

Primary intracranial leptomeningeal glioma with persistent hypoglycorrhachia

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Metastatic involvement of the leptomeninges by malignant gliomas, such as glioblastoma multiforme and medulloblastoma, is not unusual. However, gliomas grossly appearing to arise in the leptomeninges are rare, and may assume one of two forms: (1) the meningeal tumour may be entirely extracerebral and have no demonstrable connexion with the underlying neuraxis, or (2) it may grow largely in the subarachnoid space, but with definite connexions to the superficial layers of the adjacent cortex. An example of the second type is offered in the present case, where a well-differentiated astrocytoma was grossly identifiable only in the subarachnoid space of the right Sylvian fissure, but microscopically it extended into the cerebral perivascular spaces and invaded the cerebral cortex through breaks in the adventitia-glia membranes. The exact site of origin cannot be determined, but it is assumed that the existence of subarachnoid glial heterotopias facilitated this unusual pattern of growth. In addition, this tumour was associated with persistently low spinal fluid glucose levels, a finding which is usually associated with leptomeningeal involvement by an infectious process or a rapidly growing neoplasm.

CASE REPORT

CLINICAL HISTORY This was a 61-year-old former policeman who was admitted to the Seattle Veterans' Administration Hospital on 18 October, 1963. Since late July 1963, the patient's family had noticed increasing confusion, disorientation, and hallucinations. During the week preceding his admission, they had noted that the patient's right eye was 'turning out', and his admission was precipitated by headache and increasing somnolence.

In the past, the patient had developed bilateral proptosis, but investigation three years before admission revealed normal thyroid function. He had had glaucoma for several years which had left him almost blind. He had

been a moderate to heavy drinker all his adult life. In recent years he had complained of 'pain all over' and had become addicted to Dilaudid.

On admission, the patient was a large, well-nourished, white male who responded to questions with single words or short phrases. The general physical examination was within normal limits except for bilateral exophthalmos and glaucoma. The neurological abnormalities included marked impairment of vision, only light perception on the left and blindness on the right. Because of cataracts the fundi could not be visualized. There was complete internal and external oculomotor nerve palsy on the right. The right pupil measured 4 mm in diameter and the left 2 mm. Both were unreactive to light. There was a questionable left leg weakness with an equivocal plantar response.

Laboratory tests included normal blood sugar, serum protein, alkaline phosphatase, calcium, and electrolytes. Blood V.D.R.L. was negative. The erythrocyte sedimentation rate was 17 mm/hr. The initial lumbar puncture showed a pressure of 240 mm. The cerebrospinal fluid was xanthochromic and contained 14 white cells and 300 red cells/cu. mm; the protein was 248 mg% and the glucose 36 mg%. The electrocardiogram showed sinus tachycardia with ischaemia. Radiograph of the chest was normal. Those of the skull showed demineralization of the entire sella turcica, particularly of its floor, but no enlargement or bony destruction. Pneumoencephalogram was interpreted as showing symmetrical enlargement of the ventricular system, including the third and fourth ventricles. Carotid arteriograms filled both posterior cerebral arteries, and the left was definitely elevated at the base.

Electroencephalogram showed diffuse slowing, particularly in the anterior leads, with occasional random sharp waves which were maximal in the right anterior temporal leads. There was also intermittent diffuse high voltage delta activity.

A trans-nasal sphenoid bone biopsy on 7 November was reported as showing normal marrow.

The patient became more confused and somnolent. On 16 November he developed left parotitis which responded to antibiotics. On 18 November he had the first of several generalized convulsions. Subdural taps at this time were negative. Cerebrospinal fluid examination showed further decrease in glucose to 6 mg%, but no change in cells or

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protein. No organism was demonstrated on smear and culture of the fluid. The E.E.G. showed increased abnormality consisting of left frontal slowing.

