A Rare Combination of Multicentric Gliomas: A Problem of Interpretation

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ABSTRACT

Bastian, Frank O., and Parker, Joseph C. Jr.: A rare combination of multicentric gliomas: A problem of interpretation. Amer. J. Clin. Path. 54: 839-844, 1970. Cases of multicentric gliomas of similar morphology have been well documented, but the simultaneous occurrence of a glioblastoma multiforme and a distinctly separate astrocytoma has been rarely recognized and inadequately described. Both a glioblastoma multiforme and a cystic piloid astrocytoma (spongioblastoma polare) were observed at autopsy in a 62-year-old woman thought to have an occult malignancy with multiple metastatic intracranial neoplasms. This case supports the occurrence of multicentric gliomas on the basis of the development of multiple primary foci, which has been illustrated previously by experiments in animals.

MULTIPLE PRIMARY NEOPLASMS in different viscera were first reported by Billroth in 1879. Subsequent reports have shown that these occurrences are not as rare as previously thought, and the incidence in various organs ranges from 2 to 7% of the population of cancer patients. Multiple primary tumors arising in single organs or in paired organs tend to occur more frequently and have been referred to as multicentric primary neoplasms. Although a solitary neoplasm often possesses adjacent areas of well-differentiated and poorly-differentiated anaplastic degeneration, true multicentricity depends on the inability to demonstrate direct continuity or evidence of metastasis between the tumors.

Well-documented multicentric gliomas of similar morphology are rare. The combination of an astrocytoma and glioblastoma multiforme is even more uncommon and not well documented in the literature. In a review of more than 15,000 autopsies at the Duke University Medical Center only one patient with this type of multicentric glioma was found. This report deals with the case and the problems it presented.

Report of a Case

A 62-year-old Negro woman was admitted to Duke University Medical Center because of difficulty walking. For three weeks prior to admission she had complained of fronto-orbital headaches and had trouble dressing herself, but she had continued working until two weeks before admission. Three days prior to admission, while bathing, she suddenly lost the use of her left arm and leg and tended to fall to her left side, but she did not lose consciousness. For the previous 35 years she had been hypertensive, and recently she had been treated medically for this problem.

Pertinent physical findings on admission
included weakness of the left upper and lower extremities with left ankle clonus, hypalgesia, and questionably decreased vibratory and position sense over the left lower extremity and left homonymous hemianopsia. Plantar responses were flexor. The patient was normotensive.

An electroencephalogram showed localized slow waves over the right cerebral hemisphere. The brain scan demonstrated a prominent focus of increased activity over the right frontal lobe in the parasagittal region and a much smaller focus over the right parietal area (Fig. 1). Right and left carotid arteriograms showed abnormal vascular patterns, one in the right superior frontal area and the other in the right lateral parietal area. Multiple metastatic tumors were considered to be the most probable explanation for the abnormalities observed in the brain scan and carotid arteriograms.

On the basis of these studies, and without any operative intervention, the patient was treated with 3,000 rads to the whole head in interrupted doses over a period of approximately four weeks. She gradually became disoriented, obtunded, and difficult to manage, developed bowel and bladder incontinence, and was rehospitalized. At this time she was comatose, with a stiff neck and deviation of the head and eyes to the right, a left central facial paralysis, and left hemiparesis. Steroids were given without any significant improvement, and the patient remained comatose until her death, five months after the onset of the initial neurologic symptoms.

Postmortem Examination. The pertinent findings at autopsy included congestion of the lungs with foci of acute pneumonitis, arterionephrosclerosis, and diffuse hemosiderosis of the spleen and abdominal lymph nodes. Prominent radiation derma-
Fig. 2. Serial coronal sections of the brain illustrate two distinctly separate lesions: a glioblastoma multiforme (seen in the third and fourth cuts at right) in the right superior frontal gyrus, and a cystic piloid astrocytoma (spongioblastoma polare; in the second and third cuts at left) in the right parieto-occipital lobe.

titis, with hyperkeratosis and absent associated skin appendages, was evident over the entire scalp. A stasis ulcer 3 cm. in diameter was located over each lateral malleolus.

The brain weighed 1,100 Gm. and had two distinctly separate lesions in the right cerebral hemisphere (Fig. 2). A well-circumscribed, partially necrotic, hemorrhagic mass, 3 cm. by 2.5 cm. by 2 cm., was located in the right superior frontal gyrus. A 4.5 cm. by 4.5 cm. by 2.5 cm. cyst in the right lateral parieto-occipital area contained a small blood clot within a clear serous fluid. A yellow-tan, firm nodule 3 cm. by 2 cm. by 2 cm. was present in the inferior lateral.
wall of this cyst. Extensive cerebral edema was present around both of these lesions, especially the right superior frontal mass, and had produced a swollen right cerebral hemisphere with a prominent shift of all structures to the left. A cystic infarct, 2.5 cm. by 0.5 cm. by 0.5 cm., was located in the left thalamus just above the partially compressed midbrain. No other significant lesions were observed.

