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Case Report

Cutaneous syncytial myoepithelioma: A potential pitfall in the differential diagnosis of superficial dermal tumors

Abstract

In the spectrum of myoepithelial tumors of the skin, cutaneous myoepithelioma is composed solely of myoepithelial cells. Cutaneous syncytial myoepithelioma as a rare histological variant of cutaneous myoepithelioma has been first described in the last decade. This tumor is benign and rarely shows recurrence when incompletely resected. In addition to its distinctive common histological and immunohistochemical features, cutaneous syncytial myoepithelioma shares the same changes for most cases in molecular testing (EWS RNA binding protein 1 gene rearrangement). The differential diagnosis of other superficial dermal tumors is one of the major difficulties in the diagnosis of this tumor. In the current study, we present our findings of a 56 year-old woman who was diagnosed as cutaneous syncytial myoepithelioma.

Abbreviation

CK: Cytokeratins; CM: Cutaneous Myoepithelioma; CSM: Cutaneous Syncytial Myoepithelioma; EBFH: Epithelioid Benign Fibrous Histiocytoma; EMA: Epithelial Membrane Antigen; EWSR: EWS RNA Binding Protein 1; FISH: Fluorescence in Situ Hybridization; JXG: Juvenile Xantogranuloma

Introduction

Myoepithelial cell neoplasms represent a histologically broad spectrum and well defined tumor group, especially for salivary glands [1]. Extra-salivary gland representatives of these neoplasms are rare and include bone, respiratory tract, breast and retroperitoneum [1-4]. CM and soft tissue myoepitheliomas have relatively newly been defined [5-7].

CM generally affects male adults (with peak incidence in the 3. and 5. decades, and a male to female ratio of 3:1) and extremities as anatomical localization [1,6-8]. It is composed solely of myoepithelial cells and regarded as a subgroup of cutaneous mixed tumor. These tumors usually present as a solitary, slow growing papule and histologically demonstrate a wide spectrum of features including epithelioid, spindled, histiocytoid or plasmocytoid cells showing solid, lobulated or reticular growth patterns in a myxoid or hyalinized stroma [7,9]. Immunohistochemically, neoplastic cells express EMA (epithelial membrane antigen) and S100 protein. Other markers like cytokeratins (CK), GFAP, SMA and p63 show variable

expression [6,7,9]. As a rare histologic variant, CSM has been lately described and to the best of our knowledge, there are only 42 cases reported in the literature [8]. This variant demonstrates tightly packed histiocytoid-spindle cells growing in a sheet like pattern within a limited stroma. These tumors are negative for CK by immunohistochemistry unlike CM and have distinctive molecular characteristics [8]. These tumors are benign such as CM and rarely recur when incompletely resected [7,8]. At this point, we present our findings of a 56 year-old woman represented clinically by a papule on her left thigh and diagnosed as CSM in our department.

In November 2018, a 56 year-old woman with no significant clinical history presented at an external hospital for a papule on her left thigh. Complete excision of this lesion was performed by a plastic surgeon. The case was referred for a second opinion by the primary pathologist with the initial diagnosis of neurofibroma to the Pathology Department of Pamukkale University Hospital.

Results

The lesion was described as a solitary, well-circumscribed, 0.6×0.4cm white papule in the primary pathology report. The slides obtained from two paraffin blocks were evaluated. On histopathological examination, hypergranulosis and irregular acanthosis were observed in the epidermis covered with compact keratin layer. The tumor was well-circumscribed, localized in the superficial dermis and the overlying epidermis

showed pseudoepitheliomatous hyperplasia (Figure 1). The tumor consisted of ovoid to histiocytoid and spindle shaped cells with indistinct cell borders and focally clear/pale eosinophilic cytoplasm. Nuclei were monomorphic with vesicular chromatin. No significant atypia or necrosis were observed (Figure 2). Surgical margins were intact. Immunohistochemically, the tumor cells were positive for EMA, SMA and Vimentin. S100 protein was also diffusely positive in neoplastic cells (Figure 3). Melanocytic markers (HMB45 and SOX-10), CEA, CD34 and TFE-3 were all negative. Desmin couldn't be assessed due to the technical problems. Ki-67 proliferation index was 7%. In molecular testing, a FISH (fluorescence in situ hybridization) analysis showed EWS RNA binding protein 1 (EWSR1) gene rearrangement with a break-apart probe with 90.2% positive cells (Figure 4). The final diagnosis was CSM in the current case. Since the surgical margins were clear, no further treatment was recommended.

