SARCOMA ARISING IN GLIOBLASTOMA OF THE BRAIN *

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This paper will describe three primary, malignant brain tumors, each of which was composed of two dissimilar malignant tissues. One, of glial origin, was essentially like that in glioblastoma multiforme. The other, mesenchymal in origin and character, and resembling a spindle cell fibrosarcoma, is believed to have originated secondarily in the walls of the hyperplastic blood vessels seen so commonly in glioblastoma.

Tumors of this sort were described in the older literature some 60 years ago and the term gliosarcoma, analogous to the term carcinosarcoma, was restricted to such tumors by some investigators of that period. Subsequently, the existence of such tumors was discounted, the term gliosarcoma being applied to tumors which resembled sarcoma, but were thought to be nonetheless of glial origin. More recently, the term has been almost completely discarded as the glial origin of most of these tumors has been firmly established, and most would now be designated as glioblastoma multiforme. It is considered unwise to attempt to resurrect the term gliosarcoma for use in its original sense, because of the confusion which might result.

REPORT OF CASES

Case 1

The patient (P63993) was a white woman, 69 years old, with hypertension, who was well until about 2 months before death, when she began to drop objects from her left hand. A few weeks later, progressive paresis of the left foot became apparent and she became bedridden about 5 weeks prior to death. On examination, the patient was alert but disoriented and appeared severely ill. There was slight nuchal rigidity and a severe left hemiplegia with a positive Babinski sign on the left. She was incontinent. She was thought to have a metastatic neoplasm of the brain, but a thorough investigation of the gastrointestinal and genitourinary tracts, chest, and skull showed no evidence of abnormality. The electro-encephalogram showed severe slowing on the entire right side. A ventriculogram showed marked dilatation of the lateral ventricles, with the entire ventricular system deviated to the left. The third ventricle was markedly pushed over to the left, and more so superiorly than inferiorly. The posterior portion of the right lateral ventricle was deviated downward. Immediately following ventriculography, a right parietal osteoplastic flap was turned

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down. A mass was found in the inferior parietal region attached to the dura over an area about 15 mm. in diameter. The mass was first thought to be a meningioma. A complete removal of the tumor was performed. The patient's condition remained poor, without a return of consciousness, and she expired 9 days postoperatively. Permission for necropsy was not obtained.

The surgical specimen consisted of a roughly globular mass of firm, yellow, gray, and tan tissue, measuring approximately 45 mm. in diameter and weighing approximately 41 gm. It was attached at one aspect to a small fragment of a dense collagenous membrane, 20 by 30 mm. in size, which resembled dura. The tumor mass was irregularly lobulated and well circumscribed, appearing encapsulated in some areas but not in others. On section, the tumor was quite firm and varied in appearance, being white in some areas, yellow, gray, or tan in other zones, and it contained foci of hemorrhage.

On section, two discrete though intermingling types of neoplastic tissue were apparent in hematoxylin and eosin preparations (Fig. 1). In one zone, the cells were moderate to small in size, with round, elongated or irregular, deeply chromatic nuclei. The cytoplasm of most of these cells could not be distinguished, but a few possessed a somewhat hyaline, eosinophilic cytoplasm, the margins of which were not sharply defined. The cells varied considerably in size, shape, and staining characteristics, and fairly numerous mitotic figures could be seen. In places, large, bizarre, giant forms were noted. The cells were arranged without order in a coarsely reticulated, eosinophilic matrix. These cells infiltrated individually into the adjacent normal cerebral parenchyma. The walls of some of the blood vessels in this area showed hypertrophy and hyperplasia of the endothelial and adventitial cells, and these changes were marked in places. The cells of some of these markedly hyperplastic vessels could be seen to pass outward, infiltrating the surrounding tissues, in which circumstance they were indistinguishable from the second neoplastic tissue to be described. This first tissue was considered to be of glial origin, in the nature of a glioblastoma multiforme.

The cells of the second tissue were considerably larger, with moderately chromatic, reticulated, ovoid, or elongated nuclei, between which ran coarse, deeply stained eosinophilic fibers. These cells showed moderate to marked variability in size, shape, and staining characteristics, and a moderate number of mitotic figures. The cells were generally arranged in long parallel rows which tended to interweave. In places they formed columns, on each side of which the more irregular glioblastomatous tissue was present. This tissue also assumed the form, on section, of circular islands of varying size, surrounded by glio-

blastomatous tissue (Fig. 2). The smaller islands could not be distinguished from the hyperplastic blood vessels. This tissue was considered to be a spindle cell fibrosarcoma arising from blood vessel walls. Large zones of necrosis were present, apparently involving both tissues.

In phosphotungstic acid-hematoxylin preparations,[1] the fine fibers of the gliomatous tissue were stained blue. The coarse fibers of the sarcomatous tissue and portions of the blood vessel walls were stained tan. With the azocarmine technique,[2] the fine fibers of the gliomatous tissue were stained red; the coarse fibers of the sarcomatous tissue, blue. The Wilder silver method for reticulin[3] stained some of the fibers of the sarcomatous tissue.

Summary. A 69-year-old woman died within 2 months of the onset of symptoms of a brain tumor lying superficially over the right inferior parietal area. The tumor was circumscribed, firm, and generally gray or white. Section revealed it to be composed of a mixture of glioblastomatous and sarcomatous tissues. The latter was thought to have arisen from the walls of the blood vessels of the former.

