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Case report

Gliosarcoma: A rare primary CNS tumor. Presentation of two cases

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ABSTRACT

Introduction: Gliosarcoma is a very rare primary mixed tumor in the central nervous system, with a biphasic pattern consisting of glial and malignant mesenchymal elements. Its onset is between the fourth and sixth decade of life, and it has a male/female ratio of 1.8/1. Here we present two cases of Gliosarcoma treated in our department.
Discussion: The monoclonal or biclonal origin of its biphasic nature is still subject to debate; hence the importance of its diagnosis and histogenesis.
Results: Standard treatment consists in surgical resection of the tumor followed in some cases by external radiotherapy and chemotherapy.

1. Introduction

Gliosarcoma (GS) is a very rare primary mixed tumor in the central nervous system, with a biphasic pattern consisting of glial (anaplastic astrocytes) and malignant mesenchymal elements. Its onset is between the fourth and sixth decade of life, and it has a male/female ratio of 1.8/1. The monoclonal or biclonal origin of its biphasic nature is still subject to debate; hence the importance of its diagnosis and histogenesis. Treatment consists in surgical resection of the tumor followed by external radiotherapy, and chemotherapy in some cases. Here we present two cases of GS treated in our department.

2. Clinical cases

2.1. *Case #1*

A 58-year-old male consulted for left-sided hemicranial cephalea, long-standing dizziness and instability, downfall and expressive aphasia. Brain MRI showed a multinodular cystic lesion in the left temporal region measuring 5 cm, and an anterior portion of the uncus with a mass effect shifting the midline.

A left-side frontotemporal craniotomy and complete macroscopic resection were performed. Histological

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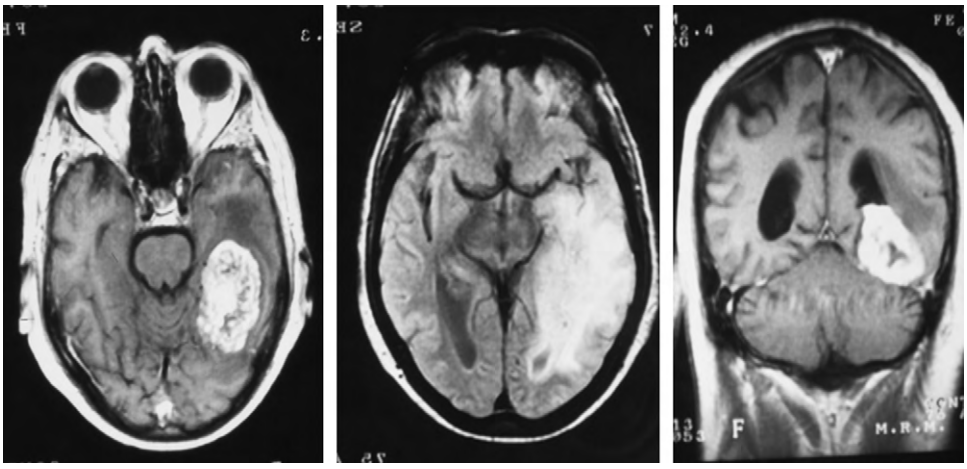

Fig. 1 – MRI-hyperintense lesion.

examination showed a biphasic pattern tumor, with unusual fusiform areas in a collagenized stroma, and areas of glial cell proliferation in a fibrillar matrix with vascular proliferation and necrosis, which were positive for reticulin staining. Immunohistochemistry showed glial protein expression in the glial component and positive vimentin in both. A post-operative period passed without complications, bringing a gradual improvement in the language aphasia with no neurological deficit. Post-operative MRI showed some post-operative changes, a cystic cavity with mild edema, and enlargement of the left temporal horn.

The patient was then referred to our department and underwent a post-operative radiotherapy treatment using an isocentric field technique, with 6 MV photons, receiving a total dose of 60 Gy in 30 fractions (2 Gy per fraction). Adjuvant Temozolamide therapy was administered. The treatments were followed by a free disease period of 5 months. Then the patient moved to another city and we could not continue his follow-up.

2.2. *Case #2*

A 59-year-old male consulted for right-side hemiparesia and global aphasia. Neurological examination revealed no further deficit. Brain CT revealed lesions in the left frontoparietal region and in the paraventricular white matter, which were interpreted as an infarction of the middle brain artery. Brain MRI also showed a hyperintense lesion in the frontoparietal region mimicking a tumor. Neuronavigator-assisted left frontoparietal craniotomy and an extended biopsy of the lesion were performed.

