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PATHOLOGY

Gleason grading of prostatic adenocarcinoma with glomeruloid features on needle biopsy

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Glomerulations in prostatic adenocarcinoma are characterized by dilated glands containing intraluminal cribriform structures with a single point of attachment, resembling a renal glomerulus. On prostate biopsy, glomerulations are exclusively associated with carcinoma and not associated with benign mimickers. However, the Gleason grading of carcinoma with glomerulations on needle biopsy remains controversial. We prospectively collected 45 prostate needle biopsies containing carcinoma with glomeruloid features from our consult files for a 9-month period and examined the association between glomerulations and the presence of concurrent high-grade carcinoma. Glomerulations were overwhelmingly associated with high-grade cancer on the same core, composed of either Gleason pattern 4 (n = 36, 80% of cases) or Gleason pattern 5 (n = 2, 4% of cases). Only a minority of glomerulations were surrounded exclusively by pattern 3 cancer (n = 7, 16% of cases) on the same core. Most of the cases with surrounding pattern 4 cancer were scored as 3 + 4 = 7 (n = 24, 66%), whereas a smaller fraction were scored as 4 + 3 = 7 (n = 9, 26%), and only a minority were 4 + 4 = 8 (n = 3, 9%). In most cases, glomeruloid change was present on the same core as the highest Gleason score carcinoma of the case. None of the pattern 3 cases and only a minority of the pattern 4 cancers had higher Gleason score carcinoma on additional cores (n = 5, 14%). Glomeruloid structures are a rare but diagnostic feature of prostatic carcinoma on needle biopsy. Our data indicate that glomerulations are overwhelmingly associated with concurrent Gleason pattern 4 or higher-grade carcinoma. In several cases, transition could be seen among small glomerulations, large glomeruloid structures, and cribriform pattern 4 cancer. These data suggest that glomerulations represent an early stage of cribriform pattern 4 cancer and, until follow-up data are available, are best graded as Gleason pattern 4.

Editorial Comment

The grading of prostatic adenocarcinoma with glomeruloid structures is controversial (1-3). Some urological pathologists do not assign a grade to this pattern and just grade the surrounding tumor. Other experts in the field feel that all glomeruloid structures should be assigned a Gleason pattern 4.

The glomeruloid feature in adenocarcinoma of the prostate refers to an architectural pattern of growth that mimics the renal glomerulus (1,3,4). Glomeruloid structures have been described in Wilm's tumor (5) probably representing differentiation of neoplastic cells toward a primitive form of renal glomerulus and are sometimes present in gliomas (6). In a rare case of adenoma (hamartoma) of bladder in siblings, spaces, often

cystic, lined with neoplastic epithelial cells with hyperchromatic nuclei were crowded at one of the poles which strikingly resembled primitive glomeruli (7).

This distinctive pattern of prostate cancer was first described in 1995 by Epstein in his book Prostate biopsy interpretation and called the lesion glomerulations (8). In 1998, Pacelli et al. (1) published a series of prostatic adenocarcinoma with glomeruloid features in biopsies and radical prostatectomies. The frequency of adenocarcinoma with glomeruloid features in 100 needle prostatic biopsies was 3% in Pacelli's series.

Glomeruloid structures appear to be a specific but uncommon finding in prostate cancer. They are not seen in benign prostatic tissue, nodular hyperplasia, basal cell hyperplasia, atypical adenomatous hyperplasia, or prostatic intraepithelial neoplasia (3,4).

In Lotan and Epstein's study glomeruloid structures were associated to Gleason pattern 4 or 5 in more than 80% of the cases. In only 16% of the cases were associated exclusively to Gleason pattern 3. The authors suggest that glomerulations represent an early stage of cribriform pattern 4 cancer and, until follow-up data are available, are best graded as Gleason pattern 4.

In a similar study based on 264 needle biopsies, we found 28/264 (10.6%) biopsies showing glomeruloid structures; 9/28 (32.14%) biopsies the glomeruloid structures were surrounded by Gleason low-grade tumor and in 19/28 (67.85%) biopsies surrounded by Gleason high-grade tumor (9). All patients in our study were submitted to radical prostatectomy. Comparing the findings for several clinicopathologic variables between patients with and without glomeruloid structures, no statistical significance was found and at 5 years, the PSA progression-free survival rates were 57% and 52% for patients without and with glomeruloid structures (log-rank, $p = 0.26$). Glomeruloid structures were associated more frequently with Gleason high-grade surrounding tumor, however, the presence of this architectural pattern was not associated to any other adverse clinicopathologic findings. It seems in our study that glomeruloid feature per se should not interfere in the grading of a tumor.

