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 immunoprofile. 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 pain. 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-
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. 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. 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, 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, 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. 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 nuclei, atypical mitoses and necrosis. 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.

Genetically, a proportion of soft tissue and skin myoepitheliomas with tubuloductal differentiation have recurrent PLAG1 rearrangements, similar to mixed tumors of the salivary glands, 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, rearrangements of PUS (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, 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

| 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+; CD99+; CD56+ 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+                                                |

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

**Case Report**

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.

References

1. Fisher C. Unusual myoid, perivascular, and postradiation lesions, with emphasis on atypical vascular lesion, postradiation cutaneous angiosarcoma, myoepithelial tumors, myopericytoma, and perivascular epithelioid cell tumor. Semin Diagn Pathol 2013;30:73-84.
2. Thway K, Fisher C. Myoepithelial tumor of soft tissue: histology and genetics of an evolving entity. Adv Anat Pathol 2014;21:411-9.
3. Gleason BC, Fletcher CD. Myoepithelial carcinoma of soft tissue in children: an aggressive neoplasm analyzed in a series of 29 cases. Am J Surg Pathol 2007;31:1813-24.
4. Hornick JL, Fletcher CD. Myoepithelial tumors of soft tissue: a clinicopathologic and immunohistochemical study of 101 cases with evaluation of prognostic parameters. Am J Surg Pathol 2003;27:1183-96.
5. Kilpatrick SE, Hitchcock MG, Kraus MD, et al. Mixed tumors and myoepitheliomas of soft tissue: a clinicopathologic study of 19 cases with a unifying concept. Am J Surg Pathol 1997;21:13-22.
6. Michal M, Miettinnen M. Myoepitheliomas of the skin and soft tissues. Report of 12 cases. Virchows Arch 1999;434:393-400.
7. Thway K, Bown N, Miah A, et al. Rhabdoid variant of myoepithelial carcinoma, with EWSR1 rearrangement: expanding the spectrum of EWSR1-rearranged myoepithelial tumors. Head Neck Pathol 2015;9:273-9.
8. Neto AG, Pineda-Daboin K, Luna MA. Myoepithelioma of the soft tissue of the head and neck: a case report and review of the literature. Head Neck 2004;26:470-3.
9. Fisher C. The diversity of soft tissue tumours with EWSR1 gene rearrangements: a review. Histopathology 2014;64:134-50.
10. Hollmann TJ, Hornick JL. INI1-deficient tumors: diagnostic features and molecular genetics. Am J Surg Pathol 2011;35:e47-63.
11. Bahrami A, Dalton JD, Krane JF, Fletcher CD. A subset of cutaneous and soft tissue mixed tumors are genetically linked to their salivary gland counterpart. Genes Chromosomes Cancer 2012;51:140-8.
12. Bahrami A, Dalton JD, Shivakumar B, Krane JF. PLAG1 alteration in carcinoma ex pleomorphic adenoma: immunohistochemical and fluorescence in situ hybridization studies of 22 cases. Head Neck Pathol 2012;6:328-35.
13. Antonescu CR, Zhang L, Shao SY, et al. Frequent PLAG1 gene rearrangements in skin and soft tissue myoepithelioma with ductal differentiation. Genes Chromosomes Cancer 2013;52:675-82.
14. Hallor KH, Teixeira MR, Fletcher CD, et al. Heterogeneous genetic profiles in soft tissue myoepitheliomas. Mod Pathol 2008;21:1311-9.
15. Rekhi B, Sable M, Jambhekar NA. Histopathological, immunohistochemical and molecular spectrum of myoepithelial tumours of soft tissues. Virchows Arch 2012;461:687-97.
16. Antonescu CR, Zhang L, Chang NE, et al. EWSR1-POU5F1 fusion in soft tissue myoepithelial tumors. A molecular analysis of sixty-six cases, including soft tissue, bone, and visceral lesions, showing common involvement of the EWSR1 gene. Genes Chromosomes Cancer 2010;49:1114-24.
17. Flucke U, Menzel T, Verdijk MA, et al. EWSR1-ATF1 chimeric transcript in a myoepithelial tumor of soft tissue: a case report. Hum Pathol 2012;43:764-8.
18. Flucke U, Palmedo G, Blankenhorn N, et al. EWSR1 gene rearrangement occurs in a subset of cutaneous myoepithelial tumors: a study of 18 cases. Mod Pathol 2011;24:1444-50.
19. Kurzawa P, Kattapuram S, Hornick FJ, et al. Primary myoepithelioma of bone: a report of 8 cases. Am J Surg Pathol 2013;37:960-8.
20. Brandal P, Panagopoulos I, Bjerkheggen B, et al. Detection of a t(1;22)(q23;q12) translocation leading to an EWSR1-PBX1 fusion gene in a myoepithelioma. Genes Chromosomes Cancer 2008;47:558-64.
21. Brandal P, Panagopoulos I, Bjerkheggen B, Heim S. t(19;22)(q13;q12) Translocation leading to the novel fusion gene EWSR1-ZNF444 in soft tissue myoepithelial carcinoma. Genes Chromosomes Cancer 2009;48:1051-6.
22. Xu T, Liao Z, Tang J, et al. Myoepithelial carcinoma of the head and neck: a report of 23 cases and literature review. Canc Treat Comumn 2014;2:24-9.
23. Biagno G, Tagarelli A, Scahiavetti A, et al. Myoepithelial carcinoma treatment in children: a report from the TREP project. Pediatr Blood Cancer 2014;61:643-6.
24. Noronha V, Cooper DL, Higgins SA, et al. Metastatic myoepithelial carcinoma of the vulva treated with carboplatin and paclitaxel. Lancet Oncol 2006;7:270-1.
25. Takayama O, Yokoyama J, Ito S. Therapeutic experience of recurrent myoepithelial carcinoma by superselective intra-arterial chemotherapy infused high-dose CDDP. Auris Nasus Larynx 2006;33:235-8.