Rhabdoid Variant of Myoepithelial Carcinoma, with *EWSR1* Rearrangement: Expanding the Spectrum of *EWSR1*-Rearranged Myoepithelial Tumors

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Received: 19 April 2014 / Accepted: 24 June 2014 / Published online: 4 July 2014
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Abstract Myoepithelial and mixed tumors represent a heterogeneous group of neoplasms for which classification is incomplete and continues to evolve. Those arising in the soft tissues appear to represent subgroups that are genetically distinct from those that occur within salivary glands. We describe a case of soft tissue myoepithelial carcinoma with rhabdoid morphology, which presented as an enlarging neck mass in a 40 year old male, and in which *EWSR1* rearrangement was demonstrated by fluorescence in situ hybridization. This neoplasm showed diffuse INI1 loss, making distinction from other INI1-negative rhabdoid tumors difficult. This expands the range of reported histologic features of *EWSR1*-rearranged myoepithelial neoplasms, and highlights the significant morphologic and immunohistochemical overlap between this and other INI1-negative malignant rhabdoid neoplasms.

Keywords *EWSR1* · Malignant rhabdoid tumor · Myoepithelial carcinoma · Translocation

Introduction

While myoepithelial tumors are well characterized within the salivary glands, those that occur in other sites such as soft tissues are often difficult to diagnose due to their marked morphologic and immunophenotypic heterogeneity. *EWSR1* gene rearrangement is now increasingly described in a subset of soft tissue myoepithelial neoplasms, resulting in fusion with one of a small group of genes (*POU5F1*, *PBX1* and *ZNF444*) in tumors with histologic features that differ considerably from the well characterized neoplasms with translocations involving *EWSR1* such as Ewing sarcoma [1]. The number of tumors reported to harbor fusions between *EWSR1* and these partner genes remains small, and these range from neoplasms histologically and immunophenotypically consistent with myoepithelial tumors, to those for which histology does not conform to any recognized tumor type. We describe herein a case of myoepithelial carcinoma with distinct rhabdoid morphology harboring *EWSR1* gene rearrangement, which arose in the neck of a 40 year old male. The immunohistochemical features were consistent with myoepithelial tumor, and included loss of INI1 expression. The fusion partner remains unknown, but commonly characterized fusion partners of *EWSR1* (*FLI1*, *ERG*, *ATF1*, *CREB1*, *POU5F1*, *NR4A3* and *WT1*) were excluded by reverse transcription polymerase chain reaction. Rhabdoid morphology is rarely described in myoepithelial neoplasms, and this expands the histologic spectrum of *EWSR1*-rearranged myoepithelial tumors, highlighting the potential for overlap with other INI1-negative rhabdoid neoplasms such as malignant rhabdoid tumor and epithelioid sarcoma.

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Fig. 1 **a** Myoepithelial carcinoma with rhabdoid morphology. The majority of the neoplasm is composed of sheets of large polygonal cells with eccentric ovoid vesicular nuclei, often prominent nucleoli and abundant eosinophilic cytoplasm which often have a glassy, homogeneous appearance. **b** In areas there is marked pleomorphism, with enlarged polygonal cells which are often bi- or multinucleate, and prominent nucleoli. **c** There is a pronounced nested architecture

in other parts of the tumor, with polygonal and plasmacytoid cells intersected by paucicellular fibrous septa. **d** Less frequently, the cells are much smaller and more uniform, with rounded nuclei and amphophilic or clear cytoplasm. **e** Other foci show nested distributions of smaller cells which are again uniform, with ovoid vesicular nuclei and clear cytoplasm. **f** There is perineurial invasion by clusters of ovoid and plasmacytoid cells

Case Report

A 40 year old Caucasian male presented with a 6 months history of a progressively enlarging right neck mass, which had been causing mild pain and discomfort. He was otherwise fit and well, with no past medical history of note. Magnetic resonance imaging (MRI) scan showed an 8 cm diameter lobulated encapsulated mass at the right common carotid artery bifurcation, which appeared to originate either from the vagus nerve or the superior sympathetic ganglion, and was suspected to be a large schwannoma. Computed tomography (CT) scans of the thorax, abdomen

and pelvis showed no evidence of metastatic disease or any other significant abnormalities. Fine needle aspiration cytology of the mass was inconclusive, showing spindle cells with irregular nuclei. The patient underwent right neck exploration, where the mass was excised with its local (levels II–III) lymph nodes. Operatively this was a large mass enveloping the internal and external carotid arteries, internal jugular vein, 10th and 12th cranial nerves and sympathetic chain.

