Coordinate Expression of Cytokeratins 7 and 20 and Other Immunohistochemical Markers in Prostate Adenocarcinoma and Bladder Urothelial Carcinoma

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Abstract

Background:

Morphologic features alone can usually be used to distinguish prostatic adenocarcinoma and urothelial carcinoma of the urinary bladder. Poorly differentiated tumors, however, can occasionally have features of both neoplasms, making determination of site oforigin difficult. Immunohistochemical studies were performed using the following panel of antibodies: cytokeratin (CK) 7, CK 20, 34bE12 , p53, prostate-specific acid phosphatase (PSAP), and prostate-specific antigen (PSA) and evaluated their usefulness for distinguishing high-grade forms of these tumors.

Methods:

We examined prostate adenocarcinoma in 50 radical prostatectomy specimens , and urothelial carcinoma of the bladder in 25 cystectomy specimens. immunohistochemically stained by the avidin-biotin complex technique with specific monoclonal antibodies for CK-7, CK-20, 34bE12, prostate-specific acid phosphatase (PSAP), prostate-specific antigen (PSA), and P53 was performed on paraffin sections.

Results:

For prostate adenocarcinoma, 2 cases had CK-7 positivity, 3 had CK-20 focal positivity, 1 stained for both markers, and 44 were negative for both. PSA, and PSAP were positive in all but 1 poorly differentiated prostatic carcinoma. One case was positive for P53, and two cases were positive for 34bE12. For the urothelial tumors, CK-7 was positive marker in 23 cases, and CK-20 in 14 case; 14 cases were positive for both, and 3 cases were negative for both. All urothelial carcinomas were PSA, and PSAP negative. Ten cases were positive for P53, and twenty cases positive for 34bE12.

Conclusions:

A positive stain with PSA or PSAP confirms the diagnosis of prostate carcinoma. Currently, there are no markers entirely specific for urothelial carcinoma and CK-7 and CK-20 are not useful for distinguishing prostate cancer from urothelial carcinoma if each is used alone. However, if both CKs are used in conjunction, they are most helpful for ruling out prostate cancer if they are both positive, as it is extremely rare for both CKs to be expressed in adenocarcinoma of the prostate. A positive reaction with 34bE12, CK 7, or p53 also can support the diagnosis of urothelial carcinoma.

Key Words: Cytokeratin; Prostate adenocarcinoma; Urothelial carcinoma; Prostate-specific antigen; PSA; CK-7; CK-20, 34bE12 , p53, prostate-specific acid phosphatase (PSAP).

INTRODUCTION

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 benefit.

Carcinoma of the prostate is the most common

internal malignancy among men in the United States and is responsible for 10% of cancer deaths in this population [(1)].

Bladder carcinoma is the fourth and 12th most commonly-diagnosed malignancy in men and women, respectively[(2).]

Both neoplasms usually are found in patients older than 50 years; in a subset of patients, both neoplasms occur synchronously or metachronously. Indeed, for patients who undergo cystoprostatectomy for urothelial carcinoma of the bladder, the reported incidence of concurrent prostatic adenocarcinoma is reported to be from 46 to 70% [(3-5)]. We frequently encounter patients with bladder neck tumors that clinically and pathologically are not clearly urothelial carcinoma or prostatic adenocarcinoma. Cystoscopy typically reveals a mass at the bladder neck, whereas the remainder of the bladder is unremarkable. Biopsies show a tumor that is often high grade and has morphologic features of both urothelial carcinoma and prostatic adenocarcinoma.

AIM OF THE STUDY

The purpose of this study was to compare the immunohistochemical (IHC) profile of prostatic adenocarcinoma with that of urothelial carcinoma.

