Low-Grade Fibromyxoid Sarcoma

159

Definition

Low-grade fibromyxoid sarcoma (LGFMS) is a malignant soft tissue tumor classified among fibroblastic-myofibroblastic neoplasms. It is also known as Evans tumor.

Epidemiology and Presentation

LGFMS is a very rare tumor with a misleadingly bland histological appearance that typically arises in the deep soft tissues of the proximal extremities (thigh is the most common site) or trunk of young adults (median age, 34 years; range, 3–78 years) with a slight male predominance. It has been rarely described in the retroperitoneum, mediastinum, and superficial acral sites.

The lesion usually presents as a painless mass (2–20 cm in diameter) which can remain undiagnosed for years.

Pathology

The tumor is characterized by an admixture of heavily collagenized hypocellular zones and more cellular myxoid nodules. Short fascicular and characteristic whorling growth patterns are observed. Tumor vasculature is made of arcades of small vessels with perivascular sclerosis. Mitotic figures are rare.

Rarely the lesion is hardly distinguishable from sclerosing epithelioid fibrosarcoma (→ see dedicated section), a likely related neoplasm. Hybrid tumors displaying composite histologic features of LGFMS and sclerosing epithelioid fibrosarcoma have been recently described.

The hyalinizing spindle cell tumor with giant rosettes (HSCTGR), which is now accepted as a subtype of LGFMS, is much more rarely described: the immunohistochemical features and biological behavior of the two neoplasms are identical.

S. Mocellin, *Soft Tissue Tumors*, https://doi.org/10.1007/978-3-030-58710-9_159

Differential diagnosis may be needed with the following: fibromatosis (usually it lacks myxoid areas; fibrous cells are aligned in broad sweeping fascicles; cells appear more like reactive fibroblasts; distinct ectatic vessels are present; diffuse or occasionally focal nuclear beta-catenin staining); fibrosarcoma (no myxoid component; "herringbone" fascicular pattern, a diagnosis of exclusion); myxofibrosarcoma (more myxoid and less fibrous, more nuclear pleomorphism and hyperchromatism in contrast to LGFMS which is almost always bland and monomorphic with little to no pleomorphism; more developed vascular network, tumor cells aggregate around vessels); myxoid neurofibroma (wavy nuclei, background of thick collagen bundles, S100 positive); nodular fasciitis (tissue culture histology, extravasated erythrocytes, myxoid cystic degeneration); and sclerosing epithelioid fibrosarcoma (MUC4 positive like LGFMS but characterized by EWSR1 rearrangements and not by FUS rearrangements).

Biomarkers

MUC4, an epithelial glycoprotein, is constantly expressed by LGFMS. CD99 is frequently expressed (90% of cases). LGFMS stains negative for S100, desmin, cytokeratins, CD34, MDM2, SMA,[1] h-caldesmon, CD117, and nuclear beta-catenin.

The majority of LGFMS cases harbor the **chromosomal translocation** t(7;16)(q34;p11), which results in the formation of the FUS-CREB3L2 fusion gene.[2] A minority of cases have been shown to carry the FUS-CREB3L1 fusion gene resulting from chromosomal translocation t(11;16)(p11;p11).

Though less frequently, the FUS-CREB3L2 fusion gene has been reported also in sclerosing epithelioid fibrosarcoma (→ see dedicated section), which has led to the hypothesis that the two entities are related.

Prognosis

Despite the low-grade histological appearance, LGFMS is a malignant, often late-metastasizing tumor. Disease relapse and metastasis rates are low during the first years of follow-up, but they increase over time (up to >60% and >40%, respectively). No histological feature is known to correlate with prognosis.

[1] SMA: smooth muscle actin.

[2] FUS-CREB3L2 fusion gene: it derives from the fusion of FUS (fused in sarcoma, also known as TLS: translocated in liposarcoma) located on chromosome 16p11 and CREB3L2 (cAMP responsive element-binding protein 3-like 2) located on chromosome 17q33. FUS encodes a multifunctional protein component of the heterogeneous nuclear ribonucleoprotein (hnRNP) complex, which is involved in pre-mRNA splicing and the export of fully processed mRNA to the cytoplasm: this protein belongs to the FET family of RNA-binding proteins which are involved in regulation of gene expression, maintenance of genomic integrity, and mRNA/microRNA processing. CREB3L2 encodes a member of the oasis bZIP transcription factor family.

Therapy

Surgery is the mainstay of treatment.

Suggested Readings

Doyle (2011) MUC4 is a highly sensitive and specific marker for low-grade fibromyxoid sarcoma. Am J Surg Pathol 35(5):733–741

Fletcher (2020) WHO classification of tumours of soft tissue and bone (5th edition)

Lau (2013) EWSR1-CREB3L1 gene fusion: a novel alternative molecular aberration of low-grade fibromyxoid sarcoma. Am J Surg Pathol 37(5):734–738

Linos (2014) MUC 4-negative FUS-CREB3L2 rearranged low-grade fibromyxoid sarcoma. Histopathology 65(5):722–724

Maretty-Nielsen (2013) Low-Grade Fibromyxoid Sarcoma: Incidence, Treatment Strategy of Metastases, and Clinical Significance of the FUS Gene. Sarcoma 2013:256280

Mohamed (2017) Low-grade fibromyxoid sarcoma: clinical, morphologic and genetic features. Ann Diagn Pathol 28:60–67

Prieto-Granada (2015) A genetic dichotomy between pure sclerosing epithelioid fibrosarcoma (SEF) and hybrid SEF/low-grade fibromyxoid sarcoma: a pathologic and molecular study of 18 cases. Genes Chromosomes Cancer 54(1):28–38

Puls (2020) Recurrent fusions between YAP1 and KMT2A in morphologically distinct neoplasms within the spectrum of low-grade fibromyxoid sarcoma and sclerosing epithelioid fibrosarcoma. Am J Surg Pathol 44(5):594–606

Saab-Chalhoub (2019) Low-grade fibromyxoid sarcoma of acral sites: Case report and literature review. J Cutan Pathol 46(4):271–276

Scheer (2020) Low-grade fibromyxoid sarcoma: a report of the Cooperative Weichteilsarkom Studiengruppe (CWS). Pediatr Blood Cancer 67(2):e28009