Soft Tissue High Grade Myoepithelial Carcinoma With Round Cell Morphology: Report Of A Newly Described Entity With EWSR1 Gene Rearrangement

M. El-Kabany, R. Al-Abdulghani, A. E. Ali, I. M. Francis, S. A. Hussein

Department of Pathology, Hussain Makki Al-Juma Center for Specialized Surgery, Kuwait City, Kuwait

Abstract

The case of soft tissue malignant myoepithelioma is presented including clinicopathological, immunohistochemical and cytogenetic findings. A 36-year-old Saudi male patient suffered from large mass involving right scapula and right shoulder joint measuring 14x13x11 mm. Core biopsy revealed sheets and lobules of poorly differentiated small malignant cells with marked atypia and frequent mitosis. Initially, immunohistochemistry was reactive for vimentin, pan-cytokeratin, EMA and CD99. The case was negative for desmin, SMA, CD34, S-100 protein and GFAP. FISH analysis exhibited negativity for SS18 (18q11.2) gene rearrangement and positivity for EWSR1 (22q12) gene rearrangement and a diagnosis of Ewing/PNET was considered. Clinical behavior and therapeutic response did not match the diagnosis with re-evaluation. Wedge biopsy demonstrated aggregates of epithelioid cells besides calponin and P63 positivity. Final diagnosis of malignant myoepithelioma with EWSR1 gene rearrangement was issued; a new entity with aggressive course. Myoepithelial carcinoma of soft tissue exhibits a wide spectrum of cytomorphology with overlapping phenotype similar to other soft tissue sarcoma like synovial sarcoma, mesenchymal chondrosarcoma, epithelioid sarcoma as well as Ewing/PNET. Moreover, a new finding of EWSR1 gene rearrangement is recognized in malignant myoepithelioma with different fusion partners. Hence, myoepithelial carcinoma should be kept in mind in diagnosis of soft tissue tumors even with unusual phenotype and gene rearrangement.

Keywords

Soft tissue myoepithelioma, soft tissue myoepithelial carcinoma, CD99, P63, EWSR1 (22q12).

Introduction

Myoepithelial carcinoma is a well recognized entity in salivary glands and in breast, where it is thought to arise from myoepithelial cells and thus shows a similar immunophenotypic pattern to its benign counterparts(1). Soft tissue myoepithelioma is an extremely rare neoplasm in a wide age-range with a peak in the fourth decade. Most cases are benign but about 40% of cases exhibit malignant features(2). It is thought that myoepithelial carcinoma is the malignant counterpart of benign myoepithelioma and mixed tumors. Some cases may show frank ductular epithelial differentiation with straightforward diagnosis, whereas others may show a predominantly solid proliferation of spindle or small round cells mimicking soft tissue sarcoma(3). By immunohistochemistry they express pan-keratin, S-100 protein and calponin in about 90% of cases; positivity for epithelial membrane antigen and glial fibrillary acidic protein in about 50% to 60%, and positivity for smooth muscle actin, P63, and desmin in 10% to 40% of cases(4).

Cytogenetic analysis of salivary myoepithelioma shows 12q12 involved in a translocation with a previously unreported partner (1q), and nonrandom del (9) (q22.1q22.3) and del (13) (q12q22)(5). On the other hand, soft tissue myoepithelial carcinoma, so far revealed only some clonal aberrations in the form of hypodiploidy and hyperdiploidy as well as loss
of material from 17p<sup>6,7</sup>. In the current work, we describe the clinical, morphological and immunohistochemical profiles of soft tissue mass with EWSR1 gene rearrangement positive for (22q12) Break Apart.

**Case Report**

The patient is a 36 year old Saudi gentleman, presented in October 2009 with a 6 month history of limited movement and pain in his right shoulder. The patient received physiotherapy without improvement. On examination, there was markedly decreased range of motion due to severe pain on mobilization of the right arm. Axial C-T identified a large 14x13x11 mm. heterogeneous mass in the region of the right scapula involving most muscles around the right scapula and right shoulder joint (Figure 1). A tiny core biopsy was obtained, which revealed sheets and lobules of poorly differentiated round cells exhibiting high N/C ratio and prominent mitosis with intervening thin walled blood vessels and foci of necrosis (Figure 2).

Phenotypically, the cells revealed positive reaction for vimentin and focal staining for pan-cytokeratin and EMA. Moreover, they demonstrated diffuse membranous positivity for CD99 (Figure 3) and cytoplasmic staining for Bcl-2. Other antibodies for LCA, CD20, desmin, SMA, CD34, Oct<sup>3</sup>, synaptophysin, S-100 protein and GFAP were non-reactive. The proliferating index for Ki67 was 80%. A diagnosis of small round cell tumor favoring Ewing/PNET was suggested with recommendation for molecular testing to confirm the diagnosis and to exclude poorly differentiated synovial sarcoma. The biopsy however was tiny and there was no tissue available for cytogenetics.