MATERIALS AND METHODS

In this study we examine 75 cases of bladder and prostate carcinoma from Al- Emam Al-Hussein teaching hospital, Al- kademyia teaching hospital, AL-Hayat privet hospital in Al- Hilla. The period of study lasting one year from Augest 2011 till Augest 2012. We studied prostatic adenocarcinoma in 50 radical prostatectomy specimens. The Gleason scores ranged from 5 to 10 as follows: 5, 5 cases; 6, 14 cases; 7, 28 cases; 8, 9, and 10, 1 case each (chart 1). Organ-confined (pT2) tumors were found in 11 (22%) of the cases, and 39 (78%) of the tumors were pT3 (extraprostatic extension and/or seminal vesicle invasion). We also studied urothelial carcinoma of the bladder in 25 radical cystectomy specimens. These cases were graded according to the World Health Organization/International Society of Urological Pathology Consensus Classification of Urothelial Neoplasms of the Urinary Bladder: papillary urothelial neoplasm of low malignant potential, 3 cases; Low grade papillary urothelial carcinoma, 7 cases; and high-grade papillary urothelial carcinoma, 15 cases (chart2). Of the high-grade carcinomas, 4 were confined to the bladder, and 11 cases had tumor invading into the prostate stroma, prostatic ducts, or rectal wall. All specimens were formalin-fixed, paraffin embedded, and subsequently immunohistochemically stained by the avidin-biotin complex technique with specific monoclonal antibodies for CK-7, CK-20, 34bE12, prostate-specific acid phosphatase (PSAP), prostate-specific antigen (PSA). The IHC reactions were scored as positive for any percentage of cell reactivity. The p53 stains was scored differently, at least 20% of the tumor cell nuclei had to stain to be considered positive. Statistical analyses were performed using Fisher's Exact Test. All comparisons were made at a significance level of P, 0.05.

RESULTS

CK-7

CK-7 stained positive in 46 (92%) of 50 of the benign atrophic prostate glands and in some basal and secretory cells in benign prostatic acini. The lining epithelium of the prostatic urethra and seminal vesicles also was stained positively. CK-7 stained intensely in benign urothelium in 10 (40%) of the 25 cases. Prostate adenocarcinoma was positive for CK-7 in 2 (4%) of 50 cases one of them was Gleason score 4 and the other was Gleason score 6, fig (1). Interestingly, some entrapped atrophic prostate glands were intensely stained in a background of negatively stained malignant acini. In urothelial carcinoma, 23 (92%) of 25 cases stained intensely positive for CK-7. The staining was positive in 100% of the cases of low malignant potential and low-grade urothelial carcinoma, out of 15 high grade malignant potential were stained positive {3 (75%) of 4 organ-confined high-grade, and 9 (81.1%) of 11 high grade tumors that had invasion to adjacent structures}chart3. In the latter cases, the staining highlighted the foci of urothelial carcinoma that extended into the prostatic ducts and invaded the prostate stroma. The difference in CK-7 staining between prostate and urothelial carcinomas was statistically significant ($P < .0001$) table (1).

CK-20

CK-20 was rarely positive in benign prostatic acini (1/50 [2%]). Focal positive staining was observed in 3 (6%) of 50 prostate adenocarcinomas fig (2). CK-20 expression had no association with pathologic tumor stage.

Interestingly, all of these cases had a Gleason score of 7 or more. On the other hand, CK-20-positive staining was found in 14 (56%) of 25 urothelial carcinomas fig (3). This CK-20 expression was observed across all grades: 2 (66%) of 3 low malignant potential, 5 (71.4%) of 7 low-grade, and 7 (46.6%) of high grade tumors {3 (75%) of 4 high-grade (organ-confined), and 4 (36.3%) of 11 high-grade tumors that invaded adjacent structures}chart4. In most of these cases, the whole thickness of the urothelium was moderately to intensely stained, and the urothelial carcinoma that invaded the prostatic ducts was variably positive. The difference in CK-20 staining between prostate and urothelial carcinomas was statistically significant ($P = .0012$) table (1) .

