Myoepithelial carcinoma of the paracecal mesentery: aggressive behavior of a rare neoplasm at an unusual anatomic site

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Abstract

Myoepithelial tumors of the soft tissues represent a rare group of neoplasms that vary in their clinical behavior, pathologic features and genetics. They are histopathologically typified by a *myoepithelial* immunohistochemical phenotype, of expression of one or more epithelial markers, S100 protein and smooth muscle actin. Because of their rarity and occurrence over a wide age range and at a variety of anatomic sites, they can be difficult to diagnose due to the lack of familiarity by physicians, which is compounded by their spectrum of histologic features and morphologic overlap with several other neoplasms. Recent genetic insights have aided classification, and it is increasingly understood that soft tissue myoepithelial neoplasms can be stratified into two distinct morphologic and genetic subgroups. We describe a case of a 44-year-old man who was diagnosed with a primary myoepithelial neoplasm of the paracecal mesentery, which showed aggressive local recurrence after four years. The tumor was composed of cords of ovoid cells within chondromyxoid stroma, and displayed a characteristic pancytokeratin, S100 protein and smooth muscle actin-positive *myoepithelial* immunoprofile. Primary myoepithelioma has not been previously described at this site, and this case highlights this varied family of tumors, emphasizes the need to consider myoepithelial tumor in the differential diagnoses of carcinoma variants occurring in the bowel or mesentery, and also adds to the number of reported myoepithelial neoplasms showing markedly aggressive behavior.

Introduction

Soft tissue myoepithelial tumors are a heterogeneous group of neoplasms with morphologic, immunohistochemical and ultrastructural features of myoepithelial differentiation. Because of their varied histologic, immunophenotypic and genetic features, they can be difficult to diagnose, and this is compounded by their rarity and their occurrence over a wide age range and at a variety of anatomic sites. However, recent genetic discoveries have significantly aided their classification. Histologically, about one third are mixed tumors of either eccrine or apocrine type, while two thirds lack ductular differentiation.[1-4] We present a case of myoepithelial tumor arising as a primary neoplasm in the paracecal mesentery of a 44-year-old male, which recurred in the form of aggressive local disease three years later. Primary and recurrent tumors showed similar features, of cords of ovoid cells within chondromyxoid stroma (a *mixed tumor* phenotype), with a characteristic *myoepithelial* immunoprofile of epithelial markers, S100 protein and smooth muscle actin immunoreactivity. *EWSR1* rearrangements were undetectable with fluorescence *in situ* hybridization (FISH), further supporting its designation as mixed tumor-type soft tissue myoepithelial neoplasm. This case highlights the need for diagnostic awareness of myoepithelial neoplasms, as they can arise at unusual anatomic sites and have potential for aggressive clinical behavior. As their genetic features become increasingly better characterized, their recognition and accurate documentation have become of even greater clinical importance, because of the potential for specific targeted treatments in future.

Case Report

A 44-year-old Caucasian male had previously had a right hemicolectomy for a paracecal mass. He had no significant past medical history, although his father and paternal grandfather had both been diagnosed with bowel cancer over the age of 70 years. The histology had shown myoepithelioma of uncertain malignant potential, arising from the paracecal mesentery, which had partially infiltrated the large bowel wall but which showed no origin from bowel mucosa. Three years later, the patient presented with abdominal distension and lower abdominal pressure. On examination there was a palpable lower right quadrant mass. He was found to have multifocal recurrent intra-abdominal disease. Imaging revealed multiple lesions up to 8.8 cm within the mesentery and abdominal wall (Figure 1), which were confirmed by biopsy on laparoscopic evaluation to be recurrent myoepithelial tumor. He was subsequently treated with 6 cycles of single agent doxorubicin with stable disease by response evaluation criteria in solid tumors for a total of 8 months. On treatment his symptoms improved. He then developed abdominal pain and imaging revealed progressive intra-abdominal disease and he was commenced on gemcitabine and docetaxel. He received 6 cycles of this combination schedule, and after 6 cycles, repeat imaging demonstrated progressive disease. His symptom of abdominal pain also worsened on this schedule. On the basis of an excellent performance status, he was offered participation in a clinical trial assessing molecular and radiological markers of response to the VEGFR tyrosine kinase inhibitor, pazopanib. He continued on the clinical trial for 7 months, but unfortunately his disease progressed. He was subsequently treated within a Phase I trial, but the first restaging scan after 6 weeks on trial showed progressive disease. His symptoms are currently well controlled and he is on active surveillance. Due to the location of the metastatic disease, no radiation has been administered as it could potentially result in toxicity.

