EXTRACRANIAL METASTASIS OF Glioblastoma Multiforme

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(Received for publication July 20, 1960)

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XCEPT for meningiomas, which often infiltrate the dura mater and skull, one of the most outstanding and well-established features of primary intracranial tumors is their tendency to remain concealed within the dural sac, inside the craniospinal bony cavity. This usually holds true even when a recurrence develops after operation or when a glioma spreads by way of the cerebrospinal fluid pathways, as occurs often with medulloblastomas, ependymomas, oligodendrogliomas, and sometimes with sarcomatous involvement of the leptomeninges.

Nevertheless, exceptions to this rule may occur and one of us reported in 1952 a case of very vascularized primary sarcoma (angiosarcoma) of the cerebellum in a 4-year-old boy which was removed surgically. A course of deep roentgen-ray therapy totalling 9,000 r was given after the operation. A year and a half later, a growth had developed in the muscles of the neck. The tumor, 5×2×3 cm. in size, was removed and a full course of roentgen-ray treatment totalling 10,000 r was given immediately after the second operation. Microscopical sections demonstrated that it was a fibrosarcoma. Investigations carried out to detect neoplastic growth elsewhere in the body gave negative results and the patient, who now has been followed for over 8 years, still is in good health. Therefore, it seems that the cerebellar sarcoma was a primary one, and the growth outside the skull, a metastasis.

Earlier than this, the same senior author saw a cerebral glioma in a young adult with a long-standing history. At operation some tumor was found underneath the galea, outside the skull. Unfortunately, this patient was operated upon shortly after the end of the Spanish Civil War, and the pathological specimens were lost. However, microscopical description of the tissue found outside the bone, as well as that within the brain, supported the diagnosis of glioma.

In reviewing the literature we have been able to collect 81 cases of primary intracranial tumors and 1 of the cauda equina that gave rise to metastasis outside the cerebrospinal cavity.

As always happens when surveying the literature covering a long span of time (1886–1959), there are some cases in which the histopathological identification of the lesions is difficult to establish because of insufficient data, as in the case reported by Lindner under the diagnosis of “dural endothelioma” with metastasis in the urinary bladder; 1 published by Davis of “spongioblastoma” of the left temporal lobe with metastasis in the right arm, lymph glands of the axilla, wall of the chest and lung, and 1 of “glioblastoma” with pulmonary metastasis reported by Mittelbach. Lindner’s case, as pointed out by many authors, could have been one of urinary carcinoma with metastasis to the brain and the other 2, as stated by Willis, pulmonary carcinomas with cerebral metastasis.

In other instances there may have been merely a co-existence of two different tumors, as in the case reported by Wohlwill of a cerebellar medulloblastoma associated with a gangioneuroma in a supraclavicular lymph node, and the first case of Barden and...
Lewey in which the metastasis looked like an Ewing's tumor. The authors thought the latter could represent metaplasia, but Willis doubted that this could happen.

There are also cases in which the metastases were not verified histologically—the cases of medulloblastomas reported by Pendergrass and Wilbur and Russell and Rubinstein, of a cerebral oligodendroglioma, in which a node developed in the neck; and Pendergrass and Wilbur's case of endothelioma of the anterior and middle fossae.

The difficulty is greater when the reports deal with tumors classified as chorionepitheliomas of the pineal region. The case of Goldzieher and Case 1 of Tompkins et al., in which there were metastases in the lungs, seem to be well proved, but Case 2 of the latter authors is doubtful, because the seminoma found at necropsy could have been the primary lesion. Even more difficult to recognize are some of the cases of meningial fibroblastomas and fibrosarcomas, such as those reported by Dérvéci et al., Brandt, and Baumann which pose the question as to which was the primary lesion, the cerebral or the extracranial. The same is true of the melanoma in the right temporal lobe and lung reported by Foot and Zeek (Case 1), and of the pituitary adenocarcinomas reported by Gilmour and Köhlmeyer, the former showing associated tumors in the liver and urinary bladder and the latter supposed metastasis in the liver.

Finally, there are cases that we know only by references, such as the fibrosarcoma of the Rolandic area with metastasis in the lung, reported by Power in 1886; the medulloblastomas with metastasis to bone cited by Zülch; the meningioma of Dublin the meningioma of Dublin with metastasis in the lung and pleura; and the cases of meningioma with metastasis in the lung, and meningial fibrosarcoma with metastasis in the kidney, reported by Christiansen et al.