CK-7 and CK-20 Coexpression

For coexpression of CK-7 and CK-20, only 1 case (2%) of 50 prostate tumors stained positive for both markers, and this expression was observed only focally. 14 (66.66%) of 25 cases of urothelial carcinoma were positive for both CK-7 and CK- 20. These were 2 (66.66%) of 3 cases of low malignant potential, 5 (71.4%) of 7 low-grade cases, 3 (75%) of 4 organ-

confined high-grade cases, 4 (36.36%) of 11 high grade cases with prostate invasion. Finally, 12% (3/25) of urothelial carcinomas versus 88% (44/50) of prostate tumors were negative for both markers. The differences were statistically significant (P <.0001) table (2).

P53

It is expressed in 10 cases (40%) of urothelial carcinomas fig (4), distributed in all grades. Only one case (2%) of prostatic adenocarcinoma was positive to P53 this was of gleason grade 7 table (1).

PSA and PSAP

Forty nine cases (98%) of prostatic adenocarcinoma were positive for PSA, only one case was negative which was Gleason grade 7. Also 49 cases (98%) were positive for PSAP which was Gleason grade 8 fig (5) table (1). Both markers were negative in urothelial carcinoma.

34bE12

34bE12 expressed in twenty cases (80%) of urothelial carcinoma. Two of negative cases were of low grade papillary carcinoma, and three were of high grade papillary carcinoma. On the other hand it was expressed only in two cases (4%) of prostatic carcinoma fig (6) table (1).

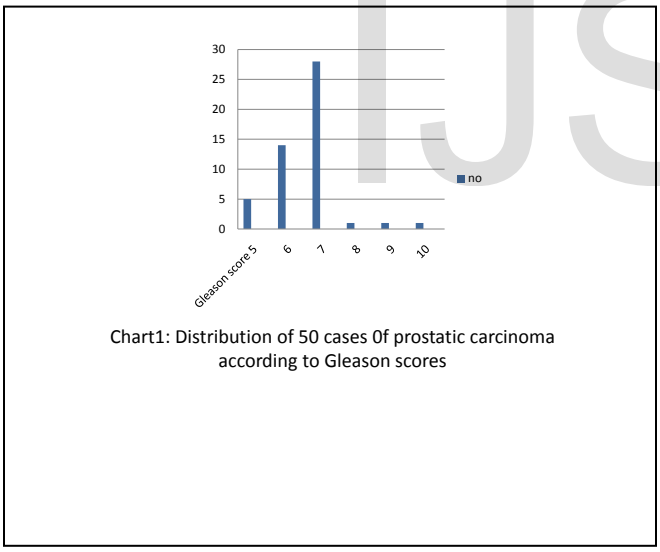


Chart1: Distribution of 50 cases 0f prostatic carcinoma according to Gleason scores

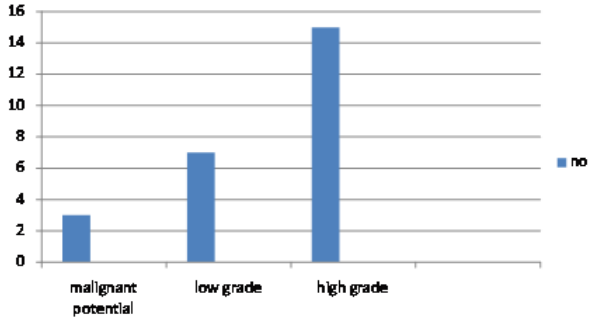


Chart2: Distribution of 25 cases of urothelial carcinoma according to WHO classification

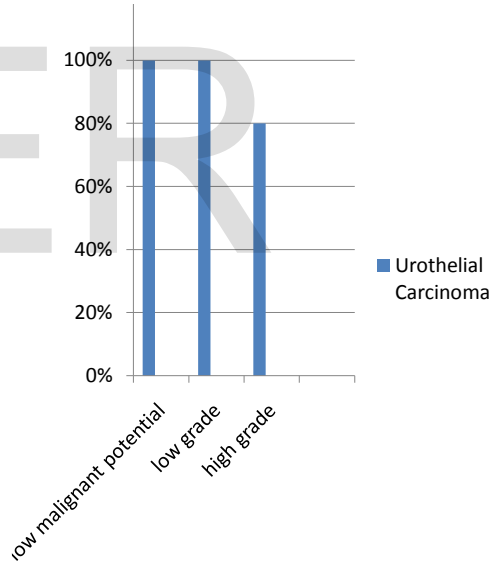


Chart3: percentage of CK7 of 25 cases of papillary urothelial carcinoma according to grade.

