Development of Extracranial Metastases from a Malignant Astrocytoma in the Absence of Previous Craniotomy*†

Case Report

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The occasional development of extra-neural metastases from an intracranial glioma is now well recognized. It is widely agreed, on clinical and experimental grounds, that the determining factor in this process is access of the tumor cells to the lymphatics, or to veins outside the nervous system.\textsuperscript{14,15} Surgical intervention, often in the form of repeated craniotomies, is presumed to play a decisive part in providing this access. Some 50 acceptable examples of glioma meta-stasizing outside the nervous system are now on record, but not a single well-documented case can be found in which some form of surgery did not precede this complication. Many of these reports point to the massive extracranial encroachment of the growth through the operative defect as a probable important contributory factor in the development of distant deposits.

In 1959, a case was recorded of a metastasizing cerebellar medulloblastoma in which the pathway of extracranial extension and metastasis was demonstrably independent of the site of previous craniotomy.\textsuperscript{13} A large frontal secondary mass had excavated the orbit and the ethmoidal sinus, and this in turn had provided the route for blood-borne and lymphatic dissemination.

We are reporting a further example of malignant glioma that developed extra-neural metastases through a pathway which had not been opened by an antecedent decompression. It is, to our knowledge, the first on record in which this complication, verified at postmortem, arose in the absence of any surgical procedure.

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Case Report

Clinical History. A 37-year-old man was admitted on July 25, 1964, following three generalized clonic fits. After the first of these, weakness was noted in the left leg; the third fit started with twitching of the right leg. No abnormal physical signs were found. Lumbar puncture yielded clear cerebrospinal fluid under a pressure of 240 mm, with one white cell and a protein content of 44 mg/100 ml. Skull x-ray, brain scan, and electroencephalogram were normal, and the patient was discharged on August 4 on anticonvulsant medication.

He was re-admitted 16 days later, following two further right-sided seizures. The right tendon reflexes were slightly increased, there was slight dysphasia, and the plantar responses were flexor. An electroencephalogram and brain scan were again normal, but carotid arteriograms disclosed a slight shift of the pericallosal arteries to the right, with premature and protracted arteriovenous filling above the corpus callosum. A pneumoencephalogram demonstrated marked depression of the roof of the left lateral ventricle in its mid-portion. A left parasagittal intracerebral tumor was diagnosed. Because of its location in the medial aspect of the dominant hemisphere, it was felt that any operative procedure at this stage would carry a considerable risk of severe and permanent damage to motor and speech activity. It was decided to begin a course of radiotherapy and to withhold surgery as long as the patient's condition did not deteriorate. Therefore no biopsy was performed; 6075 rads were delivered in 50 days by 6-MEV x-rays through wedged anteroposterior and opposed lateral ports to the left parietal area.

The patient remained in good health and seizure-free until December 1, when he had a minor fit involving the right arm. A brain
scan on December 9 was again normal. In the subsequent 6 weeks, he developed blurring of vision, unsteadiness of gait, and dysphasia. By July 1965, the seizures had recurred with increasing frequency, and he was unable to work.

He was re-admitted on August 15 in a lethargic state, with a right-sided spastic hemiparesis affecting the leg more than the arm. There was some impairment of cortical sensibility on the right. On his last admission, on September 3, he was thin and pale, and complained of severe low-back pain. He pursued a steadily downhill course and developed bladder spasms. His hemoglobin dropped from 13.0 to 7.4 mg% in 2 months, and he died in coma on December 15, 1965, 17 months after the onset of symptoms.

**Gross Postmortem Examination.** The left cerebral hemisphere was enlarged and its convolutions flattened. The left medial frontoparietal region was occupied by an intracerebral tumor (Fig. 1) which measured 3×3.5×5 cm and extended to the surface, where it adhered to the thickened leptomeninges. Most of it was yellow and necrotic, soft, ragged, and focally hemorrhagic, but its peripheral portions were firmer, granular, grayish-white, and poorly demarcated from the adjacent white matter. At its rostral and caudal ends, the cortex of the superior, medial frontal, and parietal regions was broadened and pale, and showed complete loss of demarcation from the underlying white matter, suggesting diffuse replacement by an astrocytoma.

