Malignant Myoepithelioma of the Larynx: Case Report and Literature Review

Carlos Alberto Cavalcante de Barros Junior¹, Genival Barbosa de Carvalho¹, Renan Bezerra Lira¹, Mauro Kasuo Ikeda¹, Felipe D’ Almeida Costa², Daniele Sismeiro Carnevalli², Marcelo Luiz Balacin², Gislaine Cristina Lopes Machado Porto², Joel Rodrigo Beal Lusa³, Clóvis Antonio Lopes Pinto³, and Luiz Paulo Kowalski¹

¹Department of Head and Neck Surgery and Otorhinolaryngology, Brazil
²Department of Anatomic Pathology, Brazil
³Department of Radiology, A.C. Camargo Cancer Center, Brazil

Abstract

The Malignant myoepithelioma (MME) is an extremely rare type of tumor of the salivary glands. There are few case reports. In this report we present a case of laryngeal MME with aggressive behavior and a review of the literature regarding the diagnosis, treatment options and standard prognosis of this tumor.

INTRODUCTION

Malignant myoepithelioma (MME), also known as myoepithelial carcinoma, is an extremely rare type of tumor of the salivary glands, comprising less than 1% of tumors occurring in this topography [1]. There are few series analyzing the pattern and prognosis of these neoplasms and the management of these cases relies on these small series in several other case reports.

Most of these tumors affect the parotid gland, and secondarily, submandibular glands, while only rarely occurring in the minor salivary glands of the upper aerodigestive tract [2,3]. There are few reports of MME in the larynx, with approximately seven cases reported in the literature in the English language.

In this report we present a case of laryngeal MME with aggressive behavior, having no possibility of treatment with curative intent, as well as a review of the literature regarding the diagnosis, treatment options and standard prognosis of this tumor.

CASE PRESENTATION

A 78-year-old white male patient was admitted with complaints of cervical tumor associated with progressive dysphonia and weight loss with three months of evolution. At first consultation there were already signs of severe respiratory distress and laryngeal stridor, and at video nasolaryngoscopy the presence of an extensive tumor in the subglottic larynx was observed, with extension to the trachea, causing stenosis of about 50% of the glottis.

Bronchoscopy was performed and a large tracheal lesion was found, extending through the left posterior wall of the hypopharynx, promoting bulging of the hypopharynx and larynx palsy on the left. There were no signs of active bleeding, but the lesion was friable and bled at the slightest touch of the device (Figure 1).

On the same day of admission, the patient underwent transcervical tracheostomy and biopsy of the lesion. CT staging of the neck showed large cervical mass arising from visceral compartment obliterating the entire subglottic larynx and trachea, with extra-laryngeal extension and signs of invasions of thyroid gland, perivertebral space and common carotid arteries bilaterally (Figure 2A and B). On post-contrast sagittal CT, it was possible to characterize the large lesion length in the craniocaudal plane, extending from the hyoid to the upper mediastinum. Also, a greater displacement of the entire larynx was shown, implying that the probable center of origin of lesion was subglottic or tracheal. There was regional cervical lymphadenopathy at levels IV and V. Chest tomography showed multiple pulmonary nodules and consolidations with the appearance of secondary neoplastic involvement. CT scan and upper abdomen showed no alterations.

Pathological findings

Grossly, the surgical intraoperative specimen measured 1.5 x 0.8 cm. There were multiple fragments of brown and granular material with softened areas.

Microscopic examination of the intraoperative specimens revealed isolated, pleomorphic and polymorphous cells containing abundant clear or eosinophilic cytoplasm in a myxoid stroma intermingled with extensive necrosis. In the periphery, the thyroid gland exhibited usual architecture. The frozen section diagnosis was poorly differentiated carcinoma. More material was submitted to further analysis. We received multiple fragments of tissue that showed the same gross appearance which measured 1.5 x 0.9 cm. After being formalin-fixed, paraffin embedded and the tissue undergoing HE staining, the tumor cells showed some morphologic variation comprised of epithelioid and plasmacytoid cell subtypes in a stroma extensively necrotic. The epithelioid cells were polygonal, possessing central nuclei with coarse chromatin and prominent nucleoli. These cells had clear and abundant cytoplasm. The plasmacytoid cells had eccentrically located nuclei and eosinophilic cytoplasm. The tumor cells occurred mostly isolated or occasionally crowding and overlapping, sometimes forming nests. In some areas, the tumor infiltrated the adjacent thyroid gland.