Wilkelman and Mastragostino in 1952 made a thorough study of the problem of intracranial tumors with extracranial metastasis. The first authors collected 45 cases from the literature, but considered as well proven only the 6 cases of meningiomas reported by Towne, Cushing and Eisenhardt (case of Dorothy May Russell), Jurow, Russell and Sachs, Dublin, and Hamblet and 1 of hemangioblastoma (Abbott and Love). All the others, including the gliomas, were considered as proven insufficiently. Mastragostino collected 30 cases from the literature, to which he added a personal observation of an ependymoma of the right lateral ventricle with pulmonary metastasis. He did not take into account the cases of malignant pituitary adenomas or adenocarcinomas, and made only brief mention of 11 more cases which he considered as proven insufficiently or known merely by references. The same year Willis, in his interesting book *The Spread of Tumours in the Human Body*, referring to metastases from gliomas, stated that "it is doubtful if lymph-borne or blood-borne metastasis outside the nervous system and its membranes has ever occurred."

Table 1 shows the histological types in the 81 cases of supposed primary intracranial tumors with extracranial metastasis that we have been able to find in the literature. In 52 the pathological identity seems well estab-

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**TABLE 1**

*Intracranial tumors with extracranial metastasis*

<table>
<thead>
<tr>
<th>Histological Type</th>
<th>Proven Cases</th>
<th>Doubtful Cases</th>
<th>Total</th>
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<tr>
<td>Gliomas</td>
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<tr>
<td>Medulloblastomas</td>
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<tr>
<td>Ependymomas</td>
<td>8</td>
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<tr>
<td>Glioblastomas multiforme</td>
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<td>8</td>
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<tr>
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<td>1</td>
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<td>3</td>
</tr>
<tr>
<td>Astroblastomas</td>
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<td>1</td>
</tr>
<tr>
<td>&quot;Glioma&quot; not classified</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>33</strong></td>
<td><strong>29</strong></td>
<td><strong>62</strong></td>
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<tr>
<td>Meningeal tumors</td>
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<tr>
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<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Pineal tumors</td>
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<td>4</td>
</tr>
<tr>
<td>Tumors of choroid plexus</td>
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<tr>
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<td>2</td>
<td>—</td>
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<tr>
<td>Carcinoma</td>
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<tr>
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<td>1</td>
</tr>
<tr>
<td>Pituitary adenocarcinomas</td>
<td>—</td>
<td>10</td>
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</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>52</strong></td>
<td><strong>29</strong></td>
<td><strong>81</strong></td>
</tr>
</tbody>
</table>

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A. LEY, D. CAMPILLO AND C. OLIVERAS
lished, being questionable in 29. The largest group is constituted by the gliomas, 33 cases, followed by the meningeal tumors, 29, which comprise a rather complex group that includes not only the common meningocytic or exothelial meningiomas, but also the sarcomatous growths arising from the meninges and from the perivascular connective tissue of the cerebral blood vessels.

Lately we have been able to observe 2 cases of glioblastoma multiforme: 1 with an orbital extension and the other invading the dural sinuses and metastasizing to the lymph nodes of the neck. A brief summary of their histories follows.

CASE REPORTS

Case 1. Emidgio N.Z., a 28-year-old man, came to the Neurosurgical Clinic of the senior author on March 22, 1958. The main complaints were headaches and vomiting for 8 months. During the last month he had also noticed diplopia, blurring of vision and tinnitus aurium.

Examination. The patient showed mental dullness. There was mild rigidity of the neck. Visual fields showed concentric reduction, more marked in the upper right quadrants. There was bilateral choked disc, more marked on the left, where some hemorrhages could be seen. There was mild generalized hypotonia with absence of tendon reflexes and preservation of the cutaneous abdominalis. The left plantar response was normal, while the right could not be elicited. Blood pressure was normal. Electroencephalogram showed irritative signs in the left temporal leads. Roentgenograms of skull and chest were normal. Left carotid angiography showed upward displacement of the middle cerebral artery (Fig. 1). The anteroposterior projection showed the anterior cerebral artery displaced towards the right. In the floor of the middle fossa, behind the carotid artery, some abnormally large and irregular vessels could be seen (Fig. 1). These vessels were not so well visualized in the anteroposterior views, but they seemed to be situated at the base of the temporal lobe. A diagnosis of left temporal tumor was made.

Operation. On March 31, 1958 a large infiltrating glioma of the left temporal lobe was disclosed. The tumor, which invaded the whole anterior pole of the lobe, extended medially to the uncus and hippocampal gyrus. An extensive lobectomy, which apparently included most of the tumor, was done, leaving the temporal horn of the ventricle opened.

Microscopical Examination. The growth removed at operation was a very densely cellular tumor with marked polymorphism of nuclei and cytoplasm. Its boundaries were ill-defined and here the neoplastic cells were intermingled with fibrous astrocytes (Fig. 2). Numerous mitoses, some of them atypical, were present. Silver stains showed a very rich network of glial fibrils. There were extensive areas of necrosis and hemorrhage. The tumor was rich in blood vessels, some being very large, with abnormal walls covered by thick layers of reticulin. Some vessels were sur-

Fig. 1. Case 1. Left carotid arteriogram, lateral view.
rounded by glial cells with sucker feet, resembling astroblasts (Fig. 3). Some areas were composed mainly of spongioblasts, with pseudopalisading. In others astrocytes and undifferentiated elements predominated. Very large cells with multiple nuclei (Fig. 4) were present. Histological diagnosis: glioblastoma multiforme.

