Prostatic Adenocarcinoma Diagnosed by Urinary Cytology

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Abstract

Prostatic adenocarcinoma rarely may involve the urinary bladder. Prostatic adenocarcinoma and high-grade transitional cell carcinoma (TCC) may coexist and account for the malignant cells seen in urinary cytology. Differentiating prostatic adenocarcinoma cells from those of TCC is important for therapy but remains difficult. A 10-year retrospective search identified 250 patients with high-grade carcinoma in urinary cytology. Among them, 6 cases of tissue-documented prostate adenocarcinoma were identified. The cytologic features of these cases were compared with those of 15 similarly documented cases of high-grade TCC. By using these criteria, 2 additional cases of prostatic adenocarcinoma were diagnosed prospectively. An oval nucleus with smooth borders; fine, powdery, evenly distributed nuclear chromatin and a large prominent nucleolus when present; and lack of significant pleomorphism are most helpful to differentiate prostatic adenocarcinoma from high-grade TCC. Recognizing these cells may be the first clue for the diagnosis of prostate adenocarcinoma.

Prostatic adenocarcinoma cells can be detected rarely in urinary cytology specimens. In many of these instances, the patients have a known history of prostate adenocarcinoma, usually of a high grade, which extends to the bladder mucosa and sheds tumor cells in the urine. On the other hand, hematuria due to involvement of the bladder neck or prostatic urethra rarely can be the initial presentation of prostate adenocarcinoma. In this setting, prostatic adenocarcinoma may be first diagnosed by urine cytology. In addition, prostatic adenocarcinoma and transitional cell carcinoma (TCC) can occur simultaneously in a patient. In all of these situations, differentiating prostatic adenocarcinoma from high-grade TCC is important for diagnostic and therapeutic purposes.

Although low-grade TCC, well known for a lack of cytologic atypia, may not enter in the differential diagnosis, high-grade TCC can be confused with prostatic adenocarcinoma. Yet, cytologic features that help separate these 2 malignant neoplasms have not been well characterized. In the present study, we attempted to develop criteria for this potentially problematic differential diagnostic dilemma by retrospectively comparing the cytologic features of known cases of prostatic adenocarcinoma with those of high-grade TCC in urinary cytology specimens. We subsequently were able to use these cytologic criteria to prospectively diagnose 2 additional patients with prostate adenocarcinoma who initially presented with hematuria with malignant cells in the urinary cytologic specimen.

Materials and Methods

The computer files were searched for cases diagnosed as “carcinoma not otherwise specified,” high-grade TCC, or prostatic adenocarcinoma from urine and bladder washing specimens between January 1987 and March 1997. Cases of low-grade TCC were excluded since, as mentioned, this type
of carcinoma lacks cytologic atypia and usually is not considered in the differential diagnosis of prostatic adenocarcinoma. A total of 6 cases of biopsy-confirmed unequivocal prostatic adenocarcinoma on urinary cytology were available for the study. The cytologic features of these cases were compared with urinary cytology specimens from 15 cases of high-grade TCC. The diagnosis in all of these cases was confirmed by a biopsy.

To develop differential diagnostic criteria, the cytologic features of the malignant cells of prostatic adenocarcinoma and high-grade TCC were compared and contrasted with special attention to 12 features: (1) cellularity, (2) shape of cell fragments, (3) size, (4) shape of individual cells, (5) pleomorphism, (6) cell borders, (7) cytoplasmic features, (8) nuclear shape, (9) nuclear border, (10) nuclear chromatin, (11) nucleolus, and (12) background. These criteria were used in a prospective study between April 1997 and April 1999 to determine whether prostatic adenocarcinoma can be recognized in urinary cytology specimens. Prostatic adenocarcinoma was diagnosed prospectively in 2 voided urine specimens and 1 bladder wash specimen from 2 patients.

Results

Pathologic Findings

During this 10-year period, 23 cases were diagnosed as “carcinoma not otherwise specified”; retrospective review, including tissue correlation, reclassified them as 16 high-grade TCCs, 1 squamous cell carcinoma, but the rest remained unclassifiable owing to a lack of tissue follow-up. Two hundred eighteen cases of high-grade TCC were diagnosed initially. Two of these cases on retrospective review, including follow-up biopsies, were prostatic adenocarcinoma. Nine cases were diagnosed initially as prostatic carcinoma. A total of 6 cases of biopsy-confirmed unequivocal adenocarcinoma on urinary cytology were available for the study. The cytologic features of these cases were compared with urinary cytology specimens from 15 cases of high-grade TCC. The diagnosis in all of these cases was confirmed by a biopsy.

