Primary malignant craniopharyngioma: a case report and review of literature

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Abstract: Background and Importance: Malignant craniopharyngioma (MCP), first described in 1987 by Akachi, is an exceedingly rare disease that is characterized by cytological atypia, high mitotic activity and poor prognosis. By now, only 19 cases of MCP were reported of which only 3 cases were primary type. Clinical Presentation: We presented the diagnosis and treatment of fourth primary MCP. The patient was preoperatively diagnosed as craniopharyngioma (CP) and underwent a total tumor resection. Histopathological examination showed that tumor cells had an increased nuclear-cytoplasm ratio, a high mitotic activity and Ki-67 > 20%. The patient was diagnosed as MCP. Adjuvant radiotherapy was followed after surgery and the patient remained no progression in the next 8 months follow-up. Conclusion: The mechanism, diagnosis and treatment for MCP is still challenging. Surgical resection followed by radiotherapy has demonstrated an effective treatment and chemotherapy still needs researches to demonstrate its therapeutic efficiency.

Keywords: Malignant craniopharyngioma, primary type

Introduction

Craniopharyngioma (CP), first named by Cushing in 1932, is a benign epithelial neoplasm that predominantly occurred in sellar and suprasellar region. Malignant craniopharyngioma (MCP) has been rarely reported since it was first described by Akachi in 1987 [1]. Since then, only 19 cases of MCP have described. Most MCP (16 cases) was supposed to develop by the malignant transformation of CP (secondary type), which was presumably related to the radiotherapy. Furthermore, there have also been more exceptional rare cases (3 cases) that the MCP developed de novo (primary type). Here we presented diagnosis and treatment of the fourth case of primary MCP.

Case report

A 33-year-old female patient was admitted into our department with the main complaints of progressive visual disturbance for one year coupled with paroxysmal headache for one week. Ophthalmological examinations identified visual acuity in the left eye of 20/100 and in the right eye of 20/50 with bilateral temporal hemianopsia. The bilateral optic nerve were mild atrophied. Bilateral pupilary light reflexes were normal and other neurological examinations demonstrated no deficits. The pituitary function examinations demonstrated low level of cortisol, others normal, including growth hormone, thyrotropin, prolactin, sexual hormone and so on. CT and MRI scans showed a lobulated, non-calcified, cystic-solid lesion in the suprasellar region measuring 3.0 cm × 3.0 cm × 2.5 cm. The cystic part of the lesion was slight hypointense on T1-weighted and distinct hyperintense on T2-weighted MRI. The solid part, however, was hyperintense on both T1-weighted and T2-weighted MRI with obvious heterogeneous enhancement (Figure 1A-E). Based on the history, examination and neuroimaging results, preoperative diagnosis was made as craniopharyngioma. The patient underwent a total removal of the tumor via the frontobasal interhemispheric approach following a right frontal craniotomy. Histologic morphology of the biopsy demonstrated that the tumor cells with uniform epithelial appearance proliferated and invaded into the rounding fibrous tissue. Nests of cells showed moderate to severe pleomorphism and had an increased nuclear-cyto-
plasm ratio and a high mitotic count. Immunohis-
tochemical staining of the specimen displayed
tumor cells were positive for CK5/6, CK8/18,
CK56, p53, p63 and Syn, but negative for EMA,
SMA, NSE, ChrA GFAP and CK20. The Ki-67
immunolabeling was more than 20% in the
atypical cells (Figure 2A-F). Pathological diag-
nosis was the primary malignant craniopharyn-
giuma, or we may call it “craniopharyngio-carci-
noma”. The patient came to local hospital to
receive radiotherapy and he remained no pro-
gression in the next 8 months follow-up.

Discussion

Craniopharyngioma is a neoplasm that originat-
ing from remnants of the Rathke’s pouch, a
derivative of oral ectoderm, which accounts for
5-10% and 1.2-4.6% of adolescent and adult
brain tumors respectively [2, 3]. Craniopharyn-
gioma usually presents as a cystic-solid and
calcification mass or lobulated lesion in inter-
and suprasella region. The patients may have
clinical manifestations such as visual and
docrine abnormalities, malfunction of neuro-
hypophysis and hypothalamus. The typical neu-
roimaging displays of CP are the characteristic
“egg-shell” calcification on CT scans and spe-
cific hyperintensity on T1WI because of the lipid
in the cysts [4]. Although craniopharyngioma
always presents local aggressive behavior and
frequent recurrence and requires postopera-
tive radiotherapy [5], it shows no atypia and
mitotic figures and is regarded as the Grade I
tumor in 2007 WHO classification of tumor of
CNS [6].