Postoperative course was uneventful, except for a transitory disturbance of speech, which disappeared in a few days, leaving only a mild nominative defect. A course of deep roentgen-ray treatment totalling 6,000 r was given and the patient was discharged from the hospital much improved.

Readmission. He reentered the hospital 4½ months later because in the previous week a progressive and painful swelling had developed in the left orbital region. The eyeball protruded slightly and the eyelids were swollen (Fig. 5). We thought it might be an inflammatory process of the orbit (cellulitis) but the ophthalmologists did not agree with this diagnosis. Roentgenograms showed no abnormality in the optic channel, superior orbital fissure or posterior walls of the orbit. Left carotid angiography showed signs of the old tumor, which did not appear so vascularized as before operation, the abnormal vessels having disappeared. Nothing abnormal was seen in the orbital region.

2nd Operation. A biopsy of the orbital growth was made.

Microscopical Examination. The histological appearance of the orbital tumor was the same as that of the cerebral tumor. Necrotic areas were more prevalent and the cells were disposed in pseudopalisades around the necrotic areas. Connective tissue was limited to the wall of the blood vessels, which were abnormal in size and number. Silver stains showed very atypical glial cells with marked polymorphism of nuclei and cytoplasm (Fig. 6). Numerous glial fibrils also could be seen. Diagnosis: metastatic glioblastoma.

Course. Roentgen-ray treatment to the orbit was given, but there was no improvement. The exophthalmos progressed and extensive chemosis developed with secondary ectopia. Detachment of the retina followed and the patient lost his vision in the affected eye. His general condition deteriorated rapidly and he died at home 7 months after the cranial operation. Necropsy was not done.

Case 2. Manuel L.S., a 22-year-old male, entered the clinic on Dec. 21, 1956. His main complaints were: paroxysmal headaches, predominating in the right frontal region, blurring and diminution of vision, and deafness in the right ear for 2½ months.

Examination. Visual acuity was diminished (0.17 RE and 0.9 LE), and visual fields showed...
left homonymous hemianopia. There was choking of the optic discs. Roentgenograms of skull and chest were not relevant. Right carotid angiography showed marked forward and upward displacement of the middle cerebral artery (Fig. 7), and mild displacement of the anterior cerebral artery to the left. Diagnosis: right posterior temporal tumor.

Operation. On Jan. 17, 1957 a large deeply seated, very vascularized, cystic glioma with ill-defined limits was found in the temporo-occipital region. The tumor was removed partially.

Microscopical Examination. The tumor was a densely cellular glioma. The cells varied in size and shape. Some were small astrocytes, others spongioblasts (Fig. 8). In some places cells with “sucker feet” were grouped around the blood vessels like astroblasts. There were numerous gigantic and monster cells with multiple nuclei (Fig. 9). Many mitoses could be seen. The vessels were very numerous, some of them of very large size and thrombosed. Perivascular infiltration by small round cells was very prominent. Diagnosis: glioblastoma multiforme.

Postoperative course was uneventful and deep roentgen-ray therapy, totally 3,550 r in the neoplastic focus, was given.

On discharge from the hospital on March 24, he had complete left homonymous hemianopia. The papilledema had receded, leaving signs of secondary optic atrophy.

Shortly thereafter, the patient went back to his work, complaining only of poor vision in the right eye and occasional nocturnal enuresis. In September 1958, 1 year and 8 months after operation, headaches recurred. In January 1959 he had to give up his work and was readmitted to the neurosurgical clinic.

Examination. There was no tension in the trephine openings of the skull. Vision was diminished markedly (0.25 RE, 0.66 LE). Visual fields showed left homonymous hemianopia. There was also marked bilateral optic atrophy.

Electroencephalogram showed generalized slowing of rhythm with a focus of delta waves in the right occipital region. Right vertebral angiography was performed, but it was not very revealing, so that encephalography with air was done. This showed some lateral and upward displacement of the posterior part of the body of the lateral ventricle, the occipital horn of which had been amputated.

2nd Operation. On Feb. 9, 1959 the operative wound was reopened. The dura mater was bulging and attached to the underlying brain. The cerebral cortex was much altered and the tumor was
exteriorized in the lower part of the operative field. A wide occipital lobectomy was performed, including part of the tumor. The falx and the tentorium were invaded largely by the growth which also extended forward into the centrum ovale, so that it could be removed only partially. The sinus rectus and lateralis did not appear invaded.

**Microscopical Examination.** The tumor showed the same appearance as the one removed at the first operation.

**Course.** Roentgen-ray therapy totalling 12,000 r was given and the patient left the hospital on May 20, 1959. The only neurological abnormalities were marked diminution of vision in both eyes and left homonymous hemianopia. The fundi showed no changes from the previous examination. A persistent anorexia and loss of vision ensued until he became amaurotic.