The patient became decerebrate and hypotensive and developed bronchopulmonary infection. However, by 25 November, following intensive antibacterial and anti-convulsant medication as well as support for the hypotension, the patient improved and became more responsive. In addition to the right third nerve palsy, he now showed a definite left hemiplegia.

On 4 December the spinal fluid pressure was still elevated; there were only three white cells, the sugar 32 mg%. Cell block of this sample did not show abnormal elements.

He died suddenly on 14 December 1963.

General necropsy findings The autopsy was performed by Dr. Frank Thorne, who found evidence of aspiration pneumonia, passive pulmonary congestion with acute pulmonary oedema, pulmonary emphysema with interstitial fibrosis, Laennec's cirrhosis, and acute adrenal haemorrhage (unilateral). He also noted that the posterior clinoids were eroded away from within by an infiltrating mass in this area. The sphenoid and ethmoid sinuses, the orbit, and the cavernous sinus were free of tumour.

Neuropathological findings The fresh brain weighed 1,600 g. Following fixation in 10% formalin, it showed no evidence of atherosclerosis. The leptomeninges were slightly thickened over both frontal lobes and over the base. There was a moderate degree of bilaterally symmetrical cortical atrophy of the frontal poles. No evidence of transtentorial or cerebellar tonsillar herniation was seen. Coronal sections of the cerebral hemispheres revealed a slight degree of symmetrical dilatation of the lateral and third ventricles. A small area of softening was present in the right insula. In the right Sylvian fissure there was a coating of homogeneous gray-white tissue which spread over the cortical surface and completely encased the blood vessels in this area. This tissue also spread along the medial surface of the right temporal

lobe (Fig. 1a, b) and infiltrated the right oculomotor nerve in the middle cranial fossa, but the nerve was free of tumour as it emerged from the midbrain.

In the depth of the left superior frontal sulcus was an area of recent haemorrhagic infarction measuring approximately 1 cm in its greatest extent. A similar lesion was present in the right parieto-occipital region. No abnormality was visible on sections of the brain stem and cerebellum.

Microscopically, the mass in the right lateral fissure consisted of dense glial tissue (Fig. 2). There were two predominant cell types (Fig. 3): one was a typical fibrous astrocyte with numerous processes well stained by Holzer's technique (Fig. 4) but not by Gridley's reticulin (Fig. 5) or van Gieson's collagen stains. The nuclei of these cells were large, ovoid and vesicular; the nucleolus was not prominent. The other cell type consisted of thin spindle-shaped cells, only a few of which stained for reticulin or collagen. Since all cell types were stained by Holzer's technique, it was not possible to define specifically most of these bipolar cells, but it was the impression that they represented bipolar spongioblasts. The cells were well differentiated, and no mitoses were seen.

There was a definite space containing pia mater separating the leptomenigeal tumour from the underlying cerebral cortex, which contained a marked diffuse gliosis (Fig. 2). At several points, however, glial tissue formed narrow bridges through the pia between the tumour and the cortex. These glial bridges extended into the perivascular spaces in the superficial layers of the cortex. The perivascular spaces were markedly distended by this extension of the tumour, and in a few places the perivascular tumour broke through the adventitial reticular fibres to enter the surrounding brain tissue (Fig. 5), at which point it was impossible to separate neoplasm from diffuse gliosis.

The tumour was also identified in the right oculomotor nerve and in the pituitary fossa. The tumour disrupted the fibres of the oculomotor nerve, and many large macro-

