

PATHOLOGY

False positive labeling of prostate cancer with high molecular weight cytokeratin: p63 a more specific immunomarker for basal cells

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Occasional nonspecific staining of prostate cancer cells with high molecular weight cytokeratin (HMWCK) can lead to false-negative diagnoses. We compared p63 and HMWCK immunostaining to check their specificity for basal cell identification. Out of 6887 prostate cancer cases sent in consultation to one of the authors over 1.5 years, we identified 22 (0.3%) cases with HMWCK labeling of cancer cells, including 20 needle biopsies and 2 transurethral resections of prostate (TURP). Cases were sent in consultation because of the confusing immunostaining pattern, where prostate cancer cells labeled with HMWCK at the outside institutions. In 6 cases, p63 immunostains were also received from the outside institution, whereas in the remaining 16 cases p63 immunohistochemistry was performed at our institution. In 14 cases, we used either an extra destained hematoxylin and eosin slide or a negative control slide for immunohistochemistry with antibodies to p63, and in the 2 remaining cases submitted unstained slides were used. The Gleason scores were 3+3=6 in 20 cases and 4+4=8 in 2 cases. The size of the tumor on needle biopsy ranged from 0.5 to 6.0 mm (mean 1 mm) and on the 2 TURP cases consisted of 44 and 68 cancer glands, respectively. The number of tumor cells positive for HMWCK in each of the needle biopsy cases ranged from 3 to 48 (mean 13 cells), whereas on the 2 TURP cases 26 and 10 cells were labeled with HMWCK. Corresponding stains for p63 on the same cases were negative in 18 cases. In 3 of 4 cases, p63 labeled 1, 1, and 2 tumor cells, respectively. The fourth case had 5 positive cells on p63 staining with 4 positive for HMWCK. To assess whether overstaining was a factor, we evaluated the intensity of HMWCK staining in the basal cells of the benign glands, which was moderate in 6 and strong in 16 cases. The cytoplasm of benign secretory cells showed focal weak (n = 3), diffuse weak (n = 1), and focal moderate (n = 2) staining for HMWCK. HMWCK labeling of prostate cancer cells is uncommon and does not seem to be solely attributable to overstaining. p63 is a more specific marker for basal cells than HMWCK, with less labeling of tumor cells. Recognition of this phenomenon and performing stains for p63 when it occurs can help prevent underdiagnosing prostatic carcinoma.

Editorial Comment

On a previous published study from the same Institution, it was shown that prostate adenocarcinoma cells may show aberrant expression for p63 immunostaining (1). In this study they describe another rare occurrence of aberrant expression: positivity for high-molecular weight cytokeratin (HMWCK). Both p63 and HMWCK are markers for basal cells which are absent in neoplastic acini.

Both are important reports of a pitfall for the pathologist while diagnosing prostate cancer. It is important for the urologist to know that immunohistochemistry is used only in some selected cases with difficult differential diagnosis and not routinely in all cases showing adenocarcinoma. More importantly, the urologist must know that even using immunohistochemistry the diagnosis may not be definitive, that is, it may be yet "suspicious but not diagnostic of adenocarcinoma".

Why this happens? There are several benign conditions mimicking adenocarcinoma that show absence of basal cells in some of the acini: partial atrophy (2), adenosis, small branches of normal acini, and atypical PIN (PINATYP) (3). In small lesions using immunohistochemistry, these conditions may show absent basal cells in all of the acini, and in absence of other criteria for the diagnosis of cancer the pathology report is still "suspicious but not diagnostic of adenocarcinoma".