Among the cases of high-grade TCC, 15 cases were chosen for comparative purposes. Within this group, a total of 17 urinary specimens and 4 cell blocks were available. The diagnosis in all of these cases was confirmed by cystoscopic biopsies (15 cases) and also a cystoprostatectomy (4 cases). Four of these patients also had a history of prostatic adenocarcinoma. One patient underwent a cystoprostatectomy.

Cytology of Prostatic Adenocarcinoma

The neoplastic cells were present as clusters and single cells. The clusters of cells were usually 3-dimensional syncytial fragments Image 11. Some fragments showed glandular arrangements in some areas Image 28. The cells were hyperchromatic with high nuclear/cytoplasmic ratios. The cells were 2 to 6 times the size of the background neutrophils. The single neoplastic cells were round or oval with well-defined cell borders. The cytoplasm was dense and sometimes finely granular. The nucleus was round, usually eccentric, and had a prominent nuclear border. The nuclear chromatin was fine, powdery, and evenly distributed. Nucleoli were seen only in some tumor cells but, when present, were large, prominent, and centrally placed. Cellular pleomorphism was not a striking feature in any of the cases Image 31. The background usually was clean with no tumor diathesis.

Immunohistochemical stains for prostate-specific antigen performed in 1 cell block were positive.

Cytology of Transitional Cell Carcinoma

The neoplastic cells were present as clusters or single cells. The clusters of cells were usually 3-dimensional syncytial fragments Image 41. These cells had significantly more cytoplasm than did the prostatic adenocarcinoma cells, resulting in a much lower nuclear/cytoplasmic ratio. These cells measured 4 to 10 times the size of a neutrophil in the background. Single neoplastic cells were rounded or spindle-shaped (Image 4). The cell borders were irregular, delicate, and fragmented, with multiple cytoplasmic blebs. The cytoplasm was vacuolated, wispy, and delicate. An ecto-endoplasmic separation of the cytoplasm with perinuclear clearing was prominent in many cells. The nucleus was usually oval or irregular and centrally placed. Some degenerated cells had a pyknotic nucleus. The nuclear borders were irregular with grooves and nuclear blebs. The nuclear chromatin was coarse and irregularly distributed throughout the nucleus with areas of chromatin clearing. Multiple chromocenters were present. A nucleolus was present rarely but, when present, usually was small, round, or irregular and centrally or eccentrically placed Image 51. Cellular pleomorphism was prominent.
The background was variable. Ten cases showed tumor diathesis, and 5 cases did not.

Nine cytologic features, listed in Table 1, were most useful for distinguishing prostatic adenocarcinoma from high-grade TCC. These features were used successfully in 2 cases of prostatic adenocarcinoma prospectively diagnosed out of 57 cases and 74 specimens of high-grade carcinoma. No cases of prostatic adenocarcinoma were missed by using these criteria. The urine in both cases showed large syncytial fragments of neoplastic cells and few single cells. The presence of an oval nucleus with well-defined cell borders and a fine, evenly distributed chromatin pattern was helpful for suspecting the diagnosis of prostatic adenocarcinoma in the syncytial fragments. A prominent nucleolus was present in all the neoplastic cells in 1 case and only in rare neoplastic cells in the second. There was no pleomorphism in either case.
These characteristic nuclear features and lack of pleomorphism in the syncytial fragments were most reliable for suspecting the diagnosis of prostatic adenocarcinoma. Unlike the cases reviewed retrospectively, few single cells were present in these 2 cases. An ultrasound-guided prostate biopsy performed 1 week before the urinary cytology was available for review in both cases.

Clinical Findings

The clinical features of 8 cases of prostatic adenocarcinoma (6 identified retrospectively and 2 identified prospectively) diagnosed by urinary cytology are summarized in Table 2. Three patients presented with hematuria with no history of prostatic adenocarcinoma, and the diagnosis of prostatic adenocarcinoma in 2 of the patients was first suggested by urine cytology findings. Five patients had a 1- to 10-year history of prostatic adenocarcinoma, with a Gleason score of 8 to 10, treated by radiation therapy. Seven patients had metastatic adenocarcinoma at the time of positive urinary cytology. Six of 8 patients died of the disease within 1 year of bladder involvement. One patient was lost to follow-up, and 1 was alive with disease 9 months after diagnosis.

