Spinal Gliosarcoma: A Light, Immunohistochemical and Ultrastructural Study*

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ABSTRACT

Gliosarcomas are mixed tumors of the brain containing both malignant neuroectodermal and mesenchymal components. Over 100 cases have been reported within the brain; however, to our knowledge, this is the first reported case located primarily within the spinal cord. Along with a review of the literature, the light, immunohistochemical and ultrastructural findings of a spinal gliosarcoma are reported in a 41-year-old woman with a previously diagnosed oligodendroglioma of the cerebellum 15 years earlier and a concurrent pituitary adenoma. The spinal tumor appears to be morphologically identical to its intracranial counterpart.

Introduction

Extragonadal tumors which contain both malignant epithelial and mesenchymal elements are encountered infrequently. These tumors are classified as carcinosarcomas or mixed tumors. Within the central nervous system, the concept of gliosarcoma (GS) or mixed glioma and sarcoma was accepted after the publication of three such cases by Feigin and Gross in 1955.1 The term gliosarcoma is attributed generally to Stroebe, who first used the term in an article in 1895.2 For a tumor to be classified as a GS, it has to be composed of two distinct malignant cell populations. The glial component shows positive immunoreactivity for glial fibrillary acidic protein (GFAP) and the sarcomatous cells are invested by reticulin fibers.3 Most commonly, the glial component is a glioblastoma multiforme (GBM), but the sarcomatous elements may vary although the histological picture is frequently one of fibrous histiocytoma.4,5,6,7 Gliosarcoma is 2 to 8 percent as frequent as glioblastoma multiforme,7,8 currently, there are well over 100 cases described in the literature. In a recent study, no sig-
significant difference was found between GS and GBM with regard to age, gender, tumor location within the brain, size, and survival. The clinical and morphological features of a spinal GS developing in a 41 year old woman who had been previously diagnosed and treated (15 years earlier) for an oligodendroglioma of the cerebellum are reported here.

Materials and Methods

In 1973, at age 26, the patient was treated for an oligodendroglioma of the cerebellum by surgical removal that was followed by radiation therapy and a shunt operation at the National Naval Medical Center Bethesda, Maryland.

Thirteen years later in 1986, the patient underwent decompressive laminectomy (T-6 to L-2) for adhesive arachnoiditis and paraplegia. Shortly thereafter, a one centimeter pituitary adenoma without evidence of recurrence of the cerebellar tumor was discovered by magnetic resonance imaging. Treatment for the pituitary adenoma was determined to be unnecessary.

In 1988, at age 41 and 15 years after the removal of the oligodendroglioma, the patient underwent laminectomy with subtotal resection of a cystic intraspinal sausage-like tumor which filled the spinal canal from T-12 to L-2 and appeared to have arisen from the ventral surface of the spinal cord. The morphological material for this report derives from this operation. The patient received post operative radiation therapy. Less than a year after the removal of the spinal tumor, the patient had increased pain in the left flank, for which she underwent open thoracic cordotomy. Computerized tomography of the pelvis revealed a large, intraspinal tumor in the lumbar sacral canal extending beyond the neural canal anterior to the sacrum into the lower pelvis. Again there was no evidence of recurrence of the cerebellar tumor. The patient died two months after the cordotomy. An autopsy was not performed. The patient did not have any family history of multiple tumor syndrome.

Small pieces of tissue for morphological examination were available from the 1988 resection of the thoracic lumbar tumor. These were formalin fixed, paraffin embedded and stained with hematoxylin and eosin and Wilder’s reticulin stain. The same paraffin embedded blocks were used for immunohistochemistry with antisera against vimentin, glial fibrillary acidic protein (GFAP)* and S-100 protein.† Immunoreactivity was revealed by the avidin-biotin complex (ABC) method with appropriate positive and negative controls. Tissue for electron microscopy was fixed in 3 percent glutaraldehyde, post fixed in 1 percent osmium tetroxide, and embedded in plastic. Thin sections were stained with uranyl acetate and lead citrate.

Results

A prominent light microscopic feature of this intraspinal neoplasm was the presence of numerous tumor giant cells exhibiting hyperchromatic multinucleation along with abundant, finely vacuolated, acidophilic cytoplasm. Noted together with the giant cells were slender elongated tumor cells surrounded by collagen and larger plump cells with abundant cytoplasm (figure 1). Frequent mitoses, some bizarre in shape, were noted. Wilder’s reticulin stain showed an investment of the individual giant and spindle cells. Between the sarcomatous appearing areas described were a few inconspicuous, smaller cells with irregular nuclei. Some of these cells had a more prominent eosinophilic cytoplasm. Clearly identifiable areas of glioma were not seen. Hyperplastic proliferation of

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ments were noted in addition to large numbers of mitochondria. The nuclei of all the tumor cells were highly irregular with prominent heterochromatin and nucleoli and frequent nuclear bodies. Cellular junctions were not present. Osteoblastic, chondroblastic, or rhabdomyomatous differentiation was not noticed. Degeneration and necrosis with surrounding inflammatory cells were prominent in the tissue submitted for electron microscopy.

Discussion

In our report of a spinal GS, the mesenchymal portion of the tumor was characterized by reticulin investment of the individual tumor cells, vimentin immuno-endothelial cells of small blood vessels was noted. Areas of degeneration and necrosis were widespread.