Case 2

The patient (A15698) was a white woman, 50 years of age, who was awakened suddenly by a throbbing, severe pain in the back of her head, 3 months prior to death. The headache persisted, and a few days later there was a syncopal attack. On examination, the only changes were bilateral, severe papilledema with hemorrhages. Lumbar puncture revealed xanthochromic fluid under a pressure of 240 mm., with 150 mg. per cent of protein. An electro-encephalogram showed moderate focal slowing in the right parietal region. Angiography was attempted but visualization of the carotid vessel was not obtained. Ventriculogram showed a defect in the region of the atrium of the right lateral ventricle, and a displacement of the posterior part of the third ventricle. The findings were interpreted as indicating a tumor arising deep in the region of the splenium of the corpus callosum. Immediately following ventriculography, a large, lateral, osteoplastic flap was turned down. The dura was under a marked increase in tension. On opening the dura, there was no evidence of a surface lesion. A biopsy specimen was obtained with a needle. The patient's condition remained more or less stationary and she was discharged to a nursing home after 6 weeks in the hospital. Two weeks later, she again complained of severe headache and was re-admitted. She was drowsy, disoriented, and bilateral papilledema was present. There was complete hemiplegia and a sensory defect on the left. The patient's condition deteriorated, and she expired 17 days after her second admission.

The biopsy specimen obtained by needle was not considered diagnostic. It included a group of cells which were thought to be mesenchymal, and the suggestion was made that this might represent a vascular reaction to a tumor, such as the glioblastoma.

Permission for necropsy was limited to an examination of the brain, which weighed 1,600 gm. (Fig. 4). There was a herniation of brain

substance at the operative site, with dural adhesions. The right cerebral hemisphere was larger than the left. The gyri were flattened on both sides, with concomitant narrowing of the sulci. The anterior portion of the right cingulate gyrus was herniated beneath the falx for a distance of 6 mm. The right uncus was considerably more protuberant than the left, although a distinct tentorial groove was not present. The cerebellum and brain stem were normal externally. Section of the cerebrum revealed a tumor nodule approximately 5 cm. in diameter, filling the midportion of the right lateral ventricle and extending into the tissues of the adjacent hemisphere. It was sharply circumscribed, and appeared encapsulated in areas. It was firm to hard, gray white, and presented a finely fibrillar, multilobulated, somewhat whorled appearance in most areas. Zones of hemorrhage and soft yellow zones of necrosis were present. There were a few small cysts with a gelatinous fluid. The surrounding brain was markedly edematous. The midline structures were pushed to the left for distances of 1 to 4 cm. The septum and corpus callosum were rotated. The lateral ventricles were both narrowed, except for some dilatation of the temporal horn on the right. The third ventricle was narrowed, its superior portion being deviated to the left. The aqueduct was laterally compressed. A small linear vertical hemorrhage was present in the midline of the tegmentum of the midbrain. The cerebellum was normal. The gross impression was that the tumor was a meningioma.

Microscopically, tissues of varying character were observed, complexly intermingled. One was a highly cellular tissue composed generally of small, dark cells with indefinite cytoplasmic outlines and small, round or ovoid, relatively irregular, deeply staining nuclei. These cells were diffusely distributed in a reticulated matrix. Many of the cells were large and had large, bizarre, deformed nuclei; and many mitotic figures were observed. A few of the cells contained a hyaline, eosinophilic cytoplasm with somewhat stellate outlines. These cells had infiltrated individually into the adjacent cerebral parenchyma. Large zones of necrosis were present as well as a few small protein-filled cysts. This tissue was considered glioblastomatous.

A second tissue type was composed of elongated cells with indefinite cytoplasmic outlines and elongated or fusiform, moderately stained nuclei. These nuclei were irregular in size and shape and were frequently large and misshapen. They were arranged in long parallel rows, between which coarse eosinophilic fibers were recognized. A variant of this tissue, found frequently about blood vessels, was less cellular, some of the cells being smaller and somewhat shrunken, but

characterized particularly by the presence of a slightly basophilic, mucoid, intercellular substance. These tissues were considered mesenchymal and sarcomatous.

The blood vessels of the glioblastomatous areas revealed the characteristic hypertrophy and hyperplasia of endothelial and adventitial cells to varying degrees. In places, this was marked. In some such cases the cells showed a striking variability and disorganization, with occasional bizarre, giant forms (Fig. 3). In many instances, a continuity could be traced between the tissues of the vessel wall and the tissues forming the interlacing bands of the sarcoma. Larger islands of sarcomatous tissue surrounded by glioblastomatous tissue could be found also.

The fibers of the glioblastomatous tissue generally stained blue with phosphotungstic acid-hematoxylin,[1] red with the azocarmine technique,[2] and were unstained with the Wilder silver stain for reticulin.[3] The fibers of the sarcomatous tissue generally stained tan with phosphotungstic acid-hematoxylin, blue with the azocarmine technique, and many were positive with the Wilder reticulin method. The perivascular mucoid material was slightly metachromatic with toluidine blue in an aqueous media, this property being lost when the stained paraffin sections were passed through alcohol.

Summary. A 50-year-old woman died within 3 months of the onset of symptoms of a brain tumor within the midportion of the right lateral ventricle and the tissues of the adjacent hemisphere. The tumor was circumscribed, gray, and very firm. On section, it consisted of a complex admixture of glioblastomatous and sarcomatous tissue. The latter was thought to have arisen from the walls of the blood vessels of the former.