On Aug. 23, 1959 he reentered our neurosurgical clinic, complaining mainly of very severe headaches. He was later transferred to the neurosurgical clinic of Medical School Hospital. His general condition was very poor; he was emaciated, mentally dull and amaurotic. In the right cervical region an enlarged lymph node was found.

**3rd Operation.** The cervical node was removed.

**Microscopical Examination.** The lymph node showed islands of neoplastic tissue, mainly in the periphery, underneath the capsule (Fig. 10). The boundaries between the lymphoid and neoplastic tissues were well defined. Hortega’s silver stains for glioblasts showed great variation in shape and size of nuclei and cytoplasm of the neoplastic cells. Some were monster cells, with cytoplasmic expansions of glial type (Fig. 11). Glial fibrils were very abundant in some fields (Fig. 12). Histo-
logical diagnosis: metastasis of glioblastoma multiforme in a lymph node.

Subsequent Course. The general condition of the patient deteriorated, and he died on Oct. 26, 1959, 2 years and 9 months after the first operation.

Necropsy. Nothing abnormal was found outside the skull. The operative flap was healed nor-

Fig. 6. Case 1. Photomicrograph of orbital tumor. Note glial appearance of the cells and their variation in size and shape. (del Rio-Hortega's silver stain for glioblasts.)

Fig. 7. Case 2. Right carotid arteriogram, lateral view. Note that both internal and external carotid arteries were injected.
Fig. 8. Case 2. Photomicrograph of tumor removed from right temporal lobe, showing polymorphism and gliomatous appearance of its cells. (del Rio-Hortega's silver stain for glioblasts.)

Fig. 9. Case 2. High-power view of tumor shown in Fig. 8.
Metastasis of Glioblastoma Multiforme

Fig. 10. Case 2. Section of the lymph node removed from the neck. Note neoplastic cells at the periphery between capsule and lymphoreticular tissue. (Del Rio-Hortega's silver carbonate.)

Fig. 11. Case 2. Cytological detail of neoplastic cells found in lymph node. Note polymorphism and gliomatous appearance of cells, some of which are gigantic and multinucleated. (Del Rio-Hortega's silver carbonate.)
Fig. 12. Case 2. Glial fibrils in tumor of lymph node. (del Rio-Hortega’s silver stain for glioblasts.)

nally, but the dura mater could not be separated from the underlying tissues all over the right occipital region. The right occipital lobe practically was missing and in its place there was a large mass of grayish tumor, 7×6×5 cm. in size, which adhered not only to the outer aspect of the dura mater, but also to the posterior part of the falx and tentorium. In some places both these structures were not only invaded by, but actually embedded in, the growth. Anteriorly the tumor disappeared underneath the cortex of the temporal and parietal lobes for a distance of some 2 to 3 cm., reaching the wall of the lateral ventricle. The convolutions were flattened in the left parietotemporal region, but elsewhere they looked normal. Nothing abnormal could be seen at the base of the brain, but in the undersurface of the tentorium on the right side, just underneath the tumor, there was neoplastic proliferation. After fixation in formaldehyde, coronal sections of the brain were made. They showed that the right occipital lobe had been replaced by a hard mass of tumor two-thirds the size of the left occipital lobe. The dura mater which surrounded it completely was so adherent to the tumor that it was like a capsule. The posterior part of the longitudinal sinus practically was occluded by compression by the tumor, but it was permeable and contained a blood clot. The great vein of Galen was also permeable, but the straight sinus was invaded and in some places completely obliterated by the tumor. The lateral sinus, though partially collapsed, was not invaded. The parenchyma of the parietal lobe surrounding the anterior end of the tumor and the periventricular tissue showed some softening, and the tumor bulged in the lumen of the ventricle.

The operative scar corresponding to the biopsy in the right cervical region was healed, and no macroscopical growth could be detected in this area. The carotid artery, jugular veins and lymph nodes looked normal grossly. Nothing abnormal could be found in the pleura, and the lungs showed only a mild congestion, with some pinkish foamy exudate filling the small bronchi and alveoli. The heart and large vessels were normal. In the abdominal cavity the only remarkable finding was a duodenal ulcer.

Microscopical sections of the tumor found in the brain showed fundamentally the same histological features as the one removed at operation. However, there was some fibrous reaction. The dura mater surrounding it was thickened because of fibrous proliferation, and in some places appeared infiltrated by the neoplastic cells. Sections made through the straight sinus showed infiltration of its wall by the neoplastic cells (Fig. 13), which in some places filled its lumen completely.
Fig. 13. Case 2. Microscopical section of wall of straight sinus, showing invasion of its lumen by neoplastic cells. (Hematoxylin and eosin.)