Immunohistochemistry demonstrated positive reactivity for GFAP and S-100-protein in several of the smaller inconspicuous cells, but rarely in the spindle and giant cells (figure 2). Vimentin, on the other hand, immunostained primarily the giant cells and the spindle cells. By electron microscopy, the large and bizarre multinucleated giant cells and some of the elongated cells were often dominated by dilated profiles of rough endoplasmic reticulum in addition to a normal complement of organelles (figure 3). They were surrounded by bundles of collagen. In a few of the multinucleated giant cells, centrosomes were noted containing up to eight centrioles. These plump cells often contained primary and secondary lysosomes. In some of the smaller cells bundles of intermediate fila-

**Figure 1.** Photomicrograph showing several large and irregular multinucleated giant cells. Also noted are elongated and plump cells with abundant cytoplasm (hematoxylin-eosin, original magnification ×300).

**Figure 2.** Staining of a few of the small tumor cells with the GFAP antibody. The giant cells are not stained (hematoxylin counterstain, Avidin-biotin complex method, original magnification ×640).
nopositive and GFAP immunonegative features of the giant cells and the ultrastructural findings. This portion had some similarity to a malignant fibrous histiocytoma. The isolated small cells, which were positive for GFAP and possessed intermediate filaments, indicated that a small portion of this tumor was a glioma, most likely a glioblastoma multiforme (GBM).

The presence of a mixture of GBM and sarcoma in a nervous system tumor could represent either a tumor arising from a high grade GBM with malignant transformation of the mesenchymal component into a sarcoma, or it could indicate the invasion of a primary meningeal sarcoma or malignant meningioma into the brain, which initially incites a hyperplastic neuroglial reaction that eventually undergoes a malignant transformation into a GBM. In the first and most common situation, the mixed tumor is called a gliosarcoma (GS); in the latter, it is called a sarcoglioma which morphologically is characterized by an inner core of sarcoma surrounded by a peripheral rim of glioma. The tumor described by us did not have this appearance, but consisted of a haphazard mixture of glioma and sarcoma; therefore, it belongs to the GS category. Gliosarcoma can be separated from giant cell glioblastoma by the reticulin enclosure of the individual malignant mesenchymal cells just as the presence of GFAP and intermediate filaments in GS indicate that the tumor is more than a primary or secondary sarcoma of the brain.

The possible origin of the sarcomatous component has caused considerable speculation. With the prominent vascular proliferation present in GBM, it is not surprising that an endothelial origin should be considered. Feigin et al visualized a spectrum of changes ranging from slight vascular endothelial hyperplasia to infiltrating sarcoma extending from the hyperplastic blood vessels. In an immunohistochemistry study, Factor VIII related antigen was positive not only in all endothelial cells but also in a few scattered cells, including giant cells in the sarcomatous areas. Another study demonstrated intense cytoplasmic staining for Ulex Europeus agglutinin 1 (UEA-1) in a number of sarcomatous cells, and Weibel-Palade-like bodies were noted in both vascular endothelial and adjacent sarcoma cells. Other more recent studies, however, failed to identify the presence of Factor VIII and UEA-1 outside the endothelial cells or the presence of Weibel-Palade bodies in the sarcoma cells outside the blood vessels. The endothelial cell has, therefore, been abandoned as the cell of origin for the sarcomatous component. More recent speculation about the histogenesis of the sarcomatous component has centered on undifferentiated mesenchymal cells. It may be of interest at this point to note that it is often
more useful to classify neoplasms on the basis of appropriate phenotypic differentiation markers, rather than on the basis of questionable assumptions about their origins.  

The admixture of neoplastic epithelial and mesenchymal cells, which have been noted in carcinosarcoma and gliosarcoma, have been explained as occurring by three different mechanisms.  

First of all, the epithelial neoplasm might induce a benign (pseudosarcomatous) reaction in the connective tissue. Secondly, two spatially distinct neoplasms representing a carcinoma and a sarcoma might eventually grow close enough to mingle and form a collision tumor. Finally, a single malignant clone can have the simultaneous capacity for both epithelial and mesenchymal differentiation and thus form a composite tumor. It is difficult to accept the "pseudosarcomatous reaction" as being benign when both the gliomatous as well as sarcomatous portions are represented in the metastases.  

Collision tumors do occur, but very infrequently. This leaves the composite tumor explanation as the most likely for the majority of GS.  

The proportion of the gliomatous versus sarcomatous components can vary considerably in GS from those cases in which the first biopsy revealed GBM and only tissue from later stages of the tumor showed additional sarcoma to those cases, such as ours, in which the gliomatous portion could be recognized only by immunohistochemistry. In the former instance, the additional sarcomatous tissue was mostly (8 of 12 patients) discovered following surgery, radiation therapy, and/or chemotherapy. Our patient underwent decompressive laminectomy in the same region of the spinal cord two years before the GS was diagnosed.  

Our patient appeared to have a propensity for developing tumors of the nervous system. It is highly unlikely that the GS is a metastasis from the cerebellar oligodendrogloma which was diagnosed and treated 15 years previously. No area of the spinal GS had morphologic similarity to an oligodendrogloma. There is, however, a report of a GS where the gliomatous portion was an oligodendrogloma of the temporal lobe with an angiosarcomatous component; four months later, an intramedullary and subdural GS was discovered. To our knowledge, our case is the first GS occurring primarily in the spinal cord.  

Finally, it is of interest to note that multiple intracranial tumors of different histologic types have been described. Manuelidis and Solitaire reviewed intracranial tumors associated with GBM. They found that after meningiomas, pituitary adenomas were most frequently noted in association with GBM and that multiple tumors overwhelmingly occurred concurrently. Our patient had a small pituitary adenoma discovered one and one half years before the GS was diagnosed.  

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