Case 3

A man (A15445), 24 years old, began to complain of constant throbbing headache approximately 7 months prior to death. This was followed by impairment of vision on looking to the left. His headaches became increasingly more severe and were accompanied by vomiting. On admission, the patient was alert and cooperative but shortly became drowsy. Examination revealed a left homonymous hemianopsia and bilateral choked disks. Reflexes, sensation, and motor power were normal. A right percutaneous carotid angiogram disclosed marked elevation of the middle cerebral artery. The venogram showed depression and straightening of the internal cerebral vein. A right temporal craniotomy disclosed a large mass at the temporoparietal junction, just above the sylvian fissure. Subtotal removal of the tumor was performed. The patient improved rapidly and was discharged from the hospital 2 weeks later. He received a course of high voltage x-ray therapy and remained well for about 5 months when he complained of severe low-back pain and difficulty in urination. He began to vomit again and had twitching of the left side of the body. On admission to the hospital, there was a generalized convulsive seizure with loss of consciousness. After regaining consciousness he was disoriented. There were inter-

mittent clonic movements of the right upper and lower extremities. Sensation seemed to be disturbed in both lower extremities. The course was progressively downhill, and he expired 12 days after the second admission.

The surgical specimen, weighing 11 gm., included fragments of a very cellular neoplasm (Fig. 5). The cytoplasm of the neoplastic cells could not be distinguished. The nuclei were round, ovoid, or elongated, and generally deeply chromatic. The cells varied greatly in appearance and numerous mitotic figures were present. The cells were packed in masses of viable tissue, generally about blood vessels, with large zones of necrotic débris intervening, so that an almost papillary structure was formed. The cells at the margins were even more closely packed as if by pressure from the necrotic zones. In most areas no orderly cellular arrangement could be recognized within these cell masses. In a few, the cells stained more lightly, were consistently ovoid or elongated, and were arranged in parallel rows. Some of these zones were close to the blood vessel walls. In some of these areas the azocarmine stain disclosed a few blue-staining fibers, which were generally absent elsewhere. A diagnosis of sarcoma was offered.

At necropsy, the viscera were congested, and there was bronchopneumonia of both lower lobes. The brain weighed 1,460 gm. There was a defect in the dura at the operative site, 9 by 7 cm., in the right temporoparietal area. This defect was filled by a firm, fibrotic mass, adherent to the underlying brain and projecting approximately 1 cm. above it. A similar zone of dural adhesion to brain, 3 by 2 cm., was present on the medial surface of the right occipital lobe. The gyri and sulci were normal, and there was no evidence of cingulate or uncal herniation. Section of the brain revealed a mass of abnormal tissue extending from the operative dural defect, posteriorly and medially, to reach the zone of dural adhesion at the medial surface of the occipital lobe. These tissues varied from soft to very firm, the former areas appearing necrotic. The color varied from gray-pink to yellow and brown. Small cysts were present. The neoplastic tissue extended to the ependymal surface of the ventricle. The leptomeninges of the spinal cord contained small, circumscribed, thickened areas of opacity. Distinct neoplastic tissue was not recognized on the cord.

Sections of the necropsy material revealed much of the tumor to be necrotic. The viable portion varied in appearance. Some zones consisted of elongated cells with indefinite cytoplasmic outlines and elongated, moderately chromatic nuclei. These cells were arranged in long parallel rows with coarse, eosinophilic fibers between them. There was moderate variability among these cells, but mitotic figures were not observed. Clumps of brown pigment and a few mast cells were present.

In comparison with the surgical specimen of about 6 months earlier, the tissue was far less anaplastic. In adjacent areas the tissue was less cellular, but the cells were considerably more variable in appearance. Occasional large, bizarre forms were present. Large quantities of hyalinized eosinophilic material were present between these cells. This hyaline material and the coarse fibers in the more cellular zones stained blue with the azocarmine method[2] and tan with phosphotungstic acid-hematoxylin.[1] These tissues were considered sarcomatous.

In one small zone a distinctly different type of tissue was encountered (Fig. 6). In this area small, dark cells, varying greatly in size, shape, and staining characteristics, were scattered without order in a reticular matrix. Some were large and bizarre. The nuclei were round or irregular and deeply chromatic. At the margin these cells were seen infiltrating the normal parenchyma individually for variable distances. The margin with the sarcomatous tissue was more distinct. No blue-staining fibers with the azocarmine technique were seen in this area, except in the walls of the blood vessels, many of which were hyperplastic. On phosphotungstic acid-hematoxylin stain, a few small clusters of blue-staining fibers were noted. This small area was considered glioblastomatous.

Summary. A 24-year-old man died about 7 months after the onset of symptoms referable to a tumor in the right temporoparieto-occipital region. He had been treated by subtotal removal and x-ray therapy. The surgical specimen was interpreted as a highly malignant neoplasm, probably a sarcoma. At necropsy, the bulk of the visible tumor was considered to be a sarcoma, less anaplastic than the original surgical specimen, with considerable hyalinization. A small area of tissue typical of glioblastoma multiforme was present also.

Discussion

Criteria for Diagnosis

The tumors described are of interest in that they were composed of an admixture of two dissimilar neoplastic tissues. One tissue resembled glioblastoma multiforme, containing characteristic small, dark cells diffusely distributed in an eosinophilic fibrillar matrix (Figs. 1 and 6). These fibers resembled glial fibers in that they were stained blue with the phosphotungstic acid-hematoxylin technique,[1] red with the azocarmine technique,[2] and were generally unstained in Wilder's silver preparations for reticulin.[3] The other tissue resembled fibrosarcoma, being composed of large cells with elongated or fusiform, moderately chromatic nuclei, often arranged in parallel rows along with deeply eosino-

philic coarse fibers (Figs. 1 and 5). These fibers resembled connective tissue fibers in that they were stained tan by the phosphotungstic acid technique, blue by the azocarmine method, and many were deeply stained in Wilder's silver preparations for reticulin. The two tissues were intimately interwoven in many areas. Each tissue was histologically malignant, as evidenced by mitotic figures, high cellularity, and significant atypism and variability, and zones of necrosis were present involving both tissues. The tumor grew rapidly, destroyed the normal parenchyma, and caused death in less than 1 year.

