Myoepithelial carcinoma of the posterior mediastinum: An uncommon site for a rare tumor

Eman Abdulfatah, M.D.*, Rahman Chaudhry, M.D., M.P.H., Oudai Hassan, M.D., Faisal Qureshi, M.D., Rafi Beydoun, M.D., Sudeshna Bandyopadhyay, M.D.

Department of Pathology, Wayne State University, 540 East Canfield Avenue, Detroit, Michigan 48201

Abstract

Myoepithelial carcinoma (MC) is a rare tumor that arises from myoepithelial cells; most commonly in the salivary glands, but other infrequent body sites such as the breast, lung, lower limb, upper limb, head and neck, vulva, and vagina can be involved. We report the first case of myoepithelial carcinoma arising in the posterior mediastinum of a 51 year-old male who presented with a mediastinal mass and subsequently underwent tumor debulking surgery. Grossly, the specimen consisted of multiple tan–gray firm fragments of tissue with an overall measurement of 7.0 cm in greatest dimension. Histologic examination revealed an ill-defined, infiltrative lesion with a biphasic cell population. The tumor cells were diffusely positive for epithelial and myoepithelial markers, confirming the above diagnosis. Recognition of this entity at an uncommon site may present a diagnostic challenge due to its morphologic heterogeneity and the differential diagnosis includes benign and malignant tumors, which could lead to over or under-treatment, respectively.

1. Introduction

Myoepithelial carcinoma (MC), the malignant counterpart of myoepithelioma, was first described by Stromeyer et al. in 1975 [1] and was included in the World Health Organization (WHO) classification of salivary gland neoplasms as a distinct clinicopathological entity, in 1991 [2]. MC arises from myoepithelial cells and shows both epithelial and smooth muscle cell characteristics but lack ductal differentiation [3]. They comprise less than 2% of all salivary gland carcinomas, with the parotid gland being the most common site affected [4]. However, uncommon localizations have been previously reported such as the breast, palate, maxilla, nasopharynx, liver, vulva, and vagina [1,3,5–8]. Morphologic heterogeneity is a typical histologic feature, with tumors displaying a mixture of different cell types and growth patterns. The clinical behavior of MC tends to be relatively aggressive, with a high rate of distant metastasis [9,10].

To the best of our knowledge, this is the first case of primary MC involving the posterior mediastinum. We describe the morphologic and immunohistochemical findings and discuss the differential diagnosis of this rare entity.

2. Material and methods

2.1. Case report

A 51 year-old male presented to the Urology clinic complaining of “bloody urine” for five months. As part of the workup, a computed topographic scan (CT scan) of the abdomen and pelvis showed a simple renal cyst and an incidental left atrial mass measuring 5.0 cm in greatest dimension (on higher CT cuts). Subsequently, CT scan of the chest was performed which suggested a left atrial myxoma (Fig. 1). At that time, the patient had no symptoms and was lost to follow up. Five years later, he presented with shortness of breath and palpitations. Electrocardiogram (EKG) revealed atrial flutter. Cardiac catheterization showed triple vessel coronary artery disease and transesophageal echo (TEE) showed a significant increase in the
The size of the left intra-atrial mass which was 10.0 cm in the greatest dimension, compressing the superior vena cava and right main pulmonary artery. Based on these findings, a decision was made to perform coronary artery bypass graft (CABG) and tumor debulking surgery.

Intraoperatively, the mass appeared to be mediastinal in origin (rather than atrial), coursing behind the left atrium, posterior part of the ascending aorta and involving the wall of the right and left atrium.

