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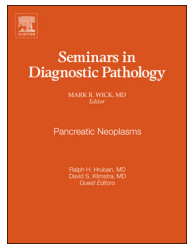


# Soft tissue tumor pathology: New diagnostic immunohistochemical markers

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ABSTRACT

Recent insights into the pathogenesis of various soft tissue tumors, along with the identification of recurrent molecular alterations characteristic of specific tumor types, have resulted in the development of many diagnostically useful immunohistochemical markers. In some cases, expression of these markers is significantly associated with distinctive clinical and histologic features, which may impart prognostic or predictive information. This review outlines new diagnostic immunohistochemical markers in soft tissue tumor pathology, emphasizing their utility in clinical practice and potential pitfalls, molecular correlates and clinical associations.



## Introduction

Over the last 10 years, many novel immunohistochemical markers for use in the evaluation of soft tissue tumors have been described. This has largely been due to new insights into the biology and pathogenesis of this diverse group of tumors, which have been quickly translated into clinically useful diagnostic markers. For example, gene expression profiling studies have identified TLE1, DOG1 and MUC4 as clinically useful markers for synovial sarcoma, gastrointestinal stromal tumor, and low-grade fibromyxoid sarcoma, respectively. Fusion protein products resulting from recurrent translocations are also useful diagnostic markers: STAT6 for solitary fibrous tumor, TFE3 for alveolar soft part sarcoma, and ALK for inflammatory myofibroblastic tumor. Other tumor types harbor molecular alterations that correlate with protein expression, such as tumors characterized by *SMARCB1* (*INI1*) loss, tumors with amplification in the region of chromosome 12q13–15, which generally show overexpression of MDM2 and CDK4 (and occasionally STAT6), tumors with deletion of the *RB1* locus, and post-radiation angiosarcoma which typically shows *MYC* amplification. Finally, so-called lineage specific markers, which tend to show nuclear staining and in general are not strictly specific to a given lineage, have also emerged as useful markers, not only in soft tissue pathology but also in general surgical pathology practice: ERG as a marker of endothelial differentiation and SOX10 for neuroectodermal differentiation.

As expected, some markers prove to be more useful in clinical practice than others, and significant overlap in staining patterns can be seen in different tumor types, which in some cases can be explained by known biologic mechanisms. This review discusses the role of these new immunohistochemical markers in the evaluation of soft tissue lesions, along with their limitations and potential pitfalls.

### *MUC4*

MUC4 (mucin 4) is a transmembrane glycoprotein normally expressed on colonic, breast and pulmonary epithelium. MUC4 is overexpressed or aberrantly expressed in various carcinomas, in particular those arising in pancreaticobiliary

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tract, breast and colon. Gene expression profiling studies of low-grade fibromyxoid sarcoma (LGFMS) identified upregulation of the *MUC4* gene, located on the long arm of chromosome 3 (3q29), in comparison to other soft tissue tumors.[1] MUC4 showed corresponding overexpression at the protein level by immunohistochemistry, and has proven to be an extremely sensitive marker for LGFMS.[2] Expression of MUC4 is detected in more than 99% of LGFMS, with only very rare cases being negative.[3] MUC4 expression in LGFMS is diffuse and cytoplasmic and is usually strong in intensity (Fig. 1). A similar pattern of expression is seen in sclerosing epithelioid fibrosarcoma (SEF), a related fibroblastic neoplasm that shows morphologic and molecular overlap with LGFMS; the overall frequency of expression in SEF appears to be greater than 90% (Fig. 1).[4–7]

MUC4 is especially useful in the evaluation of core biopsies of myxoid spindle cell neoplasms with minimal cytologic atypia, the differential diagnosis of which includes several benign soft tissue tumors, as well as LGFMS, a deceptively bland sarcoma with a significant risk of local recurrence and distant metastasis, often occurring many years after initial diagnosis. Of benign soft tissue tumors, the most common mimics of LGFMS are soft tissue perineurioma and cellular myxoma, both of which are negative for MUC4. Malignant tumors that may enter the differential diagnosis with LGFMS include low-grade myxofibrosarcoma and less commonly low-grade malignant peripheral nerve sheath tumor. Again, both of these tumor types are negative for MUC4; myxofibrosarcoma typically shows at least focal cytologic atypia, greater than that expected in LGFMS.

Expression of MUC4 is limited in other soft tissue tumors. Focal staining may be seen in approximately 20% of epithelioid GIST and 30% of ossifying fibromyxoid tumors.[2] The epithelial component of biphasic synovial sarcoma typically shows diffuse positivity for MUC4, whereas the spindle cell component of biphasic and monophasic types shows scattered positive cells in most cases. This finding likely reflects the epithelial differentiation of this tumor type. Importantly, as mentioned above, MUC4 is overexpressed in many different carcinoma types; this is particularly crucial to remember when evaluating an epithelioid tumor for which sclerosing epithelioid fibrosarcoma and carcinoma are the main diagnostic considerations. In contrast to carcinoma, sclerosing epithelioid fibrosarcoma is negative for cytokeratins; correlation with clinical history is also important in this setting.

