Low-Grade Neuroendocrine Carcinoma (Carcinoid Tumor) of the Prostate

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• A case of primary, prostatic, low-grade neuroendocrine carcinoma (carcinoid tumor) is described. The patient is an 86-year-old man who presented with symptoms of gross hematuria of several days' duration. Physical examination and a bladder biopsy specimen revealed the presence of a primary adenocarcinoma of the bladder with invasion into the muscularis propria. A cystoprostatectomy was performed, which revealed the presence of invasive adenocarcinoma of the bladder. Prostatic sampling demonstrated the presence of a low-grade neuroendocrine carcinoma (carcinoid tumor) and a small focus of well-differentiated conventional adenocarcinoma. Immunohistochemical studies using neuroendocrine markers clearly demarcated the presence of the neuroendocrine tumor. The case presented herein highlights the ubiquitous distribution of neuroendocrine neoplasms along the male genitourinary tract and the presence of 3 separate neoplasms in the genitourinary tract.

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Prostatic carcinoma is one of the leading causes of morbidity and mortality in men. However, for the most part, prostatic malignancies are those of conventional adenocarcinomas, leaving stromal malignancies and other unusual epithelial malignancies as a small percentage of prostatic primary neoplasms.[1] Primary prostatic neuroendocrine tumors, although rare, have been documented in the literature. Interestingly, of the neuroendocrine tumors, the more common are those of high-grade histologic types, such as small cell carcinomas, leaving those of low-grade malignancy, such as well-differentiated (low-grade) neuroendocrine carcinoma (carcinoid tumor), as an unusual phenomenon. The case presented herein highlights the occurrence of such a neoplasm in the prostate in association with 2 additional genitourinary tumors, including bladder adenocarcinoma and conventional prostatic carcinoma.

REPORT OF A CASE

Clinical Features

An 86-year-old man presented with gross hematuria of several days' duration. The patient had no other pertinent history of neoplasia elsewhere. A cystoscopic examination was performed, the results of which showed an abnormal mucosal lining. A bladder biopsy was performed, and the specimen was interpreted as adenocarcinoma of the bladder invading into the muscularis propria. A cystoprostatectomy was evaluated and performed. Clinically, the patient's tumor was staged as T3a.

Pathologic Features

The bladder showed a moderately differentiated adenocarcinoma composed of irregular glands with round-to-polygonal cells, hyperchromatic nuclei, and numerous mitotic figures. The tumor invaded into the muscularis propria with areas of penetration into perivesical adipose tissue. Sections of the prostate showed a well-defined tumor nodule with focal calcification (Figure, A). This tumor nodule was composed of small cells with uniform nuclei without pronounced nuclear atypia or increased mitotic activity (Figure, B and C). The cells appeared to be arranged in short cords or small cellular aggregates with vague nesting pattern dissecting collagen bundles. Adjacent prostatic glands showed glandular hyperplasia. In other areas, a small focus of prostatic conventional adenocarcinoma, Gleason 6 (3 + 3), was also found.

Immunohistochemical studies were performed in the prostatic neoplasms. Prostatic acid phosphatase, chromogranin (Figure, D), and synaptophysin showed strong positive reactions in tumor cells in the neuroendocrine component, whereas prostate-specific antigen had a negative reaction. Other neuroendocrine markers, including serotonin, showed focal weak positive staining, whereas calcitonin staining was negative. On the other hand, prostate-specific antigen and prostatic acid phosphatase showed strong positive reactions in tumor cells in the conventional carcinoma, whereas all the neuroendocrine markers produced negative reactions.

COMMENT

Primary neuroendocrine carcinomas of the prostate are rare. When these tumors occur in the prostate, they are most likely of high-grade histologic type, namely, small cell carcinoma. Interestingly, tumors of low-grade histologic type, such as well-differentiated (low-grade) neuroendocrine carcinomas (carcinoid tumors), are exceedingly rare.

Several publications of primary prostatic carcinoid tumor have appeared in the literature. However, credit for the first description of prostatic carcinoid is given to Wasserstein and Goldman,[2] who first described a single case in 1979. Interestingly, several of these descriptions of carcinoid tumor in the prostate have also been in association with conventional prostatic adenocarcinomas.[3,4] In some instances, hormonal secretion has been associated with these tumors.[5,6] A single case of primary prostatic carcinoid in conjunction with multiple endocrine neoplasia 2B

