Oral and Maxillofacial Sclerosing Epithelioid Fibrosarcoma: Report of Five Cases

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Abstract Sclerosing epithelioid fibrosarcoma (SEF) has distinctive morphology and occurs mainly in deep soft tissue of adult extremities. Approximately 59 cases of SEF have been reported, with only 12 previously described in head and neck locations. Lesions involving the oral and maxillofacial region (OMFR) and intraosseous examples are rare. We present five cases of OMFRSEF. The OMF Pathology Department Registry was searched for cases coded from 1990 to the present as “SEF,” “fibrosarcoma not otherwise specified” or “neoplasm of uncertain histogenesis.” Inclusion required OMFR location, an abundantly sclerotic sarcoma with epithelioid features, and lack of other phenotype by immunohistochemistry. Five cases of SEF included 3 males and 2 females. The age of the patients were: 19, 22, 35, 47 and 47 years. Tumor location included the infra-temporal fossa, buccal mucosa (recurrence extending into bone), anterior mandible (intraosseous primary, focally extending into soft tissue), and left parotid and submandibular gland (with metaplastic bone) regions. Tumor sizes ranged from 1.0 to 5.7 cm, median 3.5 cm. Histologically, the tumors were well

delineated and multinodular, separated by fibrous septae. The spindled to primarily epithelioid tumor cells formed moderately cellular sheets and cords of irregularly contoured medium to large, round to oval, occasionally overlapping nuclei, indistinct nucleoli, wispy eosinophilic (retracting) cytoplasm, and distinctive cytoplasmic borders, embedded in osteoid-like stroma. Hemangiopericytoid (HPC-like) vessels were observed. Despite numerous apoptotic cells, mitoses were generally low; necrosis was present in two cases. Three tumors were graded as 2/3 and two 1/3. Immunohistochemically, the tumor cells were positive for vimentin, 1 case focally for CD34, whereas all cases were negative for S100 protein, keratins, EMA, desmin, and SMA. Wide or radical excision was performed with no adjuvant therapy. Follow-up revealed that 4 cases recurred at a range of 12–120 months. One case had no recurrent/residual disease at 3 months. Metastatic disease was present in 2 cases, to chest wall and lumbar/thoracic spine at 12 and 21 months, respectively. One patient died of disease complications at 15 months. OMFRSEF occur in adults in various locations, but with a common propensity to involve bone; there is recurrent potential and morbidity with higher grade lesions. The differential diagnosis for these tumors in this site includes sclerosing carcinoma, Ewing/PNET, osteosarcoma, osteoblastoma, and benign and malignant myoepithelial salivary gland tumors. The collagen, focal spindle cell features, HPC-like vasculature, and weak focal CD34 reactivity in one case might have raised a possible relationship between OMFRSEF and low grade malignant solitary fibrous tumor, but the intraosseous propensity, epithelioid features and relative lack of CD34 make this a distinctive entity.

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Introduction

Sclerosing epithelioid fibrosarcoma (SEF), was originally described in 1995 by Meis-Kindblom et al. as an uncommon low grade variant of fibrosarcoma, found mainly in the deep soft tissue of the extremities [1, 2]. It is characterized by distinctive epithelioid cytomorphology associated with extensive stromal hyalinization. Only 12 cases involving the head and neck have been reported, three of which were intracranial [2, 3]. Additionally, tumors with definitive intraosseous origin are uncommon, despite the fact that SEF have a predilection for bone invasion [2, 4–6]. Five cases of SEF of the oral and maxillofacial region, including one intraosseous example were studied to further characterize the clinicopathologic features, biologic behavior and differential diagnosis of this uncommon malignant neoplasm.

Materials and Methods

Records from the Armed Forces Institute of Pathology Registry of Oral and Maxillofacial Pathology from 1990 to the present were reviewed for cases coded as “sclerosing epithelioid fibrosarcoma, fibrosarcoma variant or neoplasm

of uncertain histiogenesis”. Review of 45 cases from these categories revealed 5 cases conforming to established diagnostic criteria for SEF [7].