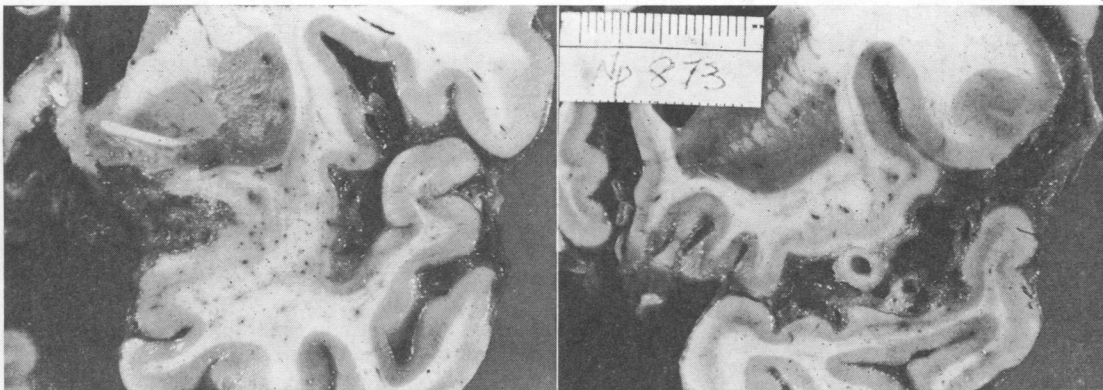


FIG. 1a.

FIG. 1b.

FIG. 1a. Leptomeningeal glioma over the right insular cortex, frontal and temporal opercula, and medial surface of the temporal lobe.

FIG. 1b. Branches of the right middle cerebral artery surrounded by the tumour.

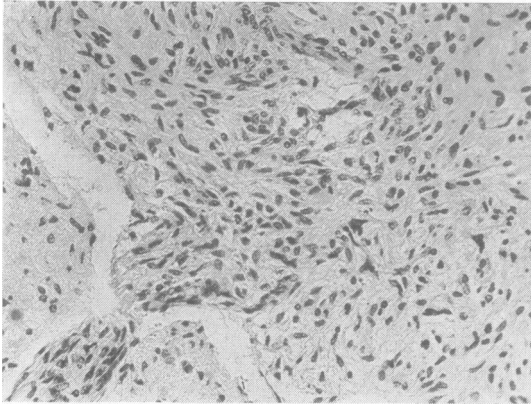


FIG. 2. *Leptomeningeal glioma (right) separated from the underlying cortex (left) by a space containing pia mater. At one point perivascular extension of the tumour is seen. (H and E, $\times 165$.)*

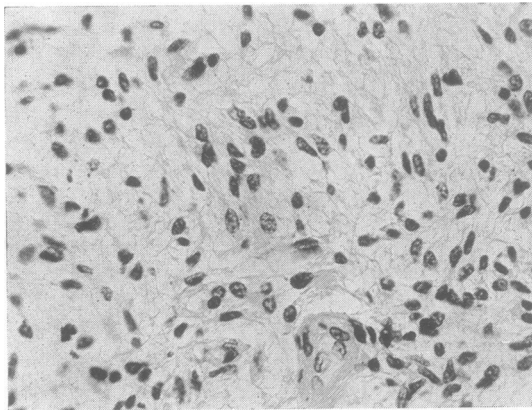


FIG. 3. *Leptomeningeal tumour composed of two predominant cell types, one with vesicular oval nuclei and the other spindle cells. (H and E, $\times 330$.)*

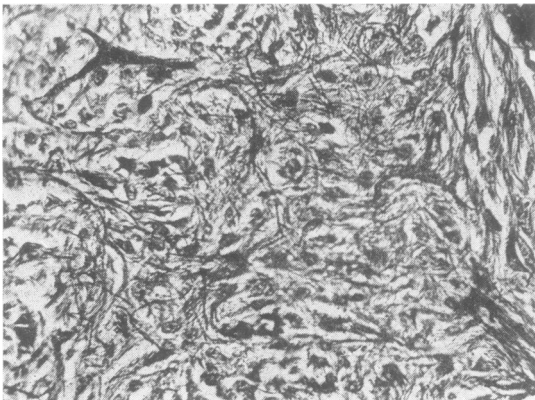


FIG. 4. *Leptomeningeal tumour containing numerous astrocytic fibres. (Holzer, $\times 330$.)*



FIG. 5. *Leptomeningeal tumour. Reticulin fibres are present only in the immediate vicinity of the blood vessels. Tumour distending perivascular space is continuous with the underlying brain only in places where the adventitia is disrupted. (Gridley, $\times 78$.)*

phages filled with PAS-positive granules were present, probably as a reaction to the degenerating myelin. Sections of the sphenoid bone, however, showed only fatty marrow.

