

manuscript, the authors reported a frequency of 24% of patients with clinically insignificant prostate cancer at radical prostatectomy. Although with some controversy (2), the same group of authors has been shown recently that a nomogram that incorporates MRI and MRSI was more accurate than clinical nomograms (clinical stage, PSA level, biopsy data) in order to predict clinically insignificant prostate cancer (3).

In a study of 89 men with biopsy-proven prostate cancer, the authors demonstrated that combined MRI and MRSI findings and three specific biologic markers that are important in proliferation, apoptosis, and cell survival (Ki-67, phospho-Akt, and androgen receptor AR values) correlated with each other and with clinically insignificant and significant prostate cancer defined at pathologic examination of prostatectomy specimens.

We agree with the authors that if a prospective study confirms their results it may represent the beginning of a new era. An era of integration of pretreatment conventional and functional MR imaging of the prostate with histopathological and specific biologic markers analyses of biopsy specimens. In the near future, this integration probably will allow better treatment selection and thus better outcome for patients with prostate cancer.

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PATHOLOGY

TMPRSS2-ERG gene fusions in “minimal” prostatic adenocarcinoma

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Background: Minimal or “insignificant” prostatic adenocarcinoma (MinPCa) is defined as tumors with insufficient virulence to threaten survival. Given recent suggestion of TMPRSS2-ERG gene fusion association with aggressive PCa phenotype, we aimed to evaluate incidence of TMPRSS2-ERG fusion in MinPCa in comparison with grade matched “non-minimal” size PCa.

Design: All 33 prostatectomies classified as containing MinPCa (2002-2003) were retrieved. Diagnosis of MinPCa (Gleason Score 6 PCa with total tumor volume < 0.5 CC, single section) was confirmed by a urologic pathologist. Tissue microarray (TMA) was constructed from the 33 cases where each tumor and paired benign tissue was represented by up to triplicate, 1mm, spots. TMA sections of 59 additional archival PCa were used as controls (26 pT2 non-minimal in size, 31 pT3a and 2 pT3b). FISH analysis was performed using break-apart probes for 5' and 3' regions of ERG. Each spot was scored for presence of TMPRSS2-ERG fusion through

deletion or translocation as well as for polyploidy (≥ 3 copies) at the ERG locus. At least 50 cells were scored per tumor.

Results: MinPCa: TMPRSS2-ERG fusion was identified in 46% (16/35) of MinPCa. In 87% (14/16) of positive tumors, fusion was due to deletion. The remaining 13% (2/16) of fusions were based on the demonstration of a split in the two juxtaposed probe signals. Ch21 polyploidy \pm fusion and duplication of ERG deletion were not observed in any MinPCa case. Control group: TMPRSS2-ERG fusion was identified in 59% (35/59) of tumors. In 77% (27/35) of positive tumors, fusion was due to deletion. Ch21 polyploidy with \pm fusion was present in 13/59 (22%) while polyploidy with duplicate ERG deletion was found in 6/59 (10%) of control tumors. On statistical analysis, there was no significant difference in TMPRSS2-ERG fusion incidence between the MinPCa and control groups ($p = 0.2$). Statistically significant higher rates of ch 21 polyploidy \pm fusion was present in control group ($p = 0.0002$). A trend approaching statistical significance for higher incidence of ch21 polyploidy with duplicate deletion was also present in the control group ($p = 0.052$).

Conclusions: TMPRSS-ERG fusion rate of 46% is present in MinPCa. The latter is not significantly different from rate of fusion in control group of non-minimal pT2 and pT3 PCa. A higher rate of Ch21 polyploidy is detected in the control group compared to MinPCa. Our finding of a comparable rate of TMPRSS2-ERG fusion in MinPCa and non-minimal PCa argues against its value as a marker of aggressive PCa phenotype.

Editorial Comment

With higher number of prostate cancer detected in stage T1c due to screening, a higher number of small adenocarcinomas have been detected on needle biopsies. Many of these small adenocarcinomas may have criteria for minimal or “insignificant” cancer: tumor in no more than 2 cores, absence of Gleason grade 4 or 5, tumor not occupying more than 50% of the core, and favorable PSA density (1). It is important to note that these criteria relate to tumor volume and not biological behavior. It would be of utmost importance to know whether a minimal or “insignificant cancer” would behave as a latent (dormant or indolent) cancer or evolve to a clinical cancer.

A notable discovery related to the molecular aspect of prostate carcinoma was the identification by Tomlins et al. (2) of a recurrent chromosomal arrangement encountered in the majority of prostate carcinomas that they studied. Possible rearrangements are of two general types. In the first, the promoter and/or enhancer elements of one gene are aberrantly juxtaposed to a proto-oncogene, thus causing altered expression of an oncogenic protein. In the second, the rearrangement fuses two genes, resulting in the production of a fusion protein that may have a new or altered activity. Tomlins et al. (2) identified recurrent gene fusions of the region of TMPRSS2 to ERG or ETV1 in prostate cancer tissues. TMPRSS2 (21q22.2) is a prostate-specific gene that is present in normal and neoplastic prostate tissue and is strongly induced by androgen in androgen-sensitive prostate cell lines. ERG (21q22.3) and ETV1 (7p21.2) are genes that encode ETS family transcription factors. TMPRSS2:ERG fusion is more frequent and occurs due to a deletion of a region on chromosome 21. TMPRSS2:ETS fusion prostate cancers comprise 40-50% of the PSA screened hospital based prostate carcinoma examined to date, making it the most common genetic rearrangement in human cancer. Emerging data suggested that TMPRSS2:ERG prostate cancer is associated with higher tumor stage and prostate specific death. Therefore, this fusion may be a marker for aggressive prostate cancer.