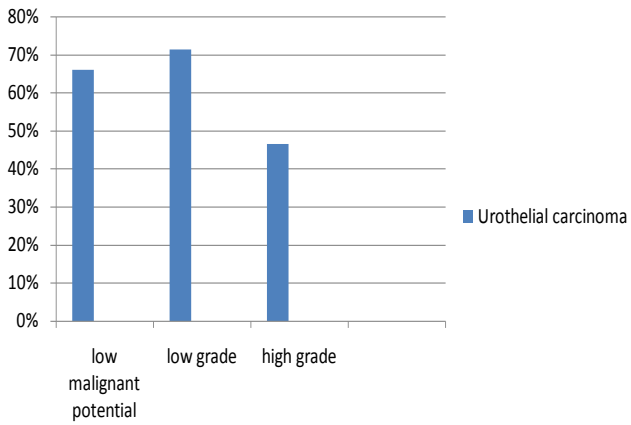
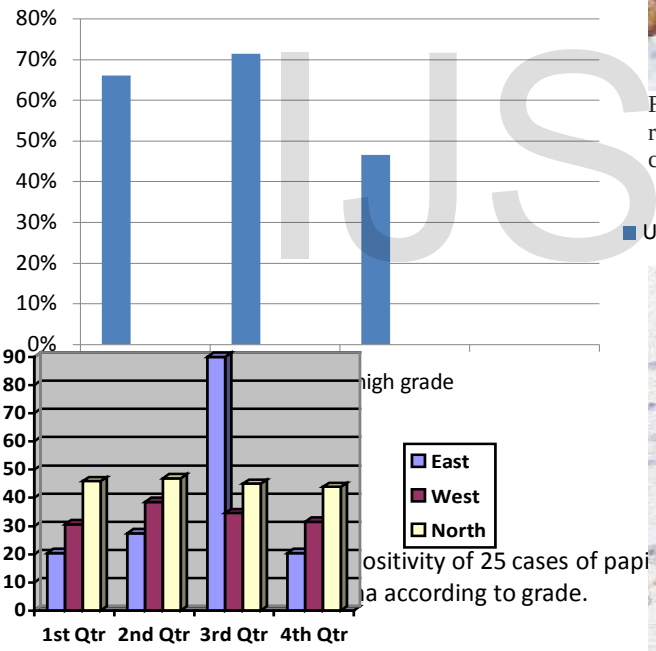


Chart4: Percentage 0f CK20 positivity of 25 cases of papillary urothelial carcinoma according to grade.



ositivity of 25 cases of papi
a according to grade.

	Both Positive	CK-7 positive	CK- 20 positive	Both Negative
prostate(n=50)	1(2%)	2(4%)	3(6%)	44(88%)
bladder(n=25)	14(56%)	23(92%)	14(56%)	3(12%)

Table 2: CK-7 and CK-20 Immunostaining in Prostate and Bladder Carcinomas.

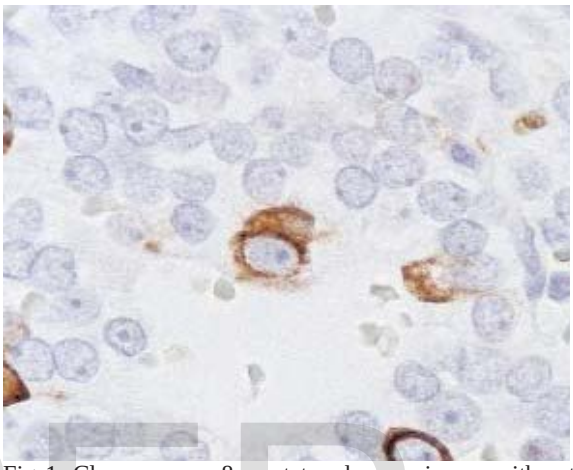


Fig 1. Gleason score 8 prostate adenocarcinoma with cytokeratin 7 reactivity. Individual cells are reactive for cytokeratin 7.

