Extraneural metastases in medulloblastoma

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ABSTRACT
Medulloblastoma is the most common childhood malignant tumor of central nervous system, but it may also occur in adults. It presents high invasive growth with spreading of tumor cells into the leptomeningeal space along the neuroaxis early in the course of the disease. Extraneural metastases are rare but frequently lethal, occurring only in 1 to 5% of patients, and are related, in the most of cases, to the presence of ventriculoperitoneal shunt. Here we characterize the clinical profile of five cases of medulloblastoma with systemic spreading of tumor cells, also comparing them to cases already described in the literature.

Key words: medulloblastoma, metastasis, extraneural.

METHOD
Along the last 13 years, we have followed-up five patients (5%) with systemic metastasis among 96 patients with medulloblastoma. There were 2 children and 3 adults (ages between 2 and 30). Three of them presented the tumor located at cerebellar vermis, and two at cerebellar hemisphere. The histological subtypes were classic in 3 cases, and desmoplastic in 2 cases. The children had bone marrow metastasis only, while the adults had several...
organs compromised. Interestingly, only one out five patients did not present hydrocephalus, consequently had no demand of ventriculoperitoneal (VP) shunt, and presented the longer interval between surgery and detection of extraneural metastasis (38 months). The adult patients that have developed abdominal metastasis had previously undergone a VP shunt procedure. However, the children did not have abdominal metastasis despite the VP shunt. No relation between age, histological types and target organs was established due to the restricted number of studied cases. Concerning the natural history of the disease, the time between the initial symptoms of the CNS disease and the onset of the metastasis ranged from 6 to 38 months, and all of them received a standard treatment: surgical tumor resection and adjuvant treatment. They have in common the short survival after the metastases were identified, despite of proper treatment.

The details of the clinical profile of these five patients are presented on Table 1.

**DISCUSSION**

The medulloblastoma metastases usually occur along the spinal cord, following the cerebrospinal outflow, or along the ventricular system, where it can implant, soak and grow. Extraneural metastases, however, are rare, and there are about 119 patients with extraneural medulloblastoma metastases previously described in the literature. The peculiarities of the brain blood barrier and the differences between the CNS and the systemic environment may explain the rarity of this occurrence. The blood brain barrier represents an obstacle for the tumoral clones, making difficult their mobility. The systemic environment, in its turn, may not offer the ideal conditions to a medulloblastoma clone to implant, soak and grow. Even with this scenario, medulloblastoma, among all pediatric CNS tumors, has the greatest potential for extraneural spread. There are few theories to explain this phenomenon. Fiorilli et al. in 2008 described some medulloblastoma molecular features that can help our understanding in this matter. He described increased expression levels of integrins and tenascins in the medulloblastoma cells. Integrin mediates adhesion of medulloblastoma cells associated to tenascin, which is expressed in the extracellular matrix, and activate pathways associated with cell survival and proliferation. This interaction may be able to guarantee proliferation and adhesion of tumor cells at remote sites, as in neuroaxis, and even out of CNS. In the following year, Osawa et al. described that in addition to other cytoskeletal proteins, ezrin plays an important role in medulloblastoma adhesion, migration, and invasion; reassuring the idea of the great metastatic potential of medulloblastoma.

Previous studies report that the systemic metastases can occur from 3 to 5% of the medulloblastoma population, but there is a lack of reports concerning some aspects of the disease, as histological type, tumor topography and survival rate. These blanks in the details of patients with systemic metastasis of medulloblastoma leave incomplete the clinical profile or the natural history of this severe condition. The present report of five cases and the review of previously reported cases have the aim to try to fulfill this gap. Summarized characteristics of the previously reported cases are presented on Table 2.

The majority of the previous reports described fewer patients, with the exception of the publications of Ebnerhart (with emphasis in pathological aspects), Campbell (including gliomas in the casuistic) and Mazloom, who performed a review of the literature and established prognostic factors to patients with extraneural metastasis, as CNS recurrence and radiotherapy. However, no

<table>
<thead>
<tr>
<th>Case</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<tbody>
<tr>
<td>Age at neurosurgery</td>
<td>2</td>
<td>30</td>
<td>29</td>
<td>30</td>
<td>7</td>
</tr>
<tr>
<td>Gender</td>
<td>M</td>
<td>F</td>
<td>F</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>Tumor topography</td>
<td>vermis</td>
<td>hemispheric</td>
<td>vermis</td>
<td>hemispheric</td>
<td>vermis</td>
</tr>
<tr>
<td>Hydrocephalus/shunt</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>--</td>
<td>+/-</td>
</tr>
<tr>
<td>Morphological diagnosis</td>
<td>classic</td>
<td>desmoplastic</td>
<td>desmoplastic</td>
<td>classic</td>
<td>classic</td>
</tr>
<tr>
<td>Overall survival (months)</td>
<td>12</td>
<td>18</td>
<td>22</td>
<td>45</td>
<td>6</td>
</tr>
<tr>
<td>Time to recurrence or metastasis (months)</td>
<td>8</td>
<td>12</td>
<td>18</td>
<td>38</td>
<td>9</td>
</tr>
<tr>
<td>Site of metastasis</td>
<td>bone marrow</td>
<td>abdomen and pelvis</td>
<td>peritoneum, lungs, bones and lymph nodes</td>
<td>bone marrow, bones, lymph nodes</td>
<td>bone marrow</td>
</tr>
<tr>
<td>Cause of death</td>
<td>severe anemia and sepsis</td>
<td>renal failure</td>
<td>ventilatory failure</td>
<td>severe anemia and sepsis</td>
<td>sepsis</td>
</tr>
</tbody>
</table>
predictive factors to extraneural metastases development were yet identified. Presence of VP shunt has been described as a risk factor to this condition by others, especially to bone marrow, bones, abdomen, and lymph nodes. Extraneural metastasis in medulloblastoma is usually considered as a late-stage complication in the natural history of the disease, however, in our series two patients presented extraneural metastasis within one year from the surgical resection of the primary tumor.

A meta-analysis of the data concerning extraneural metastasis of medulloblastoma, including our findings, allow us to conclude that: [1] the most common sites of metastasis are bone marrow and bones, followed by peritoneum, lungs and liver, [2] systemic metastasis of medulloblastoma is a rare condition, [3] metastasis aggravates the natural history of the primary condition, and [4] it is a factor that worsen the prognosis.

REFERENCES