Microscopically, the right superior frontal neoplasm was composed of prominent clusters of large cells with centrally oriented, dark, pleomorphic nuclei and scanty cytoplasm (Fig. 3). These cells were irregular in shape with some spindle forms. A pseudopalisading pattern was observed around occasional necrotic areas. In addition, many scattered mitotic figures, giant cells, and foci of hemorrhage and endothelial capillary proliferation were evident. This morphology was compatible with a glioblastoma multiforme. The cystic neoplasm in the right parieto-occipital area was lined by a thin, smooth membrane of reactive glial tissue. The firm nodule in the wall of the cyst was composed of fascicles of spindle cells with prominent cytoplasm and large, vesicular, oval nuclei (Fig. 4). Mitotic figures, giant cells, and hemorrhage were not features of this tumor. A small focus of necrosis associated with large, irregularly shaped, partially degenerated cells was located adjacent to the cyst. Compared with the previous lesion, this appeared less anaplastic and was consistent with a cystic piloid astrocytoma (spongioblastoma polare).

Both neoplasms were confined to the parenchyma of the right cerebral hemisphere. Multiple sections of the intervening edematous tissue did not reveal any direct connection between the tumors. No communication with the ventricular system or the subarachnoid space was demonstrated.

Discussion

The exact incidence of all types of multicentric gliomas is not known and varies according to different investigators. In one autopsy series multicentric gliomas were found in 0.06% of the cases. In patients with known glial tumors this incidence has ranged from 0.2% to 35.3%. Recently, Batzdorf and Malamud found five multicentric gliomas in a series of 209 autopsied patients with gliomas (2.4%). The intensity with which these lesions are sought undoubtedly influences the reported frequency of their occurrence.

Multicentric gliomas in the brain are usually of the same cell type, most often glioblastoma multiforme. This was illustrated in our review of autopsies at Duke University Medical Center by a 43-year-old man who had two left frontal craniotomies over a three-year period for a glioblastoma multiforme with prominent adjacent areas of astrocytoma. At autopsy a distinctly separate and unsuspected glioblastoma multiforme was discovered in the right frontal lobe. However, in view of the similar morphology of the two separate intracranial tumors, the operative intervention, and the clinical failure to demonstrate both tumors simultaneously, the right frontal neoplasm could easily have been a metastasis. This case exemplifies the difficulty in evaluating true multicentricity.

Case reports of multicentric gliomas of different cell types are not common. On the other hand, the development of two separate gliomas of the same cell type with different degrees of anaplasia is decidedly more unusual, and the particular combination of a glioblastoma multiforme and an astrocytoma has been rarely reported and previously not well illustrated. In his series of 21 multicentric gliomas Courville found two cases of a glioblastoma multiforme with a distinctly separate astrocytoma. These cases were illustrated by drawings and verbal descriptions. No photographic documentation of this particular combination of gliomas has been found in the literature.
Coincidence may account in part for the occurrence of multiple primary tumors of different organs.\textsuperscript{1,16} However, the greater frequency of multiple primary neoplasms within single or paired organs suggests that this cannot be explained by chance alone.\textsuperscript{11} A reasonable suggestion is that there are two phases in the development of multicentric tumors.\textsuperscript{17} The initial phase is a neoplastic transformation at a molecular level (field phenomenon) which seems to be produced by some vague stimulus and theoretically might involve the entire organ. A process of progressive atypical cellular proliferation follows and in rare instances may occur simultaneously at several sites. The stimuli for such changes may be either intrinsic or extrinsic, or both. In some conditions, such as von Recklinghausen's disease (multiple neurofibromatosis) the predilection for anaplasia within the central nervous system appears to be genetically determined.\textsuperscript{13,16-18} In other instances, chemical compounds, radiation, and viruses may induce malignant degeneration.

Multicentric gliomas have been induced experimentally in adult lower animals by chemicals (methylcholanthrene, benzpyrene, and dibenzanthracene),\textsuperscript{7,9,12} radiation,\textsuperscript{7,10} and viruses,\textsuperscript{7} indicating that differentiated adult cells can develop malignant changes \textit{de novo}. This experimental work does not support Cohnheim's embryonal rest theory, which states that gliomas originate from primitive cells displaced during the development of the central nervous system.\textsuperscript{4}

In the present case, two definitely separate and cytologically disparate, malignant gliomas in the cerebrum were demon-
strated. The obvious morphologic differences between these gliomas strongly suggested that metastasis played no role in this phenomenon. The right frontal tumor was a glioblastoma multiforme and the large cystic mass in the right parieto-occipital region was a piloid astrocytoma. There was no communication with the ventricular system or the subarachnoid space, no meningeal gliomatosis, and no direct extension from one tumor to the other. The patient did not undergo surgery for the gliomas and received radiation therapy following the clinical demonstration of both tumors.

The present case supports the occurrence of multicentric gliomas on the basis of the development of multiple primary foci. From the available clinical studies of multicentric gliomas their etiology cannot be determined. Experimental data indicate that these multiple tumors can be produced readily in lower animals by the same single stimulus (methylcholanthrene, viruses) to already differentiated normal adult tissue. An alteration in some biochemical pathway may perpetuate the malignant changes within the adult cells. With more clinical insight through further investigative ventures, the pathogenesis of these neoplasms should eventually become apparent to us.

References