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Poorly Differentiated Prostate Adenocarcinoma Vs. Urothelial Carcinoma

On many occasions, the distinction of prostate adenocarcinoma from urothelial carcinoma (transitional cell carcinoma) of bladder origin is readily made on standard H&E examination. However, when prostate or bladder tumors are poorly differentiated, it may be difficult to confidently distinguish between these two tumors, particularly in small needle biopsy specimens or in tissue fragments that show thermal artifact. In these situations, knowledge of the expected immunophenotype of poorly differentiated urothelial carcinoma and poorly differentiated prostate adenocarcinoma can be very useful in determining the definitive primary site of origin, a task that may have significant therapeutic implications.

Prostate-Related Markers

Prostate Specific Antigen (PSA) and **Prostatic Acid Phosphatase (PSAP)** are well-known to all surgical pathologists, and expression of these markers in the appropriate clinical context provides strong support for a prostatic primary origin. Non-prostatic tissues or tumors that may express PSA include breast carcinoma, anal glands in males, urethral glands, cystitis cystica/glandularis, some salivary gland tumors (particularly mixed tumor and salivary duct carcinoma), and a minority of nephrogenic adenomas of the prostatic urethra. Non-prostatic tissues or tumors that have been reported to show reactivity with PSAP include the list above, as well as rectal carcinoids, some bladder adenocarcinomas, sweat glands, rare renal cell carcinomas, and islet cell tumors. It is estimated that about 5% of high-grade prostate carcinomas may be negative with both PSA and PSAP, and expression of these markers may be focal in nature. Therefore, the absence of these

markers does not completely exclude a prostatic origin. At the recent United States and Canadian Academy of Pathology International Society of Urological Pathology companion meeting in Atlanta, Dr. Mark Wick also described the use of a new prostate marker called **Prostate-Specific Membrane Antigen (PSMA)**, that is expressed in >85% of prostate carcinomas. Unlike PSA and PSAP, this marker has not been reported in salivary or breast carcinomas. Dr. Wick noted that endothelial cells within tumors may express PSMA, so it is important to not misinterpret that finding as a reflection of true prostatic origin.

Use of Cytokeratin antibodies

High Molecular Weight Cytokeratin

(Cytokeratin HMW) (34bE12) is only rarely expressed in prostate adenocarcinoma, yet is expressed very frequently in urothelial carcinoma, even when the tumors are poorly differentiated. Therefore, identification of strong reactivity with this reagent supports a urothelial origin. The same can be said for **Cytokeratin 7**, which is frequently expressed in urothelial carcinoma, but only rarely expressed in prostate adenocarcinoma. **Cytokeratin 20** is expressed in roughly 50% of urothelial carcinomas, but a minority of prostatic adenocarcinomas are also reported to show reactivity with cytokeratin 20, so according to some authors, cytokeratin 20 is useful in this situation only when it is coexpressed with cytokeratin 7 (which favors a urothelial origin). Some authors have also advocated the use of **Cytokeratin 17**, and report that a very high percentage of urothelial carcinomas are positive with cytokeratin 17, but only 6% of prostate carcinomas express this marker.

Miscellaneous markers

Thrombomodulin is expressed in a significant percentage of urothelial carcinomas. Some authors report that up to 91% of transitional cell carcinomas express this marker, although in our laboratory I would estimate that perhaps 50% of urothelial carcinomas are positive for thrombomodulin. This marker is not expressed in prostatic adenocarcinoma, so it can be of utility in distinguishing prostate adenocarcinoma from urothelial carcinoma. Strong expression of **monoclonal CEA** also favors urothelial carcinoma, although focal expression may be observed in a proportion of prostate adenocarcinomas. **CD57 (Leu 7)** is expressed

in a high percentage of prostate adenocarcinomas, even when they are poorly differentiated. This marker is expressed uncommonly in urothelial carcinoma, although we have observed scattered positive tumor cells in a number of cases of poorly differentiated urothelial carcinoma. Prostate carcinomas often expressed **Androgen Receptors**, although at this point there have been insufficient numbers of cases of urothelial carcinoma studied to know whether or not androgen receptors would be a useful antibody in this differential diagnosis

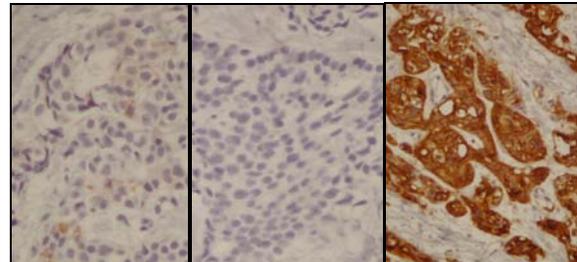
The information is provided in tabular form below:

	PSA/PSAP	CK-hmw	CK7	CK20	CK17	T-Mod	CEAm	CD57 (Leu 7)
Prostate Adenoca	+(few -)	-(foc +)	-(foc +)	-(foc +)	-(6%+)	-	-(foc +)	+(few-)
Urothelial Ca	-	+(few -)	+(rare -)	+/-	+(few-)	+/-	+(60-90%)	-(foc +)

KEY: + (few -) = Large majority of cases positive, a few negative cases may be seen
 - (foc +) = Largely negative, but scattered positive tumor cells may be seen
 +/- = Tumor may be either positive or negative
 + (rare-) = Tumor positive, but rare negative cases may be encountered

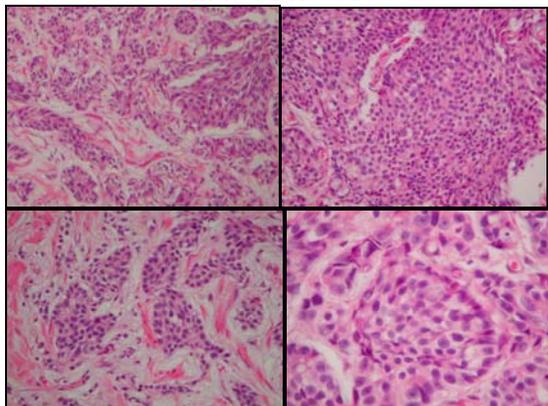
Approach to an individual case

The above information is certainly not meant to imply that all of the above antibodies need to be applied in a particular case. My usual "first-line" panel antibodies includes PSA, PSAP, cytokeratin HMW, and sometimes cytokeratin 7 or CD57. Often, a definitive diagnosis can be rendered with these initial antibodies, but if needed, additional markers as suggested above can then be used.



The PSA and PSAP stains revealed only focal weak reactivity, which was not very convincing (left panel). Immunostains for cytokeratin HMW and cytokeratin 7 were negative (middle panel), but the tumor cells showed strong diffuse expression of CD57 (Leu 7) (right panel), providing strong support for the interpretation of poorly differentiated prostatic adenocarcinoma.

Illustrative case



H&E sections tissue from the bladder neck obtained by TUR. It was not clear clinically or from H&E whether this tumor was of prostatic or urothelial origin.

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