In the glioblastomatous areas, the marked hyperplasia and hypertrophy of the cells of the vessel walls, characteristic of that tumor,[4] were clearly evident. In some vessels these changes were particularly marked and were associated with an appreciable atypism, cellular variability, mitotic figures, and disorganization, with occasional distorted, highly bizarre cells, so that the appearance suggested that a neoplastic transition had occurred (Fig. 3). In some areas, these cells extended outward from the wall to form masses of sarcomatous tissue. The clearly sarcomatous, infiltrative tissue often formed rounded nodules and masses encompassed by strands of glioblastomatous tissue, as if the sarcomatous tissue had arisen from a structure located within the existing glioblastoma (Fig. 2). It is concluded that the sarcomatous tissue did develop as a result of neoplastic change in hyperplastic blood vessel walls, the vessels themselves being present as part of the reaction to the presence of the malignant glioma.

This interpretation is made with the knowledge of some diagnostic pitfalls which tend to render a distinction between the two types more difficult. The presence of elongated spindle-shaped cells is not in itself sufficient to warrant a diagnosis of sarcoma. It is well known that in some locations, particularly in the brain stem, glial cells may assume this shape. The elongated astrocytes which form the "piloid" astrocytomas of this region, and the less mature "spongioblasts" of the spongioblastoma polare, are typical examples. The term central neurinoma applied to some of these tumors reflects the similarity to the tumors of the peripheral nerve sheaths, with their abundant collagen fibers. These gliomas of the central nervous system may be distinguished by showing that the fibers among the cells are of glial, not connective tissue, character by the staining techniques utilized in the present study.

At the same time, the mere presence of connective tissue fibers within the tumor is not in itself sufficient to warrant a diagnosis of sarcoma. Many gliomas infiltrate the subarachnoid space and there evoke a response in the arachnoid cells of the leptomeninges which

will be associated with a proliferation of connective tissue fibers. Neoplastic glial cells will then lie in relation to connective tissue fibers as well as glial fibers. It usually is possible to recognize in the section that this process is taking place in the subarachnoid space. Such areas are characterized by marked disorganization rather than presenting the orderly arrangement of cells in parallel rows seen in sarcoma and in the sarcomatous portion of the tumors being described.

A Note on Nomenclature

Although in recent years the existence of such mixed tumors of the brain has received little attention, this possibility has been the subject of considerable study in the older literature. As early as 1895, Stroebe[5] referred to tumors of glial origin within which a sarcomatous growth derived from blood vessel walls could be distinguished. He urged that the much used term gliosarcoma should be restricted to such tumors containing both elements. It would seem that others experienced greater difficulty in distinguishing these tissues or differed in their interpretation. Hildebrandt[6] and even Ewing[7] subsequently used the term gliosarcoma to refer to tumors which resembled sarcomas but were believed to be of glial origin. The terms glioblastic sarcoma[8] and glioma sarcomatosum[9] appear to be of similar significance. Wohlwill[10] expressed some doubt as to the existence of true mixed tumors as described by Stroebe, although he mentioned what he thought to be the simultaneous apposite occurrence of a glioma and a sarcoma. Globus and Strauss[11] implied that Stroebe had misinterpreted as neoplastic the hyperplastic vascular reaction seen so commonly in gliomas, particularly in glioblastoma multiforme. In any case, the term gliosarcoma was used generally for many years for some of the malignant gliomas.[7] Largely through the studies of Globus and Strauss and of Bailey and Cushing,[12] such tumors have now been firmly established as of glial (ectodermal) origin, so that the term sarcoma would be inappropriate, and most of these tumors would now be classified as gliobastoma multiforme.

While one might be tempted to resurrect the term gliosarcoma for these tumors in the sense originally described by Stroebe and as an analogue to carcinosarcoma, such an attempt would undoubtedly lead to greater confusion and is considered inadvisable.

A Historical Review

In 1905, Babes[13] described a large tumor of the right temporal lobe and the midline basal structures of a 33-year-old woman who died after an illness of at least 3 months. Microscopically, the bulk of the

tumor was considered to be a sarcoma arising from the walls of blood vessels. However, proliferating neuroglial elements were seen, particularly in zones which had become necrotic. Although it was stated that it was not absolutely certain that the glial elements participated in tumor formation, this was strongly suggested by the author.

In 1910, Merzbacher and Uyeda[14] described tumor masses in the right cerebral hemisphere of a 25-year-old man, who died after an illness of 2½ years. The tumor consisted of two adjacent neoplastic masses easily distinguished on gross examination, the point of junction being sharply defined. Microscopically, one tumor was described as a sarcoma, the other as a glioma, and some interweaving of the tissues at the line of junction could be recognized. The sarcoma was traced to the leptomeninges, and the authors expressed the opinion that the glioma had arisen secondarily as a reaction to the irritation induced by the sarcoma. Subsequently, Wohlwill[10] described tumor masses in the right frontal lobe of a 55-year-old woman who had experienced convulsive episodes since the age of 9, and had shown more definitive clinical manifestations of brain tumor for 3 years. The tumor consisted of two discrete masses separated by a clearly recognizable band of white matter. Microscopically, it was recognized that one tumor was a sarcoma, the other a glioma, and while the tumors were apposed to each other, there was only one small microscopic area of mutual infiltration. The author suggested that the two tumors were of independent origin.

