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Immunohistochemical markers of prostate carcinoma, including prostate-specific membrane antigen (PSMA).

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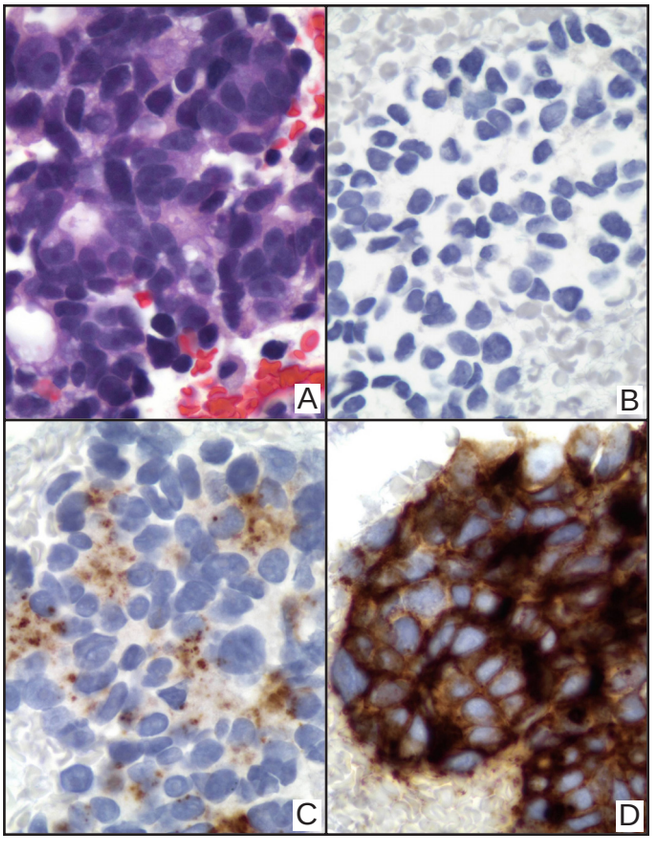
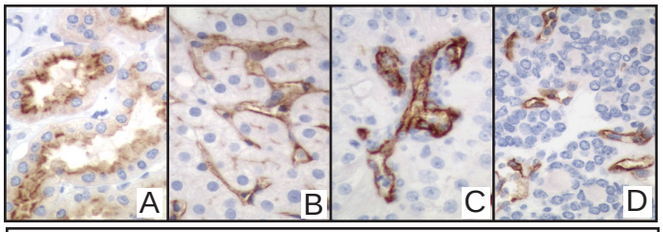
Because of morphologic overlap between prostate carcinoma and other carcinomas, immunostains may be needed to correctly identifiy the primary site. This month, we review commonly-used markers of prostate carcinoma, and discuss our newest marker prostate specific membrane antigen (PSMA).

Antibodies to **prostate specific antigen** (**PSA**) have been around for a long time. PSA has excellent specificity for prostate carcinoma. However, its sensitivity is not perfect, as a small but significant percentage of prostate carcinomas lack this marker (roughly 9% according to some studies), a finding that is more common in high-grade tumors. Since these are often the most difficult to morphologically distinguish from carcinomas of other primary sites, PSA occasionally fails us as a marker of prostate carcinoma. There are a few other tumors and normal structures that may express PSA, including breast carcinoma (~9% according to one study), some salivary gland tumors (particularly mixed tumors and salivary duct carcinoma, the latter sometimes presenting with metastatic disease), anal glands in males, urethral glands, urachal remnants, areas of cystitis cystica or cystitis glandularis, and Cowper's glands. PSA has also been reported in 36% of nephrogenic adenomas of the prostatic urethra. Rare carcinomas arising from the posterior urethral glands (Skene's glands) in females express PSA (as well as prostatic acid phosphatase), and there are reports of PSA reactivity in villous adenoma and adenocarcinoma of the bladder, as well as Paget's disease involving the male external genitalia.