The study by Albadine et al. found that TMPRSS-ERG fusion rate of 46% is present in minimal or “insignificant” prostate cancer. This finding is not significantly different from rate of fusion in control group of non-minimal confined cancer (pT2) or with extraprostatic extension cancer (pT3). The comparable rate of TMPRSS2-ERG fusion in minimal prostate cancer and non-minimal prostate cancer argues against its value as a marker of aggressive prostate cancer phenotype.

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Are nephrogenic adenomas renal stem/progenitor cell-derived lesions? An immunohistochemical study

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Background: Nephrogenic adenoma (NA) is a benign tumor-like lesion of the urinary tract that histologically resembles the developing distal nephron. Recent evidence suggests that NA is truly a “nephrogenic” lesion, arising from downstream seeding of shed renal tubular cells with implantation and proliferation in areas of damaged urothelium. This proposed pathogenesis and the rarity of the lesion suggest the possibility that NAs arise from kidney stem/progenitor cells that retain the ability to proliferate and develop into renal tubule-like structures when implanted at a distant site. Renal stem/progenitor cells have recently been identified in adult kidney tubules with several markers, including CD133 and PAX2. In our study, we investigate the expression of stem cell surface markers CD133 and CD44 as well as renal-specific transcription factors PAX2 and PAX8 by immunohistochemistry.

Design: Twenty-nine cases of NA from 2000 to 2004 were retrieved from the tissue archives, 18 of which were from urinary bladder and 19 from prostatic urethra. CD133, CD44, PAX2, and PAX8 immunohistochemical staining was performed using the avidin-biotin peroxidase method following antigen retrieval. Complete circumferential membranous staining was considered positive for CD133 and CD44. Distinct nuclear staining was required for PAX2 and PAX8 positivity.

Results: All NAs were positive for renal-specific transcription factors PAX2 and PAX8, consistent with previous studies. CD133 staining was detected focally in eight of 29 (28%) cases. The CD133 positive cells were seen in papillary surfaces, small tubules, and occasionally in the stroma. CD44 staining was detected in seven of ten cases, including five CD133 positive lesions. In the CD44 positive/CD133 positive cases, CD44 was present in the corresponding CD133 areas. CD44 expression, however, was also seen in other areas and in two CD133 negative cases. No staining for these for markers was identified in the epithelium or stroma in prostatic glands, prostatic urethra, or urinary bladder.

Conclusions: Stem cell markers CD44 (70%) and CD133 (28%) were identified in a subpopulation of cells in nephrogenic adenomas, all of which were also positive for renal-specific transcription factors PAX2 and PAX8. Therefore, we suggest that nephrogenic adenomas may arise from transplantation and proliferation of primitive renal cells into an extrarenal stem cell niche. The expression of additional stem cell markers in this regard is currently under investigation.

Editorial Comment

Nephrogenic adenomas usually arise in the setting of prior urothelial injury, such as past surgery, calculi, or trauma. An intriguing and elegant study was able to demonstrate a derivation from renal tubular cells occurring in renal transplant patients.

Mazal et al. (1) reported that the sex-chromosome pattern in examples of bladder nephrogenic metaplastic lesions in the recipient reflected the pattern of the donor patient, and was different from the chromosome pattern of adjacent urothelium in the recipient patient. An additional support for nephrogenic adenomas arising from shed renal tubular cells is positivity for PAX2. Tong et al. (2) reported that 100% of a series of 39 examples of nephrogenic adenomas stained with PAX2, a renal transcription factor which is specific for tubular epithelium. Urothelium and prostate epithelium do not stain with this antibody. These studies support that nephrogenic adenoma is not of urothelial origin and most probably originates from implanted cells shed from renal tubules.

Devaraj et al. considered the possibility that nephrogenic adenomas arise from kidney stem/progenitor cells that retain the ability to proliferate and develop into renal tubule-like structures when implanted at a distant site. They investigated the expression of stem cell surface markers CD133 and CD44 as well as renal-specific transcription factors PAX2 and PAX8 by immunohistochemistry. Renal stem/progenitor cells have recently been identified in adult kidney tubules with several markers, including CD133 and PAX2. Stem cell markers CD44 (70%) and CD133 (28%) were identified in a subpopulation of cells in nephrogenic adenomas, all of which were also positive for renal-specific transcription factors PAX2 and PAX8. These findings suggest that nephrogenic adenomas may arise from transplantation and proliferation of primitive renal cells into an extrarenal stem cell niche.

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BASIC AND TRANSLATIONAL UROLOGY

Oestrogen receptor expression and neuronal nitric oxide synthase in the clitoris and preputial gland structures of mice

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Objective: To study the presence of oestrogen receptors (ER) and neuronal nitric oxide synthase (nNOS) in the mouse clitoris.

Materials and Methods: A series of sections of the pelvic area, including the preputial glands and clitoris, of 10 mice were assessed by immunocytochemical studies specific for ER-alpha and -beta, and nNOS; selected sections were also stained with Masson's trichrome.

Results: ER alpha was detected in the epithelium of the gland of the clitoris, and in the glandular tissue, preputial and apocrine gland. ER alpha was detected in the nuclei of stromal cells around the cavernous tissue and near the epithelium of the clitoris. Cytoplasm ER alpha was detected in a few cells in an area ventral to the clitoral