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TLE1 Immunostains in the Diagnosis of Synovial Sarcoma

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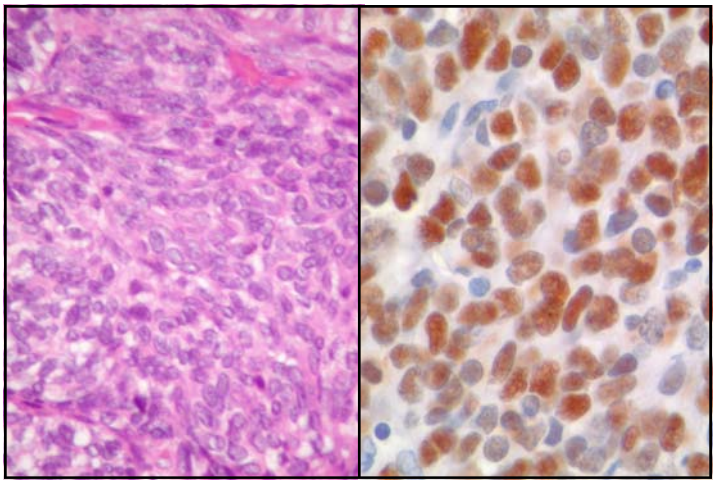
The diagnosis of synovial sarcoma can be a challenging task, particularly on small biopsy specimens, as the morphologic features of this tumor can be mimicked by a variety of other neoplasms. This month we call attention to a paper published in the February 2007 edition of the *American Journal of Surgical Pathology* describing the utility of immunostains for TLE1 in the diagnosis of this tumor. TLE immunostains are now available at ProPath.

Synovial sarcoma occurs in three morphologic varieties: monophasic, biphasic, and poorly differentiated. It has been known for some time that synovial sarcoma is associated with a specific chromosomal translocation, t(X;18), that results in the fusion of the SYT gene on chromosome 18 to either the SSX1 or SSX2 gene on the X chromosome, resulting in the production of a SYT-SSX fusion protein. Identification of this translocation in the appropriate setting is regarded by many to be diagnostic of synovial sarcoma. However, the methodologies used for this purpose (cytogenetics, fluorescent in situ hybridization, and reverse-transcriptase polymerase chain reaction) are not readily available in many diagnostic settings, and a reliable immunohistochemical marker of synovial sarcoma would be highly valued.

A number of gene expression profiling studies of synovial sarcoma have identified overexpression of a number of members of the Transduction-Like Enhancer (TLE) gene family, particularly TLE1. For that reason, the authors of the paper hypothesized that immunostains for TLE1 protein may be helpful in the recognition of synovial sarcoma.



H&E (left) and TLE1 immunostain (right) on a monophasic synovial sarcoma. Note the numerous strongly positive nuclei on the TLE1 immunostain, a typical feature of this tumor.

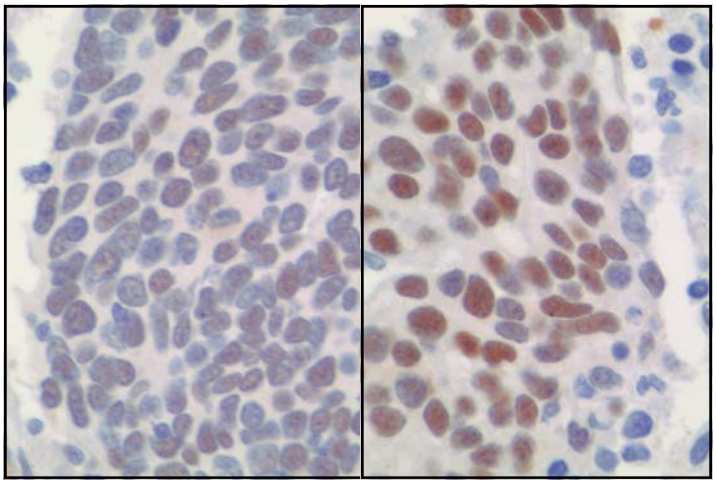
In their study, the authors performed TLE1 immunostains on multiple tissue microarrays using two different antibodies (monoclonal and polyclonal), both performing in a similar fashion. A total of 693 adult soft tissue tumors were examined, including 94 cases of synovial sarcoma that had documentation of the t (X;18) translocation. They regarded a strong (3+) immunostain as one in which >50% of tumor cells showed strong nuclear staining that was apparent with a 4x low-power objective. Moderate (2+) immunostains demonstrated 10-50% of cells with strong nuclear staining apparent on low power, or >50% of cells showing nuclear staining well above background on medium power (10x objective). Weak (1+) immunostains displayed weak to moderate nuclear staining in <50% of tumor cells. Only tumors that demonstrated 2+ or 3+ immunoreactivity were