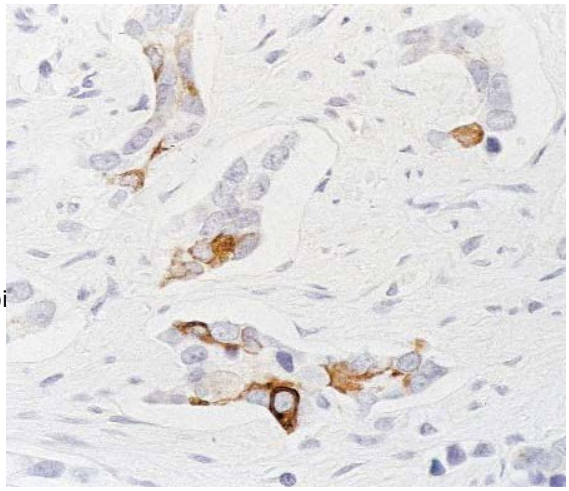


Fig 2. Gleason score 7 prostate adenocarcinoma with cytokeratin 20 reactivity .

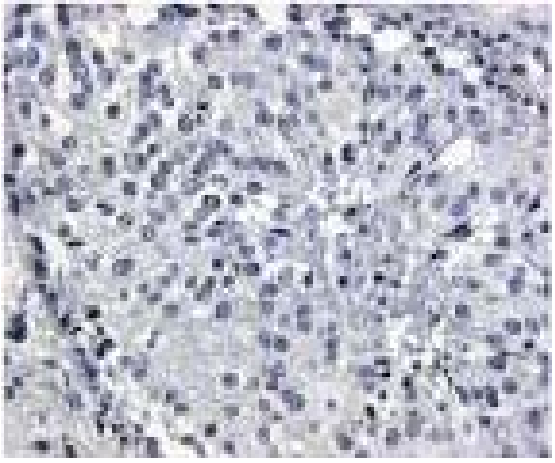


Fig 3. High-grade urothelial carcinoma extending into the prostatic ducts with focal CK-20–positive staining in the malignant cells .

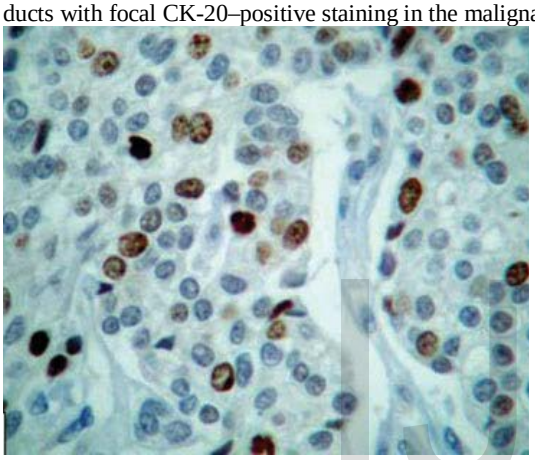


Fig 4. High-grade urothelial carcinoma with P53- positive nuclear staining.

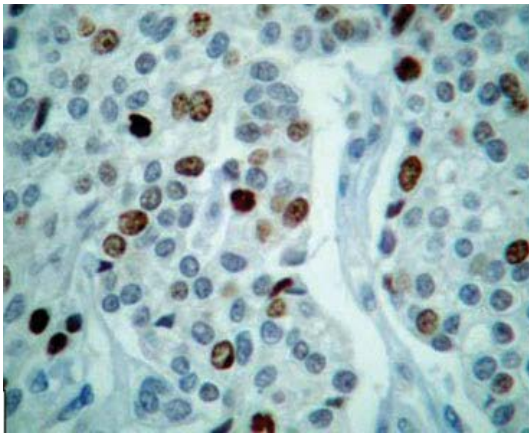


Fig 4. High-grade urothelial carcinoma with P53- positive nuclear staining.

