Sclerosing epithelioid fibrosarcoma: in-depth review of a genetically heterogeneous tumor

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First described in 1995 by Meis-Kindbloom et al. as a variant of fibrosarcoma simulating carcinoma, sclerosing epithelioid fibrosarcoma (SEF) is a malignant soft tissue sarcoma characterized by epithelioid cells in dense sclerotic stroma, frequent immunoreactivity for MUC4 and heterogeneous genetic profile with recurrent EWSR1 gene rearrangement. It typically affects middle-age adults with a predilection for the lower extremity. It is believed that SEF is closely related to low-grade fibromyxoid sarcoma (LGMS), both tumors show overlapping features in morphology, immunophenotype, and molecular profile. In this review, we discuss the clinical, morphologic, and immunohistochemical features of SEF with particular emphasis on its molecular diversity and relation to LGMS.

Key words: Sclerosing epithelioid fibrosarcoma; low-grade fibromyxoid sarcoma; soft tissue; MUC4; EWSR1.

In 1995, sclerosing epithelioid fibrosarcoma was originally recognized as a distinctive low-grade soft tissue sarcoma by Meis-Kindbloom et al. [1]. In that study, they described 25 cases of a peculiar variant of fibrosarcoma simulating carcinoma. In 1998, Eyden et al. [2] emphasized on the diagnostic criteria of SEF based on morphology, ultrastructural, and immunophenotypic features. In 2001, another study of 16 patients performed by Antonescu et al. [3] expanded our knowledge about this neoplasm and confirmed that sclerosing epithelioid fibrosarcoma is a clinicopathologically distinct tumor. It was found that a subset of SEF cases may show areas reminiscent of LGMS, suggesting a biological relationship between both tumors [4, 5]. At molecular level, the majority of LGMS cases harbor FUS gene rearrangement; however, this rearrangement is rare in pure SEF cases [6–9]. Nonetheless, EWSR1 gene rearrangement was found to be recurrent in pure SEFs [7–9]. Currently, this tumor is still a matter of interest for researchers due to its genetic heterogeneity and complexity, as well as overlapping features with LGMS.

CLINICAL FEATURES

Sclerosing epithelioid fibrosarcoma most commonly affects middle-age individuals in their fifth decade [1–3, 6, 8, 10]. The tumor was found to have a male predominance in some studies [1, 6, 10], while other studies showed striking female predominance [2, 3, 8].

SEF has a propensity for the deep soft tissue of the lower extremities, trunk, upper extremities, and head and neck region [1–3, 6–8, 10, 11]. Nevertheless, it has been reported as a primary tumor in different anatomic sites, including kidney [12, 13], pancreas [14, 15], liver [16], cecum [17], abdominal cavity [18], lung [19], bone [20, 21], oral cavity [22, 23], and pituitary gland [24].

Most patients present with a painless mass particularly in the lower extremities for few months to years. Sometimes, it is discovered due to recent change in size, new onset of pain, or trauma. Primary tumors arising in trunk, head, and abdominal cavity usually present with symptoms and signs related to mass effect.

By imaging studies, SEF can mimic other common soft tissue neoplasms. The radiological features are closely associated with the histopathologic
features and grade of the tumor. By positron emission tomography-computed tomography (PET/CT) scan, high-grade tumors are more FDG-avid, while low-grade tumors show less FDG uptake [25].

PATHOLOGIC FINDINGS

On gross examination, the tumor size is variable and ranges from 2 to 19.5 cm, with average size of 7–9 cm [1–3, 8, 11, 26]. The tumor is relatively well-circumscribed with pushing margins but it can be focally infiltrative. The cut surface of the tumor is typically lobulated, firm, and white-gray to tan. Gross evidence of necrosis can be seen in some cases. Cystic changes and foci of calcification can also occur.

Microscopically, the tumor is composed of lobules of variable cellularity, which infiltrates the surrounding adipose or skeletal muscle tissue (Fig. 1). The tumor cells are arranged in nests, sheets, cords, and single files of epithelioid cells embedded in a sclerotic stroma (Fig. 2).

The epithelioid tumor cells are small to moderate in size, generally uniform, have round to oval and sometimes angulated nuclei with small nucleoli. The cytoplasm is frequently clear but can be eosinophilic (Figs 3 and 4). The cytoplasmic clearing is mainly attributed to cellular shrinking artifact caused by encasing collagen, rather than substance accumulation. This artifact is absent in rare non-fibrosing variants of SEF, where the cells have more abundant eosinophilic cytoplasm [27]. Foci of necrosis can be seen. The mitotic rate is variable and ranges from 1 to 18 mitoses per 10 high-power fields (hpf) with a median of 4/10 hpf [1, 2, 8, 11].