Discussion

Most cases of prostate adenocarcinoma are detected in early stages, in which the urinary bladder wall is spared. Advanced prostatic adenocarcinoma may involve the bladder neck, prostatic urethra, or both and shed neoplastic cells in the urine. Recognizing prostate adenocarcinoma cells in the urinary cytology in these cases may not be problematic, since the diagnosis of prostate adenocarcinoma has been well established. However, in a small subset of patients, prostate adenocarcinoma may present initially with symptoms related to lower urinary tract obstruction or hematuria. These tumors usually involve the bladder neck, prostatic urethra, or both (stage T4) and display a high Gleason score (>8) and marked cytologic atypia. The distinction between TCC and prostatic adenocarcinoma by urinary cytology becomes important in such cases. Yet criteria that facilitate the differential diagnosis have not been well defined.

Although the cytologic features of prostatic adenocarcinoma cells in urinary cytology were described in a few previous studies, a systematic study aiming at differentiating prostatic adenocarcinoma cells from the more common TCC cells is lacking.

Our study confirms the characteristic circumstances in which prostate adenocarcinoma is diagnosed by urinary cytology. Three of the 8 patients presented primarily with hematuria and obstructive symptoms, without a history of prostate adenocarcinoma. Two of these patients had disseminated metastasis at the time of primary presentation. Such a presentation can be seen with prostatic adenocarcinoma and with high-grade TCC. In such circumstances, the distinction between prostatic adenocarcinoma and high grade TCC becomes very important.

Our study also demonstrates a characteristic cytologic profile of prostatic adenocarcinoma cells in the urinary cytology that is distinctive from that of high-grade TCC. This profile should, at the least, enable a strong suspicion for prostatic adenocarcinoma, even in the absence of a relevant clinical history at the time of cytologic interpretation. A suggestion for additional studies or a thorough review of previous case material can be initiated to confirm the diagnosis of prostatic adenocarcinoma. It should be emphasized that most prostatic adenocarcinoma that sheds cells in the urine shows marked cytologic atypia. Thus, the malignant nature of these cells in urine usually is not difficult to establish. Differentiating these cells from cells of a high-grade TCC may be problematic but should be achievable with the help of the criteria listed in Table 1. It should be noted that although the presence of prominent nucleoli is a helpful differential diagnostic criterion, our data show that this feature is a specific but not sensitive marker of prostatic adenocarcinoma. This feature was present in most tumor cells only in 4 of 8 cases in this study, whereas only occasional tumor cells showed a prominent nucleolus in the remainder. We believe that the presence of an oval or round neoplastic cell nucleus with smooth borders; fine, evenly distributed chromatin;
and a lack of significant pleomorphism should raise the suspicion of prostatic adenocarcinoma.

Since prostatic adenocarcinoma is the most frequent malignant neoplasm in elderly men,2-4 it is expected that some patients with high-grade TCC also may have prostate adenocarcinoma. Indeed, 4 of 15 patients with high-grade TCC in the present study also had a history of prostatic adenocarcinoma, and simultaneous metastases of both malignant neoplasms developed in the pelvic lymph nodes in 1 of these patients. The cystoprostatectomy specimen from this patient showed prostatic adenocarcinoma with a combined Gleason score of 7. However, in none of these patients did the prostatic adenocarcinoma involve bladder wall at the time TCC was diagnosed, and prostatic adenocarcinoma cells were not observed in their urine samples. It is interesting to note that the prostatic adenocarcinomas in these patients resulted in Gleason scores of 7 or less, in contrast with the Gleason scores of greater than 8 for the prostatic adenocarcinomas that shed tumor cells in urinary cytology.

Immunostaining for prostate-specific antigen or prostatic acid phosphatase, well known for high sensitivity and specificity, has an established role in confirming the diagnosis of prostatic adenocarcinoma, especially that of metastatic lesions. Such a role in urine cytology is, however, limited, since cell blocks, highly suitable for satisfactory immunostaining, rarely are prepared for urinary cytology specimens; on the other hand, immunostaining on prestained smears is unreliable. Indeed, material suitable for immunostaining was available for only 1 case (1 cell block positive for prostate-specific antigen) in our study. The limitation of...
immunohistochemical staining in this context highlights the importance of differential diagnostic criteria based on routine cytology preparations.

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References