Immunohistochemical stains were performed [8] on available blocks or unstained sections (summarized in Table 1). The immunostaining was scored as ‘positive’ or ‘negative’. Immunoreactivity for all antigens except bcl-2 (a nuclear marker) was cytoplasmic. Molecular evaluation for t(11;22)(q24;q12) chromosomal translocation was performed on paraffin embedded tissue. RT-PCR (t11:22) assay to detect EWS/FL-1 fusion product mRNA was performed using primers derived from EWS and FLI-1 exons. PCR products were detected by agarose gel electrophoresis followed by Southern blot analysis using probes derived from the EWS gene. RT-PCR control targets a segment of Beta-2-microglobulin mRNA. Patient follow up data was obtained.

Results

Clinical Findings and Patient Follow-up

The clinicopathological features and follow-up information for the 5 SEFs are listed in Table 2. The tumors were

Table 1 IHC dilutions and sources

IHC stain	Dilution	Source	Company
Bcl-2 (Clone 124)	1:500	Mouse/monoclonal	DAKO
CD34	Predilute	Mouse/monoclonal	Ventana
CD45ro	Predilute	Mouse/Clone A6	Ventana
CD57/Leu 7	1:50	Mouse/monoclonal	Becton Dickonson
CD68 (Clone KP1)	1:350	Mouse/monoclonal	DAKO
CD99	1:150	Mouse	DAKO
Desmin 33	1:200	Mouse/Clone M0760	DAKO
D-er-11	Predilute	Mouse/monoclonal	Ventana
EMA	Predilute	Mouse	Ventana
Factor VIII	1:1600	Rabbit/polyclonal A0082	DAKO
Factor XIIIa	1:1600	Rabbit	Calbiochem
GFAP	1:4000	Rabbit/polyclonal	DAKO
HMB45	1:50	Mouse/Clone HMB45	DAKO
Ki-67	1:80	Mouse/Clone MIB (012X101)	DAKO
MAC 387	1:1500	Mouse/monoclonal	DAKO
Melan A	Predilute	Mouse/monoclonal	Ventana
MSActin	Predilute	Mouse/Clone (HUC 1–1)	Ventana
NFP	1:200	Mouse/2F1/M0762	DAKO
Pan-cytokeratin	1:400	Mouse cytokeratins	DAKO
Cocktail (AE1/AE3)	1:400	Mouse LP34	Chemicon (A1/A3)
P63	1:100	Mouse/Clone 4A4	Santa Cruz Biotech
S100	1:600	Mouse	DAKO
SMA	1:1600	Mouse/Clone 1A4	Sigma
Vimentin	Predilute	Mouse	Ventana

Table 2 Clinicopathologic features of 5 sclerosing epithelioid fibrosarcomas (SEFs)

Case	Patient age (years)/sex	Tumor site/size (cm)	Margin status/presence of necrosis	Outside diagnosis	Treatment/recurrence/metastasis	Follow-up
1	19/M	Palate, zygomatic-temporal area, >5.0	+/Yes (piecemeal excision)	None provided	Surgery, chemotherapy, and radiation therapy/local recurrence/metastasis to chest wall	DOD, 15 mo
2	22/F	Anterior mandible, 5.7	–/No	Desmoplastic fibroma and osteosarcoma	Mandibular resection	NED, 3 mo
3	35/M	Left parotid, 3.5	+/Yes	Myoepithelial neoplasm	Surgery and radiation therapy/recurrence at 14 mo/metastasis (lower thoracic and lumbar spine) at 21 mo	AWD, 26 mo
4	47/F	Buccal mucosa, 3.1	+/No	Atypical solitary fibrous tumor	Surgery/recurrence at 60 mo	NED, 78 mo
5	47/F	Submandibular gland, 1.0 (recurrent tumor)	–/No	Myoepithelial carcinoma and pleomorphic adenoma	Surgery/recurrence at 120 mo	NED, 198 mo

AWD, alive with disease; DOD, dead of disease; NED, no evidence of disease; U, unknown

located in the following sites: infratemporal fossa area, anterior mandible, buccal mucosa, parotid, and submandibular region. The patients were comprised of the following: 19 YOM, 22 YOF, 35 YOM, 47 YOF, and 47 YOM. Presenting signs and symptoms were first noted 7 weeks to 6 months prior to diagnosis and included asymptomatic swellings, headaches and tooth mobility. Two patients presented with temporal headaches, with pain extending from the ear to eye. The intraosseous case presented as an expansile, enhancing heterogeneous (lytic) lesion involving the anterior mandible (Figs. 1, 2). The lesion had a thinned cortex and irregular margins. All patients had firm, solitary, lobulated tumors. Three of the tumors were clinically thought to be salivary gland tumors

because of presentation as firm, well-defined mass lesions adjacent to salivary gland tissue.

