Malignant meningioma metastasizing through the cerebrospinal pathways¹

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SYNOPSIS A 53 year old man presented with a malignant meningioma which was incompletely removed. The tumour subsequently metastasized through the cerebrospinal pathways causing clinical signs through invasion of the cranial nerve roots. Microscopically, the metastatic deposits displayed a papillary pattern and increased anaplastic cytological features.

Meningiomas very seldom metastasize through the cerebrospinal pathways, even when they show malignant histological features and give rise to distant visceral deposits. Only a few isolated instances of cerebrospinal spread have been recorded (see Discussion). The purpose of this paper is to describe a recently observed case, unassociated with extraneural metastasis, in which the cerebrospinal deposits demonstrated an unusual histological papillary pattern accompanied by markedly anaplastic cytological features.

CASE REPORT

The patient, a 53 year old white right-handed male, was admitted to the Palo Alto Veterans' Administration Hospital in August 1971, complaining of disorientation, headaches, confusion, memory loss, gait difficulties, and urinary incontinence. There was no previous history of neurological disease. He had had a nervous breakdown in 1946. On examination, he was oriented in place and person but not in time, exhibited very poor recent memory, perseverated, and was very slow in thought and speech. A hard non-mobile mass was palpable in the mid-frontal region to the right of the midline. Mild papilloedema was present. The left arm was weaker than the right, and his gait was unsteady. Other motor and sensory modalities, including reflexes, were normal. Skull radiographs revealed a parasagittal area of trans-

lucency measuring 4 cm in diameter which involved the inner and outer tables of the right frontal bone, accompanied by new bone formation.

Carotid angiography demonstrated a frontal parasagittal mass measuring 9.5 × 7 cm. At bifrontal

FIG. 1 Surgical specimen. Typical meningioma showing areas of whorling. Haematoxylin and eosin, × 90.

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FIG. 2 Surgical specimen. Invasion of the brain by meningioma. Haematoxylin and eosin, $\times 50$.

FIG. 3 Surgical specimen. Cellular anaplasia and mitotic figures in invasive portion of the meningioma. Haematoxylin and eosin, $\times 360$.

craniotomy, an extensive, soft, highly vascular tumour was found eroding through the calvarium and dura mater, and deeply invading both frontal lobes and the superior sagittal sinus. Tumour implants were apparent on the wall of the frontal horn of the right lateral ventricle. Much of the tumour was removed but complete extirpation was not possible. The histological diagnosis was of a malignant syncytial, occasionally transitional meningioma (*vide infra*). The patient pursued an uneventful post-operative course, with improvement in his gait and partial clearing of his mental confusion. He was transferred to Stanford University Hospital, where he received a constant infusion of 1000 mg bromodeoxyuridine via an indwelling catheter in the right common carotid artery, concomitant with external radiation to a tumour dose of 5500 r over a 36 day period. Desquamation of the right face and scalp complicated therapy, but he remained well until April 1972, when he developed a right-sided lower facial nerve palsy. Carotid arteriography showed mild hydrocephalus but no evidence of tumour. Apart from one generalized convulsion after ethanol intake, the patient had no further trouble until his

FIG. 4 Base of brain at necropsy. Tumour deposits (arrows) in the cerebellomedullary angle.

final admission in June 1972, which was prompted by the rapid development of dysphagia, regurgitation, and dysarthria over the preceding 10 days. On examination, he was dehydrated and undernourished, and showed a persistent right lower facial palsy, now accompanied by peripheral motor involvement of

FIG. 5 Spinal cord at T2 level. Sub-arachnoid tumour deposits (arrows) attached to the nerve roots.

FIG. 6 Spinal cord at thoracic level (necropsy specimen). Anaplastic tumour transgressing the dura mater (left) and permeating a capillary (lower right). Haematoxylin and eosin, $\times 120$. Inset: Capillary permeated by tumour. Haematoxylin and eosin, $\times 360$

the 9th and 10th cranial nerves. Vision, facial sensation, hearing, and movement and sensation of all limbs were intact, and no abnormal reflexes were present. The patient showed slow mentation and spoke with difficulty. A brain scan showed a new space-occupying lesion in the midline in the fronto-temporal area. The patient's last month of life was punctuated by recurrent episodes of aspiration pneumonia, poorly tolerated nasal gastric tube feedings, and progressive physical and mental decline. He died on 10 July 1972.

