Sclerosing Epithelioid Fibrosarcoma of the Oral Cavity

Camille T. Elkins · Paul E. Wakely Jr.

Received: 24 April 2011 / Accepted: 13 June 2011 / Published online: 21 June 2011
© Springer Science+Business Media, LLC 2011

Abstract Sclerosing epithelioid fibrosarcoma (SEF) rarely occurs outside the somatic soft tissue. Until recently no consistently specific genetic alteration had been associated with SEF. Molecular testing of the *FUS* gene rearrangement involving chromosome 16 [at one time considered specific for low-grade fibromyxoid sarcoma (LGFMS) and its variant, LGFMS with giant collagen rosettes], may be a nonrandom abnormality in some cases of SEF. We present an example of a rare *FUS*-positive SEF that arose in the floor of mouth of a 56 year old male. Light microscopy, exhaustive immunohistology, and FISH examination showing chromosome rearrangement using the *FUS* break-apart probe led to an erroneous diagnosis of LGFMS with giant collagen rosettes. An outside expert agreed with that diagnosis citing the FISH results as confirmatory. Upon review almost 2 years later after local recurrence, the classic histopathologic features of SEF were noted instead. This example suggests that at least a subset if not most examples of SEF are part of the LGFMS “family” of neoplasms, and reiterates the value of careful histologic examination in an age of increasingly sophisticated and presumably specific molecular results.

Keywords Sclerosing epithelioid fibrosarcoma · t(7;16) · FISH · *FUS* gene rearrangement · Low-grade fibromyxoid sarcoma · Fibrosarcoma

Introduction

Sclerosing epithelioid fibrosarcoma (SEF), a rare variant of fibrosarcoma arising primarily in the deep somatic soft tissues, has metastatic potential despite its bland appearance [1, 2]. Primary head and neck involvement is extremely unusual [1–4], with only 3 examples reportedly arising in the oral cavity [5]. Other unusual sites of primary SEF include the ovary [6], pituitary [7], cecum [8], and liver [9]. Recently, *FUS*-*CREB3L1/L2* fusion transcripts and *FUS* rearrangements using RT-PCR and FISH were documented in 4 examples of SEF as part of a larger study of low-grade fibromyxoid sarcoma (LGFMS) [10]. These authors and others [2] have suggested that these two neoplasms may be related along a similar spectrum. We report a rare example of primary oral cavity/tongue SEF that supports this notion. Initial interpretation, and that of an outside expert consultant, misinterpreted the neoplasm as LGFMS, principally due to a positive *FUS* gene rearrangement using fluorescence in situ hybridization (FISH).

Case Report

Clinical History

A 54-year old man presented with a floor of mouth mass and 20 lb weight loss over 8–10 months. Dental examination initially discovered the mass 4 years earlier. At that time, open biopsy at an outside institution reported a “benign mass.” However, fine needle aspiration biopsy reported the lesion as suspicious for a minor salivary gland neoplasm. Neither specimen was available for our review. The patient elected to postpone surgery because he was uninsured. With progressive growth, the mass ultimately

C. T. Elkins · P. E. Wakely Jr. (✉)
Department of Pathology, The Ohio State University College
of Medicine, 414 Doan Hall, 410 West 10th Avenue, Columbus,
OH 43210, USA
e-mail: paul.wakely@osumc.edu

Fig. 1 **a** A flat “pushing” edge to this hypercellular tumor subtly infiltrates overlying glossal skeletal muscle. (H&E stain, 10×). **b** Geographic zones of hypocellular, myxoid degeneration intersect with one another. These foci are more myxoid and lack the circular

“rosette” formation seen in the typical hyalinizing variant of LGFMS. (H&E stain, 10×). **c** A broad zone of sclerosis with few cells. (H&E stain, 20×)

Fig. 2 **a** Thick collagen fibers are in a parallel alignment creating rows of epithelioid cells. A hypercellular focus surrounds myxoid change at the lower right. (H&E stain, 20×). **b** Cytoplasmic retraction

is common in areas of dense sclerosis. (H&E stain, 60×). **c** Collagen whorls produce a curlicue or scrollwork pattern and stellate-shaped nuclei. H&E stain, 60×

caused significant breathing and eating difficulty requiring tracheostomy and PEG tube placement, respectively.