In exceptional rare cases, craniopharyngioma
experienced malignant transformations, nam-
ed malignant craniopharyngioma (MCP). Be-
cause the MCP is really very rare, even the pro-
fessional monographs (2007 WHO classifica-
tion of tumor of CNS) had seldom mentioned it [6]. According to the literature, only 19 cases of malignant craniopharyngioma have been reported worldwide since the first case was described by kachi et al. [7]. Among these rare cases, only three were primary MCP and our current case is the fourth [8-10]. Two of the former primary malignant craniopharyngioma patients died in the early postoperative period (6 weeks after surgery) [9, 10]. The other received subtotal tumor resection followed by adjuvant fractionated radiotherapy and thus gained a 15-months postoperative survival [9]. In other words, the secondary MCP patients experienced a median time of 9 years (range 3-24 years) from the initial craniopharyngioma to malignant transformation. The postoperative survival was from 43 days to 5 years, respectively (Table 1). In our current case, the patient received adjuvant fractionated radiotherapy after total tumor resection and thus remained no progression over the next 8-months follow-up.

Malignant craniopharyngioma is an uncommon tumor in the sellar/suprasellar region of which the mechanism, diagnosis, treatment and prognosis is still challenging. The malignant transformation of craniopharyngioma was presumably associated with frequent benign recurrence, multiple operations and, especially, radiotherapy [5]. Researchers noted that most malignant transformation patients (15 cases) had received at least one time radiotherapy [11, 12]. However, Sofela et al. [13] draw a conclusion by comparing the dose of irradiation received before MCPs and the degree of malignancy that there was no immediate correlation between radiotherapy and malignant transformation of CP. In other words, the mechanism for primary MCP is still unknown. Some researchers suggested that the strong expression of p53 and p63 proteins were associated with the primary MCP. The mutation of p53 gene can up-regulate the expression of p53 protein and thus resulting in loss of cell cycle control, genetic instability, and neoplastic growth. The wild-type p53 protein is expressed in low levels in craniopharyngioma. But some researchers demonstrated that the secondary MCP can express a higher level of p53 protein after malignant transformation [9, 14]. These

Figure 2. The pathological results of the patient. (A and B) Tumor cells with uniform epithelial appearance proliferated and invaded into the rounding fibrous tissue. Nests of cells showed moderate to severe pleomorphism and had an increased nuclear-cytoplasm ratio and a high mitotic count. (A. 100×; B. 200×) (C) The Ki-67 immunolabeling was more than 20% in the atypical cells. (200×) (D-F) Tumor cells were positive for CK5/6 (D), p63 (E) and CK10/13 (F) (200×).
findings suggest that p53 mutation may be involved in malignant transformation of CP. P63 protein, which is codified by p64 gene, a p53 gene homologue, is found over-expressed in CP and also plays a pivotal role in cell cycle regulation and tumor differentiation [15]. In our current case, the immunohistochemical results demonstrated the tumor cells were positive for p53 and p63 which supports these hypotheses.

The differential diagnosis of MCP includes pituitary adenoma, germ cell neoplasms and metastatic tumor. Histopathologic displays without adamantinomatous pattern and wet keratin, negative expression of S-100 protein, synaptophysin, chromogranin A, NSE, and pituitary hormones are all helpful in excluding pituitary adenoma. Germ cell neoplasm dose have wet keratin as a component of its ectoderm. However, the negative expression of PLAP, AFP, b-hCG, and CD30 can distinguish it from MCP. Metastatic tumor can also be excluded since it displays no pathological feature of primary neoplasms.