Discussion

CSM represents a lately described entity and a histologic variant of CM. Fletcher published a case series with 38 individuals

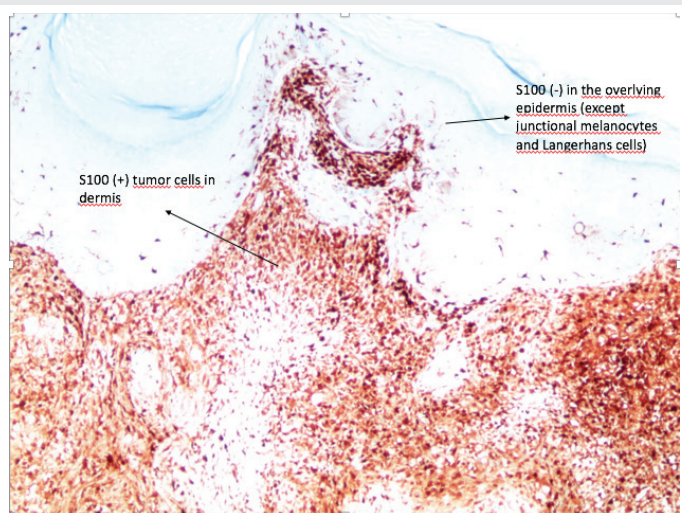


Figure 1: Well-circumscribed and unencapsulated tumor is superficially localized in the dermis. Pseudoepitheliomatous hyperplasia is observed in the overlying epidermis (H&E staining).

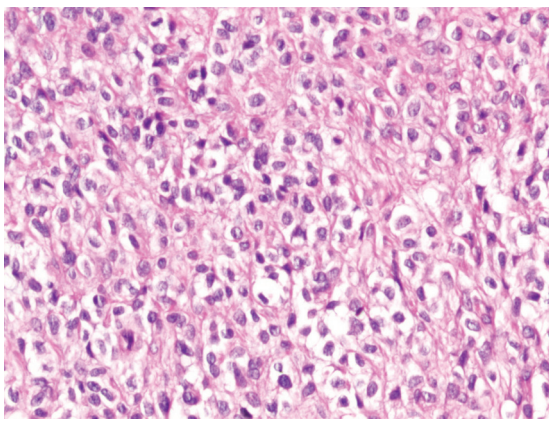


Figure 2: Ovoid to histiocytoid cells with pale eosinophilic cytoplasm arranged in syncytial/sheet-like growth pattern. Nuclei are vesiculated. No mitotic figures or area of necrosis is visible (H&E staining).

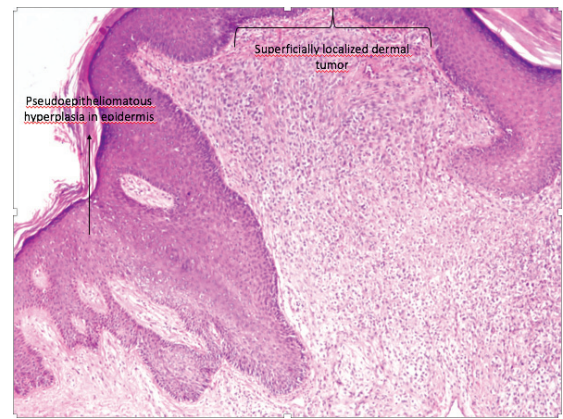


Figure 3: S100 protein is diffusely positive in neoplastic cells (Immunohistochemical staining).

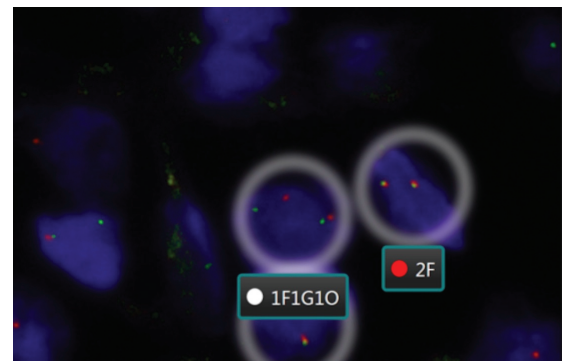


Figure 4: FISH analysis showed a cell (red point) containing 2 fusions with EWSR1 (22q12) break FISH probe.