Grossly, the specimen comprised a $10 \times 8.5 \times 6$ cm, 230 g soft cystic mass with strips of skeletal muscle and adipose tissue on its surface. Sectioning showed

extensively necrotic tumor with approximately 20–40 % solid areas composed of medium firm yellow to tan tissue. A total of 23 unremarkable lymph nodes were retrieved from the adjacent adipose tissue. Histologically, this was a partially encapsulated cellular tumor with a focally infiltrative edge. It was predominantly composed of sheets and discohesive arrays of large epithelioid or polygonal cells with pronounced rhabdoid morphology, with eccentrically sited vesicular nuclei, prominent nucleoli and moderate to abundant amounts of eosinophilic, often glassy, homogeneous cytoplasm (Fig. 1a, b). The cells were moderately to focally markedly pleomorphic (Fig. 1b), with binucleate and multinucleate forms. In other areas however, the tumor had a more nested architecture (Fig. 1c), and less frequently the cells were smaller and uniform, with blander morphology (Fig. 1d), and varied from plasmacytoid to focally clear (Fig. 1e). Infiltrative nests were present within fibrous stroma, sometimes with the formation of thick and thin hyalinised fibrous septa, and there were interspersed medium sized vessels, often with extensively hyalinised walls. Coagulative necrosis was prominent, and the mitotic index was up to 6 per 10 high power fields. There was perineurial invasion (Fig. 1f), although no lymphovascular invasion. Native ganglion cells were present within the lesion, and there were surrounding large nerves.

The tumor was diffusely positive for CD56 and positive for epithelial membrane antigen (EMA) in most cells (Fig. 2a). There was focal strong CD34 (as a cluster of cells within the tumor) (Fig. 2b), and focal smooth muscle actin (SMA) (Fig. 2c), calponin, S100 protein (Fig. 2d), neuron-specific enolase (NSE) and CD10 distributed throughout the neoplasm. There was widespread loss of nuclear INI1 expression within the entire lesion (Fig. 2e). Dot positivity for claudin-1 was also present (Fig. 2f). The tumor was negative for AE1/AE3, MNF116, CAM5.2, p63, TTF1, calcitonin, desmin, h-caldesmon, Oct3/4, CD31, CD45, CD79a, CD138, CD30, ALK, CD117, HMB45, MelanA, neurofilament, chromogranin, synaptophysin and ERG. MIB1 labelled approximately 40 % of nuclei. Molecular genetic and molecular cytogenetic analyses were performed on formalin fixed, paraffin embedded (FFPE) material for *EWSR1* rearrangements by fluorescence in situ hybridization (FISH), and for specific fusion transcripts by reverse transcription polymerase chain reaction (RT-PCR). For FISH, 1 µm thick FFPE sections were dewaxed overnight at 60 °C, treated with hot buffer wash at 80 °C (2–3 h) then proteolytic enzyme treatment at 37 °C, and washed in distilled water then an alcohol series before addition of *EWSR1* DNA break-apart probes (Abbott Laboratories Ltd, UK) or *POU5F1* break-apart DNA probes [constructed in house, based on bacterial artificial clones (BACs) RP11-116B15 and RP11-1087L18]. Hybridization was performed overnight according to