SURGICAL SPECIMEN Microscopical examination showed the pattern of a syncytial, occasionally transitional meningioma throughout most of the specimen (Fig. 1). However, some of the cells had hyperchromatic nuclei, and mitotic figures were found. In addition, there was invasion of the bone, the superior longitudinal sinus, and the brain

parenchyma (Fig. 2). In the areas of cortical invasion, mitotic figures and necrosis were conspicuous, and there was marked anaplasia of the tumour cells (Fig. 3), characterized by the presence of large nuclei with granular chromatin and prominent eosinophilic nucleoli. The anaplastic tumour cells had an unusually abundant homogeneous, glassy, and brightly eosinophilic cytoplasm with well-defined cell borders.

POSTMORTEM EXAMINATION The general necropsy revealed bilateral bronchopneumonia. In the right frontal lobe there was a large cystic surgical defect, approximately 2.5 cm in diameter, covered by adherent dura mater and extending from the surface of the brain to the lateral ventricle. The base of the cyst was surrounded by brownish necrotic material. Four firm, grey-white subdural tumour deposits measuring up to 2.5 cm in diameter were adherent to the dura mater of the posterior cranial fossa around

FIG. 7 Metastatic meningioma at necropsy. Cellular anaplasia and mitotic figures, similar to Fig. 3. Haematoxylin and eosin, $\times 360$.

FIG. 8 Metastatic meningioma at necropsy. Papillary pattern of tumour, with cells arranged radially around a fibrovascular core. Haematoxylin and eosin, $\times 225$.

the foramen magnum. Both nodular and diffuse greyish subarachnoid growths covered the ventral surface of the medulla and occupied the cerebello-medullary angles (Fig. 4). In the latter site the deposits were attached to the 7th, 9th, 10th, and 11th cranial nerve roots on the right. In the spinal subarachnoid space, small white tumour deposits ranging from pinpoint granular excrescences to masses up to 0.75 cm in diameter were noted at the C8, T1, T2, T7, and L1 levels. Some of these were adherent to the arachnoid membrane, while others were attached to the spinal nerve roots (Fig. 5).

Microscopically, a small focus of residual tumour was found in the floor of the site of surgical resection in the frontal lobe. Distant leptomeningeal spread, with invasion of cranial and spinal nerve roots, was confirmed. At one thoracic level, the subarachnoid deposit had transgressed the arachnoid membrane and the spinal dura mater and capillary permeation by tumour was seen at that point (Fig. 6). In all these areas the histological picture was uniform and resembled the anaplastic pattern found in the areas of cortical invasion of the surgical specimen. The

tumour was composed of large irregular cells with abundant bright eosinophilic cytoplasm and clearly defined borders. The nuclei varied in size and shape, and were hyperchromatic and often multiple; bright prominent eosinophilic nucleoli and mitotic figures were seen (Fig. 7). Some areas demonstrated a prominent papillary pattern formed by radially oriented cells arranged around fibrovascular cores (Fig. 8). The brain around the cystic surgical defect showed radiation changes, characterized by fibrin extravasation, demyelination, spongiosis of the white matter, and astroglial proliferation. Haemosiderin-laden macrophages and gitter cells were numerous.