describing the clinicopathologic features of CSM in 2013 [8]. 27 men and 11 women were involved in the study with a 2.5:1 ratio. The age range of the patients was between 2 months and 74 years (median, 39 years). In terms of tumor location, there was a predilection for the extremities compared to the other affected sites like back, chest, buttock, nose and cheek. Most of the initially proposed diagnoses by the primary pathologists were epithelioid sarcoma, neurofibroma, perineuroma/sclerosing perineuroma, cellular neurothekoma, granular cell tumor, myofibroma and smooth muscle neoplasms [8]. Median tumor size was 0.8cm (range 0.3cm to 2.7cm). Local recurrence was observed in only one patient with positive surgical margin after local excision [8]. On histopathologic examination, CSM has limited/no stromal component and consists of ovoid to spindled or histiocytic cells with pale eosinophilic cytoplasm arranged in a syncytial fashion [10,11]. Tumors display minimal or no mitotic activity (range 0-4 per 10 high power fields). Necrosis or lymphovascular invasion is not observed in any cases. Adipocytic metaplasia or chondro-osseous differentiation may be seen [8]. All tumors show EMA and S100 positivity. Despite most tumors are negative for cytokeratins (CK), rare tumors can show focal positivity. Variable positive reactivity is seen with myoepithelial markers as GFAP, SMA and p63 [8,10-12].

In the current study, we also reported a CSM case with dermis-located and well-circumscribed tumor displays a

syncytial/sheet-like growth pattern. A wide spectrum of superficial dermal tumors is included in the differential diagnosis of this rare entity.

Epithelioid sarcoma is one of the clinically important mimickers of CSM. The presence of dermal epithelioid cell proliferation and the immunohistochemical expression of EMA protein are common features for both tumors. However, epithelioid sarcoma usually affects distal extremities of young adults and shows granuloma-like pattern of epithelioid cells around areas of necrosis on histopathologic examination. Epithelioid sarcoma shows lack of expression of myoepithelial markers and positive expression of CD34 and CK, whilst CSM is positive for myoepithelial markers and negative for the latter [8,10,11].

Dermal melanocytic neoplasms such as Spitz nevi should be considered in the differential diagnosis of CSM. Although Spitz nevi show dermal proliferation of epithelioid cells with abundant eosinophilic cytoplasm, these cells lack the typical syncytial growth pattern of CSM. Both tumors are S100 (+), whereas CSM lacks of expression of MelanA and HMB45 [10,11].

Epithelioid benign fibrous histiocytoma (EBFH) is a well-circumscribed dermal neoplasm with uniform, medium to large angulated epithelioid cells. The epithelioid cells with indistinctive cell borders and eosinophilic cytoplasm represent the same histological pattern as CSM. Compared to CSM, EBFH has a more hyalinized stroma with marked vascular structures. Different from CSM, binucleated cells may be seen in EBFH. Immunohistochemically, both neoplasms are EMA (+), on the other hand, EBFH lacks reactivity for myoepithelial markers including S100 [8,10].

Juvenile xanthogranuloma (JXG) is a neoplasm that usually affects infants and young children. This neoplasm is composed of histiocytic cells and lacks the characteristic multinucleated giant cells especially in the early-stage lesions, so it should be considered in the differential diagnosis of CSM. JXG is negative for EMA and S100 protein, but shows CD68 and CD163 positivity [10,12].

As a histologic variant of neurothekoma, cellular neurothekoma may also mimic CSM due to the composition of this tumor with spindle and epithelioid cells with abundant eosinophilic cytoplasm and indistinctive cell borders. Immunohistochemically, cellular neurothekoma exhibits no positivity for EMA or S100 [11].

EWSR1 gene is located on the long arm of chromosome 22 at position 12.2 [13]. Although its function is not fully understood, EWSR1 protein takes part in cellular processes, cell signaling and RNA transport [14]. Mutations of EWSR1 gene are seen in a wide range of tumors including Ewing sarcoma, desmoplastic small round cell tumor, extraskeletal myxoid chondrosarcoma, clear cell sarcoma of soft tissue, myxoid liposarcoma and soft tissue myoepithelial tumors [15]. Rearrangement of this gene has been detected nearly half of CM cases [16]. Fletcher reported EWSR1 gene rearrangement was found in most CSM cases. Pre-

B-Cell Leukemia Homeobox 3 (PBX3) has been determined as a fusion partner of EWSR1 in one study [17].

In conclusion, CSM is a lately described entity and represents a diagnostic challenge in terms of superficial dermal tumors. Because of its rarity and diagnostic difficulties, most CSM cases are referred to experienced pathologists with various initial diagnoses. Since EWSR1 gene rearrangement is seen in most cases, molecular testing can help to confirm the diagnosis of this tumor in addition to some prominent histopathological and immunohistochemical features. CSM rarely shows local recurrence when incompletely resected, otherwise it presents as a benign tumor.

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