Histological examination revealed a malignant brain tumor with a biphasic pattern, with glial tissue and a mesenchymatous component. The glial component had characteristics of glioblastoma, cellular atypia, ischemic necrosis, an increased mitotic rate and expression of fibrillary acidic protein. The mesenchymal component had groups of fusocellular cells. Immunohistochemistry was positive for vimentin and reticulin fibers. Infiltration of adventitia and a muscular layer on the wall of a vessel for gliomatosis cells positive for fibrillar glial protein was revealed.

The patient was referred to our department, where an adjuvant three-dimensional conformal radiotherapy treatment was performed, with 6 and 18 MV photons, delivering a total dose of 60 Gy in 30 fractions (2 Gy per fraction). The patient responded well until 8 months later, when there was a sudden decline in his general condition, leading to death soon afterwards.

3. Discussion

Malignant gliomas account for 35–45% of all adult brain tumors, and approximately 85% are glioblastomas.[1] So, glioblastomas account for 29.7–38.2% of all adult brain tumors. Gliosarcoma constitutes approximately 2% of all glioblastoma, and accounts for 0.59–0.76% of all adult brain tumors (Figs. 1–3).

GS was described for the first time in 1895 by Stroebe[2] and defined as a subtype of glioblastoma by Feigin and Gross[3] in 1955 and Rubinstein[4] in 1956.

GS is currently defined as a morphological variant of glioblastoma multiforme, which accounts for between 1.8 and 8% of cases. It typically affects older men, with onset between the fourth and sixth decades of life and a male/female ratio of 1.8/1, although some cases of infantile gliosarcoma have also been described.[5]

It is normally located in the supratentorial region with a slight preference for the temporal lobes,[6] although it can also affect the frontal, parietal and occipital lobes.[7] In some cases, metastatic extraneural dissemination has been described to occur via the blood to lung, bone and lymphatic ganglion tissues, as well as intraaxial, brainstem and spinal cord dissemination.[6,8,9] It is clinically and radiologically indistinguishable from glioblastoma multiforme.[10]

Patients' clinical profiles may include a syndrome of endocranial hypertension such as cephalea, dizziness, vomiting, papilledema, convulsions and motor deficit. CT shows a well-defined hyperdense lesion with a marked perilesional edema, necrotic areas and a mass effect. MRI showed a hyperintense lesion in T1. An isointense lesion is visible in the T2 sequence.[11,12]

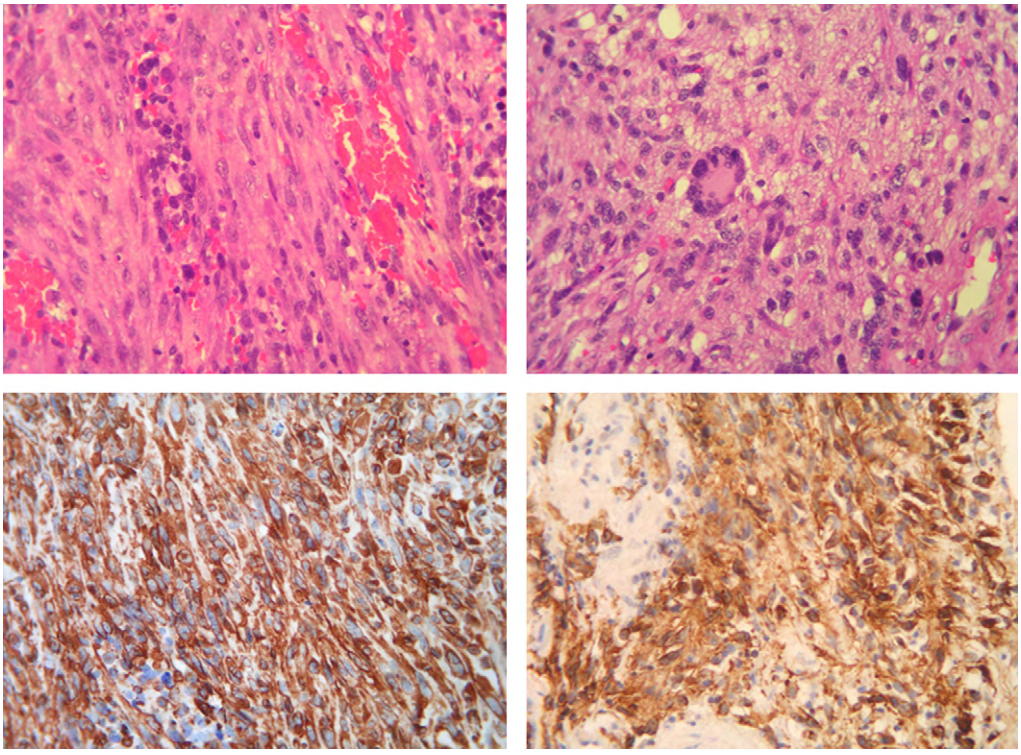

Fig. 2 – Histology: mesenchymal and glial components. HE 400×. IHC, GFAP, and vimentin.

