

Primary Diffuse Leptomeningeal Gliomatosis

Peter Bailey and Yves Robitaille

ABSTRACT: A review of the literature on primary diffuse *meningeal* gliomatosis (DMG) yielded three cases and we report a fourth. DMG is a syndrome characterized by extensive basal and spinal chronic meningitis with mental confusion, headaches, diplopia, papilledema and cranial nerve palsies. The cerebrospinal fluid (CSF) has a markedly elevated protein content, moderate mononuclear pleocytosis and a normal or low glucose. This picture invariably leads to the diagnosis and treatment of tuberculous or fungal meningitis despite persistently negative cerebrospinal fluid (CSF) cultures. Reaction of exfoliated CSF cells with glial fibrillary acidic protein (GFAP) immunoperoxidase labelled antibody is suggested as a diagnostic tool. A basal meningeal biopsy appears to be the only alternative diagnostic approach.

RÉSUMÉ: Gliomatose Leptomeningée Diffuse Primaire La gliomatose leptomeningée primaire est une entité rare, dont il n'existe que 3 cas bien documentés. Nous en décrivons un quatrième, qui se présenta comme un syndrome caractérisé par une arachnoidite basale et spinale chronique avec confusion, maux de tête, diplopie, papilloedème et paralysie des nerfs crâniens. Le liquide céphalo-rachien (LCR) montra une hyperprotéinorachie sévère, une pleiocytose mononucléaire modérée et une glycorachie normale ou légèrement abaissée. Ce tableau conduit invariablement à un diagnostic de *méningite* TB ou fongique persistente malgré de nombreuses cultures négatives. La GFAP liée à l'immunoperoxidase sur cytologie de LCR apparaît comme une épreuve de grande utilité diagnostique. La seule alternative efficace dans ce contexte serait une biopsie des meninges de la base.

Can. J. Neurol. Sci. 1985; 12:278-281

The accurate diagnosis of neoplastic meningeal disease is becoming more important with the advent of increasingly effective tumour therapy for both extra and intracranial neoplasms (Olson et al., 1974). Meningeal involvement is also recognized as the initial presentation of a small but still significant number of malignancies (Posner, 1978). Primary gliomas confined to meningeal tissues are very rare (Khang-Loon Ho et al., 1981). Sixteen cases have been reported; in 13 of these, evidence of a focal tumour mass led to prompt diagnosis. However, primary diffuse meningeal gliomatosis remains a more formidable diagnostic challenge since, as yet, there are no reports of a satisfactory "in vivo" diagnosis (Khang-Loon Ho et al., 1981; Korein, et al., 1957; Sumi et al., 1968). In this paper we review the clinical management in the light of data derived from the literature and recent experience with a new case.

CASE REPORT

The patient was a 53 year old chemist with a one year history of depression and nonspecific headache. One month prior to admission, he noted increasing headache, fatigue and decreasing ability to concentrate. Three days prior to admission, there was a sudden onset of painless horizontal diplopia. On examination, the only abnormality was a partial left abducens nerve palsy. Past history was unremarkable except for depression, prostatitis and a right L3 discectomy eight years previously.

Initial hematologic and biochemical studies were within normal limits. The chest radiograph revealed old granulomata at both apices of the lungs. Skull radiograph and electroencephalogram were normal. The plain cranial computerized tomograph scan (CT) disclosed a mildly dilated ventricular system and a small low density lesion in the region of the left medial occipital lobe. An infusion CT-scan showed marked enhancement of the tentorial region and, to a lesser degree, of the region of the Sylvian fissures and posterior parasagittal region (Figure 1). A subsequent 4-vessel angiogram was normal. CSF was xanthochromic with an opening pressure of 200 mm water. It contained 167 cells (70 red blood cells and 97 lymphocytes) per mm³. CSF protein was 8.8 g/L, CSF glucose 3.22 mmol/L and serum glucose 6.22 mmol/L. Gram stains, smears and cultures for bacteria, mycobacteria, fungi and parasites were negative. No neoplastic cells were noted.