Bone scan and bone marrow aspiration and biopsy came negative with CT scan evidence of enlarged right axillary lymph nodes and free lungs. The clinicians decided to start chemotherapy VIDE as whatever the case is synovial sarcoma or PNET he would benefit. After 3 cycles there was a marked decrease of the shoulder mass to be 8.3x3.3cm. However after 6 cycles the tumor continued to grow. A second multidisciplinary meeting was held and it was decided to obtain more tissue for molecular testing. The second
wedge biopsy showed scattered epithelioid islands composed of cells with abundant pale cytoplasm which were not present in the first biopsy, in addition to the population of round tumor cells. Areas of geographic necrosis were also present. The epithelial islands were positive for pan-cytokeratin as well as EMA. The whole biopsy was positive for bcl2. Based on this histological and immunophenotypic picture a diagnosis of poorly differentiated synovial sarcoma was considered and the tissue was sent for molecular testing for confirmation. FISH analysis, using Vysis LSI SS18 (18q11.2) Dual Color, break Apart rearrangement probe was negative for SS18 arguing strongly against poorly differentiated synovial sarcoma. However, FISH, Vysis LSI EWSR1 (22q12) Dual Color, Break Apart Rearrangement Probe identified a clear evidence of EWSR1 gene rearrangement (Figure 5). This genetic profile was suggestive of Ewing/PNET. Nevertheless, as the histological features where unusual, extended markers were done for calponin and P63 (Figure 4). Diffuse positivity was recognized and the diagnosis of soft tissue myoepithelial carcinoma was finally issued associated with EWSR1 gene translocation.

By this time, the patient had an ulcerated tumor over the right shoulder complained of constant pain and had very limited function of the right arm. A decision was then taken to disarticulate the arm. The patient developed metastatic deposits in bone, lungs and liver within 10 months after presentation (Figure 6).

Discussion

Myoepithelial carcinoma (malignant myoepithelioma or malignant mixed tumor) is the malignant counterpart of benign myoepithelioma and mixed tumor where they lack ductal differentiation. They were considered besides oncocytomas of soft tissue as members of the same myoepithelial-derived tumor family(8). While the benign group harbors minimal or no atypia with uniform small nuclei revealing fine chromatin and inconspicuous
nucleoli, the malignant type features large nuclei with coarse chromatin, prominent nucleoli and frequent mitosis. Cell type varies among cases and within the same tumor with occasional predominance of solid proliferation small, spindled or plasmacytoid cells. In small or core biopsies, such tumor growth may mimic other spindle cell sarcoma such as extraskeletal myxoid chondrosarcoma or synovial sarcoma\(^9\) or even PNET. Moreover, with identification of some aggregates of large epithelioid cells the differential diagnosis of epithelioid sarcoma can be included\(^3\). Final diagnosis then would be based on immunohisto-chemical and cytogenetic study.

In the present case positive staining for vimentin, cytokeratin, EMA as well as CD99 narrowed the differential diagnosis to poorly differentiated synovial sarcoma and PNET for further cytogenetic study which revealed negativity for SS18 (18q11.2) and positivity for EWSR1 (22q12) gene rearrangement. Hence, a diagnosis of PNET was issued but it did not go with patient’s clinical behavior or response to therapy. This required re-evaluation of the case that demonstrated calponin and P63 positivity despite the reported expression of calponin in synovial sarcoma\(^10\). Fletcher, C.D. (Personal communication) appreciated that as many as 50\% of myoepithelial carcinoma arising in soft tissue have EWSR1 gene rearrangement with different fusion partners than those seen in Ewing/PNET. About 90\% of Ewing/PNET demonstrated a characteristic t(11;22)(q24;q12) in which the FL1 genes are juxta-opposed to EWS gene to form chimeric protein translocation or to minor extent to ERG gene or rarely to other genes like ETV1, EIAF or FEV\(^11\).

Although translocation involves the EWS gene on chromosome 22 can be seen in several other malignant neoplasms such as Ewing/PNET, desmoplastic small round cell tumor and malignant melanoma of soft tissue as well as mesenchymal myxoid chondrosarcoma\(^12\). The mere presence of it may reflect a variant of myoepithelioma with clonal selection that may reflect its resistance to chemotherapy and more aggressive behavior. In a very simplistic fashion, one can consider three varieties of cancer. The first is a homogeneous population of sensitive cells, representing those tumors for which chemotherapy works immediately and dramatically. The second type, made up of a homogeneous population of refractory cells, results in early therapeutic failure. The vast majority of cancers, however, are those with a heterogeneous population of both sensitive and resistant cells. Here, therapy is a continual experiment of Darwinian clonal selection, with resistant clones emerging out. Sometimes in the setting of relapse, newly emergent clones can be detected by the presence of genetic markers not present in the original sample. Yet, sometimes these cells appear the same as in the original disease. Even more baffling, sometimes retreatment with the original agents may yield a good response\(^13\).

The unusual immunohistochemistry of the present case such as positivity for CD99 and lacking some myogenic marker such as desmin and SMA as well as negativity for S100 protein and GFAP may have correlation with the aberrant EWSR1 gene rearrangement in some myoepithelial carcinoma. Hence, in soft tissue sarcoma with dual expression of cytokeratin and vimentin such as synovial sarcoma, rhabdoid tumor and epithelioid sarcoma we can add myoepithelial carcinoma to the list. Moreover, it must be included in the differential diagnosis of CD99 positive small round cell tumor with EWSR1 gene rearrangements such as Ewing/PNET and mesenchymal myxoid chondrosarcoma.

**Conclusion**

Myoepithelial carcinomas exhibit a wide spectrum of cytomorphic features and diverse clinical outcomes. As a result of their morphologic heterogeneity, they can be confused easily with many tumors. Myoepithelial carcinomas have been under-recognized in the past. Awareness of its heterogeneous histological patterns, immunohistochemical profile and cytogenetic markers is crucial for accurate identification and should be kept in mind in diagnosis of soft tissue tumors.
References


