Primary Diffuse Leptomeningeal Gliomatosis

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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 présente comme un syndrome caractérisé par une arachnoidite basale et spinale chronique avec confusion, maux de tête, diplopie, papilleodème et paralysie des nerfs craniens. Le liquide cérébrospinal (LCR) montrait une hyperprotéinorachie sévère, une pleocytose mononucléaire modérée et une glycérachie normale ou légèrement abaissée. Ce tableau conduit invariablement à un diagnostic de méningite TB ou fungique persistante malgré de nombreuses cultures négatives. La GFAP liée à l'immunoperoxidase sur cytologie de LCR apparait comme une épreuve de grande utilité diagnostique. La seule alternative efficace dans ce contexte serait une biopsie des meninges de la base.


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 occipital region. 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-flucytosine. Progressive deterioration led to an akinetic mute state and the patient died on the 81st day of hospitalization.
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 radiculine 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, 80-90 Å wide, were visualized in the more differentiated cells with lower nuclear-cytoplasmic ratios (Figure 4).

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 spondyloisthesis (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 μL/L and a modest pleiocytosis with usually less than 100 monocytic cells. Hypoglycorrachia 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.

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.
Table 1: Reported Cases of Diffuse Leptomeningeal Gliomatosis

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

* 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.

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REFERENCES