2.2. Histology and Immunohistochemistry

Tissue sections were fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned at 4-μm thickness, and stained with hematoxylin and eosin. The immunohistochemistry was performed and evaluated at Wayne State University (Detroit Medical Center, Detroit, MI), where the Ventana BenchMark Autostainer (Ventana Medical System, Tucson, Arizona) was used on 4-μm thick formalin-fixed and deparaffinized sections with the following

![Computed Tomography of the chest showing heterogeneous non-enhancing mass extending superiorly to the inferior surface of the right main pulmonary artery.](image)

**Table 1**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Source/Clone</th>
<th>Dilution</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokeratin</td>
<td>DAKO/AE1AE3</td>
<td>1:500</td>
<td>Positive</td>
</tr>
<tr>
<td>CK5/6</td>
<td>DAKO/DC10</td>
<td>1:200</td>
<td>Positive</td>
</tr>
<tr>
<td>Calponin</td>
<td>DAKO/CALP</td>
<td>1:600</td>
<td>Positive</td>
</tr>
<tr>
<td>P63</td>
<td>DAKO/4A4</td>
<td>1:300</td>
<td>Positive</td>
</tr>
<tr>
<td>SMA</td>
<td>DAKO/1A4</td>
<td>1:400</td>
<td>Positive</td>
</tr>
<tr>
<td>GFAP</td>
<td>DAKO/6F2</td>
<td>1:400</td>
<td>Positive</td>
</tr>
<tr>
<td>S100</td>
<td>DAKO/polyclonal</td>
<td>1:1000</td>
<td>Negative</td>
</tr>
<tr>
<td>Calretinin</td>
<td>DAKO/Calret</td>
<td>Ready-to-use</td>
<td>Negative</td>
</tr>
<tr>
<td>Vimentin</td>
<td>DAKO/Vim3B4</td>
<td>1:400</td>
<td>Negative</td>
</tr>
<tr>
<td>Caldesmon</td>
<td>DAKO/h-CD</td>
<td>1:500</td>
<td>Negative</td>
</tr>
<tr>
<td>CD99</td>
<td>DAKO/12E7</td>
<td>Ready-to-use</td>
<td>Positive (cytoplasmic)</td>
</tr>
<tr>
<td>Bcl-2</td>
<td>DAKO/124</td>
<td>Ready-to-use</td>
<td>Negative</td>
</tr>
<tr>
<td>CD34</td>
<td>Immunotech</td>
<td>1:100</td>
<td>Negative</td>
</tr>
<tr>
<td>Desmin</td>
<td>DAKO/D33</td>
<td>1:200</td>
<td>Negative</td>
</tr>
<tr>
<td>WT-1</td>
<td>DAKO/6 F-H2</td>
<td></td>
<td></td>
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</tbody>
</table>
markers: AE1/AE3, CK5/6, calponin, p63, smooth muscle actin (SMA), GFAP, WT1, calretinin, vimentin, caldesmon, CD99, bcl-2, CD34, S-100 and desmin (Table 1).

2.3. Cytogenetic studies

Tumor cells were micro-dissected from tissue block. Fluorescent in-situ hybridization (FISH) analysis of the SS18 gene rearrangement was performed at Detroit Medical Center University Laboratories (Detroit, MI) using the LSI SS18/18q11.2 dual color break apart DNA probe (Vysis Inc.).

3. Results

3.1. Gross and microscopy

Grossly, the specimen consisted of tan–gray, firm fragments of tissue with an overall measurement of 7.0 × 7.0 × 3.0 cm. Histological examination revealed an ill-defined infiltrative tumor, with a biphasic cell population, spindle and epithelioid, in varying proportions, which blended with each other in a hyalinized and occasionally myxoid stroma (Fig. 2B). The predominant spindle cell areas consisted of solid sheets and fascicles of closely spaced cells with scant amount of eosinophilic cytoplasm and monotonous, hyperchromatic, ovoid nuclei (Fig. 2C-D). In other areas, few pseudoglandular structures which consisted mainly of epithelioid cells with eosinophilic cytoplasm and round nuclei were identified. Nuclear atypia as well as mitosis was minimal and no areas of necrosis were appreciated.

