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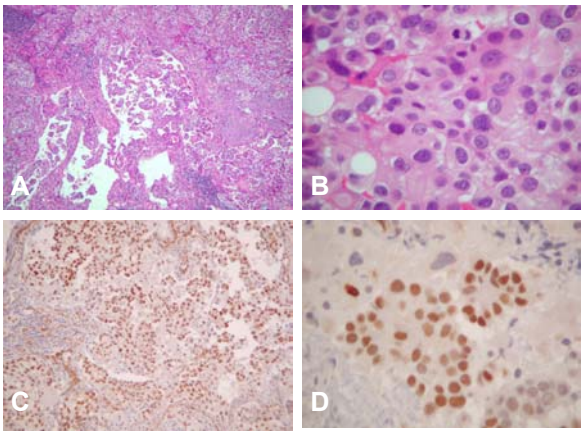
Wilms Tumor Gene Protein (WT1)

Wilms tumor gene (WT1) is a tumor-suppressor gene located at chromosome 11p13 that is involved in Wilms tumor development, and the WT1 gene product has been found to be expressed during the development of the urogenital system. In the past several years, antibodies against the WT1 gene product applicable to formalin-fixed paraffin-embedded tissue have become available, and these antibodies have found utility in diagnostic surgical pathology in several settings. These antibodies may stain both the nuclei and the cytoplasm of cells, but from the standpoint of using this antibody in diagnostic pathology, it is important to evaluate only the presence or absence of nuclear immunoreactivity (similar to estrogen and progesterone receptor antibodies, where any cytoplasmic reactivity should be ignored).

WT1 as a Marker of Mesothelial Cells and Mesotheliomas

A number of recent studies have shown that nuclear reactivity with WT1 can be of great utility in the diagnosis of malignant mesothelioma. Our experience with this marker at ProPath is similar to that reported in the literature, and we have found WT1 to be an extremely useful reagent for the recognition of mesothelioma. (The two "positive" mesothelioma markers that we always order in potential mesothelioma cases include calretinin and WT1, which in our experience have been superior to cytokeratin 5/6, N-cadherin, and thrombomodulin as "positive" markers of mesothelioma). WT1 also shows nuclear staining of benign and reactive mesothelial cells, and we have also observed nuclear staining in reactive submesothelial fibroblasts in some cases of reactive pleuritis. In a male patient, significant nuclear expression of WT1 in a malignant epithelial tumor provides strong supportive evidence for mesothelioma, as we are not aware of strong nuclear expression of this marker in other types of epithelial tumors occurring in male patients. In the case of female patients however, it must be kept in mind that certain female genital tract adenocarcinomas also characteristically express strong nuclear WT1 (discussed below). Indeed, we have seen a number of cases of WT1-positive primary serous adenocarcinomas of the female genital tract presenting as pleural effusions, but if an appropriate panel of antibodies is applied to the pleural fluid material, it is very easy to distinguish serous adenocarcinoma from mesothelioma.

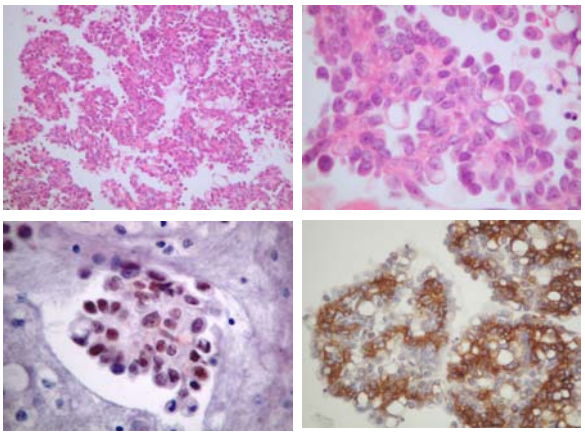


Unusual case of pleural mesothelioma presenting as a cervical lymph node metastasis in a 49 year old male. H&E stains (A&B showed a malignant epithelial tumor, originally diagnosed as adenocarcinoma. Immunophenoptyping at ProPath revealed mesothelioma, with strong expression of WT-1 (C&D). Subsequent workup revealed primary pleural mesothelioma.