The patient's mental status remained normal over the first eight days. Subsequently, nuchal rigidity developed with associated bilateral 6th nerve palsies and confusion. He was started on isoniazid and rifampin. By day 13, there were signs of gross mental deterioration. A wedge biopsy taken from the left occipital cortex and overlying leptomeninges showed mild subpial and white matter gliosis without malignant cells. He deteriorated further, and developed areflexia and ataxia, at which time pyridoxine was added. Sequential CT-scans showed progressive ventricular enlargement and on the 25th day, a ventriculoperitoneal shunt was inserted. It subsequently blocked and had to be replaced. The CSF protein rose to 19.0 g/L, at which time a cisternal puncture showed some atypical but not clearly malignant cells. He was then started on prednisone, amphotericin and 5-fluocytosine. Progressive deterioration led to an akinetic mute state and the patient died on the 81st day of hospitalization.

Received April 18, 1985

From the Departments of Neurology and Neuropathology, Montreal Neurological Hospital

Reprint requests to: Dr. Y. Robitaille, Montreal Neurological Hospital, 3801 University Street, Montreal, Quebec H3A 2B4

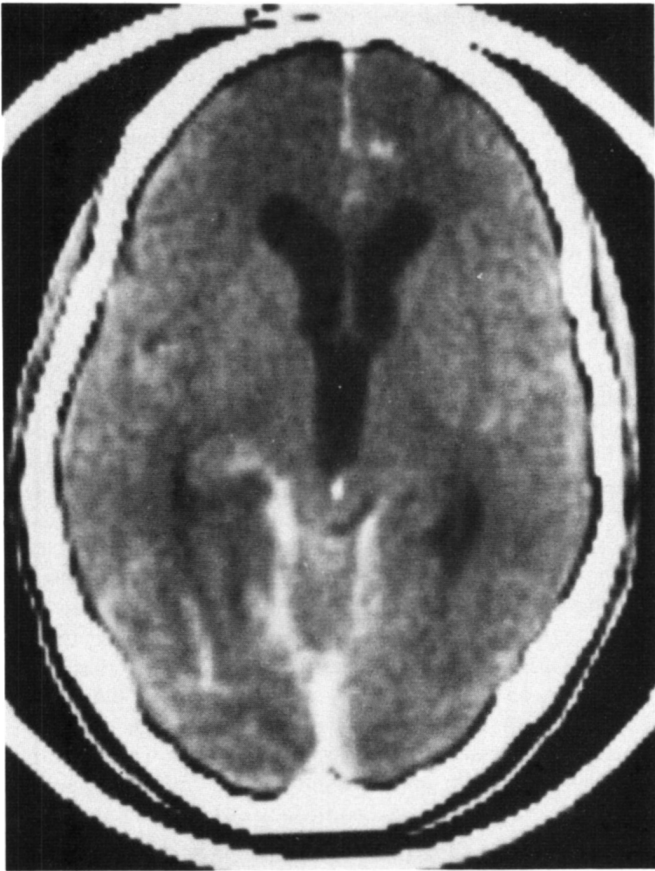


Figure 1 — Infused CT scan disclosing mild ventricular dilatation with a left medial occipital hypodense region and pathological enhancement of the tentorium cerebelli.

PATHOLOGY

A complete autopsy was performed. The brain and entire spinal cord were resected. Numerous representative sections were made and stained with hematoxylin-eosin, the Kluver-Barrera method of luxol fast blue stain for myelin, Holmes Silver Stain, L.C.T., Gram, Grocott, Ziehl-Neelsen, and Giemsa stains. Immunoperoxidase-labelled polyclonal antibodies against IgG, IgA, IgM, C₃, lysozyme and glial fibrillary acidic protein (GFAP) (Dako Corp., Cedarlane Labs., Whitby, Ontario) were applied to three representative paraffin blocks of the lesion according to standard peroxidase-anti-peroxidase techniques. Sections of gliomas and lymph nodes were used as controls. Each test was supplemented with slides challenged against normal rabbit serum antibody. After post-fixation in 3% glutaraldehyde, two representative epoxy resin embedded thin sections were stained with uranyl acetate and lead citrate, then screened with a JEOL 100CXII transmission electron microscope.

