GLIOSARCOMA

Report of four cases with immunohistochemical findings

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ABSTRACT - Gliosarcoma (GSa) is a rare primary central nervous system neoplasm (CNS) characterized by biphasic histological pattern with both glial and sarcomatous components. Our objective is to describe the clinical, morphological and immunohistochemical features of four cases of GSa and to discuss its pathogenetic mechanisms. The male:female ratio was 3:1. The mean age was 39 years, ranging from 19 to 48. Headache was the commonest clinical symptom. All patients underwent craniotomy with microsurgery and total resection of the tumor. Diagnosis was suspected due to microscopic architecture and confirmed by detection of reticulin fibers through histochemical techniques. Immunohistochemical analysis was positive for p53 in both glial and sarcomatous cells in all four cases. EGFR was focally positive in glial cells in one case. Our findings support monoclonal origin of GSa involving the TP53 tumor-suppressor gene. However, alternative pathways cannot be ruled out.

KEY WORDS: brain neoplasms, gliosarcoma, immunohistochemistry.

Gliosarcoma: relato de quatro casos com achados imuno-histoquímicos


PALAVRAS-CHAVE: neoplasias cerebrais, gliosarcoma, imuno-histoquímica.
describe its clinical and pathological features. Immunohistochemical analyses were performed to confirm diagnosis, assess histogenetic origin and evaluate the proliferation index in all cases.

**METHOD**

The cases were selected from the files of the “CNS Tumor Bank”, which is part of the section of Neuropathology of the Department of Pathology, Federal University of Parana, in Curitiba, from 1990 to 2002. This tumor bank collects around 95% of brain tumors diagnosed in the city of Curitiba, a 1.5 million inhabitants city in Southern region of Brazil. Clinical data were obtained by reviewing the medical records of all patients.

Histologic sections from all four cases were reviewed and original available paraffin-embedded blocks were recut and stained with hematoxylin/eosin and reticulin. The sarcomatous component was classified and both components were quantified. Mitotic figures per high power field were counted and type and extension of necrosis assessed.

Immunohistochemical study using the avidin-biotin method was performed with antibodies to GFAP, vimentin, CD34, p53, EGFR and Ki-67. Positive and negative controls were obtained for each antibody. GFAP and vimentin were classified as focal positivity, diffuse positivity and negative. CD34 and EGFR were classified as negative or positive. Ki-67 and p53 were considered positive only when nuclear staining was present and were graded as + when less than 1% of nuclei were stained; ++ when between 1% and 5% were stained, and +++ when more than 5% of stained nuclei were observed.

**RESULTS**

The CNS Tumor Bank of Curitiba has 3873 biopsy cases, with 92.4% of these corresponding to CNS primary tumors. From the CNS primary tumors, we obtained 5 GSAs (0.13%). Due to lack of appropriate material from one of the cases, we were able to histologically review and perform immunohistochemical analysis in only four cases.

**Clinical findings**

**Case 1.** A 43-years old male had experienced headaches over the 40 days before seeking medical assistance and a progressive loss of strength and sensation in the left lower limb. On admission he was confused, with left side hemiplegia. Both CT and MRI showed an irregular enhancing lesion in the right parietal and temporal lobes with a significant mass due to surrounding edema, causing a midline shift to the left. The patient was placed on corticosteroids and submitted to microsurgery through a right temporo-parietal craniotomy. The tumor, which was grayish and hard, was macroscopically totally removed without significant blood loss. The patient improved the motor deficit mainly in the left upper limb and was discharged on the 5th postoperative day. He died 3 months after the procedure.

**Case 2.** A 44-years old male presented with the clinical picture resembling uncinate fits one month before admission, which consisted in the anomalous perception of the smell of paints, followed by fainting spells and nonspecific headaches. He was taken to the hospital due to recent mental confusion, memory deficits and expressive aphasia, which were evident on clinical examination, besides right hemiparesis. Both CT and MRI showed an irregular infiltrating enhancing mass lesion in the left fronto-temporal lobes with slight surrounding edema (Figure 1). The patient was submitted to temporal lobectomy including the mesial structures. He received adjuvant radiotherapy during the following month. He persisted aphasic, but not confused during the next three months, without other clinical signs, when the symptoms recurred. He died 6 months after the surgical procedure.

**Case 3.** A 48-years old male had complained of pain in the left temporal area for 4 years, which he presumed was an earache. The patient was previously blind of the left eye and 2 months before admission, headaches worsened and he developed a left palpebral ptosis. He was initially seen by an ophthalmologist, who diagnosed glaucoma. Further work-up, including CT and MRI showed an irregular infiltrating enhancing mass lesion in the left temporo-parietal lobes with surrounding edema and compression of the left cerebral peduncle. On admission he was blind of the left eye with associated left palpebral ptosis. Left facial numbness, right hemiparesis and right hyperreflexia were also present. The patient was placed on corticosteroids and submitted to left temporo-parietal craniotomy. The tumor, which was grayish, soft and bloody, was macroscopically totally removed. The patient received radiotherapy during the following month and died 5 months after the surgical procedure.