WT1 as a Marker of Serous Adenocarcinomas of Female Genital Tract

Serous carcinomas of the ovary (and surface serous carcinomas of the peritoneum) have also been found

to characteristically express nuclear WT1 in a high percentage of cases. Not surprisingly, uterine serous carcinomas also show expression of nuclear WT1. In some cases, endometrioid and clear cell carcinomas may express this marker, although they generally do so in a very focal fashion, in contrast to the characteristically widespread expression in serous tumors. Ovarian mucinous carcinomas are negative for WT1. Since WT1 reactivity has not been described in significant numbers of pancreaticobiliary or GI tract adenocarcinomas, WT1 can be a useful marker to distinguish serous carcinomas from those tumors. At ProPath, we have also observed nuclear reactivity with WT1 in a number of other female genital tract tumors and tissues, including normal endometrial stroma and endometrial stromal sarcomas, normal uterine smooth muscle cells and uterine leiomyosarcomas, granulosa cell tumors, thecomas, and mixed mullerian tumors (in both the epithelial and stromal elements). Nuclear expression of WT1 is also described in fallopian tube epithelium, but not in normal endocervical or endometrial glandular epithelium.



50 year old female who presented with pleural thickening underwent removal of pleural fluid, revealing a malignant epithelial tumor (A&B, H&E stains). The WT1 stain (C) was strongly positive, and Ber-Ep4 was also strongly positive (rendering mesothelioma very unlikely). Based on the strong WT1, a diagnosis of metastatic papillary serous adenocarcinoma was rendered, and the patient was subsequently found to have primary ovarian serous adenocarcinoma.

WT1 in Other Tumors and Tissues

A number of investigators have also identified expression of nuclear WT1 in desmoplastic small round cell tumor (88% of cases in one series), although some authors report that the 6F-H2 clone does not mark these tumors. As might be expected, nuclear reactivity with WT1 is also been reported in a significant number of Wilms tumors of the kidney. In contrast, WT1 is characteristically negative in Ewings sarcoma / primitive neuroectodermal tumor, so WT1 can be a useful marker in the differential diagnosis of these "small blue cell tumors". Metanephric adenoma has also been reported to express nuclear WT1, as well as some types of leukemia. We have also observed strong staining of glomerular epithelial cells, and WT1 showed focal positivity in one case of eccrine carcinoma that we recently studied at ProPath.

REFERENCES:

Foster MR et al: Immunohistochemical Analysis of Nuclear vs. Cytoplasmic Staining of WT1 in Malignant Mesotheliomas and Primary Pulmonary Adenocarcinomas. Arch Pathol Lab Med 125 (10): 1316-1320, 2001.

Oates J et al: HBME-1, MOC-31, WT1 and Calretinin: An Assessment of Recently Described Markers for Mesothelioma and Adenocarcinoma. Histopathology 36 (4): 341-7, 2000.

Goldstein NS et al: WT1 is an Integral Component of an Antibody Panel to Distinguish Pancreaticobiliary and Some Ovarian Epithelial Neoplasms. Am J Clin Pathol 116 (2):246-52, 2001.

Shimizu M et al: Immunohistochemical Detection of the Wilms Tumor Gene (WT1) in Epithelial Ovarian Tumors. Int J Gynecol Pathol 19 (2): 158-163, 2000.

Yaziji H et al: Immunohistochemical Analysis of Gynecologic Tumors. Int J Gynecol Pathol 20: 64-78, 2001

Hill DA et al: WT1 Staining Reliably Differentiates Desmoplastic Small Round Cell Tumor from Ewings Sarcoma /Primitive Neuroectodermal Tumor. An Immunohistochemical and Molecular Diagnostic Study. Am J Clin Pathol 114 (3):345-53, 2000.

Barnoud R et al: Immunohistochemical Expression of WT1 by Desmoplastic Small Round Cell Tumor: A Comparative Study with Other Small Round Cell Tumors. Am J Surg Pathol 24 (6):836, 2000.

Barnoud R et al: Desmoplastic Small Round Cell Tumor: RT-PCR Analysis and Immunohistochemical Detection of the Wilms Tumor Gene WT1. Pathol Res Pract 194 (10):693-700, 1998.

Ordonez NG: Desmoplastic Small Round Cell Tumor: II: An Ultrastructural and Immunohistochemical Study with Emphasis on New Immunohistochemical Markers. Am J Surg Pathol 22 (11):1314-1327, 1998.

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