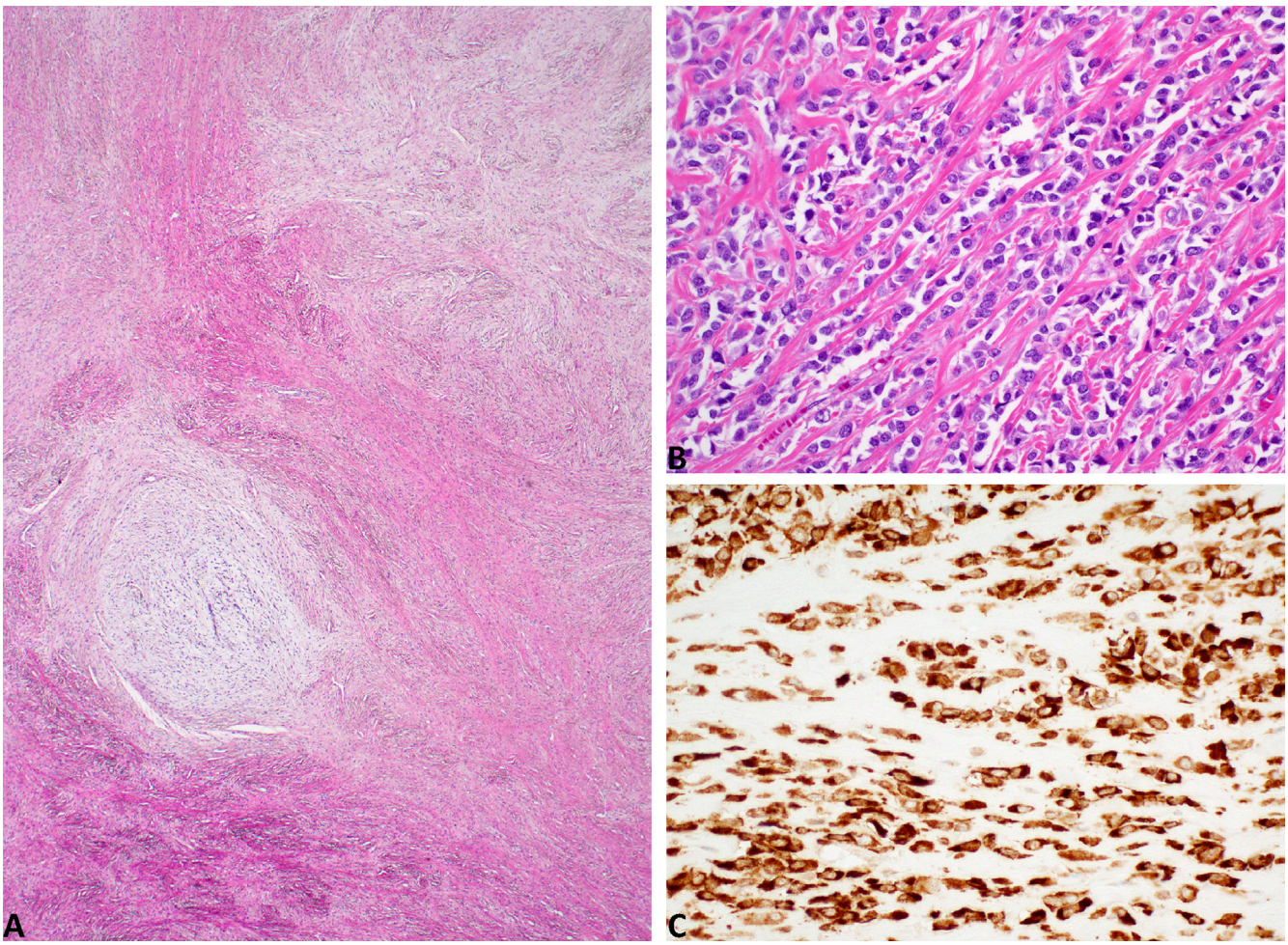


**Fig. 1 – Low-grade fibromyxoid sarcoma (LGFMS) showing characteristic alternating fibrous and myxoid areas (A). The related sclerosing epithelioid fibrosarcoma (SEF) composed of cords of epithelioid cells with pale or clear cytoplasm embedded in a densely sclerotic stroma (B) shows diffuse cytoplasmic expression of MUC4 (C).**