All patients had their tumors surgically excised; available records indicated that one patient received adjuvant chemotherapy and two received post-operative radiation therapy. Follow-up revealed local recurrences in four patients and metastatic disease in two. To date, 3 patients are alive without disease, 1 is alive with disease, and 1 has died of disease complications 15 months after initial presentation.

The contributors' diagnoses are listed in Table 2. Diagnoses from contributing pathologists included a variety of malignant and benign entities including pleomorphic

Fig. 1 CT scan demonstrating an expansile enhancing lesion of the anterior mandible

Fig. 2 Preoperative image showing an expansile mass filling the anterior mandibular vestibule

adenoma, desmoplastic fibroma, osteosarcoma, atypical solitary fibrous tumor, myoepithelial neoplasm, and myoepithelial carcinoma.

Gross Pathology

Tumor sizes ranged from 1.0 to 5.7 cm with a median of 3.5 cm. All tumors were grossly described as encapsulated and multilobular. Other characteristics of the tumors included gritty texture, hemorrhage and color ranging from grey-white to yellow-tan.

Histopathological Findings

Morphologically, all cases of SEF were relatively well circumscribed with pushing margins and focal infiltration into adjacent soft tissue or bone (Figs. 3, 4). At low power,

the lesions demonstrated areas of varying cellularity with a conspicuously hyalinized stroma. At higher magnification, distinct nests and strands of epithelioid cells were evident within dense sclerosis (Fig. 5). The tumor cells had round to oval nuclei that were variably angulated, with a moderate amount of clear to eosinophilic cytoplasm, which retracted in fixed tissue, with distinctive cytoplasmic borders (Fig. 6). The nuclei were overlapping and the nucleoli were indistinct to small. The mitotic activity was generally low (1–2/10 hpf), except case 5 which had more cellularity as well, and necrosis was observed in two cases. This group of tumors included minimal areas of conventional fibrosarcoma, represented by occasional short fascicles and parallel arrays of fusiform cells intermingled with more delicate strands of collagen (Fig. 7). Hypocellular myxoid zones resembling myxoma or myxofibrosarcoma were sometimes focally present. One tumor exhibited focal metaplastic bone formation (case 5), but no cases had true osteoid, despite the osteoid like or keloid collagen like

Fig. 3 Well circumscribed tumor with pushing margins and focal infiltration into adjacent bone

Fig. 5 Distinct nests and strands of epithelioid cells embedded within a dense sclerotic matrix

Fig. 4 Low power field of a lobular, relatively hypocellular mass with a conspicuously hyalinized stroma

Fig. 6 Tumor cells with round to oval nuclei and pale eosinophilic to clear cytoplasm

Fig. 7 Focal areas with histologic features of traditional fibrosarcoma, with interlacing short fascicles arranged in parallel arrays

appearance of the stroma. Tumor was present at the inked surgical margin in 3 of the 5 cases. Tumors were graded as follows: three cases were grade 2/3 and two were 1/3, using the French Federation Grading Scheme.

Immunohistochemical Results

The immunohistochemical findings are summarized in Table 3. Immunohistochemical stains on paraffin-embedded tissue demonstrated that 4 of 4 SEF's were positive for

Fig. 8 Tumor cells displaying immunoreactivity for vimentin

vimentin (Fig. 8) and 3 of 3 cases were immunoreactive with CD99. Bcl-2 and CD34 were reactive in one case, with only focal weak positivity for CD34.