manufacturer's protocols. RT-PCR was performed to assess for *EWSR1-NR4A3*, *TAF15-NR4A3*, *EWSR1-FLI1*, *EWSR1-ERG*, *EWSR1-WT1*, *EWSR1-ATF1*, *EWSR1-CREB1* and *EWSR1-POU5F1* fusion transcripts, according to standard or previously described methods [2, 3]. FISH using break-apart probes for *EWSR1* at 22q12 showed an atypical rearranged signal pattern in approximately 95 % of cells. These comprised cells with one paired (normal) *EWSR1* signal and an isolated green (telomeric) signal. This was in keeping with the presence of a translocation involving the *EWSR1* gene at 22q12 with loss of the translocation product with the red (centromeric) part of the gene (Fig. 3), i.e. loss of the der(22) derivative chromosome. This was performed at two independent cytogenetics laboratories, who obtained similar results. There was no FISH evidence of *POU5F1* gene rearrangement at 6p21. *EWSR1-NR4A3*, *TAF15-NR4A3*, *EWSR1-FLI1*, *EWSR1-ERG*, *EWSR1-WT1*, *EWSR1-ATF1*, *EWSR1-CREB1* and *EWSR1-POU5F1* fusion transcripts were undetectable by RQ-PCR.

The findings were interpreted as myoepithelial carcinoma with rhabdoid morphology. Tumor extended in areas to the inked margin, but all retrieved lymph nodes were free of tumor. Post operatively, as this was a large malignant high grade soft tissue tumor which had been completely excised macroscopically but with a positive microscopic margin close to the carotid vessels, the patient was recommended adjuvant radiotherapy to the right neck to reduce the risk of local recurrence. The patient has completed radiotherapy and is well with no new symptoms to report, 7 months after surgery.

Discussion

We describe a case of myoepithelial carcinoma with extensive rhabdoid morphology and harboring *EWSR1* gene rearrangement, arising in the neck of an adult male. Myoepithelial neoplasms represent a clinically, behaviorally and histologically varied group. These, along with mixed tumors (which contain ductal or glandular elements) have been well characterized in the salivary glands but are increasingly documented in a range of other sites, including those in which myoepithelial cells are normally found in relation to various ductal structures (such as the skin, lung, breast and larynx) and also where myoepithelial cells are usually absent, such as superficial and deep soft tissues and bone. Their unifying feature is the morphologic and immunohistochemical evidence of myoepithelial differentiation, but this encompasses a large spectrum of different histologic appearances and varying immunoprofiles. Soft tissue myoepithelial tumors show a wide age distribution, although the peak incidence is in the 4th decade. They

Fig. 2 **a** Most cells show strong expression of epithelial membrane antigen. **b** Although very focal, there are areas of strong CD34 expression in a sheet-like pattern. **c** Focal positivity for smooth muscle actin is also present. **d** Many cells show nuclear expression of

S100 protein. **e** The tumor shows widespread loss of nuclear INI1, in contrast to the retained INI1 seen within the nuclei of small interspersed lymphocytes, the lymphocyte cluster on the left and in endothelial cells. **f** There is distinct, dot-like positivity for claudin-1

occur most frequently in extremities, followed by the head and neck and trunk [4–7], and can arise within subcutis or deep soft tissue. Grossly they are lobulated and can appear circumscribed but are often microscopically infiltrative tumors composed of spindled, epithelioid, clear or plasmacytoid cells arranged in nests, cords or files. Malignant histological features include nuclear pleomorphism, conspicuous nucleoli, atypical mitoses and necrosis [1, 4]. In a large study of 101 soft tissue myoepithelial tumors, benign and low grade neoplasms had a local recurrence risk of 18 % and a negligible risk of metastasis, while malignant neoplasms had greater propensity for local recurrence (42 %), with approximately one-third eventually metastasizing to the lymph nodes, lungs, or soft tissues [5].

Myoepithelial tumors express S100 protein, cytokeratins and EMA [1] with varying combinations of SMA, calponin, CD10, p63 and glial fibrillary acidic protein. The immunophenotype varies markedly between cases, but a minimal requirement might be expression of S100 protein and an epithelial marker [1]. INI1 expression is lost in approximately 10 % of adult soft tissue myoepithelial carcinomas [8–10], which can lead to diagnostic confusion with epithelioid sarcoma [10] or malignant rhabdoid tumor. The *INI1/SMARCB1* gene at chromosomal band 22q11.2 encodes a member of the SWI/SNF chromatin remodeling complex which is a negative regulator of the cell cycle and functions as a tumor suppressor gene [11, 12]. INI1 is ubiquitously expressed in most cell nuclei, but is lost in

