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Importance of identification of prostatic adenocarcinoma in urine cytology

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Background Prostate carcinoma (PCa) occasionally involves the urethra and/or bladder. In these cases, PCa cells may be detected in urine. The purpose of this study was to describe the salient cytomorphologic, immunocytochemical, and epidemiologic features of PCa cells detected in urine cytology slides via a retrospective case series review.

Materials and Methods We retrospectively identified 28 cases with urine cytology either suspicious or positive for PCa. Clinical and histopathologic data were reviewed.

Results We identified 23 prostatic acinar adenocarcinomas (PAAs) and 5 prostatic adenocarcinomas with ductal features (PDAs). Urine cytology was the first evidence of disease in 6 (26%) patients with PAA and in 4 (80%) of the patients with PDA. In patients with PAA, 17 had a previous history of PAA, with positive urine cytology in the setting of disease recurrence or persistence within the bladder or urethra. The PAA in urine presented as single or small clusters of atypical cuboidal glandular cells with large, eccentric, round, or oval uniform nuclei containing conspicuous nucleoli, and scant to moderate delicate or granular cytoplasm, whereas the PDA presented as atypical columnar glandular cells in flat nests or 3-dimensional clusters, and with prominent nucleoli.

Conclusions Using standard urine cytology, we were able to detect PCa cells in the urine. Although rare, PCa was first diagnosed by urine cytology in select cases, with a higher frequency in patients with PDA. Clinicians should be aware that PCa cells can be identified by urine cytology as this can lead to an earlier diagnosis and treatment.

Introduction

Prostatic carcinoma (PCa) is the most common urologic malignancy diagnosed in American men and second leading cause of cancer death in males.[1] Investigators have previously considered the utility of urine cytology in the

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diagnosis of PCa. Although infrequent, prostate cancer cells have been reported to be shed into the urine; the clinical significance is unclear, however. One of the barriers is that the identification of PCa cells via cytology can be challenging. The use of multiple immunofluorescent stains for alpha-methylacyl-CoA racemase (AMACR), NKX3.1 (a prostatic tumor suppressor gene), nucleolin, and ETS-related gene (ERG) have shown excellent specificity, but poor sensitivity (36% or 22.7%).[2,3]

As most prostate cancers originate in the peripheral zone, the shedding of PCa cells in the urine may be a marker of more advanced disease. Additionally, although there is no evidence to support its use as a screening tool, the presence of malignant cells of prostatic carcinoma in urine samples may be the first evidence of disease in some cases. The aim of this study was to investigate the significance of prostatic carcinoma cells in urine cytology.

Materials and methods

Case selection

The research was approved by the institutional review boards of Cleveland Clinic and Northwestern University. We retrospectively identified the cases with urine cytology either suspicious or positive for adenocarcinoma and follow-up surgical biopsy diagnosis from pathology databases at Cleveland Clinic (1983 to 2016) and Northwestern Memorial Hospital (2007 to 2016).

Clinicopathological correlation

For each patient, clinical and histopathologic data were reviewed and recorded, including age, year of initial diagnosis, urine cytology, surgical pathology, Gleason score, tumor stage, tumor location, and clinical outcome. Available urine cytology slides and selected histological specimens were retrieved and reviewed.

Urine cytomorphology

Urine specimens were collected by either voiding or washing. The collected urine specimens were prepared with ThinPrep and stained with Papanicolaou stain.

The ThinPrep-prepared urine specimens were evaluated by cytology board-certified cytopathologists for diagnosis. The rendered diagnoses were recorded. The slides were reviewed and the diagnosis was confirmed by either Y.Z. or X.L.

Histology and immunohistochemical results of biopsy

Biopsies were performed via cystourethroscopy. The biopsied specimens were fixed with formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin stain.[4] Immunohistochemical studies were performed with appropriate positive and negative controls.[4] The antibodies used in the study included NKX3.1 (SKU-422, Biocare Medical, Concord, CA), PSA (A0562, DakoCytomation, Carpinteria, CA), PIN-4 (QAR3123, Biocare Medical), and GATA3 (SC-268, Santa Cruz, Dallas, TX). The hematoxylin and eosin and immunohistochemical slides were retrieved, reviewed, and recorded by either Y.Z. or X.L.

Statistics

Yates's correction test was used for statistical analysis.

Results

Patient demographics and clinical findings

On average, there were 5924 urine specimens in Cleveland Clinic and 4669 in Northwestern Memorial Hospital per year. In total, 28 patients (0.011%) were identified with urine cytology interpretation as "suspicious for/positive for adenocarcinoma" and confirmed to be PCa. There were 23 patients with acinar type (Table 1) and 5 with ductal type (Table 2). The mean age of patients with prostatic acinar adenocarcinoma (PAA) was 74.2 years (SD: 9.0 years). The mean age of patients with prostatic ductal adenocarcinoma (PDA) was 65.6 years (SD: 8.0 years). There was no statistical significance between the ages of the two groups ($P > 0.05$).

The main clinical presentations were hematuria (19 of 28 [67.9%]; 16 PAA and 3 PDA, $P > 0.05$ [70.0% PAA and 60.0% PDA]), and obstruction/stricture/urinary retention (15 of 28 [53.6%]; 11 PAA and 4 PDA, $P > 0.05$ [47.8% PAA and 80.0% PDA]) (Tables 1 and 2). Prostate cancer involvement of bladder and urethra was confirmed on cystoscopy in 21 patients (75%). No obvious lesion was identified in the bladder or urethra in 2 cases (7.1%). Cystoscopic information was unavailable in 5 cases (17.9%).

In patients with PAA, 17 had a history of PAA diagnosed previously within 2 months to 12 years, but re-presented with secondary involvement of the bladder or urethra in 12 of 17 cases (70.6%) (Table 1 and Fig. 1). The initial diagnosis of adenocarcinoma was first suggested by urine cytology in 6 patients (26.1%). Most patients (17 of 23, 73.9%) had a documented Gleason score ≥ 8, and 4 cases (17.4%) were designated "poorly differentiated PCa". Two patients were lost to follow-up. Of the remaining patients, 10 died of disease (range: 4-60 months; mean: 15.8 months) and 11 patients were alive with disease.

There were 5 patients identified with PDA, and a positive urine cytology was the first evidence of disease in 4 patients (80%). The remaining PDA case recurred with a pagetoid carcinoma involving the bladder mucosa and urethra 19.5 years after initial PCa diagnosis. Follow-up information was available for all 5 patients with PDA, ranging from 12 to 168 months. One patient died of disease, 1 patient was alive with disease, and 3 were alive without disease.