General autopsy findings revealed bronchopneumonia of the left lower lobe and splenic congestion. The search for an extracerebral primary tumour remained negative. The brain weighed 1600 grams. A very extensive network of adhesions was noted along the inferior cerebellar surface without evidence of intracerebellar tumour. The dura was thickened but otherwise unremarkable. The brain itself was soft, with diffuse gyral swelling. All major arteries were patent. The spinal cord was entirely covered by a thick gray and yellow exudate which filled

the subarachnoid space with many dural adhesions. The cord itself was soft at all segments.

Microscopically, the brain showed extensive recent anoxic-ischemic damage with marked neuronal necrosis and vascular congestion. Basal and spinal meninges were extensively infiltrated by small neoplastic round and oval shaped cells often organized in a papillary perivascular distribution without luminal invasion. Outside the left medial occipital region, there was little hemispherical meningeal involvement. Multiple sections of cerebellum revealed few foci of subpial invasion. There was focal radicular infiltration (Figure 2). Intramedullary extension was not found despite marked involvement of the cauda equina. There were several microscopic foci of necrosis in the tumour, but no mitotic figures were seen. Rosettes were absent and none of the cells revealed silver-positive processes on Holmes silver stains. All stains for micro-organisms or parasites were negative.

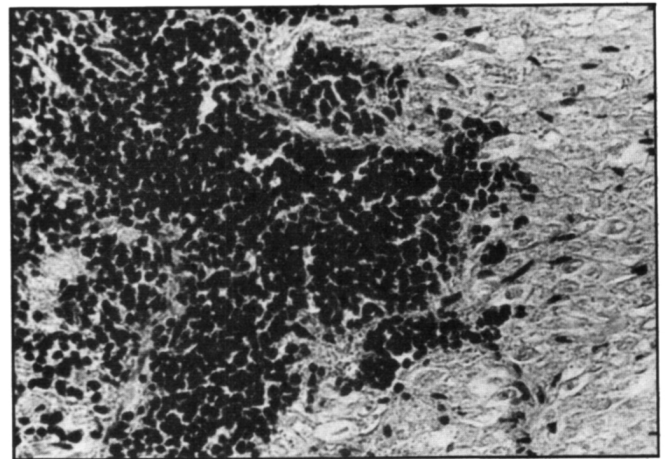


Figure 2 — H.E. Stain x 32. Neoplastic undifferentiated small cells focally infiltrate posterior thoracic nerve root.

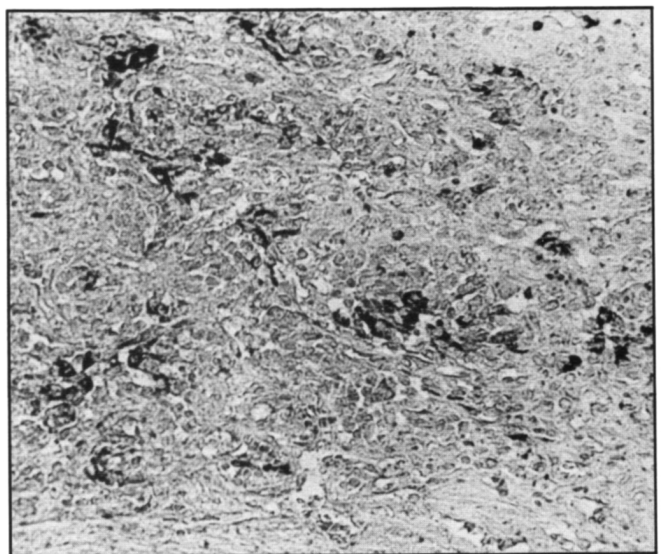


Figure 3 — x32. Representative section challenged against immunoperoxidase labelled GFAP antibody. A few neoplastic cells react strongly to outline abortive processes.