In 1934, Bailey and Ley[15] reported the case of a 6-year-old boy who had had one convulsive episode at 8 months of age, and developed definitive signs of brain tumor 4 months prior to death. At two operative procedures, large masses of tissue recognized as perithelial sarcoma were removed, but, in addition, some of the tissues removed at the second operation appeared to represent an astroblastoma. At necropsy, a large tumor mass in the right temporal lobe proved to be largely astroblastomatous, with a small mass of residual sarcomatous tissue in one area. The sarcomatous area was grossly separated from the glioma by a band of compressed brain. The authors expressed the opinion that the glioma was primary, and that the sarcoma arose at a later date from blood vessels. This may be the same case as that designated case 85 in the comprehensive study of brain tumors of children by Bailey, Buchanan, and Bucy[16] some years later.

In 1949, French[17] described a brain tumor in the right fronto-temporo-parietal area of an 18-year-old girl, who died 27 months after the onset of symptoms. Surgical material removed at the first oper-

ation, about 24 months before death, was typical of an astroblastoma. The biopsy material at a second operation, about 20 months before death, contained fragments of two different types of tissue. On section, one tissue was astroblastomatous while the other was characteristic of a perithelial sarcoma. No fragments containing both tissue types were seen. At necropsy, the remaining neoplastic tissue examined was all astroblastomatous, but much of the tumor had been inadvertently lost. The author expressed the opinion that he was dealing with two dissimilar tumors which arose independently in the same portion of the brain.

An additional report of the simultaneous occurrence of glioma and sarcoma is that by Nichols and Wagner[18] of a 69-year-old woman with a sarcoma in one cerebral hemisphere and a spongioblastoma polare in the other (case 7).

It would appear that the tumors described by Babes,[13] Bailey and Ley,[15] and French[17] may be similar to those described in this paper. The tumors described by Merzbacher and Uyeda[14] and Wohlwill[10] are less likely to be of this nature, while the situation described by Nichols and Wagner[18] is almost certainly unrelated.

The Significance of the Observations

These tumors are of limited significance in a clinical sense. Glioblastoma multiforme shows a poor response to any known therapeutic procedure, and the prognosis is not altered by the presence or absence of a superimposed sarcomatous change in its blood vessels. The sarcomatous tissue is very much harder than the glioblastomatous tissue, and the neurosurgeon who anticipates a glioblastoma might be misled by the consistency of such tumor into thinking that he is dealing with a benign meningioma. This would be particularly true when the tumor presents itself on the surface of the brain and appears to form a circumscribed mass, as in case 1 of this report. Glioblastoma also has been reported to assume such apparently circumscribed surface forms.[19]

These tumors may prove to be of greater significance because of the contribution their study might make to our knowledge of the pathogenesis of neoplasms. The relationship of one neoplastic tissue to the induction of neoplastic change in another tissue is of fundamental interest. This problem has been studied statistically by comparing the observed incidence of neoplastic change in more than one tissue with the incidence calculated on the supposition of unrelated coincidence. The most recent such study, that of Watson,[20] concludes

that the incidence of true multiple tumors is statistically coincidental and that the data did not support the thesis of either a constitutional tendency to develop a second cancer or of the development of an immunity to such second cancer. Earlier studies, such as those of Bugher,[21] Slaughter,[22] and Warren and Ehrenreich,[23] suggest that the observed incidence is significantly greater than that expected by chance.

More direct information has been sought in studies on tumors of other organs analogous to those being described in the brain. Such tumors, the carcinosarcomas, are believed by some to be composed of mixed malignant epithelial and mesenchymal tissues. These tumors have been most difficult to analyze, and their very existence is a matter of controversy. Saphir and Vass[24] reviewed 153 previously reported cases of this type, and accepted only 3 or 4. Willis[25] was reluctant to accept any human case of this type, although he believes that some animal tumors might be of this character. Harvey and Hamilton,[26] on the other hand, aware of all diagnostic pitfalls, are convinced of their existence, and reported 6 cases of their own.

In animals, tumors of this type have been induced by carcinogenic agents.[27] Experimental data have been interpreted as indicating the malignant transformation of the connective tissue stroma of transplanted animal tumors.[28-31] In some of these reports it is conceded that the true sarcomatous nature of the morphologically sarcoma-like neoplastic tissue is not conclusively demonstrated.[31] Others are convinced of the accuracy of such designation[29,30] and one report offers evidence of this based on the cultural growth characteristics of the neoplastic tissue and its inhibitory effect on the growth of fibroblasts *in vitro*, a property characteristic of sarcoma.[29] The major difficulty arises in attempting to distinguish carcinoma cells which assume a spindle shape and are arranged in parallel rows, from neoplastic fibroblasts similarly arranged. Since there is almost always a connective tissue stroma with carcinoma, the presence of connective tissue fibers among the tumor cells is not a distinguishing feature. In this regard, the presence of an essentially ectodermal, glial stroma in the brain greatly simplifies this problem. This stroma is composed mainly of astrocytes and their processes, with the oligodendroglia and the microglia, the latter of mesenchymal origin, contributing to only a slight degree. These glial fibrillary processes may be differentiated from collagenous fibers by the staining methods which have been described. In consequence, it is often possible to distinguish a tissue composed of elongated or spindle-shaped glial cells from one composed of fibro-

blasts by the staining characteristics of the accompanying fibers.