Immunohistochemical examination was performed. Cytokeratin and EMA applied as epithelial markers revealed a positive reaction. S100 protein was positive. Lack of immunostaining was observed for p63, TTF1, CD10, smooth muscle actin and desmin. Ki67 showed strong reaction in 40% of the neoplastic cells.

Based on the histopathological and immunohistochemical findings, the final diagnosis was malignant myoepithelioma. The tumor was invading the perithyroid tissue and thyroid parenchyma (Figure 3A, H&E, 4x), with extensive necrotic areas (Figure 3B, H&E, 4x). The neoplastic cells were arranged in a reticular pattern, with eosinophilic cytoplasm and irregular hyperchromatic nuclei (Figure 3C, H&E, 20x). Epithelial membrane antigen was diffusely positive (Figure 3D, EMA immunostain, 10x), together with S100 protein (Figure 3E, S100 immunostain, 10x). The proliferative index was high (Figure F, Ki-67 immunostain, 10x).

Additionally, the patient had severely compromised cardiac function, with global ejection fraction of 31% documented by scintigraphy. The patient developed progressive clinical deterioration and died by clinical complications ten days after the diagnosis.

DISCUSSION

The term myoepithelioma was introduced by Sheldon in 1943 [4] and the first report of myoepithelial carcinoma was in 1975 by Stromeyer [5,6]. It is a very rare condition as, in 1985, Barnes et al., while reviewing cases of myoepitheliomas in head and neck, found only three malignant cases. Thus, only in 1991 was this neoplasm introduced among pathologies of the World Health Organization (WHO) [1].

It does not seem to have a predilection for sex, affecting various age groups and the mean age among the accounts reported is 55 years [7,8]. In the first reports, the diagnosis of MME was made when identifying the presence of a predominantly epithelial pattern with some degree of tubular differentiation [9]. Other larger series, most currently accepted, suggest that diagnostic confirmation would be compulsorily by the unquestionable identification of malignancy, characterized by an infiltrative pattern, cellular atypia, which may or may not be present, areas of necrosis and the presence of nuclear pleomorphism associated with an exclusively epithelial histology, and no ductal and/or acinar lineage being identified [7,8]. These tumors are classified as high- and low-grade, based on histopathological characteristics such as size, pleomorphism, membrane alterations in the cell nucleus, nucleolus size, density and chromatin aberration [7,8-13]. Di Palma and Guzzo, however, classified the tumors as low grade when occurring from a pleomorphic adenoma and high grade when occurring de novo and observed that cases that had worse outcomes showed marked cellular atypia [14]. This finding, however, was not observed in other series [2,7,8-13].
Nagao et al. showed in their case report that MME characteristically presents intense cell proliferation, usually with rates of mitosis higher than 7 per 10 HPF and Ki-67 generally above 10% [7]. Savera et al. have identified very peculiar histological features of myoepithelial carcinoma: the presence of more than one morphological cell type, multinodular architecture, multicellular peripheral rings, myxoid hypocellularity and necrotic center [8].

It was noted in these studies that the myoepithelial cells present with five different histological types: epithelioid, plasmacytoid, stellate, spindle and clear cell. Cases of two other miscellaneous histological types, association with epithelioid cells with plasmacytoids and spindle with epithelioid cells, are also accepted as they may occur [10]. The origin of these tumors is still the subject of research, with Hungerman et al. [11] through a genomic hybridization study, noting that the origin of MME occurs from an abnormality on chromosome 8. It is believed that about 60-70% of these neoplasms occur from a mixed benign tumor, especially pleomorphic adenoma, and the remainder de novo derived from a myoepithelioma [7,8].