DISCUSSION

Different criteria have been used to define malignancy in meningioma. These include rapid recurrence, local invasiveness, atypical histological features, high mitotic index, and the production of remote metastases. Recurrence is a

well-known characteristic of meningiomas as a whole, irrespective of other biological or microscopical features, and has been estimated to occur in 21% of cases (Simpson, 1957). This complication appears to be primarily dependent on, and inversely proportional to, the extent to which the tumour can be entirely extirpated, and varies from 9% in those tumours that have been apparently completely excised to 34% in those in which only partial removal was attempted. It therefore does not by itself constitute a firm criterion of malignancy. Local invasion of the dura mater, the great venous sinuses, and the overlying bone is a well-known and frequent characteristic of meningiomas, but is usually associated with benign cellular features and is again not generally regarded as indicating true malignancy (Russell and Rubinstein, 1971). By contrast, invasion of the neural parenchyma is well recognized to denote a malignant trend. Kernohan and Sayre (1952) based their criteria for malignancy in meningiomas largely on histological grounds and have placed the emphasis on giant cells, increased cellularity, and the presence of mitotic figures. The occurrence of giant cells

with hyperchromatic nuclei does not, however, necessarily convey a sinister significance; on the other hand, that of unusually large numbers of mitotic figures is often indicative of aggressive growth and may herald early recurrence (Rubinstein, 1972). The progression of the histological pattern of a typical meningioma to that of a spindle-cell sarcoma (Russell, 1950), to an increasingly anaplastic cytological picture (Riley, 1971), or to a papillary pattern (Russell and Rubinstein, 1971) have all been described as identifying a malignant meningioma.

The development of remote metastases is generally regarded as constituting an absolute criterion of malignancy in meningiomas. Approximately 50 cases with extraneural metastases have been described (Shuangshoti *et al.*, 1970), the most common sites of metastatic spread being the lungs, liver, pleura, lymph nodes, bones, and kidneys. Even rarer is the development of metastases through the cerebrospinal fluid circulation. The interest of the present case lies in the development of this pathway of spread in a neoplasm which demonstrated at the time of its first occurrence a number of cytological

TABLE
REPORTED CASES OF MENINGIOMAS WITH CEREBROSPINAL METASTASES

Authors	Sex	Age (yr)	Site of primary tumour	Surgical procedures	Histological features of primary tumour	Metastases	
						Cerebrospinal	Extraneural
1. Kalm (1950)	M	48	Tentorial	None	Mixed fibroblastic and angio-blastic, invasive	Invading medulla and spinal roots	None
2. Winkelman (1954)	F	60	Sphenoidal ridge	One	Transitional, typical	In ventricle and sub-arachnoid space	None
3. Hoffmann and Earle (1960)	F	39	Frontal	Three	Fibroblastic, poorly differentiated	Invading brain and spinal cord	None
4. Russell and Rubinstein (1963)	M	78	Foramen magnum	One	Endotheliomatous, typical	In leptomeninges of lateral orbital gyrus	None
5. Shuangshoti <i>et al.</i> (1970)	F	21	Occipital	One	Angioblastic, malignant	In leptomeninges of spinal cord	Lung, thyroid, breast, lymph node, retro-peritoneum, vulva
6. Riley (1971)	F	38	Occipital	Four	Fibroblastic, malignant	To cauda equina	Lungs
7. Miller and Ramsden (1972)	M	45	Frontal	Two	Transitional, malignant	To cauda equina, brain stem, cranial nerves and choroid plexus	None
8. Present case	M	53	Bifrontal	One	Syncytial and transitional, malignant	To dura mater of skull and spinal cord, in leptomeninges of medulla, cerebellum, and spinal cord, invading nerve roots	None

features that already raised the suspicion of malignancy and became more evident in the subsequent recurrence and in the cerebrospinal deposits.