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Grading of invasive cribriform carcinoma on prostate needle biopsy: an interobserver study among experts in genitourinary pathology

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The distinction between cribriform Gleason pattern 3 and 4 prostate cancer is controversial. Out of 3590 prostate cancers sent to one of the authors over 7 months, 30 needle biopsy cases were selected that possibly represented cribriform Gleason pattern 3 cancer. Thirty-six digital images were taken and sent to 10 experts in prostate pathology. Consensus was defined when at least 7/10 experts agreed on the grade. Sixty-seven percent (n = 24) of images reached consensus (23 pattern 4; 1 pattern 3). Of the 12 nonconsensus images, 7 were favor pattern 4 (6/10 experts agreed), 1 was favor pattern 3 (6/10 experts agreed), and 4 were equivocal (< 6 experts agreed). The most common criteria used to call pattern 4 in the 23 consensus pattern 4 images were in frequency: irregular contour, irregular distribution of lumens, slit-like lumens, large glands, number of glands, and small lumens. In the only consensus pattern 3 image, criteria used were regular contour, small glands, regular distribution of lumens, and uniform round lumens. Discrepancy between experts was qualified as primarily objective (different criteria present) in 38%, subjective (different interpretation of the same criteria) in 12%, and mixed (both objective and subjective) in 50%. The most frequent situation with different interpretations of the same criteria were regular versus irregular contour and small versus large glands, with the former more common. Even in this highly selected set of images thought to be the best candidates for cribriform pattern 3 from a busy consult service, most experts interpreted the cribriform patterns as pattern 4. Moreover, most of the cribriform foci investigated (73%) were associated with more definitive pattern 4 elsewhere on the needle biopsy specimen. In conclusion, most of the small cribriform cancer foci seen on needle biopsy should be interpreted as Gleason pattern 4 and not pattern 3.

Editorial Comment

The cribriform pattern (glands in glands) is a very peculiar arrangement frequently seen in adenocarcinoma of the prostate. In metastases of unknown origin, this pattern seen in older men is almost always adenocarcinoma from the prostate. Obviously this pattern is not exclusively seen in prostate cancer. It may also be seen in carcinoma of the breast, gastrointestinal tract and other organs.

In the standard Gleason grading, cribriform pattern could correspond to patterns 2, 3, or 4. In the revised Gleason grading published in 2005 (1), cribriform pattern should never correspond to pattern 2, and very rarely to pattern 3. Most of the times it corresponds to grade 4. Cribriform pattern 3 is only diagnosed for well circumscribed glands of the same size as normal glands.

Reference

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INVESTIGATIVE UROLOGY

Localization and expression of inducible nitric oxide synthase in biopsies from patients with interstitial cystitis

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Purpose: Interstitial cystitis is a chronic inflammatory disease of the bladder and luminal nitric oxide has been shown to be increased in the bladder in patients with interstitial cystitis. We analyzed endogenous nitric oxide formation and inducible nitric oxide synthase gene expression in the bladder of patients with interstitial cystitis to obtain further knowledge of the localization of inducible nitric oxide synthase in the bladder mucosa.

Materials and Methods: Six patients with interstitial cystitis and 8 controls were studied. In these 2 groups endogenous nitric oxide formation was measured and inducible nitric oxide synthase expression in bladder biopsies was analyzed at the transcriptional and protein levels by real-time polymerase chain reaction and Western blot, respectively. Immunohistochemistry for inducible nitric oxide synthase was also performed.

Results: Patients with interstitial cystitis had higher inducible nitric oxide synthase mRNA expression and nitric oxide formation than controls ($p < 0.01$ and < 0.001 , respectively). Inducible nitric oxide synthase protein expression was up-regulated in the interstitial cystitis group. Immunohistochemistry showed that inducible nitric oxide synthase was predominantly localized to the urothelium in patients with interstitial cystitis but inducible nitric oxide synthase-like immunoreactivity was also found in macrophages in the bladder mucosa.

Conclusions: The increased levels of endogenously formed nitric oxide in patients with interstitial cystitis correspond to increased inducible nitric oxide synthase mRNA expression and protein levels in these patients. Furthermore, inducible nitric oxide synthase was found to be localized to the urothelium but it was also found in macrophages in the bladder mucosa. Whether high levels of endogenously formed nitric oxide are a part of the pathogenesis in interstitial cystitis and whether it has a protective or damaging role remain to be elucidated.