Physical examination noted a firm mass centered in the anterior floor of mouth that involved the entire tongue such that it nearly made contact with the hard and soft palates. The mass effaced the lingual cortex of the mandible, but did not invade bone. CT scan showed a large homogenous mass involving the floor of mouth and intrinsic musculature of the tongue, but no lesions elsewhere. The patient underwent radical resection of the superior neck and floor of mouth mass and tracheal stomaplasty. A pathologic diagnosis of LGFMS with giant collagen rosettes was made internally, and outside expert consultation was sought. The consultant pathologist agreed with the internal diagnosis, citing the positive *FUS* gene rearrangement result as confirmatory for LGFMS.

The patient subsequently suffered from ankyloglossia, but was free of disease until 18 months later at which time the mass was noted to have locally recurred. He then underwent a total oral glossectomy and selective neck dissection. This second specimen was interpreted as representing SEF, rather than LGFMS. It had 20% necrosis, and once again, a positive *FUS* gene rearrangement by FISH. Review of the initial surgical specimen showed the histopathologic features that were typical of SEF. At present, just over 2 years since his initial surgery, PET/CT

imaging showed extensive metastatic disease involving both lungs and the right hemipelvis, thereby negating any radiation therapy to the head and neck.

Pathology

The original specimen consisted of a 9.8 cm well circumscribed off-white whorled rubbery mass with areas of tan-yellow softening. Tan-pink mucosa partly covered the external surface. The mass abutted all margins. H&E-stained sections showed a well circumscribed, unencapsulated proliferation of uniformly-sized cytologically bland cells in a diffusely hyalinized collagenous stroma of variable density. Most of the neoplasm was highly cellular with foci of markedly hyalinized stroma and few cells Fig. 1. Infiltration of a minor salivary gland was noted at the tumor periphery. The variable amount and thickness of hyalinizing stromal collagen throughout the lesion created a range of patterns, including: solid hypercellular foci; nested cell groups; interconnecting hypocellular myxoid zones; a curvilinear pattern with collagen whorls; and thin anastomosing cell cords Fig. 2. Thin zones of non-sclerotic hypercellularity commonly cuffed myxoid nodules. Eosinophilic collagen was noted to envelope cells, either individually; as thick strands in groups of five or fewer cells (imitating the pattern seen with “malignant osteoid”);

Fig. 3 Interphase FISH shows 1 yellow fusion signal and split orange and green signals indicating a rearrangement of the *FUS* gene at 16p11

as thin wavy tendrils surrounding cell nests; or in broad sheets producing markedly hypocellular or nearly acellular zones. Nuclei were rounded, oval, to stellate, with variably angulated contours, euchromatic evenly dispersed chromatin, indistinct nucleoli, and minimal pale cytoplasm that merged with the abundant surrounding collagen. Cell retraction was commonplace. Distinctly absent were collagen rosettes, ductal differentiation, dystrophic calcification, multinucleated giant cells, and osseous metaplasia, as well as foci of conventional LGFMS. A 50-field count revealed 3 mitotic figures per 10 high power field; atypical mitoses were absent. Necrosis was found in approximately 10% of the original specimen.

Immunohistology showed diffuse positive staining with vimentin, and equivocal expression of bcl-2, CD57, and CD99. No staining occurred with a host of antibodies, including: EMA, CD31, CD34, pan-keratin, smooth muscle actin, S-100, CD20, CD3, CD68, HMB-45, Melan-A, myogenin, CD30, synaptophysin, chromogranin, p63, Factor XIIIa, calponin, CD56, HHF-35 actin, smooth muscle myosin heavy chain, CD117, and S-100. A Ki-67 proliferation index was <15%. A trichrome stain was diffusely positive.

Fluorescence in situ hybridization (FISH) performed on 100 interphase cells using a commercially available LSI dual-color break-apart probe (Vysis; Abbott Park, IL, USA) showed single and dual split signals involving the *FUS* gene on two separate occasions in over 90% of cells Fig. 3.

Discussion

SEF is a fibrosarcoma variant that simulates infiltrating carcinoma because of its epithelioid morphology [1].

