Malignant Transformation in Craniopharyngiomas

ABSTRACT
Craniopharyngiomas are histological and cytological benign epithelial tumors of the central nervous system which may be aggressive and tend to recur after excision. Malignant transformation in craniopharyngiomas is extremely rare; only around 15 reports are found in literature. In this report, we describe a case of squamous cell carcinoma, in a 58-year-old woman, developing from a previous benign craniopharyngioma. The patient was diagnosed with a recurrent craniopharyngioma in 2011. During the subsequent months, she experienced evolution of the recurrent tumor and then was submitted to a partial resection plus radiotherapy in another Institution. In 2012, the tumor recurred with involvement of sellar, suprasellar region, basal cisterna, and medial fossa, with midbrain compression and central skull base destruction. Histologic evaluation revealed cellular anaplasia and a high mitotic activity in a lesion with foci of craniopharyngioma. Radiation might have been a contributing factor to the malignant transformation in this case.

Keywords: Craniopharyngiomas; Malignant transformation; Squamous cell carcinoma

RESUMO

Palavras-Chave: Craniofaringiomas; Transformação maligna; Carcinoma de células escamosas

César Batista Gonçalves da Cruz¹
Antonio Aversa do Souto¹
Priscila da Costa Mendes de Souza²
Daniel Bulzico¹
Márcio Cristianni³
Leila Chimelli³
Paulo Antonio Faria³

¹MD, Division of Neurosurgery, National Institute of Cancer, Rio de Janeiro, RJ, Brazil.
²MD, Estácio de Sá University, Rio de Janeiro, RJ, Brazil.
³MD, Division of Pathology, State Institute of Brain, Rio de Janeiro, RJ, Brazil.

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INTRODUCTION

Craniopharyngiomas are benign epithelial tumors of the central nervous system that characteristically arise in the infundibulohypophyseal axis in the sellar and suprasellar areas. They comprise approximately 3% of all intracranial tumors and have a bimodal age distribution; most of these tumors occur during the first two decades of life, and a small proportion in the seventh and eighth decades.

These general slow-growing tumors may reach large sizes before becoming clinically symptomatic. Although benign, craniopharyngiomas may be aggressive, invading the neighboring tissue and adhering to blood vessels and nerves. They have a well-recognized predisposition to recur after surgical excision, particularly if the resection is incomplete. Locally aggressive and recurrent craniopharyngiomas are histologically and cytologically benign. Malignant transformation in craniopharyngiomas is a distinctly rare occurrence. There have been 15 cases reported in the English and Japanese literature (Table 1). In addition, there is a single case report, in the veterinary literature, of a spontaneous occurrence, metastasis, of a malignant craniopharyngioma in an albino rat, an event which is as uncommon in animals as it is in humans. Most of the malignant craniopharyngiomas reported have had a previous history of radiotherapy (75%). In the reported cases, the age of the patients varied from 10-66 year-old (mean of 30.8 years). There was