Tumor had invaded the dural leaflet along its medial convexity and spread along its inner surface, where it was firm, grayish, and granular. The superior longitudinal sinus was occupied by growth along its middle third (Fig. 2).

Behind this largely necrotic mass and laterally to it, the left centrum ovale at the level of the splenium was softened, sunken, waxy-yellow, and occasionally spotted with tiny hemorrhages, suggesting diffuse irradiation damage. No metastases were found in the ventricles or in the leptomeninges of the brain and the spinal cord.

Examination of the rest of the body revealed absence of red marrow in the bodies of the thoracic, lumbar, and sacral vertebrae, and replacement by grayish-yellow sclerotic growth (Fig. 3). A separate mass of firm grayish-white tumor, approximately 10 cm long by 1.5 cm thick, occupied the abdominal para-aortic region and had invaded the psoas muscle. Four enlarged pelvic, two enlarged inguinal, and one pancreatic lymph node were replaced by similar tumor. The lungs showed focal purulent bronchopneumonia. The spleen was slightly enlarged and weighed 260 gm. The kidneys were congested and flabby, and showed ill-defined red blotches throughout the medulla. The other organs were normal.

**Microscopic Study.** Sections from the intracerebral tumor revealed an extensively necrotic glioma displaying all the stages from a well-differentiated to a highly malignant astrocytoma. The cingulate cortex and white matter were diffusely infiltrated by small stellate glial cells forming microcysts in relation to which fine and coarse neuroglial fibrils were well demonstrated with Mallory's phosphotungstic-acid hematoxylin (Fig. 4). In many other areas, considerable dedifferentiation was found, with increased cellular density, hyperchromatism of the nuclei, mitotic figures, and multinucleated giant-cell formation. The astrocytic character of the tumor was, however, often preserved (Fig. 5), and neuroglial fibrils remained demonstrable. No pseudopalisades were found. Anaplastic cells infiltrated the leptomeninges, transgressing the dura in places and extending beyond it. The lumen of the superior sagittal sinus was occupied by tumor mixed with thrombotic material, some of which was fresh, some organized and re-canalized.

In addition to the considerable necroses, widespread alterations were found in the tumor and the adjacent edematous white matter. These consisted of punctate hemorrhages, thromboses in small and large veins, some of which had a telangiectatic appearance, focal fibrinoid necroses of the blood vessel walls, and transudation of fibrinoid material throughout the brain parenchyma. There was also, in the surrounding cortex and white matter, marked astrocytic hyperplasia, spongy vacuolation of the subcortical bands, and multinucleation and giant-cell formation of scattered neuroglial elements with nuclear hyperchromasia and atypicality. These changes were interpreted as the result of irradiation.

The vertebral bone marrow was extensively
Fig. 1. Left medial frontoparietal intracerebral tumor. Coronal section.

Fig. 2. Dura from cerebral convexity, showing invasion of superior sagittal sinus by tumor.

Fig. 3. Replacement of lower thoracic and lumbar vertebral bodies by tumor.
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Infiltrated by small anaplastic glioma cells (Fig. 6). The residual marrow showed myelofibrosis, and there was almost complete absence of hemopoiesis.

The pelvic and pancreatic lymph nodes and the large retroperitoneal mass were largely replaced by secondary malignant astrocytoma which displayed the same anaplastic features as the primary site and included a number of large multinucleated giant cells (Fig. 7). In the retroperitoneal mass and pancreatic lymph node, several veins were permeated by tumor (Fig. 8).

The spleen, kidney, liver, and adrenal gland showed active extramedullary hemopoiesis, with various primitive forms suggesting hemocytoblasts and derivative components, as well as a number of nucleated erythrocytes. Scattered megakaryocytes were also found throughout these organs. In addition, the kidney was the seat of a severe chronic pyelonephritis.

The lungs showed purulent bronchopneumonia. Ten sections failed to reveal microscopic tumor emboli.