The striking feature is the presence of thick densely eosinophilic collagen bands and strands enclosing the tumor cells (Fig. 5). Stromal myxoid changes can also occur. The vasculature usually consists of irregular, thin-walled, ectatic vessels.

Other histological findings that had been observed are the presence of foci of hyaline cartilage, calcifications, and metaplastic bone formation. Some tumors can display cellular zones of intersecting fascicles of spindle cells “fibrosarcoma-like areas” [1], while other tumors can show areas reminiscent of LGFMS with alternating hypocellular and hypercellular areas of spindle to stellate cells in a fibromyxoid stroma (Fig. 6) [4–8, 10].

ULTRASTRUCTURAL FEATURES

The tumor cells in SEF are found to generally display features of fibroblasts and myofibroblasts [1–3]. The cytoplasm contains moderate numbers of mitochondria, abundant rough endoplasmic reticulum (RER) network, and large Golgi apparatus. Collagen secreting granules sometimes can be seen. Cytoplasmic arrays of “vimentin-type” intermediate filaments are present in most cases. The nucleus has smooth outline, evenly dispersed chromatin with small one to several nucleoli.

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Initial studies revealed that SEF shows consistent reactivity for vimentin [1–3], which was part of the diagnostic criteria proposed by Eyden et al. [2]
Later on, Doyle et al found that MUC4 is a sensitive and relatively specific marker for SEF [10]. In that study, 69% of pure SEF cases showed strong diffuse cytoplasmic staining for MUC4 (Fig. 7). Further studies performed later confirmed this finding [7, 8]. Staining for epithelial membrane antigen (EMA) is variable and ranges from 27% to 88% (Fig. 8) [1, 3, 11]. SEF is generally negative for smooth muscle actin (SMA), desmin, and CD34. Cytokeratin AE1/AE3 and S100 stains are also negative; however, focal and weak positivity was observed in few cases [1].

It is essential to mention that MUC4 lacks specificity as it can be positive in other epithelioid soft tissue tumors. The glandular component of synovial sarcoma can sometimes show reactivity for MUC4 [10]. Focal reactivity in ossifying fibromyxoid tumor, epithelioid gastrointestinal stromal tumor, and myoepithelial carcinoma has also been observed [10].

MOLECULAR PATHOLOGY

The molecular alterations found in SEF are more diverse and complex than was initially thought. The
first attempt to explore its genetic profile was made by Gisselsson et al. [28], who found amplification of 12q13 and 12q15 sequences in a single case. There were few additional attempts to karyotype this tumor in the following few years [29, 30]. In 2012, Doyle et al. [10] found that 38% of MUC4-positive pure SEF cases had FUS gene rearrangement by fluorescent in situ hybridization (FISH), but was absent in the MUC4-negative cases, suggesting a relation between MUC4 expression and FUS rearrangements. In the same year, Wang et al found that FUS rearrangements are rare in pure SEF. In that study, only 9% of pure SEFs were positive for FUS rearrangement [6].

For the first time in 2014, two large studies by Arbajian et al. and Carlos-Prieto-Granda et al. found recurrent EWSR1 gene rearrangement in pure SEF, predominantly EWSR1-CREB3L1 fusion, and less frequently EWSR1-CREB3L2 [7, 8]. In both studies, all hybrid SEF/LGFMS cases, unlike pure SEF cases, carried FUS-CREB3L2 gene fusion, suggesting a genetic dichotomy between the two tumors [7, 8]. In 2017, Arbajian et al. [9] found similar results, EWSR1-CREB3L1 and EWSR1-CREB3L2 fusions were predominant in pure SEF, while FUS-CREB3L2 was found to be predominant in hybrid SEF/LGFMS. In that study, they also described previously unreported gene fusions in few cases of pure SEF including FUS-CREM, FUS-CREB3L2, and PAX5-CREB3L1 [9]. EWSR1-CREB3L3 gene fusion had also been described in a single case [31].