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Interval from benign to malignancy (years)</th>
<th>Symptoms</th>
<th>Ki-67</th>
<th>Radiotherapy history</th>
<th>Follow-up</th>
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</thead>
<tbody>
<tr>
<td>Akachi et al.</td>
<td>F</td>
<td>10</td>
<td>3</td>
<td>Headache and visual symptoms</td>
<td>NA</td>
<td>Yes</td>
<td>DOD 8mo after MT</td>
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<tr>
<td>Nelson et al.</td>
<td>F</td>
<td>49</td>
<td>35</td>
<td>Ill nerve palsy, hemiparesis and altered mental status</td>
<td>NA</td>
<td>Yes</td>
<td>D 11w after surgery</td>
</tr>
<tr>
<td>Suzuki et al.</td>
<td>M</td>
<td>11</td>
<td>8</td>
<td>Altered mental status</td>
<td>NA</td>
<td>Yes</td>
<td>DOD 2mo after MT</td>
</tr>
<tr>
<td>M</td>
<td>14</td>
<td>5</td>
<td></td>
<td></td>
<td>NA</td>
<td>Yes</td>
<td>DOD 2mo after MT</td>
</tr>
<tr>
<td>Virk et al.</td>
<td>M</td>
<td>34</td>
<td>10</td>
<td>Visual symptoms</td>
<td>NA</td>
<td>Yes</td>
<td>DOD 10mo after MT</td>
</tr>
<tr>
<td>Kristopaitis et al.</td>
<td>F</td>
<td>42</td>
<td>15</td>
<td>Visual symptoms and seizures</td>
<td>NA</td>
<td>Yes</td>
<td>A 5y after MT</td>
</tr>
<tr>
<td>Sakai et al.</td>
<td>M</td>
<td>14</td>
<td>11</td>
<td>Blindness</td>
<td>NA</td>
<td>Yes</td>
<td>DOD 3y after MT</td>
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<tr>
<td>Yue and Da</td>
<td>F</td>
<td>21</td>
<td>14</td>
<td>Headache and visual loss</td>
<td>&gt; 50%</td>
<td>Yes</td>
<td>DOD 6mo after MT</td>
</tr>
<tr>
<td>Rodriguez et al.</td>
<td>M</td>
<td>31</td>
<td>0</td>
<td>Headache</td>
<td>15%</td>
<td>No</td>
<td>DOD 6w after surgery</td>
</tr>
<tr>
<td>M</td>
<td>63</td>
<td>5</td>
<td>Mental disturbance</td>
<td>55%</td>
<td>Yes</td>
<td>DOD 2mo after MT</td>
<td></td>
</tr>
<tr>
<td>Boonerid et al.</td>
<td>F</td>
<td>46</td>
<td>0</td>
<td>Headache and progressive visual loss</td>
<td>44%</td>
<td>No</td>
<td>D 6w after surgery</td>
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<tr>
<td>Ishida et al.</td>
<td>M</td>
<td>11</td>
<td>5</td>
<td>Visual loss</td>
<td>27%</td>
<td>Yes</td>
<td>A 10mo after MT</td>
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<tr>
<td>Aquilina et al.</td>
<td>M</td>
<td>12</td>
<td>8</td>
<td>Headache and facial numbness</td>
<td>&gt;70%</td>
<td>Yes</td>
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<tr>
<td>M</td>
<td>13</td>
<td>7</td>
<td>Mental disturbance</td>
<td>&gt;50%</td>
<td>Yes</td>
<td>DOD 10mo after MT</td>
<td></td>
</tr>
<tr>
<td>Lauriola et al.</td>
<td>F</td>
<td>66</td>
<td>0</td>
<td>Visual loss</td>
<td>&gt; 50%</td>
<td>No</td>
<td>DOD 15mo after MT</td>
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<tr>
<td>Gao et al.</td>
<td>F</td>
<td>41</td>
<td>4</td>
<td>Headache and visual loss</td>
<td>NA</td>
<td>No</td>
<td>DOD 3mo after MT</td>
</tr>
<tr>
<td>Ujikufu et al.</td>
<td>M</td>
<td>42</td>
<td>10</td>
<td>Progressive visual loss and altered mental status</td>
<td>NA</td>
<td>Yes</td>
<td>D 6w after surgery</td>
</tr>
<tr>
<td>Aversa do Souto et al.</td>
<td>F</td>
<td>58</td>
<td>20</td>
<td>Progressive visual loss and altered mental status</td>
<td>&gt;30%</td>
<td>Yes</td>
<td>D 1w after surgery</td>
</tr>
</tbody>
</table>

F: female; M: male; y: years; mo: month; w: weeks; NA: Not applicable; MT: Malignant transformation.
no gender correlation, and the interval between the benign to malign transformation was of 3-35 years (mean of 8.3 years). The one-year survival after diagnosis of malignant transformation was of 20% and the mean survival was of 6.8 months. There were strong expressions of p53 and p63 proteins in the malignant craniopharyngioma, and an increase from 10 to 51% in the primary tumor to >90% in the malignant craniopharyngioma.8

CASE PRESENTATION

In 2011, a 58-year-old female patient with a previous history of craniopharyngioma resection done twenty years before and further radiotherapy, was admitted in other department with visual disturbance, sudden right visual loss, and complete ophthalmoplegia in the right eye.