Discussion

The interest of this case lies in the exclusion of antecedent craniotomy as a possible mechanism for the extracranial extension of a glioma, and in the demonstration that the local conditions determining such a development may in time be met in the natural course of the tumor’s progress within the cranial cavity. It is evident that direct invasion of the superior longitudinal sinus by tumor provided the pathway for distant dissemination. This event acquires special significance if it is recalled that spontaneous
dural sinus invasion by a malignant glioma is extremely uncommon. A single example has been briefly recorded elsewhere,\textsuperscript{14} in which a left parietal glioblastoma penetrated the adjacent sagittal sinus and the tributary veins of the region (postmortem examination in that case was unfortunately restricted to the head). The rarity of this event is presumably due to the structure of the venous sinuses, which are enclosed in dense dural tissue, and to the natural resistance of the dura to penetration by a subjacent glioma. Even when the glioma has become firmly united to the dura as a result of leptomeningeal invasion, microscopic examination of such cases reveals that only the inner layer of the dura is infiltrated. The smaller veins within the central nervous system, on the other hand, are poorly supported by the yielding tissue which surrounds them, and their collapse ahead of the advancing tumor has been postulated to be the reason why they too are virtually never permeated by gliomas.\textsuperscript{16} Whatever the explanation, a contrast is offered here to the behavior of meningiomas and pituitary adenomas. Venous and dural sinus permeation is not infrequent in these tumors, but since it has usually not resulted in remote metastases it has not been considered significant.

Yet, in view of the several examples of meningioma and pituitary adenoma which developed extracranial deposits in the absence of craniotomy,\textsuperscript{4,14} we must presume that such penetration provides a natural pathway for distant spread in some cases.

In previously-operated gliomas, invasion of a main sinus or of meningeal veins has been recorded at the primary site in at least six examples with extraneurial metastases.\textsuperscript{6,8–10,13,15} Probably in these instances surgery has, through the production of an artificial defect in the dura, mechanically facilitated infiltration and transgression of this tissue by tumor; surgery may also have made metastases more likely by simply prolonging the life of the patient. In a number of other cases in this group, venous permeation was demonstrated only in distant metastases, particularly in the lungs.\textsuperscript{1,3,5,7,11} The invasion, as in the present example, of veins within a secondary paravertebral mass was illustrated in a metastasizing glioblastoma by Wisiol, \textit{et al.}\textsuperscript{17} Collectively therefore, these reports suggest that although venous permeation by a glioma is extremely rare, it should, when demonstrated at the primary site, be regarded as a harbinger of distant dissemination.

The spontaneous invasion of the superior
longitudinal sinus in the natural course of the malignant astrocytoma’s evolution was, in our case, presumably determined by the combination of three favorable circumstances: the proximity of the medial frontal-parietal tumor to the dura and the related venous sinus; the histological type of tumor, consistent with a somewhat slower clinical progress than in the classical glioblastoma; and the effects of irradiation which, by controlling the tumor growth within the cerebral hemisphere and prolonging survival, may have provided the time interval necessary to permit transdural spread. The predilection of secondary deposits for the vertebral marrow and the para-aortic, pelvic, and inguinal lymph nodes, combined with the absence of demonstrable tumor deposits in the pulmonary circulation, suggest that the spread may have first been blood-borne to the spine by way of the vertebral system of veins and then subsequently directed to the regional lymph nodes.

The presence of a myelofibrosis of sufficient severity to cause clinical anemia and to stimulate extramedullary hemopoiesis is noteworthy. In this case it resulted from the vigorous fibroblastic reaction evoked in the bone marrow in response to its permeation by glioma cells. A similar reaction has been observed microscopically in examples of cerebellar medulloblastoma with extraneural metastases, and, clinically, a severe anemia was also found terminally in such cases.

**Summary**

We have reported a case of malignant astrocytoma which spontaneously invaded the superior longitudinal sinus and metastasized to the vertebral marrow, and to the aortic, pelvic, and inguinal lymph nodes. We believe this to be the first report of an intracranial glioma which spread in this manner in the absence of a previous surgical procedure.

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**References**