Histopathological diagnosis of a MME invariably passes through a broad immunohistochemical study. In the study of Nagao et al. and Savera et al., the most frequently expressed markers were cytokeratins CAM5.2, AE1:AE3, S100 protein, vimentin, smooth muscle actin and calponin. In the study of Suba et al. [12], findings were very similar to those in Shubhada et al. that reviewed 51 cases and found the most expressed markers were vimentin (100%); calponin (98%) and S100 protein (82%) [13].

The biological behavior of this neoplasm is highly variable and the prognostic factors are not yet well defined. Several authors have attempted to identify any specific factor that would predict an increased risk of recurrence and metastasis. Nagao et al. [7] found that tumors with high cell proliferation, extensive invasion into adjacent tissues, perineural infiltration and cellular pleomorphism are related to worse prognosis and p53 expression was associated with higher rate of recurrence and death. The same was observed in the large series of Shubhada et al. [13] where higher recurrence rate was observed in tumors with stellate, clear and fusocellular cells, large tumor size and the presence of bone and perineural invasion. High incidence of metastases was observed in the presence of involved margins, large areas of necrosis and a high rate of cell replication, characterized by a mitotic count higher than 4 per 10 HPF and a high Ki-67, in addition to nuclear atypia and fusocellular characteristics [13,14]. These findings were also present in our case, which had a Ki-67 estimated at 40%, as well as large size and extensive necrosis and similarly evolved with a very aggressive pattern. Other authors also noted that a large tumor size is closely linked to a higher chance of distant metastases, both in salivary glands and the breast [15,16].

Some authors have suggested that some immunohistochemical markers can be related with the prognosis. According to Mao et al. [17,18], the expression of calponin may be related to a worse prognosis, which was not tested in this report. According to Jiang et al. [19,20] the expression of p63 and a high value of Ki-67 are

<table>
<thead>
<tr>
<th>Series</th>
<th>Age</th>
<th>Gender</th>
<th>Primary site</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrahim et al. (1991)²</td>
<td>71</td>
<td>Male</td>
<td>Hypopharynx and larynx</td>
<td>Chemotherapy and radiotherapy</td>
<td>Death from disease</td>
</tr>
<tr>
<td>Savera et al. (2000)³</td>
<td>36</td>
<td>Male</td>
<td>Supraglottic</td>
<td>Partial laryngectomy</td>
<td>Lost to follow-up</td>
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<tr>
<td>Ganly et al. (2006)¹⁷</td>
<td>70</td>
<td>Male</td>
<td>False cord</td>
<td>Radiotherapy</td>
<td>Alive without disease</td>
</tr>
<tr>
<td>Ganly et al. (2006)¹⁷</td>
<td>76</td>
<td>Male</td>
<td>Infrathyroid epiglottis</td>
<td>Laryngectomy and dissection</td>
<td>Death from other cause</td>
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<tr>
<td>Mao et al. (2010)³⁸</td>
<td>61</td>
<td>Male</td>
<td>Subglottic</td>
<td>Laryngectomy and radiotherapy</td>
<td>Death from disease</td>
</tr>
<tr>
<td>G. Yu et al. (2011)³⁹</td>
<td>78</td>
<td>Male</td>
<td>Glottic</td>
<td>Total laryngectomy</td>
<td>Alive without disease</td>
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<tr>
<td>Jiang et al. (2012)²⁰</td>
<td>62</td>
<td>Male</td>
<td>Glottic</td>
<td>Laryngectomy and radiotherapy</td>
<td>Death from disease</td>
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<td>Present case</td>
<td>78</td>
<td>Male</td>
<td>Subglottic</td>
<td>Transtumoral tracheostomy</td>
<td>Death from disease</td>
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associated with a greater chance of local recurrence and distant metastases. In this report, although p63 was negative, Ki-67 had a value considered very high (40%).