Other incidental findings included atrophy of both optic nerves, but with no definite trans-synaptic atrophy in the lateral geniculate bodies. The area of necrosis at the depth of the right superior frontal sulcus involved the deeper layers of the cortex, contained marked vascular proliferation and was heavily infiltrated by gitter cells. The similar small focus of haemorrhagic necrosis in the right parieto-occipital cortex involved its whole thickness and was surrounded by gitter cells around the margins. There were patchy areas of ischaemic degeneration of Purkinje cells of the cerebellum.

DISCUSSION

The presence of a tumour at the base of the brain in the middle fossa was suspected clinically on the basis of the mental changes, the right third nerve palsy, and the abnormalities revealed by radiographs of the skull and angiograms. Involvement of the sub-arachnoid space was suggested by the hypoglycorrhachia. Chronic meningitis, reticuloendotheliosis (Hand-Schüller-Christian type), and basal tumour (primary or secondary) were considered in the differential diagnosis, but repeated cultures, India-ink preparations, and cell blocks of the spinal fluid were all unrevealing. The sphenoid bone biopsy showed normal bone marrow only, and there was no diabetes insipidus. The nature of the suspected tumour could not be established during life.

At necropsy there was a well-differentiated astrocytoma in the subarachnoid space over the right Sylvian fissure which was separated from the under-

lying brain by an intervening pial membrane. However, the perivascular spaces of the superficial cortex was widely distended by extensions of the tumour which invaded the brain through breaks in the adventitia-glia membrane. In addition, there were glial strands between the tumour and the subjacent cortex. Except for diffuse gliosis in the superficial layers in the adjacent cortex, probably due to local compression, there was no evidence of tumour anywhere in the brain. Although one cannot exclude the possibility of origin from the diffuse cortical gliosis (? glioma) or from a small and undiscovered nodule of more definite intracerebral glioma, the appearance of the lesions suggested that this was an example of a leptomeningeal glioma arising from a heterotopic glial nest in the leptomeninges. This tumour extended to the underlying cortex along the Virchow-Robin spaces and, through defects in the pia mater, infiltrated the superficial layers of the cortex. Most of the glial proliferation in the cortex appeared to be a reaction to the tumour.

Leptomeningeal glial heterotopic nests have been known since Wolbach's original description in 1907. Freeman (1926) described heterotopic cortical tissue on the ventral surface of the pons. Buckley and Deery (1929) reported glial heterotopias over the frontal lobe. Cooper and Kernohan (1951) found glial heterotopias in 1% of a series of 100 consecutive necropsies but 25% in association with other central nervous system malformations. In 50 cases of glial heterotopias, 57% were located over the medulla oblongata, 10.5% in the midbrain, 15% in the pons, 20% in the spinal cord, 8% over the cerebellum, and only 4% over the cerebral cortex.

Oberling (1922, 1924) suggested that the meninges were of neuroectodermal origin, the glial heterotopias arising from primitive cells included in the meninges. Sensenig (1951), however, believed that only part of the pia mater was of neural crest origin, most of the leptomeninges being of mesodermal origin. Cooper and Kernohan (1951) thought that the heterotopias resulted from a protrusion of the superficial layers of the spinal cord or brain through a defect in the pia mater, the stalk eventually becoming pinched off.

Leptomeningeal glioma completely isolated from the underlying brain was first described by Bailey (1936). Since that report, Abbott and Glass (1955) and Daum, Le Beau, and Billet (1963) have described similar cases. In the first two cases the tumour was an astrocytoma, in the last an astroblastoma. In 1922 Oberling described a glioma in the subarachnoid space over the cerebellum which was connected to the cerebellar cortex by a series of glial bridges. He suggested that the tumour had arisen primarily in the leptomeninges and had secondarily gained attach-

ment to the underlying cerebellum. A similar tumour, again over the cerebellum, was reported by Walker (1941) in a patient with neurofibromatosis.

