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PATHOLOGY

Small cell carcinoma of the prostate. A morphologic and immunohistochemical study of 95 cases

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Small cell carcinoma of prostate is rare, with the literature consisting of case reports and small series. The current work analyzes the morphology and immunohistochemistry of 95 cases of prostatic small cell carcinoma diagnosed at our institution. Specimens included 55 needle biopsies, 27 transurethral resections, 4 radical prostatectomies, and 9 biopsies from metastatic sites (some patients with > 1 procedure). Patients ranged in age from 44 to 92 years old (mean: 69 y). Although serum prostate-specific antigen (PSA) in some cases was very high (up to 1896 ng/mL), the median value was only 4.0 ng/mL. Of cases with available information, 33/78 (42%) had a history of usual prostatic adenocarcinoma. The interval between the diagnosis of small cell carcinoma and prior usual prostatic cancer ranged from 1 to 300 months (median 25 mo). Pure small cell carcinoma was seen in 54/95 (57%) of cases with the remaining cases admixed with prostate adenocarcinoma. In cases with adenocarcinoma, there was a sharp demarcation between small cell carcinoma and adenocarcinoma in 20.5% of cases; in the remaining cases there was gradual merging of the 2 components. In mixed cases, small cell carcinoma predominated (median: 80% of the tumor); the Gleason score of the adenocarcinoma was > or = 8 in 85% of these cases. In 61 cases (64%), small cell carcinoma was classic “oat cell” morphology with remaining the “intermediate cell” variant. Of the 95 cases: necrosis was seen in 40% (2% to 95% of the tumor); giant bizarre cells in 19%; Indian filing in 21%; rosette formation in 29%; focal vacuolated cytoplasm in 18%; and desmoplasia in 20%. Most (88%) of small cell carcinoma were positive for at least 1 neuroendocrine marker. In the small cell carcinoma component, 14/73 (19%) were positive for PSA, 17/61 (28%) positive for prostein (P501S), and 15/59 (25%) positive for prostate-specific membrane antigen, although often very focally. Stains for thyroid transcription factor-1 were positive in 23/44 (52.3%) cases. In this, the largest study of prostatic small cell carcinoma, we highlight the presence of morphologic features that may result in its underdiagnosis. Other more classic histologic features of small cell carcinoma along with rosettes are critical for its accurate diagnosis. P501S and prostate-specific membrane antigen were better in identifying the prostatic origin of small cell carcinoma than PSA, although the majority (60%) of prostatic small cell carcinomas were negative for all 3 markers.

Editorial Comment

The variant small cell carcinoma of the prostate must be recognized by the pathologist. These rare tumors have an aggressive course and the average survival of patients is less than a year. Most of these tumors show neuroendocrine differentiation demonstrated by immunohistochemistry with markers like NSE, synaptophysin, or chromogranin. Due to these unique features small cell carcinomas are not histologically graded.

Approximately half of the tumors are associated with conventional prostate adenocarcinoma. It is important to note that neuroendocrine differentiation may occur during progression of prostate conventional carcinomas. Therefore, the tumor may be a conventional adenocarcinoma in the prostate and small cell carcinoma in a metastatic site. In this very large series of Wang and Epstein’s the median value of serum prostate-specific antigen was 4.0 ng/mL. In mixed cases, small cells predominate and the Gleason score of the conventional component is high (> or = 8 in 85% of the cases).

A review of the literature of genitourinary small cell carcinoma, Mackey et al. (1) found cisplatin chemotherapy to be beneficial for bladder tumors but only surgery was prognostic for prostate small cell

carcinomas. Others suggest treating small cell carcinoma of the prostate with the same combination chemotherapy used to treat small cell carcinoma in other sites like, for example, “oat cell carcinoma” of the lung (2-4).