In 2019, Kao et al. performed molecular analysis on a subset of SEFs that are MUC4-negative and lack EWSR1 and FUS fusions [26]. They found that some cases do carry YAP1 and KMT2A gene rearrangement, while the control group of LGFMS cases lacked these genetic alterations. In 2020, Puls et al. [11] also identified recurrent fusions between YAP1 and KMT2A in cases that are morphologically in the spectrum of SEF and LGFMS. One case in that study showed PRRX1-KMT2D gene fusion. In the same year, a study performed by Massoth et al. [32] revealed that KMT2A-rearranged sarcomas commonly exhibit sclerosing epithelioid sarcoma-like morphology and complex YAP1-KMT2A-YAP1 fusions, which provided another evidence that KMT2A gene rearrangement can occur in a subset of cases of SEF. In 2021, the largest reported series to date of 51 cases of SEF was performed by Warkme and Meis [33]. Their results were congruent with the previous studies; EWSR1 gene rearrangement was the most common genetic alteration with predominance of EWSR1-CREB3L1 fusion. Only few cases in that study showed FUS gene rearrangement and a small subset of cases revealed YAP1-KMT2A fusion. Recently, we also identified a novel HEY1-NCOA2 gene fusion in a case of intra-abdominal hybrid SEF/LGFMS, adding another layer to the molecular complexity of this neoplasm [34].

**DIFFERENTIAL DIAGNOSIS**

Tumors that are characterized by epithelioid cells and sclerotic stroma as the main features should be considered. The most important differential diagnosis is metastatic carcinoma. Lack of history of a previous primary carcinoma, absence of evidence of visceral disease, and negative staining for pan-cytokeratin by immunohistochemistry help distinguish SEF from metastatic carcinoma.
The differential diagnosis also includes benign fibrous proliferations and neoplasms such as nodular fasciitis, myositis ossificans, hyalinizing leiomyoma, ossifying fibromyxoid tumor, and myoepithelial tumors. Other diagnostic considerations include sclerosing lymphoma, melanoma, clear cell sarcoma, alveolar rhabdomyosarcoma, extraskeletal myxoid chondrosarcoma, and epithelioid malignant peripheral nerve sheath tumor. The dense collagen in the stroma of SEF can sometimes be arranged in delicate lace-like strands reminiscent of osteoid, and extraskeletal osteosarcoma should be excluded. A wide panel of immunohistochemical stains including cytokeratin AE1/AE3, LCA, S100, HMB-45, SMA, desmin, and SATB2 will allow distinction between these entities.

Other epithelioid tumors, such epithelioid sarcoma (ES) and epithelioid hemangioendothelioma (EHE), should be considered in the differential diagnosis. ES is typically positive for CD34 and shows loss of nuclear expression of SMARCB1 (INI-1). On the other hand, SEF is negative for CD34 and shows intact nuclear staining for INI-1. EHE is characterized by having cordlike to nested growth pattern embedded in a myxohyaline matrix. The tumor cells have characteristic intracytoplasmic vacuoles and express the vascular marker CD34 as well as CAMTA1 and/or TFE3.

**PROGNOSIS AND TREATMENT**

Sclerosing epithelioid fibrosarcoma tends to have an aggressive behavior. According to several large studies, approximately 30–53% of patients developed local recurrence, while distant metastasis rate was variable and ranged from 20% to 86% [1–3, 8, 11, 26]. The follow-up periods ranged from 1 to 11 years. The most common sites of metastasis are the lungs followed by bone, lymph nodes, and pleura [1–3, 6]. Metastases to brain, pericardium, peritoneum, bone marrow, and penile shaft had also been reported [1, 6, 11, 35, 36].

Treatment options include surgery as wide local excision or amputation followed by either radiotherapy or chemotherapy [2, 11, 26, 37]. It was found that SEF has limited response to conventional chemotherapeutic agents [37]; however, further randomized clinical trials with more patients are needed.

Recently, Arbajian et al. [9] have found that CD24 is unregulated in SEF by gene expression analysis. In that study, microdeletions in DMD gene (encoding dystrophin) were also detected by single nucleotide polymorphisms (SNP) [9]. They suggested that CD24 and DMD could be potential therapeutic targets. However, additional studies are needed to clarify the role of such therapy in SEF.

**CONCLUSION**

Sclerosing epithelioid fibrosarcoma is a rare and unique malignant tumor that occurs in middle-age adults with a predilection for the lower extremities. This tumor bears diagnostic difficulty and shows overlapping features with LGFMS. SEF tends to have an aggressive clinical course, with high risk for local recurrence and distant metastasis. The tumor is genetically heterogeneous with various genomic imbalances and fusion genes. These genetic alterations may have an impact on therapeutic modalities in the future.

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**CONFLICT OF INTEREST**

All authors declare no potential conflict of interest.

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