Intracranial Malignant Myoepithelioma: A Rare Aggressive Tumor: Case Report and Literature Review

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Introduction
Myoepithelial tumors are very rare tumors and can be benign or malignant. Salivary glands are the classical organs of origin of myoepithelial tumors, although they are known to occur in in breast, skin, soft tissues as well as lungs. Central Nervous System (CNS) is an extremely rare site of presentation of these tumors and in the CNS, sellar region is the commonest location. Myoepitheliomas may arise from the remnants of the Rathke’s cleft. Around ten such cases of intracranial myoepithelioma have been reported in the literature. With the advent and increased availability of immunohistochemical markers, there has been an increase in the number of cases of myoepithelial tumors diagnosed in the last decade. Here we report the aggressive clinical course of an intracranial malignant myoepithelial tumor in a young male patient.

Case Report
A 28-year-old male presented with complaints of holo-cranial headache, which was insidious onset, gradually progressive, moderate to severe in intensity for a duration of 3 months, without any history of trauma, not relieved with over-the-counter medications. There was also associated history of nausea and vomiting, unrelated to food intake for a month. Subsequently, the patient developed altered sensorium for 2 weeks. There were no other neurological symptoms. There was a history of fatal malignancy in his father and cancer of head and neck in his sister. Exact diagnosis and treatment history was unavailable for both.

General physical examination revealed multiple café au lait spots noted over the back. There was no organomegaly or lymphadenopathy. Patient was alert, conscious, co-operative,
not oriented to time, place and person and there were no signs of any focal neurological deficit. A Computed Tomography (CT) scan was suggestive of an ill-defined non-encapsulated heterodones lesion with patchy calcified foci within and moderate perilesional edema in left temporo-parietal parenchyma associated with midline shift. On contrast administration, heterogenous enhancement was noted. For confirmation of CT findings, a contrast enhanced magnetic resonance imaging (CEMRI) was done. The patient underwent tempo-parietal craniotomy followed by gross total excision. Intraoperatively, the tumor was hard, not sackable, and moderately vascular with calcification and showed an intertumoral cyst.

Histopathology, a biphasic tumor was noted with both epithelial and stromal components. The epithelial component was arranged in the form of glands, cribriform pattern and papillae. The stromal component was composed of spindle to polygonal cells with coarse chromatin, distributed in a myxoid background with frequent mitosis. In addition to areas of necrosis and calcification, malignant chondroid and osseous production was noted indicating chondrosarcomas and osteosarcomas differentiation. No other heterologous element was seen. The epithelial component stained positive for cytokeratin (CK), glial fibrillary acidic protein (GFAP), S100 and showed patchy p63 and calponin positivity indicating myoepithelial differentiation. S-100 and SATB2 stains were positive in chondrosarcomas and osteosarcomas components respectively. They were negative for desman and myozenin (excluding rhabdomyosarcoma), OLIG2 (excluding glial differentiation), OCT4, SALL4 and AFP (excluding germ cell tumor), synaptophysin and chromogranin (excluding neuroendocrine tumor), TLE and smooth muscle actin. Nuclear INI1 expression was retained. Fluorescence in situ hybridization (FISH) for SS18 gene rearrangement (using dual color break apart FISH probe, Vysis) was negative. The final pathological diagnosis was given as malignant mixed tumor (myoepithelioma) with osteosarcomas and chondrosarcomas elements (Figure 1, 2).

Post-operatively, FDG PET-CT was suggestive of a localized heterogeneously enhancing residual soft tissue mass (3X3cm, SUVmax 15.4), in the left tempo-parietal lobe, adjoining the occipital horn of left lateral ventricle. There was no tracer uptake elsewhere in the body. MRI brain done at 6 weeks confirmed the similar findings. Screening spine and CSF analysis revealed no evidence of drop metastases. Blood and CSF analysis performed were essentially normal and showed no elevations of tumor markers.

The patient was planned for adjuvant radiation to a total dose of 54Gy at 1.8Gy per fraction. However, two weeks after initiation of radiotherapy, the patient developed multiple episodes of seizures which were managed conservatively. A CECT done at this point of time revealed a large progressive tumor in the site of residual disease. The patient had a protracted clinical course in which he deteriorated and succumbed to the disease within a week.

Discussion

Myoepithelial tumors are very heterogenous in terms of histology, cytological morphology and immunophenotype. Besides their original described origin in salivary glands, literature has shown them to originate in various sites like breast, skin, lacrimal gland, head and neck including paranasal sinus and vulva. Intracranial myoepitheliomas have been rarely reported in the literature. Despite extensive literature search, only ten cases have been found of which half were malignant (Table 1).

Intracranial myoepitheliomas have been reported in patients from 1 year [6] to 52 years [5] of age, both in intra as well as extra-axial regions. Here, the radiological differential diagnosis in this index case was glioma considering the heterogenous enhancement with extensive perilesional edema.

The pathological appearance was also atypical. The stroma was heterogenous including chondroid and osseous metaplasia.
as has also been reported by Ghanta et al. [5]. In malignant cases, high mitotic index has been studied with mitosis as high as 11/10 high power field [3]. There are still date no specific criteria to define them as benign or malignant and it depends primarily on the clinical characteristics.

Myoepithelialomas and their malignant counterpart, myoepithelial carcinoma phenotypically resembles the myoepithelial cells. However, the neoplastic myoepithelial cells are morphologically heterogenous. Myoepitheliomas are lobulated tumors composed of cords of epithelioid or spindle cells with reticular architecture and chondromyxoid, collagenous and hyaline stroma. Variable epithelial component can be identified, as seen in the index case. Pure myoepitheliomas and mixed cell tumors lie on a morphological continuum with overlap in histological appearance and clinical behavior. The tumors, on immunohistochemistry, express a wide range of epithelial and mesenchymal markers, similar to myoepitheliomas of other primary sites. Cytokeratin and S100 are almost always positive as is seen in our case. Epithelial membrane antigen, glial fibrillary acidic protein and smooth muscle actin appear to be variably expressed.