The definite diagnostic criteria for MCP has not been published. Even the professional pathological monographs (2007 WHO classification of tumor of CNS) had rarely mentioned it. However, according to the literature reviewing, researchers have reached a consensus that the pathological displays of MCP should include the following features: a) cellularity and increased nuclear cytoplasmic ratio; b) atypia such as basilar hyperplasia and nuclear pleomorphism; c) coagulative necrosis; d) higher mitotic activity; e) other histologic features of malignancy such as vascular invasion, infiltrative growth, or coagulative necrosis [10, 16]. When CP includes more than two of the above features, it should be diagnosed as MCP. Among these features, the higher mitotic activity may be more valuable for diagnosis. Nishi et al. suggested that an increased expression of Ki-67 (more than 7%) may prognosticate a high tendency to recurrence [15]. And Boongird et al. had also brought Ki-67>7% into the diagnostic criteria [10]. However, whether or not 7% for Ki-67 works as a threshold for the diagnosis of MCP, still needs statistical analysis and further investigation. In our current case, the histologic displays included all the discussed above. Based on the patient’s history, the pathological results of nuclear pleomorphism, increased

### Table 1. Summary of 20 reported cases of MCP

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Age</th>
<th>Sex</th>
<th>Histology</th>
<th>Radiation (Y/N)</th>
<th>MC/MT</th>
<th>Therapy after MT</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary MCP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rodriguez et al.</td>
<td>2007</td>
<td>31</td>
<td>M</td>
<td>OGC</td>
<td>N</td>
<td>MC</td>
<td>Surgery</td>
<td>Dead/6 w after surgery</td>
</tr>
<tr>
<td>Boongird et al.</td>
<td>2008</td>
<td>46</td>
<td>F</td>
<td>MC</td>
<td>N</td>
<td>MC</td>
<td>Surgery</td>
<td>Dead/6 w after surgery</td>
</tr>
<tr>
<td>Launola et al.</td>
<td>2011</td>
<td>66</td>
<td>F</td>
<td>MC</td>
<td>N</td>
<td>MC</td>
<td>Surgery</td>
<td>Dead/15 m after surgery</td>
</tr>
<tr>
<td>Present case</td>
<td>2015</td>
<td>33</td>
<td>F</td>
<td>MC</td>
<td>Y</td>
<td>MC</td>
<td>RT</td>
<td>Alive/8 m after surgery</td>
</tr>
<tr>
<td><strong>Secondary MCP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Akachi et al.</td>
<td>1987</td>
<td>7</td>
<td>F</td>
<td>AC/MT</td>
<td>Y</td>
<td>MT</td>
<td>Surgery (2), RT</td>
<td>Dead/8 m after MT</td>
</tr>
<tr>
<td>Nelson et al.</td>
<td>1988</td>
<td>14</td>
<td>F</td>
<td>AC/MC</td>
<td>Y</td>
<td>MT</td>
<td>Surgery</td>
<td>Dead/11 w after surgery</td>
</tr>
<tr>
<td>Suzuki et al.</td>
<td>1989</td>
<td>3</td>
<td>M</td>
<td>AC/SCC</td>
<td>Y</td>
<td>MT</td>
<td>RT, VP shunt</td>
<td>Dead/2 m after MT</td>
</tr>
<tr>
<td>Suzuki et al.</td>
<td>1989</td>
<td>9</td>
<td>M</td>
<td>AC/SCC</td>
<td>Y</td>
<td>MT</td>
<td>Surgery</td>
<td>Dead/23 m after MT</td>
</tr>
<tr>
<td>Vink et al.</td>
<td>1999</td>
<td>24</td>
<td>M</td>
<td>AC/MT</td>
<td>Y</td>
<td>MT</td>
<td>Surgery, CT, RT</td>
<td>Dead/10 m after MT</td>
</tr>
<tr>
<td>Kostopatis et al.</td>
<td>2000</td>
<td>27</td>
<td>M</td>
<td>AC/MT</td>
<td>Y</td>
<td>MT</td>
<td>Surgery, CT</td>
<td>Alive/6 m after surgery</td>
</tr>
<tr>
<td>Sakai et al.</td>
<td>2004</td>
<td>3</td>
<td>M</td>
<td>*/MT</td>
<td>Y</td>
<td>MT</td>
<td>Surgery (5), stereotactic RT</td>
<td>Dead/3 y after MT</td>
</tr>
<tr>
<td>Plowman et al.</td>
<td>2004</td>
<td>6</td>
<td>F</td>
<td>AC/MT</td>
<td>Y</td>
<td>MT</td>
<td>Surgery, CT</td>
<td>Dead/6 m after MT</td>
</tr>
<tr>
<td>Rodriguez et al.</td>
<td>2007</td>
<td>58</td>
<td>F</td>
<td>AC/SCC</td>
<td>Y</td>
<td>MT</td>
<td>Surgery, VP shunt</td>
<td>Dead/2 m after MT</td>
</tr>
<tr>
<td>Rodriguez et al.</td>
<td>2007</td>
<td>14</td>
<td>M</td>
<td>AC/MT</td>
<td>Y</td>
<td>MT</td>
<td>Surgery</td>
<td>Dead/1 y after MT</td>
</tr>
<tr>
<td>Ishida et al.</td>
<td>2010</td>
<td>6</td>
<td>M</td>
<td>AC/MT</td>
<td>Y</td>
<td>MT</td>
<td>Surgery, CT</td>
<td>Alive/10 m after MT</td>
</tr>
<tr>
<td>Aqualina et al.</td>
<td>2010</td>
<td>4</td>
<td>M</td>
<td>*/SCC</td>
<td>Y</td>
<td>MT</td>
<td>Surgery (2), CT</td>
<td>Dead/6 m after MT</td>
</tr>
<tr>
<td>Aqualina et al.</td>
<td>2010</td>
<td>6</td>
<td>F</td>
<td>AC/SCC</td>
<td>Y</td>
<td>MT</td>
<td>Surgery (2), CT, RT</td>
<td>Alive/5 y after MT</td>
</tr>
<tr>
<td>Ujifuku et al.</td>
<td>2010</td>
<td>32</td>
<td>M</td>
<td>AC/SCC</td>
<td>Y</td>
<td>MT</td>
<td>Surgery (2)</td>
<td>Dead/43 y after surgery</td>
</tr>
<tr>
<td>Gao et al.</td>
<td>2011</td>
<td>41</td>
<td>F</td>
<td>MC</td>
<td>N</td>
<td>MC</td>
<td>Surgery</td>
<td>Dead/35 m after surgery</td>
</tr>
</tbody>
</table>