Diagnosis: local recurrence of glioblastoma multiforme, with invasion of dura mater and dural sinuses.

DISCUSSION

The extracranial metastasis of intracranial tumors may be proximal to or remote from the primitive lesion. The former arises in the skull, pericranium or soft tissues of the scalp or in the neck, as in the cases of medulloblastoma of Mittelbach54 (Case 2); ependymomas of Meredith and Sahyoun,43 Wen and Barrows71 and James and Pagel;46 oligodendrogliomas of Bailey and Bucy7 (Case 5) and Strassman;55 glioblastomas of Köhlmeier53 and Dewart et al.;57 astroblastomas of Sikl;64 meningioma of Cushing and Eisenhardt53 (case of Dorothy May Russell) and fibrosarcoma of Ley and Rosendo.46 In these cases the metastasis may be considered merely as direct extension of the intracranial growth, or caused by accidental contamination of the operative wound by the neoplastic material. In our Case 1, in which the growth invaded the orbit, there may have been simple extension through either the optic foramen or superior orbital fissure, as in another case of glioblastoma reported by Cross and Cooper21 (Case 2). We regret that in our case necropsy could not be done. However, in comparing it with the one reported by Cross and Cooper,21 we have to point out that in our case there was no clinical or radiological evidence that the growth had extended to the bone or soft tissues of the operative wound. Besides, there was no impairment of either visual or oculomotor functions, as could be expected if the growth had passed through the narrow foramina from which the 2nd to 6th cranial nerves have their exit. On the other hand, we could see, both in the angiogram (Fig. 1) and at operation, a marked proliferation of blood vessels at the bottom of the anterior pole of the temporal lobe. So the possibility of the neoplastic cells being carried to the orbit by these blood vessels through the superior orbital vein cannot be dismissed.

Remote metastases from intracranial tumors have been found in the lymph nodes of
TABLE 2

<table>
<thead>
<tr>
<th>Histological Type</th>
<th>Cervical Lymph Nodes</th>
<th>Lungs and Pleura</th>
<th>Bones</th>
<th>Liver</th>
<th>Skin and Muscles</th>
<th>Other Organs</th>
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<td>Medulloblastoma</td>
<td>2</td>
<td>8</td>
<td>2</td>
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<td>1</td>
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<tr>
<td>Astroblastoma</td>
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<td>Tumors of choroid plexus</td>
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As can be seen in Table 1, we have found in the literature 8 cases of glioblastoma multiforme with extracranial metastasis. Some of them seem dubious as to their real nature. The first was published by Davis under the diagnosis of spongioblastoma multiforme. The tumor had been removed on 2 occasions, and subsequent roentgen-ray therapy was given. Before the patient’s death 6 months after the first operation a growth was observed in the right pectoral muscle and left axilla. At necropsy tumor was found in the soft tissues of the right arm and scapular region, the left wall of the chest and 3 small nodules were present in the left lung. The microscopical appearance of these tumors was similar to that of the cerebral tumor and therefore they were interpreted as metastases. However, as Willis pointed out, “This diagnosis...is open to question; the account is very brief, and there is no mention of the condition of other viscera; the possibility that the lung might have been the primary seat of the disease is inadequately considered; the illustrations are quite compatible with a diagnosis of anaplastic carcinoma; and the fact that the cerebral growth was large and solitary does not exclude its possibly secondary nature...”

Mittelbach reported a case in which a large tumor of the right hemisphere, which invaded the dura mater, was removed partially. The histological diagnosis was heteromorphous glioma. The patient died 6 months after operation. At necropsy, a large tumor of the left cerebral hemisphere was found with extensive areas of necrosis which reached the ventricular wall. The tumor infiltrated the dura mater, over the convexity and falx. There were multiple nodules of tumor in the lung and lymph nodes of the mediastinum. Histologically, the cerebral tumor proved to be a glioblastoma multiforme. The pulmonary and lymphatic growths had the same microscopic appearance, being considered by the author as metastases. There are no illustrations of the microscopical sections in that paper, and Willis and Zülch suggested that the primary growth in this case also was
a bronchial carcinoma with a large cerebral metastasis.

Another case that has been questioned by Zülch is one reported by Gropp.\textsuperscript{41} At necropsy, a large cystic tumor was found in the left parieto-occipital lobe. In the wall of the right ventricle of the heart, just underneath the pericardium, another whitish tumor nodule, the size of a pea, was found. The cerebral tumor was considered by the author to be a glioblastoma multiforme with a metastasis to the heart. Zülch, who studied this case, thought that it was not a glioblastoma multiforme but a monocellular sarcoma arising from the adventitia of the cerebral blood vessels.