Around 45% of soft tissue myoepithelial tumors show EWSR1 gene translocation but pleomorphic adenoma gene (PLAG-1) mutations are commonly observed in salivary gland myoepitheliomas [10,11]. In the available literature, genetic studies were done in only two intracranial cases to detect EWSR1 mutations, of which only one was positive [6]. In our case, EWSR1 gene mutation was done although it yielded a negative report.

The origin of intracranial myoepitheliomas is a matter of concern. In and around the sella, they are postulated to originate from the salivary gland rests in posterior pituitary which communicate with remnants of oropharynx in Rathke’s pouch [9,12]. Tumors in middle cranial fossa may arise from ectopic salivary gland tissue remnants in middle ear [13].

There are conflicting reports regarding the optimal strategy for myoepithelial neoplasm. For localized disease, wide local excision is the mainstay of treatment. Is there any information regarding the extent of surgery and survival? Radiation therapy has been reported as an adjunctive therapy following subtotal resection or in cases of recurrence; kindly add about radiation sensitivity, radiation doses used and techniques that are preferable. If there are no details available in the literature mention the same citing that this lack of information is one of the reasons these tumours show poor results. However, given the rarity, its efficacy has not been well defined. They may be characterized by nodal metastasis which may be addressed surgically. There is no proven role of chemotherapy in such tumors. Can you find any details regarding the various chemotherapeutic agents that have been used either as adjuvant or palliative? If no information is present, kindly add chemotherapy agents used for extra cranial myoepitheliomas and that if they can be used in CNS MYO tumors [9].

**Conclusion**

Intracranial myoepitheliomas are rare. Surgical approaches require careful planning to minimize morbidity. Although commonly benign and slow growing, myoepitheliomas may invade bone and dura and in rare instances differentiate into frankly malignant lesions with metastatic potential. A metastatic workup to look for secondaries is essential. Surgical excision is the mainstay of therapy, with radiation therapy reserved for unresectable or recurrent lesions. Chemotherapy has not been effective in the management of myoepithelial neoplasms, but is reserved for unresectable, progressive, or metastatic myoepithelial carcinomas. The present case scenario solidifies the fact that conventional approach via surgery and adjuvant radiotherapy is in adequate in achieving any kind of tumour control. Further research in terms of molecular pathogenesis, identification of molecular targets for therapy, radiobiological studies to identify the radiation sensitivity of these tumours may enable a more aggressive and tailored approach towards these rare tumours.

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**Table 1: Myoepithelial tumors of central nervous system.**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Site</th>
<th>Behavior</th>
<th>Surgery</th>
<th>Chemotherapy and Radiotherapy</th>
<th>Status at final follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erdogan et al. [1]</td>
<td>47</td>
<td>F</td>
<td>Falx</td>
<td>Malignant</td>
<td>Yes</td>
<td>Scheduled for radiation</td>
<td>Stable at 4 months</td>
</tr>
<tr>
<td>Vajta et al. [2]</td>
<td>32</td>
<td>M</td>
<td>Cerebello-pontine angle</td>
<td>Benign</td>
<td>Yes</td>
<td>No</td>
<td>Disease free at 6 years</td>
</tr>
<tr>
<td>Hong et al. [3]</td>
<td>48</td>
<td>F</td>
<td>Cavernous sinus</td>
<td>Malignant</td>
<td>Yes</td>
<td>No</td>
<td>Died at 2 months</td>
</tr>
<tr>
<td>Hayward et al. [4]</td>
<td>17</td>
<td>F</td>
<td>Orbit, dura</td>
<td>Benign</td>
<td>Yes</td>
<td>No</td>
<td>Disease free at 10 months</td>
</tr>
<tr>
<td>Ghanta et al. [5]</td>
<td>52</td>
<td>M</td>
<td>Parieto-occipital</td>
<td>Benign</td>
<td>Yes</td>
<td>No</td>
<td>Disease free at 1 year</td>
</tr>
<tr>
<td>Choy et al. [6]</td>
<td>13</td>
<td>M</td>
<td>Falx</td>
<td>Benign</td>
<td>Yes</td>
<td>No</td>
<td>Disease free at 2.5 years</td>
</tr>
<tr>
<td>Gupta et al. [7]</td>
<td>2</td>
<td>F</td>
<td>Parieto-occipital</td>
<td>Malignant</td>
<td>Yes</td>
<td>Chemotherapy (intravenous and oral)</td>
<td>Disease progression at 9 months</td>
</tr>
<tr>
<td>Gowripriya et al. [8]</td>
<td>43</td>
<td>M</td>
<td>Meckel’s cave</td>
<td>Benign</td>
<td>Yes</td>
<td>Not mentioned</td>
<td></td>
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<tr>
<td>Neider et al. [9]</td>
<td>34</td>
<td>F</td>
<td>Sella</td>
<td>Benign</td>
<td>Yes</td>
<td>Radiation 54Gy in 30 fractions, chemotherapy at recurrence</td>
<td>Died at 20 months</td>
</tr>
<tr>
<td>Index case</td>
<td>28</td>
<td>M</td>
<td>Temporo-parietal</td>
<td>Malignant</td>
<td>Yes</td>
<td>Radiation</td>
<td>Died at 2 months</td>
</tr>
</tbody>
</table>
References