Pathology

Grossly, the original resection specimen comprised bowel with multiple lobulated tumor masses with attached peritoneal fat. Sectioning showed firm white tumors, without hemorrhage or necrosis. Histologically, tumor masses of the primary excision specimen were centered in the mesentery (Figure 2A-C), with focal infiltration of the bowel wall. Both pri-

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mary and recurrent tumors were composed of cords, trabeculae and clusters of relatively uniform cells with minimally to mildly atypical ovoid vesicular nuclei and small amounts of eosinophilic cytoplasm, within fibrous to fibromyxoid stroma. The mitotic index varied from 0-1/10 high power fields, and no necrosis was present. Immunohistochemically, there was diffuse strong expression of cytokeratin (CK) 14 (Figure 2D), with focal strong pancytokeratin AE1/AE3, focal, strong nuclear expression of S100 protein (Figure 2E), and focal expression of CK5/6, p63, smooth muscle actin (SMA) (Figure 2F), calponin, CD10 and D2-40. Epithelial membrane antigen (EMA), CAM5.2, CK7, CK20, CDX2, CEA, TTF-1, CD34, desmin, h-caldesmon, CD117, DOG1, HMB45 and MelanA were negative. INI1 was retained within nuclei. FISH showed no evidence of *EWSR1* gene rearrangements. Multiple sections from the rest of the large bowel wall showed unremarkable mucosa, only.

The features in both primary and recurrent cases were of soft tissue myoepithelial tumor of *mixed tumor*-type morphology.