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Precursor lesions to prostatic adenocarcinoma

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High-grade prostatic intraepithelial neoplasia (PIN) is the one well-documented precursor to adenocarcinoma of the prostate. This review article defines both low- and high-grade PIN. Unusual variants of high-grade PIN are illustrated. Benign lesions that may be confused with high-grade PIN, including central zone histology, clear cell cribriform hyperplasia, and basal cell hyperplasia are described and illustrated. High-grade PIN is also differentiated from invasive acinar (usual) and ductal adenocarcinoma. The incidence of high-grade PIN, its relationship to carcinoma (including molecular findings), and risk of cancer on rebiopsy are covered in detail. Finally, intraductal carcinoma of the prostate, a controversial entity, is discussed and differentiated from high-grade PIN.

Editorial Comment

This is a nice review on precursor lesions to prostatic carcinoma. High-grade prostatic intraepithelial neoplasia (PIN) (Figure-1) was previously described by many authors using such terms as atypical epithelial proliferation, atypical glandular hyperplasia, atypical glandular proliferation, atypical hyperplasia, dysplastic lesions, dysplastic hyperplasia, cribriform hyperplasia, and atypical primary hyperplasia (1-6). These lesions were of interest for German authors and in the 80s studied by American authors. Bostwick described 3 grades for the lesion: low, intermediate and high-grade - grades 1, 2, and 3 (7). In 1989 during an international workshop in Bethesda, USA, sponsored by the American Cancer Society in an attempt to unify nomenclature it was introduced the term prostatic intraepithelial neoplasia (PIN) (8). In the same workshop it was suggested to refer in the pathology reports only to high-grade PIN (grades 2 or 3) due to the fact that low-grade PIN (grade 1) lesions have poor reproducibility among pathologists and lack any significant association with concomitant cancer.

The presence of PIN in a biopsy means a high frequency for finding cancer in a second biopsy. This frequency varies in the literature between 26% and 53%, however, with the advent of extended biopsies this frequency today is 27%-31% (9). In a study by Herawi et al. (10) the risk of cancer on biopsy within 1 year following a diagnosis of high-grade PIN in extended biopsies was very low (13.3%). Herawi et al. concluded that for patients diagnosed with high-grade PIN on extended initial core sample, a repeat biopsy within the first year is unnecessary in the absence of other clinical indicators of cancer.

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BASIC AND TRANSLATIONAL UROLOGY

Botulinum toxin-A to improve urethral wound healing: an experimental study in a rat model

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Objectives: Tensile distracting forces caused by elements such as a muscle pull can cause widening of scars in the tissue during the wound healing process. The aim of the present study was to investigate whether induced immobilization of the urethral muscle using botulinum toxin-A (BTX-A) enhances wound healing and also reduces the amount of scar formation in an experimentally induced urethral injury in a male rat model.
Methods: Prepubertal male albino rats were divided into 2 groups: 20 rats in the BTX-A group received BTX-A injection treatment during surgery and 10 rats in the control group received 0.9% saline solution injection. The penile skin was incised circumferentially and degloved. To make the urethral injury at a location approximately 15 mm proximal to the external meatus, the urethra was cut transversally with scissors, from the 2-o'clock to the 10-o'clock position and then sutured by a single suture at the 6-o'clock position. To evaluate chronic inflammation and fibrosis, the rats were killed, and the injured portions of the urethras were harvested for histopathologic examination after a follow-up period of 21 days.
Results: On histopathologic evaluation, the control group rats had a more severe fibrotic change in the urethral tissue compared with the BTX-A injected rats, which showed a mild fibrotic change. The mean +/- SD and median fibrosis score was 2.4 +/- 0.5 and 2 in the control group and 1.5 +/- 0.5 and 1 in the BTX-A group, respectively ($P < .01$ and $P < .01$, respectively).
Conclusions: The results of our study have shown that BTX-A prevented increases in collagen content during urethral wound healing.

Editorial Comment

This is a very interesting and inventive study that certainly will open new avenue for treatment of urethral stricture disease. In fact, using biochemical and stereological methods, we have recently found that, when compared to age-matched controls, there is no fibrosis and no collagen increase in the urethral edges of