MRI scan revealed an intra and suprasellar lesion with heterogeneous contrast enhancement with displacement of optic chiasm and suprasellar cistern (Figure 1).

The patient was submitted to a partial resection through a transsphenoidal approach with an improvement on her visual loss, remaining the ophthalmoplegia in the right eye. After six months, the patient showed visual deterioration, ophthalmoplegia in the left eye and a dramatic change in her clinical condition were observed presenting dehydration, disorientation, weight loss and a decreased level of consciousness. MRI revealed an

Figure 1. A, B. T1 coronal with gadolinium showing a predominant solid selar and suprasellar craniopharyngioma. C. T1 axial view with gadolinium. D. T1 sagittal view with gadolinium.
aggressive and heterogeneous lesion involving all the sellar and supra-sellar regions, lateral extension, infiltrating the basal cistern, medial fossa, compressing the midbrain and destroying the center of skull base (Figure 2). She was then referred to our hospital.

The patient was admitted in a critical condition, both clinical and neurological, in comatose state. She was submitted to an urgent transsphenoidal approach with partial resection and internal decompression of the lesion. The patient did not show any improvement of the neurological status and died two weeks later of pneumonia and multiple organs failure.

The histopathological study showed a malignant transformation, with cellular anaplasia, a high mitotic activity and a high Ki-67 exceeding 50% (Figure 3).

**DISCUSSION**

Patients with craniopharyngiomas generally present 3 major clinical syndromes related to (a) increased intracranial pressure, (b) endocrine dysfunction caused by compression of the hypothalamic-hypophyseal axis, and (c) visual problems resulting from direct compression of the optic pathways by the tumor.

Craniopharyngiomas are hypothesized to develop from remnants of Rathke's pouch and in a strict sense are malformations, "trapped elements" of nonneoplastic tissue of the central nervous system with linear growth curves. There are two recognized histological variants of craniopharyngioma, the adamantinomatous type and the papillary variant. A mixture of both types is frequently present. In summary, cysts, calcifications, and cholesterol droplets, giving the oil machinery fluid, characterize the...
adamantinomatous variant. Papillary craniopharyngiomas show lack of the oil machinery fluid and are more typically solid rather than cystic. The papillary variant is formed microscopically of well-differentiated, stratified, squamous like epithelium and a fibro vascular stroma, resulting in the formation of prominent papillae. While adamantinomatous craniopharyngiomas are poorly circumscribed and frequently exhibit an infiltrative growth pattern, the papillary types are well-circumscribed and do not adhere to local structures. Some authors have observed that the papillary variant may be more amenable to total surgical resection and may have a more favorable outcome, but this issue is still being debated in the literature.10-14

One of the most challenging aspects in the treatment of craniopharyngiomas is the prevention of recurrence. After gross total resection, the recurrence rate is of approximately 20%, but tumors incompletely resected have recurrence rates of up to 60%.2,10 In repeated surgeries achievement of total surgical resection may be even more difficult, with each subsequent attempt coming up with higher surgical morbidity2.

Radiation therapy has shown to benefit patients with incomplete surgical resection, decreasing tumor recurrence rates to about 30%.2,9,10 Overall, there is 80% of 5-year survival rate for patients with benign craniopharyngiomas.12

A distinctly rare complication of craniopharyngioma is malignant transformation. There is little information regarding the natural history of malignant transformation of craniopharyngiomas.3-5 Nelson et al.3 first described a 48-year-old patient who had developed malignant transformation 35 years after the initial diagnosis of craniopharyngiomas. This patient died from secondary complications of upper gastrointestinal bleeding and pneumonia.3 The mechanism for malignant transformation in craniopharyngioma is currently unknown. Nelson et al.3 suggested

Figure 3. A, B, C. Histopathological study showed a malignant transformation, with cellular anaplasia and a high mitotic activity. D. high Ki-67 exceeding 50%.
a causal relationship between radiation therapy and malignant transformation of craniopharyngiomas.