Discussion and Conclusions

We describe a case of soft tissue myoepithelioma arising from the cecal mesentery of a 44-year-old male, which recurred three years after initial excision. Soft tissue myoepithelial neoplasms are a rare, diverse and incompletely characterized tumor group. Primary origin from the cecal mesentery has not been previously described, and we highlight both the unusual primary site, and the aggressive behavior of this tumor; the latter is of note as the histologic features of both primary and recurrent neoplasm were both bland, and because myoepithelial neoplasms are more frequently malignant when occurring in children.[3,4] Myoepithelial neoplasms are unified by differentiation towards myoepithelial cells (in terms of morphologic, immunohistochemical and ultrastructural features), but these otherwise constitute a varied spectrum of tumors differing in histopathologic appearances and genetics. Histologically, there are two groups: approximately up to one third (including this case) are mixed tumors of ductular eccrine or apocrine type resembling those arising within salivary glands, while the others lack ductular differentiation.[1-4] Soft tissue myoepithelial tumors occur at a wide range of sites, most frequently within extremities and limb girdles, followed by the head, neck and trunk, and can arise within subcutis or deep soft tissue,[5-8] and in visceral organs such as lung and breast. These occur approximately equally in both sexes and affect a wide age range, from infants to adults in the ninth decade. They predominate in young adults,[4] although approximately one fifth occur in pediatric patients. Clinical behavior is varied: histologically benign or low grade lesions have a reported local recurrence risk of <20% and typically do not metastasize, whereas approximately 40% of malignant myoepitheliomas recur, with metastases in about a third to lymph nodes, lungs or soft tissues.[4] Documented sites of metastasis include bone, mediastinum and brain. Histologically, there is marked variation in architectural patterns (including nests, fascicles and trabeculae) cell morphology (epithelioid, spindled, plasmacytoid or clear cell) and stroma (including hyalinized, myxoid, chondromyxoid or cartilaginous), and cellular atypia is typically minimal and mitoses infrequent. Malignant histologic features include nuclear pleomorphism with prominent nucleoli, atypical mitoses and necrosis.[4,9] Myoepitheliomas typically express a combination of S100 protein and pancytokeratins and/or EMA, and variably, other markers of myoepithelial differentiation such as SMA, calponin and p63. Loss of nuclear INI1 expression is described in about 10% of adult soft tissue myoepithelial carcinomas, and approximately 40% of pediatric myoepitheliomas.[3,10] Genetically, a proportion of soft tissue and skin myoepitheliomas with tubuloductal differentiation have recurrent *PLAG1* rearrangements, similar to mixed tumors of the salivary glands,[11-14] while *EWSR1* gene rearrangements are described in up to one half of soft tissue myoepitheliomas. *EWSR1* can partner with several genes, including *POU5F1*, *ZNF444, PBX1* and *ATF1*;[15-21] rearrangements of *FUS* (an alternative binding partner to *EWSR1*) are also reported. *EWSR1*-rearranged deep soft tissue and bone myoepitheliomas have not shown glandular/ductal differentiation nor cartilage or bony matrix,[16] in keeping with *PLAG1*-rearranged and *EWSR1*-rearranged myoepithelial neoplasms representing genetically distinct subsets. The challenge in diagnosing myoepithelial neoplasms appears attributable to the relative unfamiliarity of physicians in recognizing soft tissue myoepithelial neoplasms both clinically and histologically. Given their pathologic and genetic heterogeneity, it is likely these tumors have been significantly under recognized previously, and may have been subsumed into histologic diagnoses of other carcinoma variants, such as adenocarcinoma/mucinous carcinoma. An index of suspicion and knowledge of the heterogeneity of defining features is therefore important in their correct diagnosis. The differential diagnosis in this case includes epithelioid neoplasms more common to gastrointestinal sites, such as primary (including mucinous) carcinoma or epithelioid gastrointestinal stromal tumor (GIST) (Table 1). Adenocarcinoma

Table 1. Immunohistochemical features of myoepithelial carcinoma and neoplasms in its differential diagnosis

Diagnosis	Cytokeratin	Epithelial membrane antigen	S100 protein	Smooth muscle actin	INI1	Other
Myoepithelial carcinoma	+	+	+	Variably +	– in 10-40%	Can express other markers of myoepithelial differentiation e.g. calponin and p63; CD34–
Adenocarcinoma	+	+	–	–	+	May express CK7 or CK20 (metastatic or primary mucinous adenocarcinoma) according to specific site of origin; May express markers suggesting primary site, *e.g.* TTF1 (lung); CDX2 (colorectal); CD34–
Epithelioid gastrointestinal stromal tumor	–	–	– (rare focal positivity in some tumors)	– (expression only seen in a minority of cases)	+	CD117+; DOG1+; CD34+ in some cases
Synovial sarcoma	+ focal	+ focal	Occasional cases	Occasionally (in <10% of cases)	Can be associated with decreased immunoreactivity for INI1	TLE1+; Bcl-2+; CD99+; CD56+
Leiomyosarcoma	+ focal in some cases	–	–	+	+	Desmin+; H-caldesmon+