Molecular Evaluation

Because of the identification of CD99 reactivity in three cases, molecular evaluation for the t(11;22)(q24;q12) chromosomal translocation was performed on cases 1 and

Table 3 Immunohistochemistry results

	Case 1	Case 2	Case 3	Case 4	Case 5
Bcl-2	–	+	–		
CD34	–	+ (focal scant)	–	–	–
CD45ro	–				
CD57				–	
CD68		–		–	
CD99	+	+	+		
Desmin	–	–	–	–	
EMA			–	–	–
Factor VIII				–	
Factor 13a				–	
GFAP				–	–
HMB45	–			–	
Ki-67	40%				
MAC 387				–	
Melan A					–
MSA	–			–	
NFP	–			–	
Pan-cytokeratin	–	–	–	–	–
P63		–			–(contributors stain)
S100	–	–	–	–	–
SMA		–	–	–	–
Vimentin	+	+	+	+	

2. The results were negative for this translocation, ruling out Primitive Neuroectodermal Tumor and Ewing sarcoma.

Discussion

SEF is an uncommon, yet distinct, variant of fibrosarcoma. Originally described by Meis-Kindblom et al. in 1995 as a low grade fibrosarcoma [1], SEF is characterized by the World Health Organization (WHO) as a malignancy of deep soft tissue [7]. The tumors affect a wide variety of sites, with the majority of the reported cases arising in the extremities, limb girdle, and trunk.

The clinical and histological findings of our cases of OMFRSEF correlate with the diagnostic criteria as previously established [1, 7]. A review of the literature reveals 9 cases that involved the head and neck (excluding intracranial cases), which are summarized in Table 4, along with the current series.

Although originally described as a low grade tumor [7], OMFRSEF, in these head and neck sites, tend to have an aggressive behavior, and tend to be of higher (intermediate) grade. The current study reports 5 additional cases presenting in the oral and maxillofacial region, with four recurrences and two metastases, one death related to disease, with these tumors exhibiting intermediate grade morphology. Metastases were present in the chest wall of the patient in case 1 and thoracic and lumbar spine of the patient in case 3. Of the previously reported cases of head and neck SEF, 3 patients have died of their disease, 2 are alive with disease, and 1 has no evidence of disease. Follow-up data and disease status was not available for 3 of

the cases. Only 2 cases have been previously reported in oral and maxillofacial regions [5, 9]. Chow et al.'s review of the literature reported from 1995 to 2002 revealed recurrence or metastasis in 48% and 60%, respectively, of patients with SEF [6]. Lung is the most common site of metastasis, however kidney, chest wall, bone, liver, lymph nodes, breast and retroperitoneum metastases have been reported [1, 2, 5, 6, 10]. Therefore this previously considered low grade [1, 11] fibrosarcoma variant is now found to be of higher grade culminating in its recurrent and morbid potential, especially in head and neck and OMFR locations.

OMFRSEF have a propensity to occur in bone, particularly in these sites. SEF does not typically present as an intraosseous lesion, and only 4 primary intraosseous lesions have been previously described [2, 4, 6]. One case in the current study (case 2) also presented as a primary intraosseous tumor (anterior mandible), again confirming that SEF is not limited to soft tissue. Another of our patients had an intraosseous recurrence. A few cases reports have demonstrated that SEF also have the potential to invade into adjacent bone [2, 4]. Therefore, OMFRSEF clearly demonstrates a propensity to involve bone.

Histologically, OMFRSEF is identical to SEF of other sites. It is characterized by a multinodular proliferation of sheets, nests, or cords of uniform round to oval epithelioid cells with distinctive cell borders. The cytoplasm of the tumor cells is pale eosinophilic to clear and the nuclei are rounded, although in some areas where the tumor cells are tightly packed together, nuclear angulation may be evident. These cells are embedded in a densely hyalinized stroma. Areas of myxoid degeneration, cystic change, foci of metaplastic bone, hyaline cartilage, and calcification are

Table 4 Reported cases of sclerosing epithelioid fibrosarcoma located in the head and neck (excluding intracranial cases)