The most recent World Health Organization (WHO) classification of soft tissue neoplasms defines this neoplasm as a fibrosarcoma variant characterized by epithelioid tumor cells embedded within a sclerotic collagenous matrix and arranged in nests and cords [11]. Notably absent in SEF are the myxoid zones, the bland spindle-shaped cells with a whorling growth pattern, and the arcades of curved capillaries characteristically seen in LGFMS. Immunohistology is of value principally by its consistent expression of vimentin alone, thus enabling one to eliminate many other sclerosing forms of sarcoma, carcinoma, and melanoma from diagnostic consideration. All other purported positive markers have typically been either weakly, equivocally, or inconsistently expressed. Scattered, weak and inconsistent staining has been reported with CD34, S-100, CAM 5.2, bcl-2, and EMA [1, 2, 8, 12–14]. A positive CD99 stain led Folk et al. [5] to perform RT–PCR for the t(11; 22)(q24; q12) translocation in two cases, which were both negative. Eydin et al. [3] have proposed a rigid definition of SEF based on histopathology coupled with an absence of any positive immunohistochemical stain other than vimentin—unless the anomalous immunostains are corroborated by electron microscopy indicating only fibroblastic differentiation. Twenty-seven different immunohistochemical stains performed in our case showed unequivocal expression for vimentin only.

The head and neck is an exceedingly infrequent location for the development of SEF, and the oral cavity site is even more rare [5], with ours being the third reported case, and the first to specifically involve the tongue, to our knowledge. The largest head and neck series from the AFIP showed no examples occurring in the tongue/floor of mouth [5]. Those authors emphasized that in the oral/maxillofacial region, SEF has a predilection to arise in bone rather than soft tissue. In our case, the patient showed erosion of the mandibular bone, but the mass was strictly soft tissue-based. Primary oral SEF produces a broad differential diagnosis based on other sclerosing neoplasms in this site, including myoepithelial carcinoma, hyalinizing clear cell carcinoma, sclerosing mucoepidermoid carcinoma, and cellular pleomorphic adenoma. However, the absence of ductal differentiation and lack of epithelial/myoepithelial markers should be sufficient to exclude these entities.

LGFMS is a hypocellular neoplasm composed of bland fibroblastic cells within a collagenized stroma alternating with myxoid foci, a whorled growth pattern, delicate capillary arcades, and few mitotic figures [15]. Occasional areas have increased cellularity, atypia or necrosis. The t(7; 16) (q34; p11) resulting in a *FUS/CREB3L2* gene fusion had been considered pathognomonic for this entity [16]. Although previously considered a separate neoplasm, a variant of LGFMS sharing this cytogenetic abnormality is characterized by strikingly obvious collagen rosettes

(hyalinizing spindle cell tumor with giant rosettes) [17]. Guillou et al. [10] have recently demonstrated the presence of t(7; 16) (q32-34; p11) in 4 cases diagnosed as SEF using RT-PCR, thus implicating SEF as another potential variant of LGFMS. This suggestion was made earlier by Antonescu et al. [2] however, they had no cytogenetic or molecular data to substantiate this. Guillou et al. [10] found areas of hypercellularity and marked epithelioid morphology to mimic SEF in a small subset of their LGFMS cases. Unlike SEF, however, a very high fraction of their LGFMS cases expressed EMA, and CD99 (93 and 91%, respectively). Even more recently, Rekhi et al. [12] reported 1 case with mixed features of LGFMS and SEF involving deep soft tissue that showed positive FUS rearrangement in 60% of cells using FISH, thus supporting the notion that three distinct histomorphologic entities may exist within the neoplastic spectrum of LGFMS. Upon re-examination of this patient's original specimen, only hypocellular collagenous zones and myxoid nodules could be considered "soft" evidence that this neoplasm had any similarity to conventional LGFMS or its collagenous variant. Guillou et al. [10] emphasized that a common chromosomal abnormality in two apparently unrelated neoplasms does not signify, in and of itself, that they are actually related. This case, however, illustrates that SEF (although morphologically dissimilar) is probably part of the expanding histologic spectrum of LGFMS—analagous to the previously recognized hyalinizing variant with collagen rosettes [17].