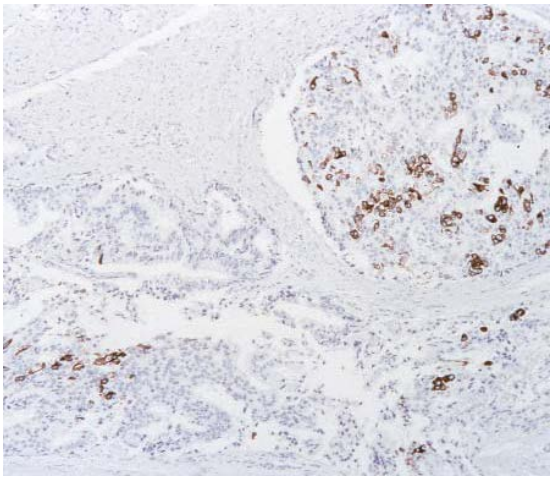


Fig 5. Prostatic carcinoma with PSAP reactivity.

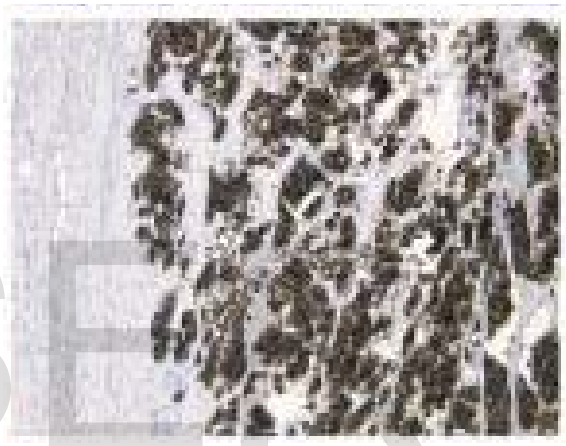


Fig 6. High-grade urothelial carcinoma with 34bE12- positive staining.

DISCUSSION

Determination of the site of origin of poorly differentiated carcinomas of the prostate and bladder, especially in the area of the bladder neck, using only H&E-stained sections continues to be a challenging diagnosis for pathologists. The differential diagnosis is poorly differentiated adenocarcinoma of the prostate involving the bladder neck vs high-grade urothelial carcinoma of the bladder with prostatic extension. Often these high-grade tumors have overlapping morphologic characteristics and, thus, can be difficult to identify correctly. This can have considerable consequences, as these tumors are treated differently.

The biggest problem with the use of immunohistochemistry in this differential diagnosis is that while PSA is a reliable marker for tumors of prostatic origin, there is no reliable positive marker for urothelial tumors. CK-7 and CK-20 have been reported to have predictable patterns of distribution in prostate adenocarcinoma and urothelial carcinoma.(6,7,8).

Our objectives in the present study were to examine the coordinate expression patterns of CK-7 and CK-20 in the spectrum of urothelial and prostate carcinomas and to determine

their usefulness for diagnosing these tumors. In addition, we also compared the contribution of CK-7 and CK-20 coexpression with PSA,PSAP, P53, and 34bE12 staining for distinguishing between the 2 cancers.