Author	Number of cases	Age/sex	Site/size (cm)	Follow-up	Disease status
Meis-Kindblom et al. [1]	2	27/M	Neck, 14.5	None	Unknown
		60/F	Posterior neck, 4.0	None	Unknown
		23/M	Subcutaneous cheek, 5.0	72 mo	AWD
		40/F	Right neck, 3.0	84 mo	DOD
Eyden et al. [9]	3	25/F	Subcutaneous forehead, 2.5	None	Unknown
Antonescu et al. [2]	3	48/M	Scalp, 4.0	30 mo	DOD
		51/M	Left neck, 3.7	13 mo	NED
		52/F	Skull base (bone), >15	65 mo	AWD
Battiata et al. [5] ^a	1	19/M	Palate, zygomatic-temporal area, U	15 mo	DOD
		19/M	Palate, zygomatic-temporal area, U	15 mo	DOD
		22/F	Anterior mandible, 5.7	3 mo	NED
Folk et al (current study), 2005	5	35/M	Left parotid, 3.5	26 mo	AWD
		47/F	Buccal mucosa, 3.1	78 mo	NED
		47/M	Submandibular gland, 1.0 (recurrent tumor)	198 mo	NED

^a The case is in the current study (case 1)

AWD, alive with disease; DOD, dead of disease; NED, no evidence of disease; U, unknown

additional features that may be present [1, 2, 9]. Although true osteoid may be controversially acceptable, if only focally in these lesions, osteoid was not identified in our cases. The sclerotic areas were histologically distinguished from osteoid. One case displayed metaplastic bone formation. Significant mitotic activity (including atypical forms) and necrosis are not common findings. Interestingly, although the sample size of our study is too small to draw definitive conclusions, it should be noted that the two tumors with the most aggressive behavior (Cases 1 and 3) contained foci of tumor necrosis. These tumors were otherwise cytomorphologically indistinguishable from the remaining cases, yet were slightly higher grade than the other tumors, using the Coindre French Federation Grading Scheme [12] based on differentiation (score of 1), necrosis present (score of 1), and higher mitotic activity than the other cases (score of 2). Total scores of 4 or 5 indicate intermediate grade, grade 2/3, requiring adjuvant therapy.

Immunohistochemically, the tumor cells of SEF do not display definitive evidence of differentiation along a specific lineage. Most examples are immunoreactive with vimentin, but variable staining for EMA, S100, AE1/AE3, Bcl-2, CD34 and CD99 has been reported [1, 2, 4, 13, 14]. The immunophenotypic features of these cases did not differ significantly from previously reported cases, with 4 of 4 cases demonstrating reactivity with vimentin, one case focally for CD34, and 3 of 3 cases showing tumor cell positivity with CD99.

The wide differential diagnosis of this tumor is reflected in the diagnoses offered by the contributing pathologists, as noted in Table 2. The SEF's circumscription, bland cytomorphology, low mitotic rate and the extensive stromal hyalinization might suggest the diagnosis of a benign entity. However, the infiltrative growth pattern suggests an aggressive neoplasm. When SEF occurs in the head and neck, specifically in the salivary gland area, the epithelioid cytomorphology and nuclear angulation can mimic salivary gland tumors, including pleomorphic adenoma, myoepithelioma, myoepithelial carcinoma, and clear cell carcinoma. The absence of ductal differentiation in SEF aids in distinguishing it from pleomorphic adenoma. In addition, the neoplastic cells of SEF are generally non-reactive for keratin, S100, smooth muscle actin or GFAP, in contrast to tumors with myoepithelial derivation.

Intraosseous SEF can mimic a variety of benign and malignant tumors, such as desmoplastic fibroma and osteosarcoma. Although a densely collagenous stroma is a feature of desmoplastic fibroma, the tumor cells are more spindle and elongated and less cellular than the plump, round to ovoid cells seen in SEF. In intraosseous cases, distinguishing SEF from an osteosarcoma with epithelioid tumor cells can be extremely difficult. Although foci of metaplastic bone and cartilage have been reported in cases

of SEF, osteosarcoma is predicated on the presence of malignant osteoid, which is more lacelike, curvilinear, and aborizing with lacunae formation. In SEF the non-osseous collagen is more fibrillar, linear and is compressed between the neoplastic cells [7].

Examples of other sarcomas with abundant dense hyalinized extracellular matrix production, specifically rhabdomyosarcoma (RMS) (hyalinizing, matrix-rich variant) can also pose difficulty in distinguishing from SEF. In both SEF and RMS (hyalinizing, matrix-rich variant) the extracellular matrix can have an osteoid-like appearance, but lacks definite lacunae or matrix calcification. Foci of metaplastic bone can be seen in both entities, but RMS will not show focal areas of more typical fibrosarcoma and the tumor cells will have a dot-like reactivity with desmin [15].