Fig. 3 Fluorescence in situ hybridization using break-apart probes for *EWSR1* at 22q12 showed an atypical rearranged signal pattern in approximately 95 % of cells. These comprised cells with one paired (normal) *EWSR1* signal and an isolated green (telomeric) signal. This was in keeping with the presence of a translocation involving the *EWSR1* gene at 22q12 with loss of the translocation product with the red (centromeric) part of the gene cells with a split *EWSR1* signal, indicating the presence of a translocation involving the *EWSR1* gene at 22q12

the majority of malignant extrarenal rhabdoid tumors, approximately 90 % of epithelioid sarcomas and 50 % of epithelioid malignant peripheral nerve sheath tumors (MPNST), and this has also been described in 4/24 extra-skeletal myxoid chondrosarcomas [13].

EWSR1 rearrangements have been described in about half of soft tissue myoepithelial tumors, most of those arising in lung and bone, and least commonly in those of the skin [14, 15]. In the group of *EWSR1* rearranged myoepithelial tumors, *EWSR1* has been found to partner one of a small number of genes: (a) *POU5F1*, documented in five myoepithelial neoplasms of extremity deep soft tissue, displaying predominantly solid or nested patterns with thin fibrous septa and clear cell morphology [14, 16, 17], (b) *PBX1*, found in a small number of myoepithelial tumors including from deep soft tissues of the extremities [14, 18] and lung and bone [19], with bland, clear or spindle cells within fibrous stroma [14, 18, 19], (c) *ZNF444*, described in a primary pulmonary myoepithelial tumor and in an occipital myoepithelial carcinoma that metastasized to lung [14, 20], and (d) in a single case *ATF1*, in a myoepithelioma of the pelvis [21].

The *EWSR1* gene is known for its ability to partner with an array of genes, resulting in several classes of well characterized neoplasms such as the Ewing family tumors, desmoplastic small round cell tumor, angiomatoid fibrous histiocytoma, clear cell sarcoma of tendons and aponeuroses, extraskeletal myxoid chondrosarcoma, primary pulmonary myxoid sarcoma and a subset of myxoid

liposarcomas. However, *EWSR1*-rearranged myoepithelial neoplasms do not appear to resemble any of the defined morphologies of well established groups of neoplasms with translocations involving *EWSR1*. Antonescu et al. [14] described a variety of morphologic patterns in *EWSR1*-rearranged myoepithelial tumors of deep soft tissues and bone, of (1) solid sheets of monotonous small cells with scant cytoplasm and ill-defined cell borders (in which Ewing sarcoma was excluded by negativity for CD99 and absence of *EWSR1-FLII* and *EWSR1-ERG* fusion transcripts) (2) a predominantly rhabdoid or epithelioid appearance, with moderate to abundant amounts of eosinophilic or clear cytoplasm and eccentric nuclei, or (3) spindle and ovoid cells within prominent sclerotic stroma. None of their *EWSR1*-rearranged neoplasms showed ductal or glandular differentiation or the formation of cartilage or bony matrix. They also found that myoepithelial tumors lacking *EWSR1* rearrangement tended to be benign, cutaneous or located superficially. Their tested group of myoepithelial tumors and related neoplasms of the salivary glands did not harbor *EWSR1* rearrangements.

Rhabdoid morphology is a rarer finding in myoepithelial carcinoma, and this feature coupled with loss of INI1 expression makes this especially difficult to distinguish from other malignant rhabdoid neoplasms. Malignant extrarenal rhabdoid tumor (MRT) can occur at all ages although most frequently arises in young children [22, 23] and comprises sheets of large polygonal cells, often with eccentric vesicular nuclei and eosinophilic intracytoplasmic inclusions representing aggregates of intermediate filaments, essentially similar to the features seen in this case. In contrast to this case, most MRT express cytokeratin. Proximal-type epithelioid sarcoma, an aggressive, rhabdoid or large cell variant of epithelioid sarcoma which predilects for the midline of the trunk and proximal limbs and limb girdles [24] is similarly composed of sheets of polygonal and epithelioid cells with large, vesicular nuclei and distinct nucleoli. It expresses both low and high molecular weight cytokeratins, with CD34 expression in about half of cases. CD34 is not usually found in myoepithelial tumors, but interestingly showed very focal but strong expression in this case. Epithelioid MPNST accounts for approximately 5 % of MPNSTs, and may be associated with a nerve or a pre-existing neurofibroma or schwannoma. It can occur in patients with NF1, although this is rarer than for classical MPNST. Epithelioid MPNST typically comprises vague nodules of cords, strands or clusters of large, rounded cells with prominent nucleoli. Many contain spindled areas which merge with the epithelioid cells, and tend to show strong and diffuse expression of S100 protein. None of these groups of rhabdoid neoplasms is associated with *EWSR1* rearrangements. Extraskeletal myxoid chondrosarcoma (EMC) can