Immunoperoxidase-labelled antibodies revealed that approximately 20% of the neoplastic cells reacted with GFAP (Figure 3). However, reactions with all major classes of immunoglobulin antibodies, C₃ complement fraction and lysozyme were negative. Control slides tested with normal rabbit serum antibody gave no evidence of nonspecific reactions.

Electron microscopy revealed round, sometimes spindle-shaped cells infrequently tied by zonulae adherentes. A few cells showed abortive processes. Cytoplasmic contents were restricted to rare mitochondria, free polyribosomes and short loops of rough endoplasmic reticulum. Intermediate filaments, 80-90Å wide, were visualized in the more differentiated cells with lower nuclear-cytoplasmic ratios (Figure 4).

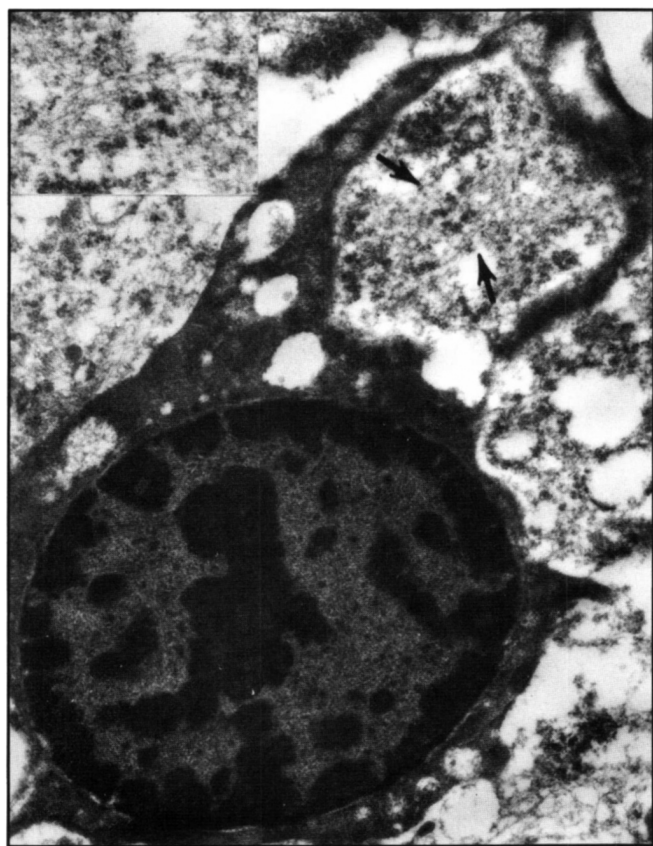


Figure 4 — *x 10,000. Representative electron microscopic picture showing small undifferentiated cells and short processes. Inset upper left displays intermediate filaments in this area outlined by arrows.*

DISCUSSION

Previously reported diffuse meningeal gliomas have been astrocytic or oligodendroglial (Table 1). In the present case, the undifferentiated nature of neoplastic cells, few of which reacted with immunoperoxidase labelled GFAP antibody, suggested a primitive neuroectodermal tumour with partial glial differentiation. Rorke (1983) has recently re-evaluated the classification of this group of tumours and has suggested that they are derived from the subependymal region and may occur throughout the neuraxis. They are considered to occur only in children. The site of origin in the present case appeared to be subarachnoid tissue, in view of the lack of subependymal or primary cerebellar involvement.