(including mucinous carcinoma) typically shows local origin from the bowel mucosa with dysplastic or *in situ* changes within the surrounding glandular epithelium, in contrast to the current case, which showed unremarkable mucosa and was seen only to infiltrate the muscularis propria from externally. Patients with conventional adenocarcinoma will tend to be older or have a history of previous carcinoma. Potential sites of origin may also be indicated with immunohistochemistry (*e.g.* with TTF-1 or CDX2, which are absent in myoepithelial neoplasms). Epithelioid GIST does not contain myxoid stroma, and >90% of GISTs express DOG1, CD117 or CD34, usually diffusely (although this can be focal in the epithelioid variant), while these markers are typically absent in myoepithelial tumors. Synovial sarcomas can arise intra-abdominally, show biphasic morphology with epithelioid cells that can form rudimentary glandular structures, and focally express cytokeratins, EMA and S100 protein, leading to diagnostic confusion with myoepitheliomas. The vast majority of synovial sarcomas express TLE1, bcl-2 and CD99, and characteristically harbor a specific chromosomal translocation, t(X;18), which has not been shown in any other neoplasm. Leiomyosarcoma can occasionally show epithelioid morphology or myxoid stroma as well as focal cytokeratin expression, mimicking myoepithelioma. However, leiomyosarcoma typically shows diffuse and strong positivity for SMA (which can be more variable in myoepitheliomas) and broad-spectrum myoid or smooth muscle markers desmin and h-caldesmon. Most neoplasms in the differential diagnosis of myoepitheliomas will show nuclear retention of INI1 (which is ubiquitously expressed in most cell nuclei), but which is absent in approximately 10-40% of myoepithelial neoplasms.

Due to the rarity and challenges in diagnosing these tumors, their management remains poorly defined. Surgical resection is generally considered the mainstay of management for localized disease, with or without radiation. The literature is too scarce to recommend an optimal schedule and chemotherapy regimen for metastatic myoepithelial carcinoma. What remains unclear is whether this entity should be approached as a soft tissue sarcoma or as a carcinoma. Although our patient did not respond to conventional chemotherapy regimens used in soft tissue sarcoma, others have reported some favorable responses with doxorubicin-based chemotherapy.[22,23] Platinum-based regimens commonly used in carcinomas were also reported to be active.[24,25] In view of the lack of prospective data, patients with myoepithelial tumors should be offered participation in clinical trials of novel agents.

In summary, we report a rare case of soft tissue myoepithelioma of the cecal mesentery.

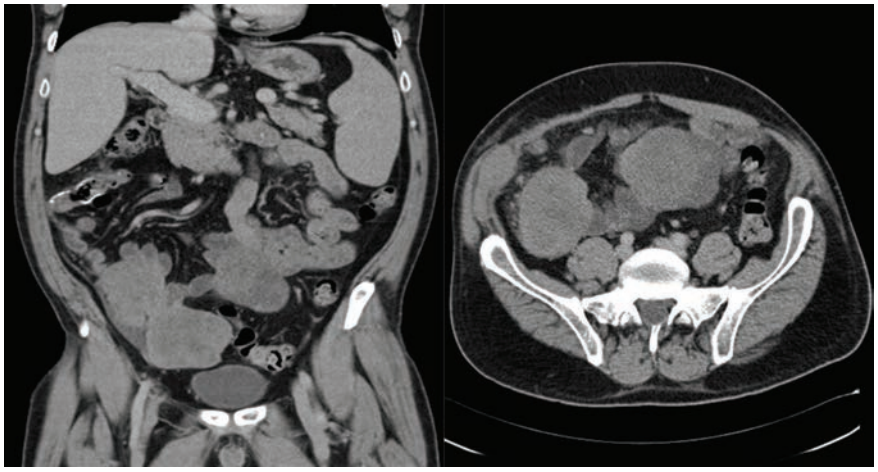

Figure 1. Computed tomography imaging of myoepithelioma of soft tissue. Coronal and transverse computed tomography scans at the time of tumor recurrence show multifocal intra-abdominal recurrent disease, comprising large tumor deposits measuring up to 8.8 cm.