Within the substance of the brain, a primary fibrosarcoma is most likely to arise from the blood vessels. The mesenchymal tissues of the brain include the blood vessels, the microglia, and the meninges. The microglial cells have the capacity to form phagocytes but it is to be doubted that they can influence the deposition of connective tissue fibers, since these are not observed in circumstances in which a marked microglial proliferation is noted, as in cerebral infarction. Neoplasms considered to be of such origin are certainly rare, and their delineation from other types of tumors has been a source of confusion.[32] There is little question that the mesenchymal cells of the vessel walls and of the leptomeninges may influence the deposition of connective tissue fibers. Neoplasms of leptomeningeal origin form the common meningioma group, while the occurrence of neoplastic change in the blood vessel walls is reflected in the relative frequency with which primary sarcomas of the brain are characterized as "perithelial."[33] The observations which are considered to implicate the blood vessels as the source of the sarcomatous elements of the tumors being reported have been described (Figs. 2 and 3).

The capacity of the cerebral blood vessels to reactive hyperplasia, particularly in relation to neoplasms, deserves emphasis. In frequency and degree this far exceeds that noted in other organs. In the brain vascular hyperplasia occurs in a variety of circumstances, including anoxia, nutritional deficiencies, and inflammation, but this is comparatively moderate. A very marked vascular hyperplasia occurs almost uniformly in glioblastomas, so that this is often included as a diagnostic criterion for the recognition of this tumor.[4] A similar change may be noted with some other brain tumors as well, including some metastatic tumors.

The relatively slight vascular hyperplasia noted with astrocytoma and the almost constant marked vascular hyperplasia with glioblastoma are of special interest because of recent studies defining a relationship between these tumors. Although considerable controversy remains, we are convinced of the accuracy of the fundamental concept offered by the Mayo Clinic group,[34] in which these tumors and some others are considered to form a single group of varying anaplasia and malignancy. Astrocytoma and glioblastoma bear the same relation to each other as adenoma and adenocarcinoma, except that intermediate forms are much more common, and the transition of the benign to the malignant form more frequently observed. In this sense, the vascular hyperplasia may be described as tending to parallel the de-

gree of malignancy within the group. Studies of these features are contemplated.

An incidental observation relates to case 3 of this report in which the glioblastomatous tissue formed only a minute fraction of the whole tumor, the bulk of which was sarcomatous. There are many reports among those dealing with mixed tumors in other organs which suggest that the sarcomatous elements possess a greater growth potential than the carcinomatous.[26,28-30] The same may be true of the mixed tumors of the brain. The possibility exists that some of the primary sarcomas of the brain, especially some of those characterized as "perithelial," may have arisen by sarcomatous change in the vessels of a glioblastoma with subsequent overgrowth of the sarcoma obscuring or destroying the glioblastoma.

SUMMARY

Three cases of primary brain tumor are described in which the neoplasm was composed of an admixture of dissimilar tissues, both malignant. One component resembled the glioblastoma multiforme; the other, a spindle cell fibrosarcoma.

Evidence is presented to suggest that the sarcomatous elements arose by neoplastic change in the markedly hyperplastic blood vessels regularly seen in the glioblastoma multiforme.

It is suggested that the sarcomatous elements may grow more rapidly than the glioblastomatous tissue, obscuring or obliterating the latter. Some of the primary sarcomas of the brain may have arisen in this fashion.

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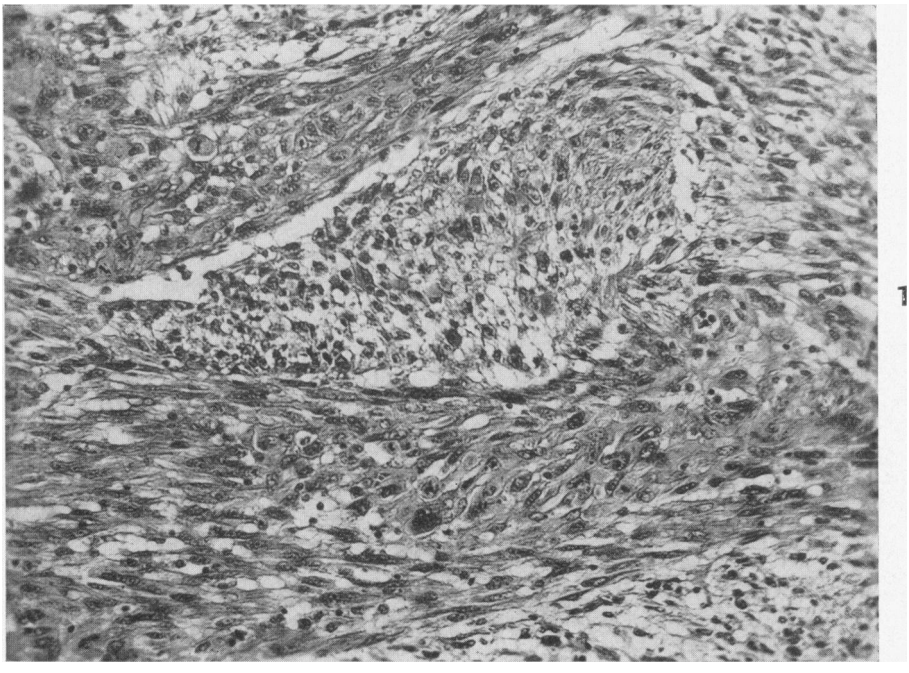
LEGENDS FOR FIGURES

FIG. 1. Case 1. Tumor, showing admixture of glioblastomatous and sarcomatous tissues. Hematoxylin and eosin stain. × 150.

FIG. 2. Case 1. Tumor, showing circumscribed islands of sarcomatous tissue encompassed by glioblastomatous tissues. Azocarmine stain. × 80.