sometimes occur as a poorly differentiated sarcoma devoid of myxoid areas [25, 26], although usually contains areas of more typical morphology, of cords and clusters of bland ovoid and spindle cells within myxoid stroma. While only a minority show INI1 loss, most INI1-deficient lesions have shown rhabdoid features [13]. EMC however lack expression of cytokeratins and EMA, and most are also negative for S100 protein. EMC also have characteristic translocations that fuse *NR4A3* on chromosome 9q22 to a variety of partners [27–32], but characteristic fusion transcripts of EMC were undetectable in this case.

It is important to note that this mass occurred in the level II region of the neck, which is a common site of tail of parotid and occasional ectopic salivary tissue. It is therefore crucial to exclude this neoplasm being a variant of salivary myoepithelial carcinoma. About half of salivary gland myoepithelial carcinomas have a demonstrable benign precursor [33], in contrast to those of the soft tissues, but a benign component was not seen in this case. Mixed tumors of the salivary glands (pleomorphic adenomas), are characterized by specific gene alterations involving *PLAG1* or *HMGA2* [34–36], but this case did not show the features of tubuloductal differentiation typical of salivary gland mixed tumors. Hyalinizing clear cell carcinoma (HCCC) typically arises from the minor salivary glands of the oral cavity of women, and is composed of infiltrative cords, nests or trabeculae of relatively uniform glycogen-rich cells with clear to sometimes eosinophilic granular cytoplasm, surrounded by hyalinized bands and foci of myxohyaline stroma [37]. The cells express cytokeratins and EMA although lack myoepithelial differentiation, and are negative for SMA, calponin and S100 protein. *EWSR1-ATF1* is a consistent finding in HCCC [38]. The morphology and immunoprofile of this current neoplasm is distinct from those of HCCC, and, moreover, it did not harbor evidence of *EWSR1-ATF1* fusion transcripts by RT-PCR. While *EWSR1* rearrangements were not previously demonstrable in classic myoepithelial tumors of the salivary glands, *EWSR1* gene rearrangement has been recently shown in a subset of salivary gland myoepithelial carcinomas, which were distinctive aggressive variants, composed predominantly of clear cells with prominent central comedonecrosis and characterized by poor clinical outcome [39].

In summary, we report a case of myoepithelial carcinoma with rhabdoid morphology and *EWSR1* gene rearrangement, for which the partner gene remains unknown. This neoplasm showed complete INI1 loss and hence significant morphological and immunohistochemical overlap with other rhabdoid neoplasms such as malignant rhabdoid tumor and epithelioid sarcoma. It seems likely that the true incidence of *EWSR1*-rearranged myoepithelial tumors is underrepresented, given their histologic similarity to a

variety of other neoplasms and non-specific immunophenotypes, and their characterization remains incomplete, not least because of the current lack of knowledge of the spectrum of their partner genes. Documentation of all myoepithelial neoplasms harboring *EWSR1* gene rearrangements is crucial for the further characterization of this group of tumors, as is the need to investigate any putative relationship between rhabdoid neoplasms and the presence of *EWSR1* gene rearrangements.

Acknowledgments The authors are grateful to Mr. John Swansbury and Dr. Toon Min (Haematology Cytogenetics, Royal Marsden Hospital and The Institute of Cancer Research) for FISH studies. The authors also acknowledge support from the NIHR RM/ICR Biomedical Research Centre.

Conflict of interest The authors have no conflicts of interest or funding to disclose.

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