The case reported by Wolf \textit{et al.}\textsuperscript{76} is very interesting because it constituted a real experiment on the production of extracranial metastasis. The patient was a girl, 14 years old. Ventriculography suggested a tumor occupying the region of the lamina terminalis. At craniectomy the tumor was considered inoperable and a ventriculopleural anastomosis was performed. Her condition improved at first, but 3 months later it deteriorated again, and she died 8.5 months after operation. At necropsy, a glioblastoma involving the wall of the 3rd ventricle was found. The glioma had spread freely in the cerebrospinal meninges and pleural cavity, where it formed multiple small nodules. Further metastases had occurred in the posterior mediastinal lymph nodes and the bone marrow of ribs, vertebrae and sternum.

The remaining 4 cases were reported by Köhlmeyer\textsuperscript{42} (Case 6), Brandt,\textsuperscript{14} Cross and Cooper\textsuperscript{21} (Case 2), and Dewart \textit{et al.}\textsuperscript{27} The histological identity of the tumors seems to be well established in all of them. However, we should point out that in the case of Dewart \textit{et al.}\textsuperscript{27} the neoplastic cells seemed to be rather uniform in size and shape, with bipolar expansions, so that it could have been a spongioblastoma which degenerated and became malignant. In the cases of Köhlmeyer,\textsuperscript{43} Brandt,\textsuperscript{14} and Dewart \textit{et al.}\textsuperscript{27} extension to the scalp developed after operation. In the case of Cross and Cooper,\textsuperscript{21} the tumor invaded not only the bone and muscle but also the orbit, as in our Case 2. In the first three mentioned, metastatic nodules were found in the lungs. In the case of Brandt\textsuperscript{14} a small neoplastic focus at the upper pole of the left kidney was also found. In the case of Dewart \textit{et al.}\textsuperscript{27} there were two metastases in the liver. In the case of Mittelbach,\textsuperscript{44} the lumen of the dural sinuses as well as the tracheobronchial lymph nodes were invaded by the neoplastic growth. In the case of Cross and Cooper,\textsuperscript{21} in addition to the pulmonary metastasis, there was neoplastic invasion of the abdominal wall.

The cases we have just discussed and the 2 personal observations presented in this paper have been grouped in Table 3. Noteworthy are the marked prevalence of metastasis of glioblastomas in males, the predominance of the primary lesion in the left cerebral hemisphere, and the relative youth of the patients, if we consider the mean age for this type of tumor.

The most common location for remote metastasis of those gliomas was in the lungs. This seems to support the assumption that the main pathway for extracranial dissemination may be the venous system, as we shall discuss later. In our Case 2, though some of the dural sinuses actually were invaded by the tumor cells, the only metastasis found outside the skull was in the cervical lymph node. As already stated, this location for metastasis is found commonly in cases of ependymomas,\textsuperscript{36,40,49,66,71} however, we cannot talk of specific location for metastasis of any special type of tumor.

Chiovenda,\textsuperscript{17} Henschen,\textsuperscript{58} Willis,\textsuperscript{73} Mastragostino\textsuperscript{69} and Winkelman \textit{et al.},\textsuperscript{74} among others, had discussed the surprising feature of the rarity of extracranial dissemination of malignant gliomas and especially of such highly anaplastic and invasive tumors as the glioblastoma multiforme. In posing the question as to “Why is dissemination from them so constantly absent?” Willis\textsuperscript{73} and Winkelman \textit{et al.}\textsuperscript{74} pointed out the absence of true lymphatics linking the central nervous system with the rest of the body, which in cases of many other malignant tumors, constitute the source of further dissemination.
They suggested also that the structure of the veins of the central nervous system does not favor invasion of them by tumors. Willis\textsuperscript{72} pointed out that the cranial sinuses are enclosed in dense dural tissue that is rarely penetrated by the neoplastic cells, while the small cerebral veins are thin-walled, so that their collapse before advancing tumors may be readily imagined.

Henschel\textsuperscript{38} advanced the idea that the neuroglial cells, even if they reach other tissues of the body, fail to survive in foreign territories so different morphologically and genetically from their own. Finally, Willis,\textsuperscript{73} Mastragostino\textsuperscript{52} and Russell and Rubinstein\textsuperscript{61} considered the possibility that the rapid evolution of some malignant gliomas does not give time for the metastasis to develop, since it has been noted that long periods of time have been involved in some of the more authenticated cases recorded in the literature.