CK-7 was observed in 92% and 2% of bladder and prostate cancer cases, respectively. Similarly, the majority(56%) of urothelial carcinomas were positive for CK-20, in contrast with a small minority of prostate cancer cases (2%). These differences obviously are significant; however, making a diagnosis based on the expression patterns of the 2 CKs alone is not feasible, as CK-7 or CK-20 expression can be seen in prostate and urothelial carcinomas. When we examined coordinate expression of CK-7 and CK-20, the results were similar with those of Wang et al9; however, there were some differences. They found that bladder urothelial carcinoma was positive for both markers in 89% of cases in contrast with 56% in the present study. Wang et al9 also found no cases negative for both CKs, while the present study showed negative results for both CKs in 3 cases (12%). In prostate adenocarcinoma, Wang et al9 found 62% were negative for both markers, whereas we observed this in 88%. Their findings for the other scenarios in prostate cancer were almost similar to what we observed. However, they examined only 13 cases. They concluded that CK-7 and CK- 20 could be used to discriminate between carcinomas of different primary sites and may be particularly helpful for determining the site of origin of carcinomas presenting as metastatic disease.

Recently, Genega et al10 reported similar expression of CK-7 and CK-20 in prostate and urothelial carcinomas. They described CK-7 positivity in 19% of prostate adenocarcinomas (all with Gleason score >6) vs 70% of urothelial carcinomas.

Only 2% and 15% of prostate adenocarcinoma and urothelial carcinoma, respectively, were positive for CK-20.

A critical review of the present study does not necessarily allow for the conclusion that CK status is very helpful. Positive and negative expression of both CKs together are suggestive only of bladder and prostate cancer, respectively.

The comparison of CK expression with PSA staining is an important consideration in the discussion of the practical application of immunohistochemistry in this setting. PSA and PSAP staining enables the correct identification of the prostatic origin of adenocarcinoma cases, which makes it the most valuable single antibody in this differential diagnosis.11 Although, PSA and PSAP staining has been reported to be negative in some poorly differentiated adenocarcinomas of the prostate, the present study found PSA and PSAP staining in all except 1 advanced prostate tumors; all urothelial tumors were negative for PSA. Therefore, whereas PSA positivity confirms the prostatic nature of a tumor, CK-7 or CK-20 positivity is not specific for urothelial carcinoma. Coordinate expression of CK-7 and CK-20 also was examined in the context of the grade of the tumor. Positive expression of both markers was found across all grades of urothelial carcinoma. There was no apparent predilection of CK staining based on the differentiation of the tumor.

Our data show that the high-molecular-weight cytokeratin antibody 34bE12 expressed in % of urothelial carcinoma. 34bE12 binds to high-molecular-weight cytokeratins. 12-15 and has been previously shown to be highly expressed in urothelial carcinoma and only rarely expressed in prostatic adenocarcinoma 16,17 It is most commonly used to label prostate basal cells and thus distinguish benign prostate lesions from prostatic adenocarcinoma (18-20). Recently, Googe et al. (21) reported a high frequency
of 34bE12 expression in primary and metastatic prostatic adenocarcinoma. However, our data and that of Yang et al. (17), shows that 34bE12 expression is rare in prostatic adenocarcinoma.

In a subset of cases, p53 immunohistochemistry may help to distinguish urothelial carcinoma from prostatic adenocarcinoma. Mutations of the p53 gene, as determined by p53 immunohistochemistry, are common in invasive urothelial carcinoma and androgen-independent prostatic adenocarcinoma but are uncommon in hormone-sensitive, localized prostatic adenocarcinoma. (22-27).

CONCLUSION

we describe an immunohistochemical panel including PSA, PSAP, 34bE12, CK 7, and p53, that may be helpful in distinguishing high-grade prostatic adenocarcinoma from high grade urothelial carcinoma in diagnostically difficult cases. A positive stain with PSA or PSAP confirms the diagnosis of prostate carcinoma.

Currently, there are no markers entirely specific for urothelial carcinoma and CK-7 and CK-20 are useful for distinguishing prostate cancer from urothelial carcinoma if each is used alone. However, if both CKs are used in conjunction, they are most helpful for ruling out prostate cancer if they are both positive, as it is extremely rare for both CKs to be expressed in adenocarcinoma of the prostate. a positive reaction with 34bE12, CK 7, or p53 also can supports the diagnosis of urothelial carcinoma.

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