Low-grade fibromyxoid sarcoma (LGFMS; Evans Tumor) is classically composed of relatively banal, hypocellular spindle cells arranged in alternating fibrous and myxoid zones. Cytogenetically, there is a recurrent reciprocal translocation involving \textit{FUS} (16p11) and \textit{CREB3L2} (7q32-34) or less commonly \textit{CREB3L1} (7p11). Within the accepted morphologic spectrum of LGFMS lie tumors previously described as "hyalinizing spindle cell tumor with giant rosettes" (HSCTGR) harboring an identical translocation.(1-3) These tumors have a propensity for late metastases to the lung which was initially surprising given their somewhat banal appearance.

Sclerosing epithelioid fibrosarcoma (SEF) is a rare malignant mesenchymal tumor characterized by epithelioid cells arranged in nests and cords embedded in a sclerotic hyalinized stroma and can mimic infiltrating carcinoma. SEF arises primarily in adults (45-65 years of age) and very often involve the deep soft tissue of the lower extremities. However, broad age and site spectra are noted. In the largest series, approximately half recurred locally with metastatic rates (mostly pulmonary) ranging from 43 to 86%. Mortality ranges from 25 to 57%. (4-7)

Several studies have noted areas reminiscent of SEF in some cases of LGFMS and vice versa, suggesting an unexpected relationship between these morphologically disparate neoplasms. In the initial SEF study by Meis and Enzinger, spindled areas resembling various fibrous tumors including LGFMS were reported in a subset of their SEF cases(5), an observation collaborated by Antonescu \textit{et al.} in their series.(4) Similarly, published series have occasionally
reported SEF-like areas in LGFMS/HSCTGR. Folpe et al. described a case of HSCTGR giving rise to a metastasis reminiscent of SEF in their study as well as noting that some cases of LGFMS to have more epithelioid areas; a finding also mentioned in other studies. (3,10,11) Evans has also described a recurrence with SEF-like features while Rehki et al. mention SEF-like areas in LGFMS in 6 of 18 of their cases. (8,11)

Intriguingly, several studies report SEF cases with a translocation identical to that of LGFMS. (8-10) In their study of cytogenetically identical LGFMS and HSCTGR tumor variants, Reid and colleagues discussed a single case of HSCTGR with SEF-like area. (9) The French sarcoma group noted 4 of their 7 tested SEF to have the same chimeric fusion transcript as LGFMS by reverse transcriptase polymerase chain reaction (RT-PCR). (10) FUS rearrangements by fluorescence in-situ hybridization (FISH) have been described in SEF. (12) We have also observed multiple cases of LGFMS with SEF-like areas (such the case presented in this session), with both conventional LGFMS and SEF-like areas harboring rearrangement of FUS (16p11) by FISH (Figure 1).

Figure 1. Schematic of fluorescence in-situ hybridization (FISH) on SEF or LGFMS using FUS (16p11) break-apart probe set. Two fluorescently-labeled probes labeled (R)ed and (G)reen hybridize to regions of chromosomal DNA flanking the FUS locus. In cells negative for FUS rearrangement, the spectral overlap of the green and red signals create a (Y)ellow signal (left). Cases positive for FUS rearrangement show nuclei with separated green and red signals (split signals) and one yellow (intact) signal (right).
Since LGFMS can include morphological variants such as HGSCT, we recently examined the prevalence of *FUS* rearrangement by FISH in cases of SEF lacking identifiable areas of LGFMS. Eighteen out of 21 patients had tumors that were analyzable by FISH and only two tumors positive for rearrangement of the *FUS* locus. Both FISH-positive tumors lacked recognizable LGFMS areas despite extensive sampling. Thus, rearrangement by FISH was only seen in 2 of 18 (11%) patients with SEF tumors while the majority of cases (16 of 18; 89%) lacked *FUS* rearrangement. In comparison, Guillou et al. noted 4 of 7 (57%) SEF tumors harbored the identical translocation seen in LGFMS by RT-PCR. Examination of *FUS* rearrangement by FISH in SEF was less successful in their series; however, other studies have detected *FUS* rearrangement by FISH in SEF. The differences in translocation prevalence may be due to the small size of the studies.

In the experience of others and ourselves, rearrangements in *FUS* detected by FISH can be detected in up to 90% of LGFMS (14-16) and up to 96% of LGFMS have been demonstrated to have *FUS/CREB3L1/2* by RT-PCR. Notably, in a few instances the translocation has not been demonstrated in LGFMS raising the possibility of another genetic aberration that could conceivably link a subset of SEF and LGFMS. Regardless, the prevalence of t(7;16) is markedly lower in SEF than LGFMS.

The presence of *FUS* rearrangement in some sclerosing epithelioid fibrosarcomas and the presence of tumors with hybrid areas suggest that some SEF are LGFMS which have a prominent SEF-like area, similar to our two SEF cases even though no LGFMS-like areas were discerned. However, certainly not all (or even the majority) of SEF are related to LGFMS at least in terms of *FUS* rearrangement.
REFERENCES