The first argument, that is the absence of true intradural lymphatic channels, seems to be valid, and can be held as one of the main causes that prevent the metastasis of intracranial tumors to remote parts of the body. The second is more questionable because, as Mastragostino\textsuperscript{52} pointed out, there are cases of primary intracranial tumors of different nature, as reported by Abbott and Love,\textsuperscript{1} Bertrand and Carvalho,\textsuperscript{12} Brandt,\textsuperscript{14} Calvo,\textsuperscript{16} Courville,\textsuperscript{20} first case of Cross and Cooper,\textsuperscript{21} Gama,\textsuperscript{31} Marburg,\textsuperscript{51} Mastragostino,\textsuperscript{52} Mittelbach,\textsuperscript{54} Russell and Sachs,\textsuperscript{62} Towne\textsuperscript{68} and our Case 2, in which the lumen of the cerebral

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
Author & Year & Age & Sex & No. of Operations & Survival from 1st Operation & Remarks \\
\hline
Davis\textsuperscript{34} & 1928 & 31 & M & 2 & 6 mos. & Soft tissues, arm and chest. \\
& & & & & Axillary lymph nodes. Lung & Bronchial carcinoma according to Willis\textsuperscript{72} \\
\hline
Mittelbach\textsuperscript{61} (Case 6) & 1935 & 39 & M & 1 & 6 mos. & Dural sinuses. Tracheobronchial lymph nodes. Lung & Bronchial carcinoma according to Willis\textsuperscript{72} and Zülch\textsuperscript{79} \\
\hline
Köhleiner\textsuperscript{13} & 1941 & 38 & M & 3 & 1 yr. & Op. flap. Lung & Bronchial carcinoma according to Willis\textsuperscript{72} and Zülch\textsuperscript{79} \\
\hline
Brandt\textsuperscript{11} & 1950 & 52 & M & 1 & 1 yr. & Op. flap. Lung. Kidney \\
\hline
\hline
\hline
Gropp\textsuperscript{21} & 1955 & 48 & M & 0 & — & Pericardium & Sarcoma according to Zülch\textsuperscript{79} \\
\hline
\hline
Ley \textit{et al.}\textsuperscript{0} & 1961 & 28 & M & 1 & 7 mos. & Orbit \\
\hline
Ley \textit{et al.}\textsuperscript{0} & 1961 & 22 & M & 2 & 2 yrs., 9 mos. & Dural sinuses. Cervical lymph nodes \\
\hline
\end{tabular}
\caption{Glioblastomas with extracranial metastasis}
\end{table}
blood vessels or sinuses was invaded by the neoplastic cells. Besides, the frequency with which parasagittal meningiomas invade the longitudinal sinus is well known, and, as we have seen in Table 1, the total number of reported extracranial metastases of meningiomas is exceedingly small.²⁹ We therefore have to admit that besides the factors that prevent the invasion of blood vessels by neoplasm there must be some other mechanisms that prevent the reproduction and progression of the neoplastic elements if they ever reach the lumen of the vessels.

Concerning the possibility suggested by Henschen³⁸ as to the inadequacy of foreign tissues for the growth of gliomatous elements, the early experiments of Freeman and Zimmerman²⁰ demonstrated that transplants of gliomas in the anterior chamber of the eye did not produce any metastasis. However, there are many proven facts that seem to contradict this hypothesis too. Among them could be mentioned, besides the cases of extracranial metastasis of gliomas that we are discussing, the observation of Weiss⁷⁹ of an ependymoma of the cauda equina operated upon four times in the course of 10 years, which metastasized to the lungs, liver, and tracheobronchial lymph nodes; another of Mallory,⁶⁰ a coccygeal glioma from which there were metastases in the lymph nodes of the groin; the case of Helmke,³⁷ in which a gliomatous proliferation from an ovarian teratoma developed in the peritoneal cavity; the cases of Askanazy³ and Hückel⁹⁹ of frontal encephalocele associated with a gliomatous proliferation in the lungs; and the 2 cases of Kimpton,⁴² 1 of a gliomatous formation in the buttock and the other of a cystic glioma in the pararectal region, not associated with any other neoplastic growth and therefore being interpreted as migrating glia from the embryonal spinal cord.

Furthermore, the feasibility of growing normal and neoplastic neuroglial cells in vitro in blood plasma or serum; the experimental production by Zimmerman⁷⁸ of gliomas in the thoracic and abdominal viscera of mice by direct injection into the caudal vein; of homogenates from experimentally induced gliomas; and the wide dissemination and growth of the gliomatous cells after ventriculopleural anastomosis in the case reported by Wolf et al.,⁷⁶ may be held as valuable experimental facts against Henschen's point of view. However, Zimmerman⁷⁷ has also proved the marked influence that an alien medium may have upon the morphology and structure of gliomatous cells.

Therefore, we must admit the suggestion made by Abbott and Love¹ as to the existence of unknown "natural barriers" which, by preventing the entrance of pathological material into the lumen of the blood vessels, isolate the brain tumors from the rest of the body. To these "barriers," we may add some other protective mechanisms that prevent the growth and dissemination of neoplastic cells through the blood stream if they succeed in breaking through the first barrier, and reach the lumen of the blood vessels. A third protection would be afforded by the resistance presented by various organs to the growth of the alien neoplastic cells of the brain or meninges.

With regard to the mechanism by which the metastasis of brain tumors to distant organs is produced, it is reasonable to assume, as Russell and Rubinstein⁶¹ suggested, that access of the tumor cells to the lymphatics and veins outside the nervous system is the determining factor in the process.