regarded as "Positive for TLE1", and those that demonstrated 1+ staining or had absent immunostaining were regarded as "Negative for TLE1".

97% (91/94) of the cases of synovial sarcoma were positive for TLE1. The cases of biphasic synovial sarcoma showed staining in both the epithelial and spindle cell elements, and all 4 cases of poorly differentiated synovial sarcoma were positive. The 3 "Negative" synovial sarcomas demonstrated 1+ reactivity, and none of the synovial sarcomas showed completely absent staining.

In contrast, most other spindle cell tumors (including those that may mimic synovial sarcoma) were negative or showed low-level staining. Notable exceptions that were also positive (i.e, showed 2+ or 3+ staining) included 40% (2/5) of hemangiopericytomas, 31% (5/16) of schwannomas, 27% (4/15) of solitary fibrous tumors, 25% (1/4) of fibroxanthomas, 17% (1/6) of cellular schwannomas, 14% (1/7) of carcinosarcomas, 14% (1/7) of clear cell sarcomas, 13% (1/8) of high grade chondrosarcomas, 8% (1/13) of Ewing sarcomas, 6% (2/35) of gastrointestinal stromal tumos (GIST), 5% (4/88) of malignant peripheral nerve sheath tumor (MPNST), and 2% (1/41) of leiomyosarcomas. All other tumors were negative for TLE1 (i.e., absent or 1+ reactivity), including cases of dermatofibrosarcoma protuberans (DFSP), desmoplastic small round cell tumor (DSRCT), malignant fibrous histiocytoma (MFH), endometrial stromal sarcoma, epithelioid sarcoma, fibromatosis, Kaposi's sarcoma, fibrosarcoma, liposarcoma, neurofibroma, perineurioma, rhabdomyosarcoma, and others.

Studies at ProPath employing our multi-tumor sandwich block preparation (that contains over 80 tumors of all different types) also identified TLE1 positivity (i.e.,2+ or 3+) in cases of cutaneous basal cell carcinoma, seminoma, dysgerminoma, breast carcinoma (3/4), breast lactating adenoma, lung adenocarcinoma (2/4), prostate carcinoma (2/2), melanoma, serous carcinoma of ovary (2/3), endometrioid carcinoma of uterus (1/2), clear cell carcinoma of endometrium, squamous carcinoma, and Merkel cell tumor (1/2). From these results, it is apparent that TLE1 immunoreactivity is certainly not specific for synovial sarcoma, and should be included among a panel of markers employed for recognition of this tumor. However, based on the reported results in the microarray study discussed above, there seems little doubt that TLE1 is a valuable marker for the accurate diagnosis of synovial sarcoma, particularly in small specimens and when genetic confirmation is not readily available.



TLE1 immunostains on a lung carcinoma (left) and a high grade ovarian serous carcinoma (right), demonstrating that a positive TLE1 immunostain is not specific for synovial sarcoma, but can be an important marker when used in the appropriate clinical context as part of a battery of additional immunostains.

Reference:

1. Terry J, Saito T, Subramanian S et al: TLE1 as a Diagnostic Immunohistochemical Marker for Synovial Sarcoma Emerging from Gene Expression Profiling Studies. *Am J Surg Pathol 31 (2): 240-246, Feb 2007.*

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