3.2. Immunohistochemistry

Based on these morphologic features, the differential diagnosis of biphasic tumors included synovial sarcoma, biphasic mesothelioma, myoepithelial carcinoma, thymoma and malignant peripheral nerve sheath tumor (MPNST). To further characterize the lesion, a panel of immunohistochemical stains was performed. The tumor cells were diffusely positive for epithelial markers including AE1/AE3 and CK5/6 and myoepithelial markers including calponin, p63, smooth muscle actin (SMA) and GFAP (Fig. 3). In addition, WT1, calretinin, vimentin, caldesmon, CD99 (cytoplasmic), bcl-2, CD34, S-100 and desmin immunostains were performed and were negative (Table 1).

3.3. Cytogenetics studies

Due to the high clinical and morphological suspicion of synovial sarcoma, fluorescent in-situ hybridization (FISH) analysis of the
SS18 gene rearrangement was performed and was found to be negative, making this diagnosis less likely (Fig. 2).

Based on the morphology, immunophenotype and cytogenetic results, the diagnosis of myoepithelial carcinoma/malignant myoepithelioma was rendered. Due to the presence of residual tumor following surgery, adjuvant radiation therapy was recommended. The patient passed away four months later due to a subarachnoid hemorrhage, not related to MC.

4. Discussion

Myoepithelial tumors are rare and distinguishing benign from malignant can be a major challenge. Although MC was described as an entity more than 40 years ago [1], it remains under recognized, and its diagnostic criteria as well as prognostic factors are still not well delineated. Given its morphologic heterogeneity, MC may be misdiagnosed, particularly when involving unusual sites. For definitive diagnosis of this tumor, histopathological characteristics and immunohistochemical profile must be utilized together [8].

Histologically, the most characteristic feature of MC is its multinodular architecture and its zonal cellular arrangement. These tumors typically display solid, trabecular and/or reticular patterns, with a variably prominent myxoid and/or hyalinized stroma. The myxoid stroma is predominantly composed of chondroitin sulfate proteoglycans, while the eosinophilic hyaline component represents basement membrane-related elements [11]. Additionally, different cell types including spindle shaped, epithelioid, plasmacytoid and clear cells are often seen within the same tumor. Focal luminal formations can be observed; however, true ducts are almost never identified, which are required to define epithelial–myoepithelial carcinoma. Various forms of metaplasia, including squamous, chondroid and sebaceous differentiation may be seen, with squamous metaplasia being the most common [12]. In our case, the tumor consisted of solid sheets of spindle and epithelioid cells, present within a hyalinized and occasionally myxoid stroma. Few pseudoglandular structures were seen, but no true ducts were identified. Moreover, none of the previously reported metaplasia was noted.

Determination of myoepithelial differentiation on the sole basis of morphology may be difficult. In such cases, the use of immunohistochemical stains might be helpful. Given that neoplastic myoepithelial cells may vary in their immunohistochemical protein expression profiles, the WHO has proposed that reactivity for a cytokeratin and at least one of the myoepithelial markers, including S100, SMA, calponin, GFAP and p63, is required to definitively diagnose MC [13]. Kane and Bagwan [14], reported S100 positivity in the majority (95%) of their reported series. Our case showed strong reactivity of the tumor cells...
with AE1/AE3, CK5/6 and myoepithelial markers including calponin, p63, smooth muscle actin (SMA) and GFAP, thus fulfilling the WHO criteria of a myoepithelial tumor. However, in contrast to the previous studies, S100 was negative.