Prostate-specific acid phosphatase (**PSAP**, also known as prostatic acid phosphatase) has also been available as a marker of prostate carcinoma for many years. In my experience it is more sensitive than PSA, particularly in poorly differentiated prostatic carcinomas. PSAP has also been described in the same normal structures and extra-prostatic tumors as PSA, except that PSAP is negative in breast cancer. Additionally (and in contrast to PSAP), PSAP is



H&E (A) of a needle biopsy from a bone lesion in a patient with a history of prostate carcinoma. The PSA immunostain performed in the original laboratory was negative (B), so the case was referred to ProPath for additional immunostains. These showed that the tumor cells were positive for PSAP (C) and intensely positive for PSMA (D).



PSMA staining of kidney tubules (A), liver sinusoids (B), and neovasculature in renal cell carcinoma (C) and thyroid follicular adenoma (D).

positive in many rectal carcinoid tumors. This is an important point to keep in mind, since some carcinoid tumors may mimic prostate adenocarcinoma very closely. However, rectal carcinoid tumors are easily distinguished from prostate carcinoma by carcinoid's strong expresion of chromogranin and/or synaptophysin, as well as the lack of PSA in rectal carcinoids. Interestingly, PSAP has also been touted as a marker of intravascular large B-cell lymphoma.

Because of the suboptimal sensitivity of PSA when used alone as a marker of prostate carcinoma, I always order both PSA and PSAP in cases where metastatic prostate carcinoma is a reasonable diagnostic consideration. Nevertheless, some authors report that 5% of high-grade prostate carcinomas lack both of these antigens, and others report that treatment of prostate carcinoma may be associated with loss of immunoreactivity to these markers in some cases. In these situations, the newly commercially-available marker **prostate specific membrane antigen** (**PSMA**) may be particularly helpful, since it has been shown to be positive in many prostate carcinomas that are negative for other prostate markers. PSMA is a transmembrane glycoprotein that functions as a folate hydrolase. It is expressed at low levels in benign prostate epithelium, but shows marked upregulation in prostate malignancies. The degree of expression of this marker seems to be inversely correlated with the degree of differentiation of the tumor. As such, high-grade prostate carcinomas tend to express this marker in a very high percentage of tumor cells, whereas lower grade tumors show more heterogeneous expression. Expression of PSMA has also been reported in the brain (weak), salivary gland, subpopulation of proximal kidney tubules, duodenal mucosa, and a subpopulation of neuroendocrine cells in colonic mucosa. Interestingly, normal endothelial cells reportedly do not express PSMA (although I have personally seen PSMA staining of benign liver sinusoids), but neovasculature of many different types of tumors expresses PSMA.

In summary, immunostains for PSA will miss a small but significant percentage of prostate carcinomas, and these tumors may often be recognized by employing additional immunostains for PSAP and/or PSMA. PSMA is particularly valuable for identifying poorly differentiated prostate carcinomas that do not express PSA and PSAP. Finally, as with all other immunohistochemical markers, it is important to be aware of the spectrum of normal and abnormal tissues that are expected to stain with these reagents, to avoid diagnostic pitfalls and potential misdiagnoses.

PSA and PSAP have been available for many years at ProPath, and we now offer immunostains for PSMA.

References:

1. Murphy GP et al: Current evaluation of the tissue localization and diagnostic utility of prostate specific membrane antigen. Cancer 83 (11): 2259-2269, Dec 1, 1998.
2. Chang SS et al: Comparison of anti-prostate-specific membrane antigen antibodies and other immunomarkers in metastatic prostate carcinoma. Urology 57(6): 1179-1113, Jun 2001.
3. Silver DA et al: Prostate-specific membrane antigen expression in normal and malignant human tissues. Clin Cancer Res 3(1): 81-85, Jan 1997.
4. Ross JS et al: Prostate specific membrane antigen (PSMA) expression in non-prostate cancers. Mod Pathol 17 (Supplement 1): 326A (abstract 1373), Jan 2004.
5. Seki K et al: Prostatic acid phosphatase is a possible tumor marker for intravascular large B-cell lymphoma. Am J Surg Pathol 28(10): 1384-1388, Oct 2004.
6. Fan CY et al: Expression of androgen receptor and prostatic specific markers in salivary duct carcinoma: an immunohistochemical analysis of 13 cases and review of the literature. Am J Surg Pathol 24(4): 579-586, Apr 2000.
7. Dabbs DJ (editor) Diagnostic immunohistochemistry, Churchill-Livingstone, Philadelphia, 2002, pages 407-409.

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