The differential diagnosis includes various primary cerebral small cell tumours of adults. Medulloblastomas previously reported in this age range were cerebellar tumours usually lateralized to one hemisphere which could not be documented either clinically or postmortem in our case (Rubinstein and Northfield, 1964). A low density lesion seen on CT-scans in the left medial occipital lobe represented a more extensive focus of meningeal invasion which had remained outside the range of the biopsy. The lack of neuroblastic differentiation in the form of Homer-Wright rosettes or silver positive neurites of the club-shaped types found in pinealoblastomas failed to support a primary pineal tumour or the source of meningeal invasion. By electron microscopy, characteristic synaptic ribbons, microtubular arrays and cilia were not seen (Varakis and Zurhein, 1976) (Fig. 4). Furthermore the lobular architecture and biphasic features provided by large neoplastic cells surrounded by lymphocytes in germinomas were not present. It was also felt that the molding effects of these undifferentiated neoplastic cells and their virtual absence from intracerebral or intramedullary Virchow-Robin spaces were more consistent with neuroepithelial cells than with those of a lymphoma, which rarely display such overwhelming meningeal growth. Immunoperoxidase studies, although confined to heavy and light immunoglobulin chain antibodies, could not confirm a primary cerebral lymphoma. The numerous scattered GFAP reactive cells did not show the extensive processes of hypertrophic astrocytes. Their abortive cytoplasmic expansions and intracytoplasmic intermediate filaments were more in keeping with focal astrocytic differentiation of an otherwise undifferentiated tumour (Fig. 3).

In accordance with previous authors (Bailey, O.T. 1934; Cooper, I.S. et al., 1951; Korein, J. et al., 1957; Sumi, S.M. et al., 1968; Khang-Loon Ho et al., 1981), we favour the possibility that the tumour may have arisen from subarachnoid cell nests. These were studied in detail by Cooper and Kernohan (1951). They found them in only 1% of 100 consecutive autopsies of neurologically asymptomatic patients. Analysis of 80 cases with various congenital malformations disclosed a 25% incidence of heterotopic glial nests in the subarachnoid space. In an unpublished series of well documented focal primary subarachnoid gliomas, Kernohan noted there was a high incidence of minor congenital anomalies including spina bifida occulta, club foot and spondylolisthesis (Kernohan et al., 1951). It is of interest that in the case reported by Korein et al (1957) an Arnold-Chiari malformation was present, which again raises the possibility that subarachnoid nests are possible sites of origin. These nests predominantly harbor mature astrocytes but ependymal differentiation occurred in over half the cases and, in several examples, small round cells were evident.

In the light of previous reports (Table 1), a distinct pattern of presentation has emerged characterized by a prodromal period ranging from 4 to 8 weeks, in which nonspecific complaints of headache, lethargy and subtle changes in mental status occurred, followed by severe behavioral abnormalities and the onset of cranial nerve palsies in two of the cases. Distinct CSF abnormalities developed in all cases, with very high protein levels ranging between 2.0 and 20.0 g/L and a modest pleiocytosis with usually less than 100 monocytic cells. Hypoglycorrhachia was recorded in one case. Hydrocephalus was present in all cases and proved to be difficult to control. Seizures occurred in two of the four patients.

Table 1: Reported Cases of Diffuse Leptomeningeal Gliomatosis

Source	Age/ Sex	Histology	Clinical presentation	CSF Findings	Course*
Korein et al., 1957	17/M	Oligodendroglioma	Seizures, headache, papilledema	Pressure 500 mm Protein 54-400 mg%	18 months
Sumi et al., 1968	61/M	Astrocytoma	Headaches, hallucinations, confusion, somnolence, diplopia (3rd nerve)	Pressure 220 mm Protein 248 mg% ≈Glucose 36/160 mg% ●WBC 14 ▽RBC 300	3 months
Khang Loon et al., 1981	55/M	Astrocytoma	Headache, confusion, papilledema	Pressure 150 mm Protein 680 mg% Glucose 59/160 mg% WBC 92 lymphocytes RBC 652	3 months
Present case	53/M	Primitive neuroectodermal tumour	Headache, diplopia (6th nerve), confusion, ataxia	Pressure 200 mm Protein 880 mg% Glucose 58/112 mg% WBC 97 (mononuclear) RBC 69	3 months

