The use of immunohistochemistry as a surrogate marker of specific chromosomal abnormalities has been expanding in the past several years. The utility of the ALK-1 antibody (as a marker of a subset of anaplastic large cell lymphoma and several other tumors) was discussed in this forum in May 2003, and the use of WT1 antibodies in the diagnosis of desmoplastic small round cell tumor represents another example.

This month, we call attention to an article published by Argani and associates (from Johns Hopkins and Memorial Sloan-Kettering) in the June 2003 issue of the American Journal of Surgical Pathology, regarding the use of an immunostain for TFE3 to assist in the identification of alveolar soft part sarcoma and other neoplasms with TFE3 gene fusions.

TFE3 is a gene that has both a leucine zipper dimerization domain and a basic helix-loop-helix DNA binding domain (don’t ask me what this means!). The TFE gene is widely expressed, although the normal gene product is not normally detectable by immunohistochemistry, presumably because of a low degree of expression. Furthermore, transcription factors often have short half lives, which could provide another reason for the difficulty of detecting the gene product by immunohistochemistry in normal cells.

In the case of alveolar soft part sarcoma, the TFE3 gene on chromosome Xp11.2 fuses with the ASPL gene on chromosome 17q25. As a result of this gene fusion, the TFE3 gene is overexpressed, secondary to its abnormal placement under the control of a novel
promoter. The authors of the study hypothesized that the overexpressed TFE3 fusion protein might be detectable in the nuclei of affected cells using immunohistochemistry with an anti-TFE3 antibody.

In the appropriate clinical setting and with the benefit of immunostains, the diagnosis of alveolar soft part sarcoma may not be particularly difficult if a large enough biopsy is obtained. However, as all diagnostic pathologists know, we are being continually asked to do more and more with less and less tissue, so arriving at a specific diagnosis of alveolar soft part sarcoma on a tiny biopsy can be problematic. Fortunately, based on the information in this study, immunostains for TFE3 appear to represent a sensitive and specific marker of alveolar soft part sarcoma.

In the study design, cases were scored as "positive for TFE3", if nuclear reactivity was readily identified on low-power magnification (using a 4x objective). Parenthetically, the authors also noted consistently stronger immunoreactivity at the edges of intact sections than in the center of tumors, an observation confirmed in a case of alveolar soft part sarcoma that we stained at ProPath. Cases that showed weak or equivocal staining at this magnification were regarded as negative.

The authors stained a variety of normal tissues and several groups of tumors. No staining was identified in normal tissues (lung, thyroid, lymph node, breast, colon, liver, gallbladder, pancreas, uterus, ovary, bone, kidney, bladder, adrenal, prostate, and skin) except for weak staining in a few glomeruli and pancreatic acini. Next, they stained 40 tumors that were previously cytogenetically characterized and known to contain the TFE3 gene fusion. As they hypothesized, they found nuclear expression of TFE3 in 19 of 19 alveolar soft part sarcomas. Of 21 additional tumors (renal cell carcinomas) known to contain the TFE3 gene fusion, 20 were positive for TFE3, and the single negative case had been fixed in Bouins fixative (one of my least favorite fixatives for immunohistochemistry). Following this, the authors studied 1476 cases of a wide variety of tumors (sarcomas, carcinomas, melanomas, lymphomas, etc.) in tissue microarrays, and only 6 tumors were positive for TFE3. These included 2 of 60 adrenal cortical carcinomas, 2 of 8 granular cell tumors, 1 of 15 distal common bile duct carcinomas, and 1 of 2 cases of high-grade myxofibrosarcoma (myxoid MFH). Finally, the authors studied 11 "test cases" of pediatric renal tumors that lacked material for molecular characterization. Based on clinical and pathologic findings, they found TFE staining in 7 of the 8 cases that were expected to be positive for TFE gene fusions. The overall sensitivity of positive TFE3 immunostaining for detecting tumors with TFE3 gene fusions was 97.5%, and the specificity was 99.6%.

In addition to its utility in the recognition of alveolar soft part sarcoma, the authors concluded that this marker is also useful in the identification of subsets of renal carcinomas (that tend to arise in children and young adults) that are associated with TFE3 gene fusions, including PRCC-TFE3 renal carcinomas, ASPL-TFE3 renal carcinomas, and PSF-TFE3 renal carcinomas.

TFE3 is now available in the ProPath Immunohistochemistry Laboratory.

References:


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