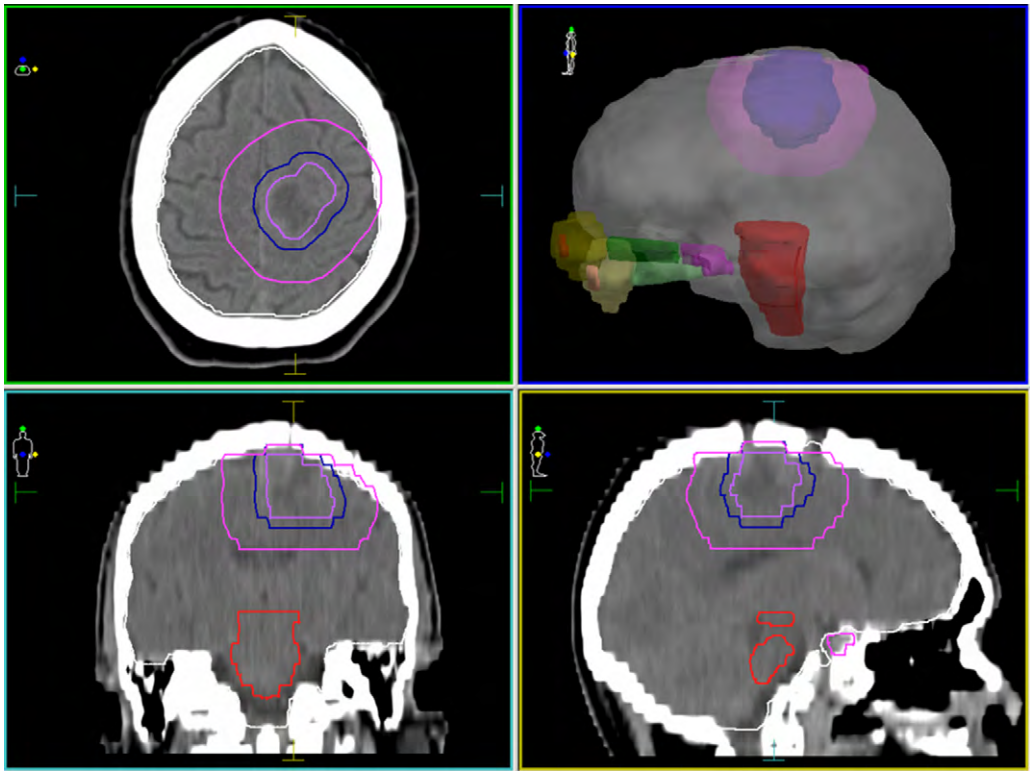

Fig. 3 – Radiotherapy plan. Inner magenta line: surgical bed; blue line: PTV2 or boost (surgical bed +5 mm) (CTV2) +3 mm (PTV2); outer magenta line: PTV1 (surgical bed +20 mm) (CTV1) +3 mm (PTV1).

Histologically it is a mixed tumor consisting of two components which are mesenchymal and glial. The sarcomatous mesenchymal tissue presents spindle-shaped cells; it may present a fishbone architecture typical of the fibrosarcomas that are either distinguished or forming disorganized fascicles and pleomorphic cells. GS has been described to show mesenchymal differentiation other than fibrosarcoma, as occurs in epilethial differentiation, myofibroblasts, cartilage, bone, angiosarcoma, smooth muscle and striated muscle.[13–19] The glial component is astrocytic and mimics glioblastoma.