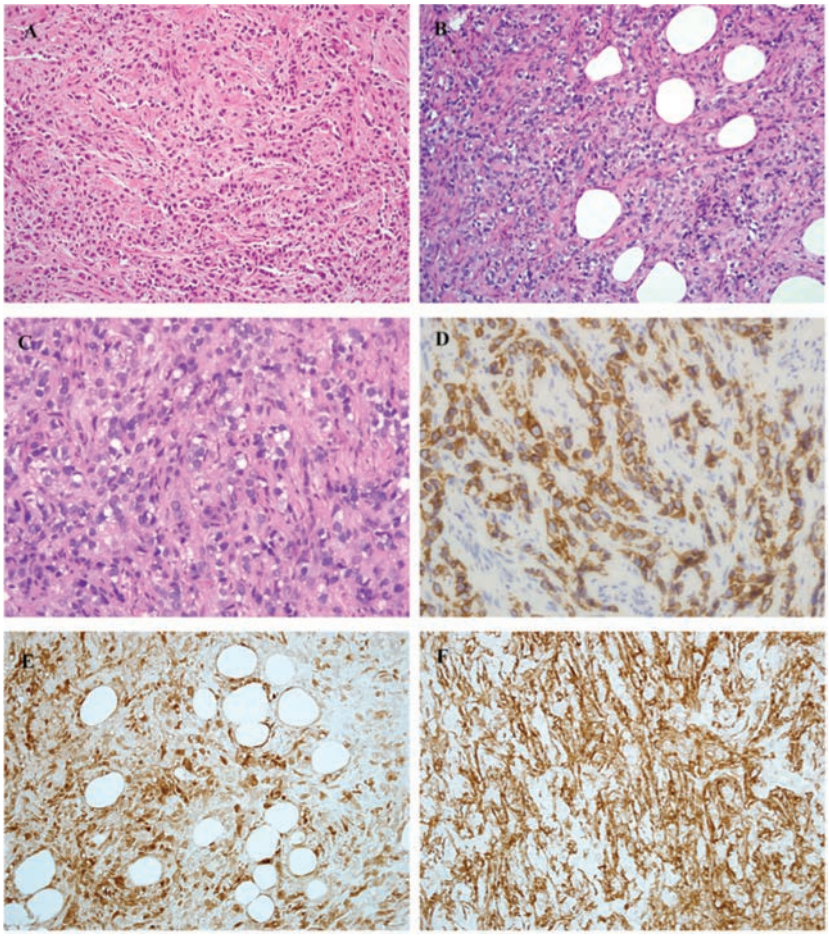

Figure 2. A-C) Histological features of soft tissue myoepithelioma of the paracecal mesentery. Tumors masses were centered in the mesentery; B) are seen to infiltrate mesenteric fat. These were composed of cords, nests and clusters of relatively uniform cells with minimally to mildly atypical ovoid vesicular nuclei and small amounts of eosinophilic cytoplasm, within fibrous stroma. Mitoses are not a prominent feature (hematoxylin and eosin; ×40, ×40 and ×100 respectively). D) Immunohistochemical features of soft tissue myoepithelioma of the paracecal mesentery. There is diffuse and strong expression of keratin CK14, which highlights the cord-like and trabecular architectural pattern. E) There is strong nuclear (and cytoplasmic) expression of S100 protein in most cells and F) focal expression of smooth muscle actin; the coexpression of these three markers is in keeping with a myoepithelial immunophenotype (×100, ×40 and ×40 respectively).

Diagnostic awareness of this entity is important for correct documentation, particularly because myoepitheliomas are still incompletely characterized, and it is important to document those with unusual behavior so that the full spectrum of disease behavior can be recognized. While there are pathologic indicators of tumors with a greater likelihood of malignant behavior, this case shows that the behavior of those with blander histological features cannot be fully predicted, and emphasizes that long term clinical follow-up is mandatory because of the risk of aggressive local recurrence, even in myoepithelial neoplasms without atypical features. Finally, because of the increasing knowledge of the genetic background of these neoplasms and the recognition that these constitute genetically distinct entities, awareness of these neoplasms and their correct diagnosis is crucial because of the likelihood that they will be amenable to specific targeted therapies in the near future.

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