Another sarcoma that poses difficulty in the diagnosis of SEF is synovial sarcoma. SEF is not typically mistaken for the classical biphasic synovial sarcoma, but can be reminiscent of the more poorly differentiated examples of the monophasic synovial sarcoma, composed of sheets of round cells. The collagen formation seen in synovial sarcoma is generally non-sclerotic and has a short ropey arrangement, whereas the collagen in SEF is arranged in sheets and is densely hyalinized and sclerotic. All of our cases, even the one with CD99 and Bcl2 positivity, were negative for keratins and other epithelial markers. Although only limited cytogenetic studies have been performed on SEF [13, 16, 17] lack of identification of the t(X;18), characteristic of synovial sarcoma, can be helpful [18].

Melanoma may be suggested by the “packeted” islands of tumor cells embedded in a dense eosinophilic collagen. However, the cells in melanoma are typically larger with more prominent centrally placed nucleoli. Although the tumor cells of SEF can be positive for S100 [1, 14], the expression is usually weak. In addition, HMB45 is negative in SEF, as it was in our cases.

Identification of conventional areas of fibrosarcoma can help distinguish this tumor from diffuse large B cell lymphoma with sclerosis. Also, the absence of lymphoid markers in SEF precludes the diagnosis of a lymphoid neoplasm.

The Ewing/Primitive neuroectodermal tumor (PNET) family of tumors may also be considered in the differential diagnosis for SEF. The sheet-like proliferation of round cells with distinct cell borders and clear to pale eosinophilic cytoplasm seen in PNET can be similar to that seen in SEF. However, the neoplastic cells in SEF tend to be blander and lack stippled chromatin and the cells are larger with more cytoplasm than the PNET tumor cells. Furthermore, rosette like areas are absent in SEF. In addition, the sheets of densely hyalinized collagenous stroma characteristic of SEF are not present in PNET. Although CD99

reactivity is noted in almost all cases of PNET [7], the tumor cells of SEF may also be reactive. PNET characteristically demonstrates strong membrane expression of CD99, whereas SEF exhibit non-specific cytoplasmic staining. Identification of the t(11;22)(q24;q12) chromosomal translocation is also helpful in distinguishing PNET from SEF. The two cases examined did not demonstrate evidence of this translocation.

Additional tumors that may be considered in the differential diagnosis of these lesions include the following: sclerosing carcinoma, leiomyoma, fibrous histiocytoma, and solitary fibrous tumor. Keratins, desmin, and diffuse CD34 are negative in SEF, separating it from these entities, respectfully.

In summary, we present five cases of OMFRSEF. These tumors occur in various OMFR sites and have a propensity to involve bone. Furthermore, even small lesions in this tightly spaced location have the potential for locally aggressive growth, local recurrence, and even more aggressive behavior such as metastasis and patient death. The histologic finding of necrosis and therefore higher grade may indicate a poorer prognosis, as seen in our cases with a more ominous clinical course (disease persistence, multiple recurrences, metastatic disease, and death due to disease). Grading of SEF according to Federation Nationale des Centres de Lutte Contre le Cancer or in English—French Federation of National Cancer Centers (FNCLCC), criteria is recommended as higher tumor grade (based on differentiation, mitoses, and necrosis) for SEF may correlate with more aggressive behavior [12].

Since SEF is recently described, relatively rare and particularly uncommon in head and neck or OMFR sites, and the histologic features of these tumors in this location may be misinterpreted as several benign and malignant soft tissue and intraosseous OMFR tumors. The diagnostic criteria for OMFRSEF should include the following: (1) a multinodular tumor separated by fibrous septa, (2) an infiltrative neoplasm with tumor cells displaying an epithelioid morphology with slight angulated or overlapping nuclei and indistinct nucleoli (3) presence of an extensively hyalinized osteoid-like stroma but with obvious fibrillar eosinophilia and (4) neoplastic cells that are immunoreactive mainly only for vimentin.

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