AC: Adamantinomatous craniopharyngioma; MC: Malignant craniopharyngioma; MT: Malignant transformation; SCC: Squamous cell carcinoma.
nuclear-cytoplasm ratio, infiltrative growth and 20% Ki-67 index, the diagnosis of primary MCP is appropriate.

The treatment for malignant craniopharyngioma arouse controversies. In most circumstances, surgical resection is still the first choice for MCP patients. Total surgical resection should be attempted. However, considering the infundibulo-tuberal CP that would bring more surgical difficulty and more severe hypothalamic injury, subtotal removal followed by adjuvant radiotherapy may be more appropriate. Adjuvant radiotherapy has demonstrated its efficiency in both maximizing tumor control and minimizing complications. Stereotactic radiosurgery has been reported to achieve 100% control rate for solid small CP at least 3 mm from the optic chiasm [17]. Intracavitary beta irradiation has also been used efficiently in controlling the size of craniopharyngioma cysts [18, 19]. Accordingly, although whether the radiotherapy can lead to malignant transformation of CP has aroused controversies, however, once the diagnosis of MCP is established, the radiotherapy should still be applied. Chemotherapy has been applied in some secondary MCP patients [5, 11, 14, 20, 21], one patient [5] gained a long-term survival (5 years), the others only gained a median survival of 6.5 months. Considering the five patients had also accepted radiotherapy, the efficiency of chemotherapy still needs further researches. Two of the previous primary MCP patents who did not accept radiotherapy had died in the early post-operative period. But the other who received fractionated radiotherapy had gained a 15-months survival after surgery. In our current case, the tumor has been totally excised and the adjuvant radiotherapy was performed after surgery. The patient has remained no progression in the next 8-months follow-up.

Conclusion

Malignant craniopharyngioma is an exceedingly rare disease and the mechanism, diagnosis and treatment for this disease is still challenging. The histological displays and immunophenotypical characteristics are still the only reliable basis for diagnosis. Total surgical resection should be attempted and adjuvant radiotherapy should be applied follow the surgery once the MCP is diagnosed. Chemotherapy still need studies to clarify the usage and efficiency.

Disclosure of conflict of interest

None.

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