In this respect, it may be convenient to point out the important role that surgical procedures may play. Though there have been a few cases, as the one reported by Gropp⁴¹ in which the extracranial extension developed before any surgical procedure was undertaken, in most instances in which distant metastases of intracranial tumors were found, the primary tumor had been operated upon previously, as in our 2 cases; some as many as three times, as the medulloblastoma of Nelson,⁵⁵ the ependymoma of Maass,⁴⁹ the oligodendroglioma of James and Pagel,⁴⁰ the meningioma of Cross and Cooper,¹¹ the fibrosarcoma of Christensen et al.,¹⁸ the papilloma of the choroid plexus of Vraa-Jensen,⁶⁹ and the glioblastoma of
Köhler, and even 17 times as in the famous case of Dorothy May Russell, reported by Cushing and Eisenhardt. It seems as if the surgical procedures may sever the “natural barriers” against brain tumors, allowing invasion of the blood vessels by the neoplastic cells. Mastragostino suggested that the surgical trauma may act in two ways: a) by facilitating aspiration of neoplastic material by the blood vessels of the stroma and its subsequent circulation in the blood stream, and b) by disintegrating the cytostromal structure of the tumor by laceration of the basal wall.

Concerning the effect of long survival on the development of extracranial metastasis, we should like to point out the following facts. Although in some cases the survival period after the first operation was rather long (4 years in the case of oligodendroglioma reported by James and Pagel; 6 years in the ependymoma of Perry; 8 years in the oligodendroglioma of Bailey and Bucy and the meningiomas of Case 1 of Cross and Cooper and Almeida Lima; and even 13 years in the case of Dorothy May Russell reported by Cushing and Eisenhardt), we have to consider that the expectancy of life with these types of tumors usually is long. On the other hand, if we restrict ourselves to cases of glioblastoma multiforme (Table 3), we find that except for our Case 2, the postoperative survival was not above average. However, in the case of Dewart et al., the operation was done more than 2 years after onset of clinical symptoms, the total evolution therefore being 3 years. The lengthy course in this case may be explained by the great isomorphism of the neoplastic cells. It could be that the primary tumor in this case was a benign spongioblastoma polare that later on degenerated, becoming a malignant spongioblastoma. In our Case 2, however, this could not be the explanation, because the course was rapid from the beginning, the patient having been operated upon 3 months after onset of clinical symptoms. So, we have to admit that a long-lasting course and repeated surgery may favor the development of extracranial metastasis. As Sherbaniuk and Shnitka and Russell and Rubinstein have pointed out, it seems as if in some cases of long duration the invasion of the pericranium and scalp has paved the way to metastasis.

In dealing with extracranial metastases, one may get the impression that they could be more frequent than was thought formerly. Mastragostino has stressed how easily they can escape detection at the ordinary clinical examination. However, we should like to point out that since we saw our first case of extracranial metastasis of a glioma in 1958, we have been making routine roentgen-ray check ups of the chest, and biopsies of any swollen lymph node or abnormal growth found in the postoperative follow up in all our cases of brain tumor. So far, the search gave positive results in only 1 instance (Case 2).

In conclusion we may say that there is still a lot of work to be done, if we want to know more about this important aspect of the natural history of intracranial tumors.

**SUMMARY**

Two cases of glioblastoma multiforme with extracranial metastasis are reported. In Case 1 a large glioblastoma multiforme was removed from the left temporal lobe of a 28-year-old man. Roentgen-ray therapy was given. Four months later a tumor developed in the left orbital region. Biopsy was done, and microscopically the orbital tumor had the same appearance as that of the cerebral tumor. Further roentgen-ray therapy was given, but the patient died 7 months after the cranial operation. Necropsy was not performed.

In Case 2 a glioblastoma multiforme was removed partially from the right posterior temporal region of a 22-year-old male. Roentgen-ray therapy was given. The patient returned to his work for nearly 2 years, and then was operated upon for recurrence. He received a new course of roentgen-ray therapy, but died 2 years and 9 months after the first operation. Just before his death a metastasis in the cervical lymph node was discovered and removed. Microscopically it showed glioblastoma multiforme. At
necropsy, intracranial recurrence of the glioblastoma, with invasion of the dura mater and dural sinuses, was found.

In reviewing the literature, 81 cases of primary intracranial tumors with extracranial metastasis were found. In 52 their pathological identity seemed well established, being questionable in the remaining 29. The largest group was constituted by the gliomas, 33 cases, followed by the meningeal tumors (29). In 8 of them the histological diagnosis was spongioblastoma or glioblastoma multiforme, but in 4 of them the diagnosis has been questioned by some outstanding pathologists.

A brief discussion follows, concerning the hypothetical causes which may both prevent or facilitate the extracranial dissemination of cerebral gliomas and other primary intracranial tumors.

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