Reticulin stains demonstrate a single-cell pattern of reticulin positivity, which correlates with basal lamina deposition ultrastructurally, whereas the pure glial areas of the same tumors are reticulin negatives.[20]

The immunohistochemical findings enable to identify the glial component of the glial fibrillary acidic protein (GFAP) and the protein S-100. Among the epithelial components are cytokeratins and immunoreactivity for p53 and, occasionally, actin, if there is a muscular component.[21]

There is some controversy regarding the pathogenesis of gliosarcoma. Some authors maintain that there occurs a sarcomotose transformation of the endolethial glioblastoma cells, while others suggest that the sarcomotose component originates in the smooth muscle cells of adventitia of vessels or pericytes, fibroblasts, and undistinguished mesenchymal cells.[4,10,22]

More recent research suggests a monoclonal origin for the two components with a phenotype dedifferentiation, based on the identical genetic alterations in the two components of the tumor, i.e. the presence of p53 and PTEn mutations, p16 deletions and a coamplification of MDM2 and CDK4.[22,23] The predominance of sarcomatosis is associated with a better prognosis and a longer period of time without recurrence.[24]

The morphological differential diagnosis should include glioblastoma, gliofibroma and other sarcomas. Occasional glioblastomas may show considerable connective tissue reaction which may be caused by meningeal invasion by tumor or organization of zones of necrosis, or as a response to marked microvascular proliferation. The lack of the mosaic pattern alternating areas of glioma and sarcoma should assist in differential diagnosis [20,25].

Gliofibroma is a much less common entity which is also a mixture of astrocytic and mesenchymal elements, mostly in a spindle cell pattern. It usually affects children and is more common in females. Several of the reported examples have been in the spinal cord. The tumor cells often have some surrounding reticulin staining and the basal lamina seen by electron microscopy. It is a biphasic tumor composed of a glial component that ranges from low-grade to high-grade differentiation, but the stromal component is a non-sarcomatous type. The prognostic of gliofibromas is usually favourable with occasionally aggressive comportment.[26,27]

Primary sarcomas of the CNS are extraordinarily rare. Metastatic sarcomas are more common, although rare. In either case there is no double glial and sarcomatous expression, which defines gliosarcoma.[25,27]

The prognosis for GS is generally poor, with an average survival of less than 8–24 months from the onset of symptoms.[6] The brain edema with increase in intracranial pressure and herniation of the temporal lobe are the immediate causes of death.

The standard treatment is the same as that administered for glioblastomas, namely surgical resection of the tumor and followed in some cases by external radiotherapy and chemotherapy.[28] The mean overall survival of patients receiving radiotherapy is longer (10.6 months) than for those treated only with surgery (6.2 months).[29]

Radiotherapy should begin 4 weeks after a surgery. Identification of the clinical target volume (CTV) is recommended, using post-surgical MR with gadolinium in a T1 sequence.

The dominant pattern of failure of glioblastoma is within the contrast enhancing lesions seen on CT or MRI, up to 80% in the field of tumor and up to 22% in the first centimeter adjacent to surgical bed.[30] These studies have been done by correlating information from CT and MRI studies of pathological tissue samples from stereotactic brain biopsies made among patients initially untreated, and serial samples of brain during surgery or autopsy The intent of the current study is to focus treatment exclusively at the enhancing residual mass following surgery.

More recent studies[31,32] of conformal radiotherapy define two or three-volume targets in relation to the contrast enhancement defined as macroscopic residual tumor volume to achieve higher dose. In volume corresponding to the GTV plus a small margin of 0.5 cm, the rate of relapse observed was as high as 78–89%. This zone corresponds to the target volume estimate that receives the highest dose. Beyond a distance of 2.5 cm from GTV the relapse rate is low, 3–9%. All these studies confirm that the main mode of relapse is local, in a defined volume around the GTV with a margin of 2–3 cm. The RTOG trials 98-03 and 08-25 recommended volumes are: CTV1 = surgical bed and/or residual tumor +20–25 mm, CTV2 = surgical bed and/or residual tumor +5 mm. The planning target volume (PTV) is an additional margin of 3–5 mm, depending upon localization method and reproducibility, at each center.

Thanks to breakthroughs in neuroimaging (CT, MRI and PET), computer dosimetry and conformal radiation techniques such as 3D-CRT, it is possible to administer uniform doses in target volumes while avoiding the effect on normal tissues.[33,34] Doses of over 60 Gy and boost on the surgical bed do not appear to influence survival. Recent studies on dose escalation with radiosurgery, an interstitial implant, or IMRT have not shown a significant increase in survival. The studies of dose hyperfractionation and intraoperative radiotherapy are controversial.[35,36,37]

GS is a chemoresistant tumor, but the literature suggests that the use of Temozolamide at the same time as radiotherapy as a first-line treatment at doses of 75 mg/m^2 per day 1 h before radiotherapy and at weekends, and after the radiotherapy treatment is concluded, as an adjuvant treatment in doses of 150 mg/m^2 for 5 cycles, slightly increases survival.[33]

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