To summarize, we report an extremely rare instance of SEF arising within the tongue and the difficulty of recognizing this neoplasm in such a location. Our case reiterates the suggestion that at least a subset of SEF neoplasms are part of the larger LGFMS "family" of neoplasms, and stresses the value of careful histologic examination in an age of increasingly sophisticated, and presumably specific, molecular tools.

References

1. Meis-Kindblom JM, Kindblom LG, Enzinger FM. Sclerosing epithelioid fibrosarcoma: a variant of fibrosarcoma simulating a carcinoma. *Am J Surg Pathol*. 1995;19:979–93.
2. Antonescu CR, Rosenblum MK, Pereira P, et al. Sclerosing epithelioid fibrosarcoma: a study of 16 cases and confirmation of a clinicopathologically distinct tumor. *Am J Surg Pathol*. 2001; 25:699–709.
3. Eyden BP, Manson C, Banerjee SS, et al. Sclerosing epithelioid fibrosarcoma: a study of five cases emphasizing diagnostic criteria. *Histopathology*. 1998;33:354–60.
4. Battista AP, Casler J. Sclerosing epithelioid fibrosarcoma: a case report. *Ann Otol Rhinol Laryngol*. 2005;114(2):87–9.
5. Folk GS, Williams SB, Foss RB, et al. Oral and maxillofacial sclerosing epithelioid fibrosarcoma: report of five cases. *Head Neck Pathol*. 2007;1:13–20.
6. Wantanabe K, Suzuki T. Epithelioid fibrosarcoma of the ovary. *Virchows Arch*. 2004;4:410–3.
7. Massier A, Scheithauer BW, Taylor HC, et al. Sclerosing epithelioid fibrosarcoma of the pituitary. *Endocr Pathol*. 2007;18: 233–8.
8. Frattini JC, Sosa JA, Carmack S, et al. Sclerosing epithelioid fibrosarcoma of the cecum: a radiation-associated tumor in a previously unreported site. *Arch Pathol Lab Med*. 2007;131: 1825–8.
9. Tomimaru Y, Nagano H, Marubashi S, et al. Sclerosing epithelioid fibrosarcoma of the liver infiltrating the inferior vena cava. *World J Gastroenterol*. 2009;15(33):4204–8.
10. Guillou L, Benhattar J, Gengler C, et al. Translocation-positive low-grade fibromyxoid sarcoma: clinicopathologic and molecular analysis of a series expanding the morphologic spectrum and suggesting potential relationship to sclerosing epithelioid fibrosarcoma: a study from the French Sarcoma Group. *Am J Surg Pathol*. 2007;31:1387–402.
11. Meis-Kindblom JM, Kindblom LG, van den Berg E, et al. Sclerosing epithelioid fibrosarcoma. In: Fletcher CDM, Unni KK, Mertens F, editors. *World health organization classification of tumours. Pathology and genetics of tumours of soft tissue and bone*. Lyon: IARC Press; 2002. p. 106–107.
12. Rekhi B, Folpe AL, Deshmukh M, et al. Sclerosing epithelioid fibrosarcoma: a report of two cases with cytogenetic analysis of FUS gene rearrangement by FISH technique. *Pathol Oncol Res*. 2011;17:145–8.
13. Bilsky MH, Scheffler AC, Sandberg DI, et al. Sclerosing epithelioid fibrosarcomas involving the neuraxis: report of three cases. *Neurosurgery*. 2000;47:956–9.
14. Reid R, Barrett A, Hamblen DL. Sclerosing epithelioid fibrosarcoma. *Histopathology*. 1996;28:451–5.
15. Evans HL. Low-grade fibromyxoid sarcoma: a report of two metastasizing neoplasms having a deceptively benign appearance. *Am J Clin Pathol*. 1987;88:615–9.
16. Panagopoulos I, Storlazzi CT, Fletcher CD, et al. The chimeric FUS/CREB3L2 gene is specific for low-grade fibromyxoid sarcoma. *Genes Chromosom Cancer*. 2004;40:218–28.
17. Reid R, deSilva MVC, Paterson L, et al. Low-grade fibromyxoid sarcoma and hyalinizing spindle cell tumor with giant rosettes share a common t(7;16)(q34;p11) translocation. *Am J Surg Pathol*. 2003;27:1229–36.