The occurrence of neoplasms after radiation therapy is well documented. Radiation therapy for craniopharyngiomas has been implicated in the development of secondary neoplasms in 5 cases. In their study about side effects of radiation therapy for benign brain tumors in adults, Al-Mefty et al. reported that the latency for secondary neoplasms ranges from 4 years to 30 years, with a median of 12.5 years. Our patient received radiation therapy for over a 20-year period, previously. Therefore, it is possible that radiation may have been a contributing factor to the development of squamous cell carcinoma in this case. However, the vast majority of cases in which radiation has been used to prevent the recurrence of craniopharyngioma have not resulted in transformation to a squamous cell carcinoma. Therefore, the radiation-induced malignant transformation is a distinctly rare event. Additional evidence that radiation may have contributed to carcinogenesis in this case is the immunohistochemical expression of p53 in the malignant craniopharyngioma. Animal research, as well as in vitro analyses of human tumors, have demonstrated that the development of delayed mutations in p53 following irradiation may be one step in the sequence leading to radiation-induced malignant transformation. The p53 tumor suppressor gene controls cellular growth after DNA damage through mechanisms involving growth arrest and apoptosis. Mutation of the p53 gene can lead to the loss of cell cycle control system, genetic instability and neoplastic growth. The wild-type p53 protein is present in very low levels in tissue, and mutations of the p53 tumor suppressor gene stabilize the p53 protein and extend its half-life, enabling detection with immunohistochemical methods. The ability to detect p53 with immunohistochemistry is closely correlated with the presence of a p53 gene mutation in some tumors, such as squamous cell carcinoma of the esophagus. In other tumors, such as squamous cell carcinomas of the head and neck, immunohistochemical expression of p53 may not always reflect mutation of the p53 gene. We can cite Xu et al. who demonstrated 60% of concordance between immunohistochemical expression of p53 and gene mutations detected by single-strand conformational polymorphism analysis in squamous cell carcinomas of the head and neck.

Although malignant transformation in craniopharyngiomas is uncommon, pathologists should be aware of its occurrence. Confusion should not be made with benign appearing tongues and nests of craniopharyngioma in surrounding areas of nervous tissue. Local invasion, particularly in adamantinomatous craniopharyngiomas, is characteristic and not a sign of malignancy. However, anaplastic features in craniopharyngiomas and high mitotic activity, particularly in patients with a previous history of radiotherapy, should be critically examined and considered.

Malignant transformation in craniopharyngioma rarely occurs but it carries a poor prognosis. The precise mechanism of the malignant transformation remains to be further studied. Radiotherapy may be relevant to the malignant transformation of craniopharyngioma. Definitive histological criteria for malignant craniopharyngioma were not well defined, but higher mitotic activity, Ki-67 > 7% and anaplastic features suggest the diagnosis of malignancy. The presence of these findings in a recurrent craniopharyngioma, especially when radiotherapy was administered, should be an alert for this threatening diagnosis, with a poor prognosis.

REFERENCES

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Cesáro Batista Gonçalves da Cruz, MD
Division of Neurosurgery
National Institute of Cancer
Rio de Janeiro, Rio de Janeiro, Brazil
E-mail: cesarbgcruz@gmail.com

Case Report

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CORRESPONDING AUTHOR

César Batista Gonçalves da Cruz, MD
Division of Neurosurgery
National Institute of Cancer
Rio de Janeiro, Rio de Janeiro, Brazil
E-mail: cesarbgcruz@gmail.com

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