

Editorial Comment

Kunkle et al. report on their experience with missed ureteral injuries at a busy inner city trauma center. This is a well written and comprehensive paper on delayed diagnosis. Tables 3 and 4 are nice meta-analyses demonstrating that roughly 11% of ureteral injuries are missed at laparotomy, resulting in an overall nephrectomy rate of 18% and death at 13%. Even in the busiest of trauma centers, external ureteral injuries are rare, typically with fewer than 10 injuries seen per year. In the literature, there are only a few series with a sizable experience, and they are all retrospective, cover long study periods (10-40 years), and are mostly treated by heterogeneous groups of physicians. Most external ureteral injuries occur from gunshot wounds. Missile path even in proximity to the ureter can cause significant delayed tissue destruction. Such injuries can be difficult to identify initially and often present in a delayed fashion. Penetrating ureteral injuries are almost always associated with multiple intra-abdominal organ injuries (such as, small bowel, colon, liver and iliac vessels. Associated injuries are often more obvious and overshadow the ureteral injury. Ureteral injuries from blunt trauma are equally rare. They usually occur in children during rapid deceleration, causing excessive hyperextension and disruption at the ureteropelvic junction. Such patients are usually poly-traumatized and have associated multiple organ injuries (mostly liver, spleen and skeletal system).

In the acute trauma setting, therefore, the diagnosis of ureteral injury can be difficult. When the ureteral injury is missed and not diagnosed till late or the primary repair fails, the complication rate increases considerably, including renal loss and even death.

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PATHOLOGY

Are There Morphologic Correlates of Prostate Cancer Associated with TMPRSS2-ERG Molecular Abnormalities?

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Mod Pathol. 2007; 20 (suppl 2): 146A

Background: Recent studies have shown that TMPRSS2-ERG fusion is common in prostate cancer, varying from 30-70% of cases in published series. The molecular abnormalities include formation of a fusion gene, in a majority of cases due to deletion of a region on chromosome 21. While the histologic features of these tumors have not been elucidated, it has been suggested that these molecular genetic events may be associated with distinct morphologic characteristics, such as cribriform architecture and the presence of blue mucin.

Design: Blinded histologic review was conducted on 67 cases comprising two tissue microarrays (TMA) on which fluorescent in situ hybridization (FISH) had previously been performed to delineate molecular abnormalities.

Results: By FISH, 37/67 cases showed molecular abnormalities, including 21 deletions, 5 translocations, and 11 cases with other abnormalities. The other 30 cases were negative on FISH analysis. 8/37 (16.7%) cases with and 9/30 (30%) cases without molecular abnormalities showed cribriform glands or glomerulations. Intralumini-

nal blue mucin was present in 15/37 (40.5%) cases with and 11/30 (36.7%) cases without genetic events. Overall, 19/30 (63.3%) cases without FISH abnormalities showed no specific morphologic features. Cribriform glands/glomerulations were present in 8/17 cases with molecular changes and 9/17 FISH negative cases.

Conclusions: In this analysis, we observe that TMPRSS2-ERG-related abnormalities do not correlate with specific tumor histology. Similarly, cribriform architecture is seen equally in cases with and without these genetic events. These findings suggest a lack of association between FISH-detected molecular changes and these morphologic findings. Further studies in larger cohorts of tissue are in progress to confirm these observations.

Editorial Comment

The paper by Fine SW et al. from the Memorial Hospital (New York) is at odds with the paper by Mosquera MJ et al. from the Brigham and Women's Hospital (Boston). Fine SW et al. observed that TMPRSS2-ERG abnormalities did not correlate with any specific or peculiar feature of prostate adenocarcinoma. One of the reasons for the discrepancy between the two papers may be related to the sophisticated techniques used in cancer molecular cytogenetic analysis.

So far, the TMPRSS2-ERG fusion is detected by molecular cytogenetic analysis available only in research laboratories. Future efforts will be directed at characterizing the expressed protein products of this gene fusion which may be detected by immunohistochemistry. This latter technique is available to all routine laboratories of pathology.

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Morphological Features of TMPRSS2: ERG Fusion Prostate Cancer

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Mod Pathol. 2007; 20 (suppl 2): 165A

Background: TMPRSS2:ETS fusion prostate cancers (PCA) comprise 40-50% of the PSA screened hospital based PCA examined to date making it the most common genetic rearrangement in human cancer. The most common variant involves TMPRSS2 and ERG. Emerging data from our group and others suggests that TMPRSS2:ERG PCA is associated with higher tumor stage and PCA specific death. The goal of this study was to determine if this common somatic alteration is associated with a morphologic phenotype.

Design: We assessed 253 PCA cases for TMPRSS2:ERG fusion status using FISH. Tumors were assessed for presence or absence of 8 morphologic features. The reviewers were blinded to the fusion status. Statistical analysis was performed to look for significant associations between morphologic features and TMPRSS2:ERG fusion status.

Results: Five morphologic features were associated with TMPRSS2:ERG PCA: blue-tinged mucin (85% of cases, n = 23/27), cribriform growth pattern (68%, n = 50/74), macronucleoli (78%, n = 39/50), intraductal tumor spread (88%, n = 38/43), and signet-ring cell-like features (82%, n = 9/11) all with p-values < 0.05. Only 24% (n = 30/125) of tumors without any of these features displayed the TMPRSS2:ERG fusion. In contrast, 55% (n = 38/69) of cases with one feature (RR = 3.88), 86% (n = 38/44) of cases with two features (RR = 20.06), and 93% (n = 14/15) of cases with three or more features (RR = 44.33) were fusion positive (p < 0.001). **Conclusions:** This is the first study to our knowledge that demonstrates a significant link between a molecular alteration in PCA and distinct phenotypic features. The strength of these findings is similar to BRCA-1/2 breast cancers and HNPCC colon cancer. The biologic effect of TMPRSS2:ERG overexpression may drive pathways that favor these common morphologic features that pathologists observe on a daily basis. These features should also be helpful in diagnosing TMPRSS2:ERG fusion PCA which may have both prognostic and therapeutic implications. Validation studies are underway.

Editorial Comment

A central aim in cancer research is to identify altered genes that play a causal role in cancer development. 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. In 2005, Tomlins SA et al. (1) identified recurrent gene fusions of the region of TMPRSS2 to ERG or ETV1 in prostate cancer tissues. These fusions may have important implications for understanding prostate cancer tumorigenesis and developing novel diagnostics and targeted therapeutics.

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 suggest 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 aim of the study by Mosquera JM et al. was to find morphological features of TMPRSS2:ERG fusion prostate cancer that may indicate more aggressive tumors. The authors found that tumors with blue-tinged mucin, cribriform growth pattern, macronucleoli, intraductal spread and signet-ring cell-like features were frequently associated with the fusion. When 3 or more features were combined, 93% of the cases presented TMPRSS2:ERG fusion.

Reference

1. Tomlins SA, Rhodes DR, Perner S, Dhanasekaran SM, Mehra R, Sun XW, et al.: Recurrent fusion of TMPRSS2 and ETS transcription factor genes in prostate cancer. *Science*. 2005; 310: 644-8.

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