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Pseudocarcinomatous epithelial hyperplasia in the bladder unassociated with prior irradiation or chemotherapy

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Pseudocarcinomatous epithelial hyperplasia in the bladder is a little known phenomenon, recognized to be associated with prior irradiation and/or chemotherapy. Whether this process can occur outside of this setting has not been studied. We identified 8 of these cases mimicking invasive urothelial carcinoma from our consultation files from 07/04 to 07/06 with no prior history of radiation or chemotherapy. The mean age at diagnosis was 65 years (range, 42 to 81 y), with 5 of the 8 males. Seven patients had a potential etiology for these changes that could either have resulted in localized ischemia or injury to the urothelium. These included case 1: atrial fibrillation, hypertension, congestive heart failure, gastrointestinal bleeding, and coronary artery vascular disease; case 2: coronary angioplasty, atrial fibrillation, hyperlipidemia, and amputation of arm for ischemia; case 3: hypertension, uncontrolled diabetes, hyperlipidemia, and atrial fibrillation; case 4: underlying arteriovenous malformation of the bladder; cases 5 to 6: history of indwelling Foley catheter; and case 7: history of radical prostatectomy for prostate cancer but no radiation. One patient had no potential contributing factors. All 8 patients presented with gross hematuria. At cystoscopy, 7 patients had polypoid lesions with 1 appearing nonpolypoid. Histologically, all cases showed epithelial proliferation of urothelium with cells having prominent eosinophilic cytoplasm. This process that mimicked invasive cancer within the lamina propria was marked in 3 cases (38%). Moderate nuclear pleomorphism was seen in 6 cases (75%). Only 1 case revealed mitotic figures. Ulceration was seen in 1 case. All cases showed some degree of hemorrhage with hemosiderin deposition identified in 3 cases (38%). Fibrin deposition was present in 1 case within the stroma, 3 cases in the vessels, and 4 cases in both. Five cases show stromal fibrosis. Edema and vascular congestion were common features (90% and 100%, respectively).

Six out of 8 cases were accompanied by moderate to marked acute and chronic inflammation. The original diagnosis included nested variant urothelial carcinoma (1 case), atypical suspicious for invasive carcinoma (5 cases), hemangioma (1 case), and eosinophilic cystitis (1 case). Patients were followed for a mean of 16.5 months (range, 10 to 34 mo), and none developed bladder cancer. As a rare response to ischemia and chronic irritation, pseudocarcinomatous epithelial proliferations in the bladder may be confused with invasive urothelial carcinoma. Pathologists must be aware of the histologic changes mimicking cancer, and recognize that it can occur outside of the setting of prior irradiation or chemotherapy.

Editorial Comment

Irradiation and/or chemotherapy induce well known lesions in the urinary bladder. They include: acute cystitis with desquamation of the urothelial cells, hyperemia, edema in the lamina propria, atypical epithelial and/or stromal cells, hyalinization and thrombosis of the vessels, and prominent telangiectatic vessels that explain the hematuria that often occurs. Late complications of radiation injury include ulcers, marked contraction of the bladder because of fibrosis, and ureteral strictures that may lead to severe pyelonephritisd and death (1).

A pitfall for the pathologist in radiation cystitis is pseudocarcinomatous proliferation of the urothelium simulating invasive urothelial carcinoma. In 2000, Baker and Young (2) reported 4 cases with this lesion. It is a reactive process and the authors point out some clues for the correct diagnosis: absence of mitotic figures, preservation or decrease of the nuclear-to-cytoplasmic ratio, prominent vacuolar change, and squamoid appearance of the epithelium.

The report of Lane and Epstein's is very important because it adds to pseudocarcinomatous epithelial hyperplasia in the bladder causes unassociated with prior irradiation or chemotherapy that must be known by the pathologist. One patient had no potential contributing factor, but 7 patients had ischemia and/or chronic irritation as possible causes for this reactive lesion mimicking invasive urothelial carcinoma. We had the opportunity to see in our Institution a biopsy of the urinary bladder of a 44-year-old male showing pseudocarcinomatous hyperplasia unassociated with prior irradiation or chemotherapy. This reactive lesion was associated to chronic cystitis due to a rectalvesical fistula secondary to diverticulitis.

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