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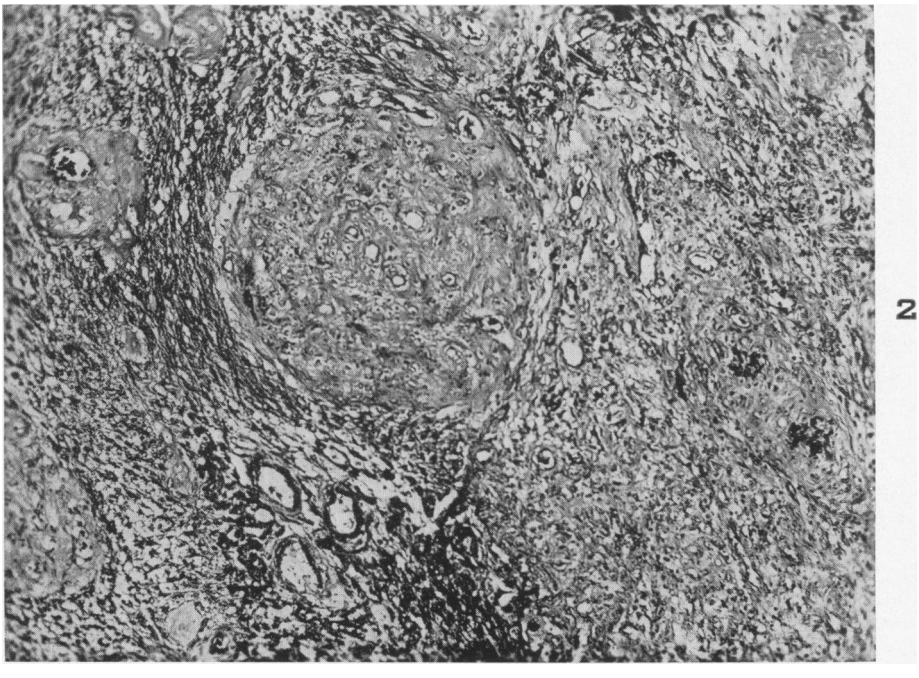

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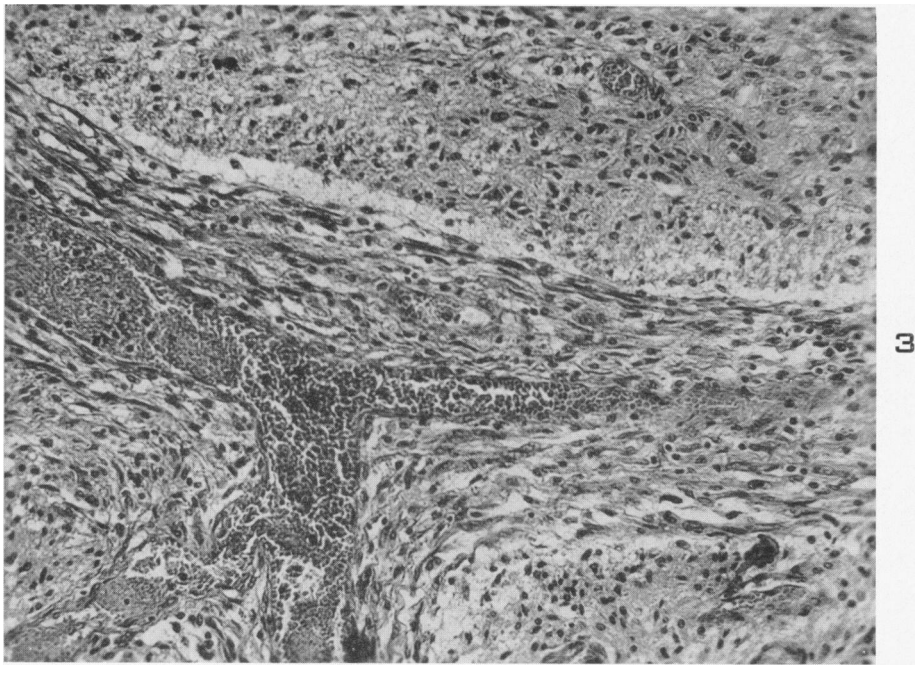
FIG. 3. Case 2. Tumor, showing variability and disorganization of the cells of a blood vessel within a glioblastomatous area. Hematoxylin and eosin stain. × 170.

FIG. 4. Case 2. Coronal section of brain showing position and gross appearance of tumor. × 7/8ths.



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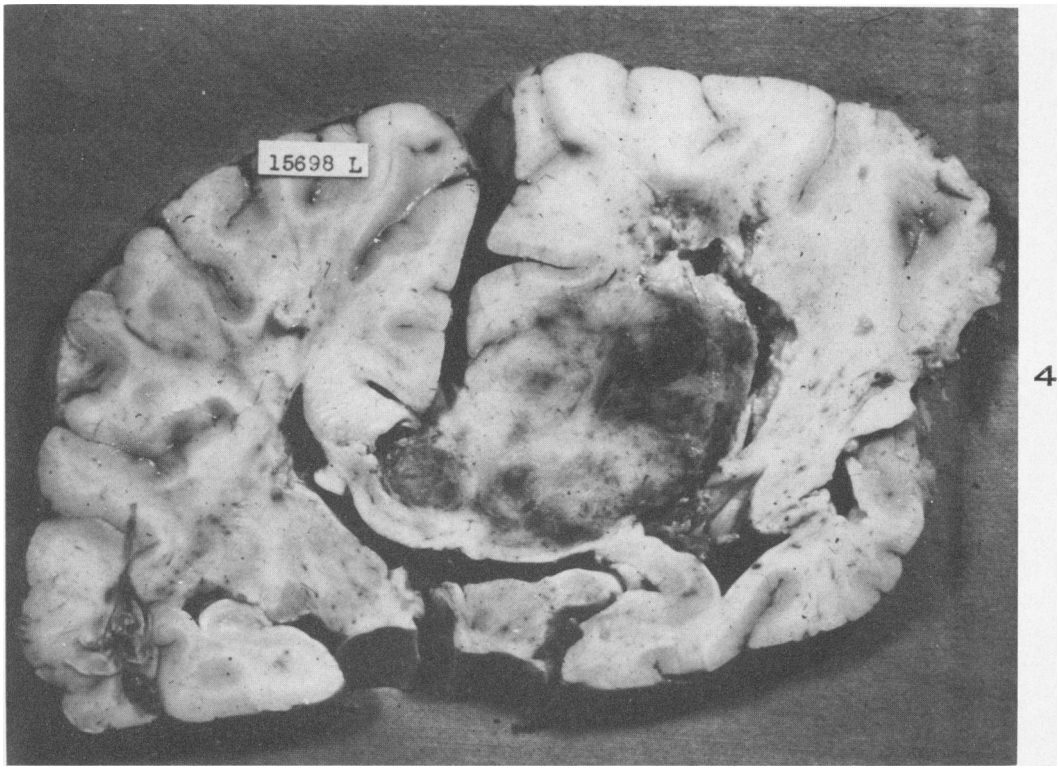