* Course = time from presenting symptoms to death

≈ Glucose = CSF glucose/serum glucose

● WBC = white blood cells

▽ RBC = red blood cells

In all patients the search for an infectious etiology was negative and routine CSF cytology did not demonstrate malignant exfoliated cells. The presence of a nonspecific inflammatory pleocytosis and the distortion of nucleocytoplasmic outlines produced by high CSF protein levels probably contributed significantly to the lack of diagnostic specificity. Weschler et al. (1984) have recently described the use of immunoperoxidase labelled GFAP antibody directed against exfoliated cells as a diagnostic technique in a patient with a known cerebral glioma. This approach may also be effective in the future diagnosis of patients with diffuse primary meningeal gliomatosis. If this is negative a biopsy of the basal meninges would remain the only alternative. The present case and that of Korein et al. (1957) underwent cerebral biopsies with sampling of the associated leptomeninges with nonspecific findings suggesting that future biopsies must focus on regions of maximal clinical and radiological abnormality.

In conclusion, we suggest that gliomatous meningitis be considered in patients with severe basilar meningitis in whom a specific etiology cannot be ascertained. Early and specific diagnostic measures are required to differentiate this condition from chronic infectious processes, since prompt antineoplastic therapy may improve the otherwise dismal prognosis in this condition.

ACKNOWLEDGEMENT

We are indebted to Frances Padden and Arlene Berg for typing the manuscript. Dr. J.D. Stewart provided helpful criticism.

REFERENCES

- Bailey OT (1936) Relation of glioma of the leptomeninges to neuroglial nests: Report of a case of an astrocytoma of the leptomeninges. *Arch Pathol* 21: 584-600.
- Cooper IS, Craig W McK, Kernohan JW (1951) Tumors of the spinal cord: Primary extramedullary gliomas. *Surg Gynecol Obstet* 92: 183-190.
- Cooper IS and Kernohan JW (1951) Heterotopic glial cell nests in the subarachnoid space: Histopathologic characteristics, mode of origin and relation to meningeal gliomas. *J Neuropathol Exp Neurol* 10: 16-29.
- Khang-Loon Ho, Hoschner JA, Wolfe DE (1981) Primary leptomeningeal gliomatosis. *Arch Neurol* 38: 662-666.
- Korein J, Feigin I, Shapiro MF (1957) Oligodendrogliomatosis with intracranial hypertension. *Neurology* 7: 589-594.
- Olson ME, Chemik NL, Posner JB (1973) Infiltration of the leptomeninges by systemic cancer. *Arch Neurol* 30: 122-137.
- Posner JB (1978) The neurological complication of systemic cancer. *Disease-a-month*: April 1978.
- Rorke LB (1983) The cerebellar medulloblastoma and its relationship to primitive neuro-ectodermal tumors. *J Neuropathol Exp Neurol* 42: 1-15.
- Rubinstein LJ and Northfield DWE (1964) The medulloblastoma and the so-called "arachnoidal cerebellar sarcoma". A critical reexamination of a nosological problem. *Brain* 87: 379-412.
- Sumi SM, Leffman H (1968) Primary intracranial leptomeningeal glioma with persistent hypoglycorrhachia. *J Neurol Neurosurg Psychiatry* 31: 190-194.
- Varakis JN and Zurhein G (1976) Experimental pineocytoma of the Syrian hamster induced by a human papova virus (JC). *Acta Neuropathol* 35: 243-264.
- Wechsler LR, Gross RA, Miller DC (1984) Meningeal gliomatosis with "negative" C.S.F. cytology: The value of GFAP staining. *Neurology* 34: 1611-1615.