**Case 4.** A 21-years old woman, who presented with headaches for 18 months, underwent surgery elsewhere six months before admission, when a right parieto-occipital tumor was removed, followed by radiotherapy. On admission she had a left hemiplegia and a left homonimous hemianopia. CT
scan and MRI showed an irregular enhancing mass lesion in the right parieto-occipital lobes involving midline structures, invading right lateral ventricle and infiltrating corpus callosum. The patient was placed on corticosteroids and reoperated through the same approach. The tumor, which was macroscopically totally removed, was grayish, soft, and bloody. The lesion, interpreted initially as a malignant meningioma, had the diagnosis of gliosarcoma established through immunohistochemical analysis. She died 4 months after the second procedure.

The main clinical findings are summarized in Table 1.

**Histological and immunohistochemical findings**

All four cases displayed sarcomatous and glial components. The glial component was remarkably similar to a glioblastoma, with nuclear pleomorphism, high mitotic index, marked vascular proliferation and foci of necrosis, either focal or geographical (Fig 2A).

The sarcomatous component consisted of groups of spindle cells arranged in a fashion that resembled fibrosarcoma in all cases (Fig 2A). In order to evaluate the mesenchymal component, histochemical study to reticulin fibers was performed and demonstrated a rich network of fibrils in all cases (Fig 2B).

The glial component comprised greater than 50% of the neoplasm in only one case. In the remaining three cases, the sarcomatous component comprised 70%, 80% and 90% of the sampled neoplasm, respectively. Mitotic figures per 5 high-power fields in the glial neoplasm ranged between 8 and 2 (mean 6.25). In the sarcomatous areas, the number of mitotic figures per 5 high-power fields ranged between 6 and 2 (mean 3).

Immunohistochemical findings are illustrated in Table 2, Figures 2C and 2D.

*Fig 1. MR images of case 2 displaying a bulging lesion with marked peripheral edema and midline deviation localized on the fronto-parietal region (A, axial view; B, coronal view). Peripheral enhancement of the lesion was observed after contrast medium injection (C).*

**Table 1. Clinical findings of gliosarcomas.**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Presenting symptom</th>
<th>Site of lesion</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>43</td>
<td>male</td>
<td>headache</td>
<td>R temporo-parietal</td>
<td>† in 3 months</td>
</tr>
<tr>
<td>2</td>
<td>44</td>
<td>male</td>
<td>olfactory allucinations</td>
<td>L fronto-temporal</td>
<td>† in 6 months</td>
</tr>
<tr>
<td>3</td>
<td>48</td>
<td>male</td>
<td>headache</td>
<td>L temporo-parietal</td>
<td>† in 5 months</td>
</tr>
<tr>
<td>4</td>
<td>21</td>
<td>female</td>
<td>headache</td>
<td>R parieto-occipital</td>
<td>† in 4 months</td>
</tr>
</tbody>
</table>

R, right; L, left; †, death.
DISCUSSION

GSa is a rare morphological variant of glioblastoma, predominant in males, with age ranging from the fourth to the sixth decades, with a slight predilection for the temporal lobes. In our present report, GSa accounted for 1.06% of all glioblastomas, with a mean age of 39. However, the occurrence of a GSa in a 22-year old patient is uncommon. We failed to observe an anatomical site of predilection. In spite of some reports of metastatic spread, none of the patients reported herein evolved with systemic dissemination.

On clinical basis, primary glioblastomas and gliosarcomas are indistinguishable, both presenting with short clinical course, low median survival and similar peak of incidence; hence the inclusion of GSa in the same clinical trials of glioblastomas. The mean duration of symptoms in our patients

Table 2. Immunohistochemical findings of gliosarcomas.

<table>
<thead>
<tr>
<th>Case</th>
<th>GFAP</th>
<th>Vimentin</th>
<th>CD34</th>
<th>p53</th>
<th>EGFR</th>
<th>Ki-67</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>G – D</td>
<td>G – F</td>
<td>G – N</td>
<td>G +++</td>
<td>G – N</td>
<td>G +++</td>
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<tr>
<td></td>
<td>S – N</td>
<td>S – D</td>
<td>S – N</td>
<td>S ++</td>
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<td>S +</td>
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<td></td>
<td>S – N</td>
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<td>G – D</td>
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<tr>
<td>4</td>
<td>G – D</td>
<td>G – F</td>
<td>G – N</td>
<td>G +</td>
<td>G – P</td>
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<td>S – N</td>
<td>S – D</td>
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<td>S ++</td>
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</tbody>
</table>

G, glial component; S, sarcomatous component; D, diffuse positivity; F, focal positivity; N, negative; P, positive; +, staining of less than 1% of nuclei; ++, staining of 1 to 5% of nuclei; ++++, staining of more than 5% of nuclei; GFAP, glial-fibrillary-acidic protein; EGFR, epidermal growth factor.
apy and/or chemotherapy in 8% of 38 tumors, with staining of both components in only one case. Previous studies have reported EGFR overexpression and amplification as absent. In our study, we detected EGFR immunostaining in only one case, which showed positivity in the glial area and negativity in the sarcomatous one.

In conclusion, GSa in our series present clinical and some genetic features similar to primary glioblastomas. An extremely low rate of EGFR overexpression remains as the most striking difference between these two entities. Furthermore, the TP53 tumor-suppressor gene mutation seems to play a pathogenetic role in GSa and the authors believe there is strong evidence concerning its monoclonal origin. However, different molecular and genetic events may participate in the pathogenesis of GSa and deserve further investigation.

REFERENCES