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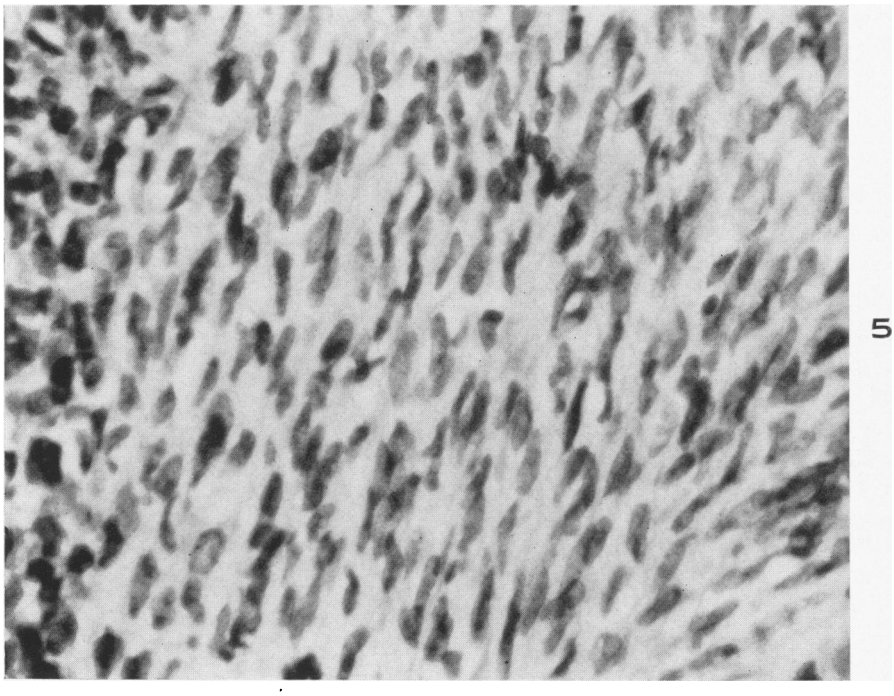
FIG. 5. Case 3. Tumor removed at surgery, showing sarcomatous features. Hematoxylin and eosin stain. × 550.

FIG. 6. Case 3. Portion of tumor in necropsy specimen, showing glioblastomatous area. Hematoxylin and eosin stain. × 530.



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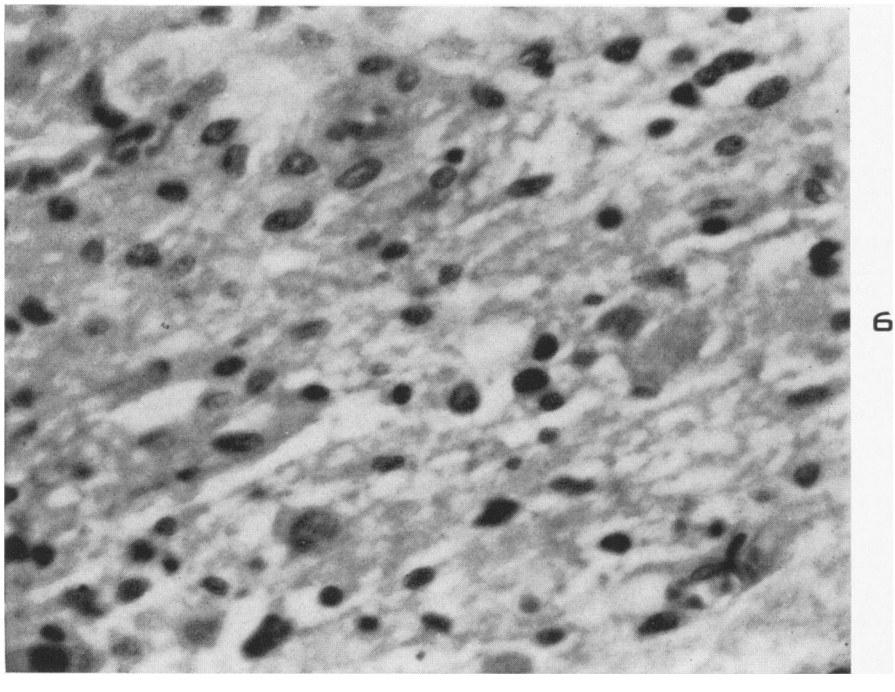

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