hodgkins lymphoma. *Cancer* 1979; **43**: 390-397.
- Marshall G, Raesmann U, Van den Noort S. Invasive Hodgkin's disease of brain. *Cancer* 1968; **22**: 621-630.
- Walton JN. Meningitis due to *Cryptococcus neoformans* (*Torula histolytica*). In: Walton JN, ed. *Brain's Diseases of the Nervous System*. 8th ed. Oxford: Oxford University Press, 1981.
- Adams RD, Victor M. *Principles of Neurology*. New York: McGraw-Hill, 1981: 454.
- De Villiers JC. Cysticercosis of the nervous system. *S Afr Med J* 1983; **63**: 769-772.
- Kuper S, Mendelow H, Proctor NSF. Internal hydrocephalus caused by parasitic cysts. *Brain* 1958; **81**: 235-242.
- Mooze PM, Cupps TR. Neurological complications of vasculitis. *Ann Neurol* 1983; **14**: 155-167.
- Delaney P. Neurologic manifestations of sarcoidosis. *Ann Intern Med* 1977; **87**: 336-345.
- Morgan SH, Hughes GRV. Connective tissue disorders. *Medicine International* 1985; **2**: 973-978.
- Wulff CH, Hansen K, Strange P, Trojaborg W. Multiple mononeuritis and radiculitis with erythema, pain, elevated CSF protein and pleocytosis (Bannwarth's syndrome). *J Neurol Neurosurg Psychiatry* 1983; **46**: 485-490.
- Jaeckle KA, Krol G, Posner JB. Evolution of computed tomographic abnormalities in leptomeningeal metastases. *Ann Neurol* 1985; **17**: 85-89.
- Ascheril GF, Hilal SK, Brisman R. Computed tomography of disseminated meningeal and ependymal malignant neoplasms. *Neurology (NY)* 1981; **31**: 567-574.
- Wasserstrom WB, Glass JP, Pisner JB. Diagnosis and treatment of leptomeningeal metastases from solid tumors. *Cancer* 1982; **49**: 759-772.
- Fishman RA. *Cerebrospinal Fluid in Diseases of the Nervous System*. Philadelphia: WB Saunders, 1981.
- Balhuizen JC, Bots GTAM, Schaberg A *et al.* Value of CSF cytology for the diagnosis of malignancies in the central nervous system. *J Neurosurg* 1978; **48**: 747-753.
- Bunn PA, Schein PS, Banks PM, de Vita VT. Central nervous system complications in patients with diffuse histiocytic and undifferentiated lymphoma: leukemia revisited. *Blood* 1976; **47**: 3-10.