The histologic differential diagnosis of MC includes biphasic tumors such as synovial sarcoma, biphasic mesothelioma, MPNST and thymoma. Synovial sarcoma, particularly the biphasic form, may show a marked resemblance to MC. The tumor consists of fascicles of spindle cells admixed with numerous glandular structures lined by cuboidal to columnar epithelium, set in a background of variably collagenous stroma [15]. Immunohistochemically, in addition to the positive staining in the epithelial component, the spindle cell element shows at least focal positivity to EMA and cytokeratin. CD99 shows membranous staining while bcl-2 shows cytoplasmic staining in either or both components. Myoepithelial markers are negative. Furthermore, 90% of synovial sarcomas show a characteristic t(X;18)(p11.2;q11.2) [16]. While our case did exhibit immunoreactivity to cytokeratin, bcl-2 and CD99 (cytoplasmic, rather than membranous), the presence of strong expression of more than one myoepithelial marker and the lack of characteristic cytogenetic abnormality, made this diagnosis less likely.

Biphasic mesothelioma should also be considered in the differential diagnosis of MC, particularly in the mediastinum. These tumors present with a diffuse growth pattern usually involving the visceral and parietal pleura and are characterized by a combination of epithelioid and sarcomatoid elements in varying proportions. Similar to MC, the tumor cells are positive to cytokeratin (AE1/AE3) and CK5/6; however, they lack immunoreactivity to myoepithelial markers. In addition, specific markers of mesothelial origin such as calretinin and WT1 are expressed in the majority of mesotheliomas [17], which help in differentiating them from MC.

Thymomas must be taken into account due to the mediastinal origin of the tumor; however these tumors involve the anterior rather than the posterior mediastinum. Microscopically these tumors are generally encapsulated, with thick fibrous septa dividing them into lobules. Type A thymoma consists of fascicles of spindle shaped epithelial cells with focal areas of glandular differentiation, mimicking MC. In addition, scant amount of T cells is present in the background [18]. Immunohistochemically, the spindled epithelial cells stain positive for cytokeratin and EMA, and the T-cell population exhibits a cortical thymocyte phenotype of TdT+, CD1a, and CD99 [19]. In our case, due to the infiltrative growth pattern, posterior mediastinal involvement, lack of co-existent lymphocytic component, and the characteristic immunoprofile, thymoma was ruled out.

MPNST, the main differential diagnosis of synovial sarcoma, shows epithelial (glandular) differentiation on rare occasions and may require distinction from MC. These tumors typically have a spindle-celled fascicular appearance and perivascular whorling of tumor cells. Immunohistochemically, 50% of the cases of MPNST are S-100 positive, whereas 20%–30% are GFAP positive. Rare cases exhibit EMA positivity; however, none of them show myoepithelial differentiation which is essential in differentiating it from MC [20].

The clinical behavior of MC tends to be relatively aggressive. In a recent study by Kong et al. [10], approximately one third of the patients diagnosed with MC of salivary glands developed distant metastasis, with lung being the most common site. A major issue regarding MC has been the assessment of tumor grading. Previous studies have shown no clear correlation between different histologic features of MC and its clinical behavior [14]. Savera et al. [12] classified MC as low grade when the tumors displayed relatively uniform small sized nuclei and as high grade when they showed marked cytologic atypia, nuclear pleomorphism and high proliferative activity. Moreover, Kong et al. showed that the presence of tumor necrosis correlated significantly with a worse clinical behavior and therefore suggested defining high grade MC on the basis of tumor necrosis. Due to the rarity of MC, particularly in unusual sites, the outcome and optimum management of these tumors remain uncertain. Case studies have shown that chemotherapy has a limited role and that surgical excision remains the mainstay of treatment. Pertaining to our case, the tumor was considered unresectable. The patient underwent a suboptimal tumor debulking surgery. Postoperative radiotherapy was initiated with symptomatic improvement; however, the patient passed away four months after surgery due to subarachnoid hemorrhage, not related to MC.

In summary, we report the first case of MC arising in the posterior mediastinum. The morphologic heterogeneity of these tumors requires supportive immunohistochemical stains to aid diagnosis, especially for tumors in unusual sites. Greater awareness of the occurrence of MC in the posterior mediastinum may lead to increased recognition of this rare entity, with subsequent improved understanding of the optimum clinical management and outcomes.

References