Primary leptomeningeal glioma appears to be more common in the spinal canal than intracranially. Among a series of 51 cases of intramedullary spinal tumours, Kernohan, Woltman, and Adson (1931) described three such tumours. In a later publication, Cooper, Craig, and Kernohan (1951) reported 15 cases of primary extramedullary glioma, nine of which were ependymoma, the rest astrocytoma.

Sumi and Lindenberg (1964) described a tumour containing neurons, myelinated nerves, oligodendrocytes, astrocytes, and microglia, lying in the subarachnoid space ventral to the pons, and appearing to have arisen from ectopic pontine tissue. The tumour was continuous with the brain stem in the left upper pontine region and bore a closer resemblance to hamartomata frequently found in relation to the tuber cinereum (Richter, 1951; Bedwell and Lindenberg, 1961) than to leptomeningeal glioma.

The consensus in all these reports is that the tumours described probably arose at a site of a heterotopic glial nest, either in the leptomeninges or on the adjacent surface of the neuraxis.

Histologically, the tumour in our patient appears to have been quite slow growing. It is difficult from the clinical history to estimate the length of time it may have been present. The onset of right oculomotor palsy in the week before admission indicated extension of the tumour to the base of the brain. The left hemiplegia is not adequately explained, but may have been due to the softening in the right insular cortex. This ischaemic necrosis may, like the haemorrhagic necrosis in the frontal and parieto-occipital cortices, have been in a border-zone between the distributions of the major cerebral arteries, and may have resulted from the prolonged hypotension noted a few weeks before death.

Another unusual aspect of this case was the finding of persistently low spinal fluid glucose levels. We have found such low values in some cases of diffuse leptomeningeal infiltration by glioblastoma multiforme and medulloblastoma, and by leukaemic, lymphosarcomatous, and carcinomatous cells. Berg (1953) found that of 57 cases of diffuse meningeal neoplasm of various types reported in the literature, 43 had spinal fluid glucose values of less than 40 mg%. The presence of hypoglycorrhachia in association with this discrete, slowly growing glioma was, therefore, of considerable interest. In the absence of any evidence of an infectious process, either by culture of the spinal fluid or by histological examination of the brain, one must conclude that the

glioma was responsible for this finding. Tegeris and Brandriss (1963) reported a similar finding in association with a cerebellar haemangioma.

The mechanism of hypoglycorrhachia is unclear. In purulent meningitis Petersdorf, Garcia, and Swarner (1959) and Petersdorf and Harter (1961) suggested the phagocytic activity of the leukocytes may be one reason for the fall in spinal fluid glucose. Berg (1953) stated that hypoglycorrhachia was more likely to occur in association with malignant tumours and that the rapidly proliferating tumour cells in contact with the subarachnoid space may be utilizing the spinal fluid glucose. That the hypoglycorrhachia in this case was due to an alteration in the blood-cerebrospinal fluid barrier to glucose similar to that postulated to occur in tuberculous meningitis (Weichsel and Herzger, 1936; Sifontes, Williams, Lincoln, and Clemons, 1953) also seems unlikely with such a circumscribed lesion. Neither of these explanations appear to be applicable to the present case. The reason for the hypoglycorrhachia remains obscure.

SUMMARY

A well-differentiated astrocytoma, presenting grossly in the leptomeninges of a 61-year-old man, is described. The pertinent literature is reviewed, and it is suggested that this tumour arose in a pre-existing heterotopic glial nest in the leptomeninges, since perivascular extension of the glioma occurred in the underlying cerebral cortex. An unusual associated finding was the persistent hypoglycorrhachia.

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