As far as we are aware, the literature contains seven previous reports of meningiomas that developed cerebrospinal metastases (Kalm, 1950; Winkelman, 1954; Hoffmann and Earle, 1960; Russell and Rubinstein, 1963; Shuangshoti *et al.*, 1970; Riley, 1971; Miller and Ramsden, 1972). The main features of these cases, as well as our own, are shown in the Table. In six of the eight cases, the development of cerebrospinal metastases was associated with cellular features of malignancy that were already apparent in the original neoplasm, and the deposits demonstrated the same aggressive character by locally reinvading the neural parenchyma or the nerve roots. In addition, two of these cases had distant metastases in the lungs. In two of the eight cases, however, both the original tumour and the metastases were histologically benign. In the case of Winkelman (1954) a sphenoidal ridge meningioma was removed and, at necropsy four years later, in addition to recurrence of the original tumour, numerous microscopic whorls of tumour cells, duplicating the original meningioma, were seen wedged in the subarachnoid space between the folia of the cerebellum and floating free within the ventricular system. In the case of Russell and Rubinstein (1963) a single metastasis was discovered in the subarachnoid space underlying a lateral orbital gyrus a few days after partial removal of a meningioma of the foramen magnum. It is open to question whether in these last two cases the deposits in the cerebrospinal pathway should, in the absence of other malignant characteristics, be regarded as aggressively spreading metastases rather than as benign, passively transported seedings. The latter have been reported in other central nervous system tumours, such as ependymomas (Fokes and Earle, 1969) and choroid plexus papillomas (Russell and Rubinstein, 1971). Why cerebrospinal seedings or, alternatively, metastases, should occur so infrequently in meningioma is unclear if one considers how often meningeal tumour cells gain access to the cerebrospinal fluid pathways both during their growth period and at the time of surgical intervention. Although the cerebrospinal fluid would

be expected to provide a good culture medium for tumour cells, it is apparent that tumour texture and friability may play a greater role in determining the potential for cerebrospinal dissemination than either the location or the intrinsic cytological character of the primary nervous system tumour (Russell and Rubinstein, 1971).

The present case falls into the first of these two categories—namely, the one in which malignant cytological features were present in both the primary tumour and the remote deposits. In seven of the cases tabulated in the Table the development of cerebrospinal metastases occurred after one or more previous operations. The case of Kalm (1950) is exceptional in that the primary tumour was first discovered at necropsy and metastases had taken place in the absence of antecedent surgical procedure. This extraordinary occurrence has been noted in a few other neoplasms of the central nervous system (Rubinstein, 1967; Anzil, 1970). An unusual feature in our case, similar to the case of Kalm, was the production of cranial nerve symptoms due to the direct invasion of the cranial nerve roots by metastases. This contrasts with the more usual causes of cranial nerve signs, which are attributable either to local pressure on the nerves or to increased intracranial pressure (Needham *et al.*, 1970).

Two further features indicative of aggressiveness of growth were noteworthy in our case. The first consisted in the development of distant subdural deposits in the posterior fossa, an event which is probably related to the transgression of the dura mater by the subarachnoid tumour at one or more points, as demonstrated in the thoracic region in this instance. A similar phenomenon has been reported in the case of medulloblastoma with extensive metastases in the subdural space (Koenig, 1971). The second feature of interest is the demonstration of capillary permeation by tumour at the site of transgression of the spinal dura mater by growth. The significance of this finding is, however, limited, in view of the frequency with which meningiomas are known to permeate the venous sinuses, as demonstrated at the primary site of occurrence in this case.

Microscopically, our case showed the typical pattern of a classical syncytial and occasionally

transitional type of meningioma in the primary tumour, but areas with more atypical cellular features were also present. The anaplastic character of the tumour was more evident in the metastatic deposits. The same phenomenon has been described in the cases of Riley (1971) and of Hoffmann and Earle (1960). In Riley's case, progressively more anaplastic histological features were noted in the successive recurrences of a meningioma which spanned a period of 16 years. Of particular interest in our case was the microscopical appearance of a papillary pattern, a feature originally noted by Cushing and Eisenhardt (1938) in a patient with a recurrent meningioma, who presented with pulmonary metastases at necropsy after 17 operations. Subsequent observations by Russell and Rubinstein (1959) and Kepes *et al.* (1971) have confirmed the occasional development of this phenomenon in extraneural metastases of malignant meningioma. Russell and Rubinstein (1971) have briefly noted the same papillary pattern in the original tumour of four cases of malignant meningioma. A detailed review of a further series studied in this department has confirmed the association of this microscopical pattern with other cytological features of malignancy and with unusually aggressive clinical behaviour (Ludwin *et al.*, in preparation).

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