MME only rarely occurs in the larynx and through a review of the literature in the English language, seven cases were found in reports and series [2,8,17-20]. In the classic series of Savera et al. [8], only one case was observed in the larynx and did not have an effective follow-up. Not in the study by Nagao et al. [7] or the large series of Shubahda et al. [13], in which the majority of tumors affected the parotid gland and the palate, were cases involving the larynx observed. Table (1) lists the cases of MME identified in the literature as well as the affected laryngeal subsites, established treatments and the final outcome. Interestingly, no cases were reported in females and almost all occurred in men with older age, with a mean of 66.5 years. This may justify why 75% of cases (6/8) had an unfavorable outcome with lethal outcome.

There are few reports of the imaging findings of malignant myoepithelioma, given the rarity of cases described in the literature [21-24]. Most of these reports describe the imaging features of epithelioma affecting major salivary glands, which are most common site of involvement [24] (Table 1).

Despite the rarity of reported cases of MME, some authors reported CT and MRI features of MME. Mozen et al. reported on unenhanced CT lesion was isodense with muscle. These same authors believe that contrast-enhanced CT disclosed inhomogeneous enhancement of the tumor, which might reflect the differences in contrast enhancement between edema and hyalinization in the stroma [23]. Faint enhancement and hyperintensity in T2 weighted imaging on MRI was also described, which could also reflect the edematous stroma. Most of them described tumors with cystic areas, likely due to collagenous or mucoid stroma, as seen in our case here. MRI is useful to identify whether there is fibrous capsule and the presence or absence of the tumor spread beyond the fibrous capsule [22-24].

For those tumors emerging from the parotid glands and accessory parotid gland, from the standpoint of the CT scan findings, the most important differential diagnoses for MME of the parotid gland include benign pleomorphic adenoma and Warthin tumor [24,25]. However, as seen in this case, the location was extremely unusual. Since there are no pathognomonic findings, and imaging findings are common to other neoplastic lesions, the differential diagnosis in this case is based especially on the probable center of origin of the lesion. Also, several imaging features as irregular tumor margins, central intratumoral necrosis, heterogeneous enhancement, invasion into adjacent structures and vascular extension suggest aggressive neoplastic appearance or malignancy.

Particularly, in this case, the differential diagnosis includes lesions arising from visceral compartment, specifically infrahyoid space, including anaplastic thyroid carcinoma, squamous cell carcinoma of larynx, primary thyroid lymphoma and other less common as neurofibromas. Anaplastic thyroid carcinoma can be identical of the lesion presented here, regarding image features. Both may present heterogeneous enhancement, hemorrhage and central necrosis. Although it would be expected to find calcifications inside the lesion in about 60% of cases in anaplastic carcinoma, was not seen in this case [26]. This discourages the differential diagnosis of squamous cell carcinoma of the subglottic larynx; the extensive lesion volume without bone involvement. Primary thyroid lymphoma is also an uncommon disease, which usually promotes expansion of the gland with heterogeneous aspect and is marked by bilateral lymphadenopathy. Conversely, neurofibromas show hypodense center, well-defined appearance and homogeneous enhancement by contrast medium. On MRI they have high signal on T2, intermediate signal on T1 and intense homogeneous enhancement by contrast medium.

Although the final diagnosis can be provided only through immunohistochemical studies, multiplanar imaging, such as multislice CT and MRI, have an important role in the staging of head and neck lesions because they provide information about resectability and the extent of disease in therapeutic planning. Bronchoscopic study has the advantage of obtaining histological sample, assess patency of airway mucosa and luminal extension of the disease, but underestimates the true extent of the lesion and involvement of adjacent structures, as seen in this case.

The most accepted treatment for MME is surgery with wide resection margins seeking free margins, while the role of chemotherapy and radiotherapy is still very controversial [7,8,12,13,17-20]. Apparently, when it affects the larynx, especially in an older male population, this neoplasm appears to have a very poor prognosis, with a high chance of local recurrence and distant metastasis [2,18,20].

CONCLUSION

Malignant myoepithelioma of the larynx is a major therapeutic challenge and perhaps the most important measure is a precise clinical and histopathological diagnosis aiming to establish the earliest possible surgical treatment.

REFERENCES