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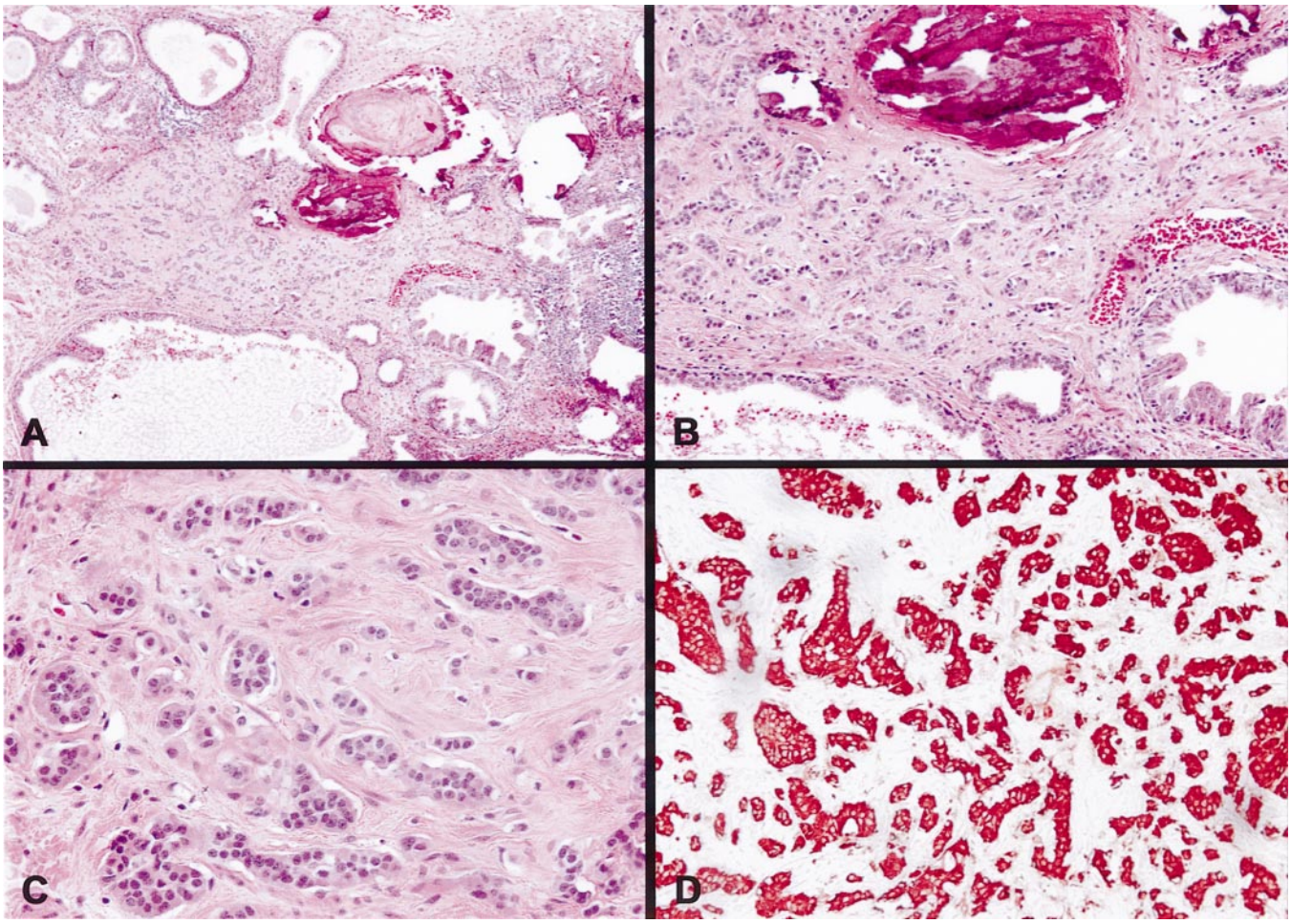

A, Low-power view of a small, well-defined tumor nodule with focal calcification. Adjacent glands show focal, high-grade prostatic intraepithelial neoplasia (hematoxylin-eosin, original magnification ×25). B, Intermediate-power view showing a nesting pattern (hematoxylin-eosin, original magnification ×30). C. High-power view showing a homogenous cell population without evidence of nuclear pleomorphism or mitotic activity (hematoxylin-eosin, original magnification ×40). D, Chromogranin immunohistochemical stain showing strong positive reaction in tumor cells (original magnification ×40).

in a child has also been documented.[7] Furthermore, the development of neuroendocrine neoplasia evolving from previous conventional adenocarcinoma has also been described.[8] However, more important is the proper identification and classification of neuroendocrine carcinoma. It is possible that in a given tumor a conventional adenocarcinoma may show neuroendocrine features, the so-called carcinoid-like growth pattern, whereas, on the other hand, a conventional prostatic adenocarcinoma may also show positive immunostaining for neuroendocrine markers. Such characteristics have been amply presented in the literature.[9–14] Some authors have speculated that the tumors in which neuroendocrine differentiation is present behave more aggressively. Thus, it becomes extremely important to determine whether a tumor is a conventional adenocarcinoma with neuroendocrine differentiation or a true neuroendocrine carcinoma of either high- or low-grade morphologic features (small cell carcinoma or carcinoid tumor). It is expected that those tumors of low-grade histologic type will behave in a more indolent fashion contrary to those of high-grade morphologic type. Even though the behavior of the carcinoid tumor is unpredictable, one would argue that most individuals have an indolent follow-up. Interestingly, a single case of prostatic carcinoid tumor with lymph node metastasis has been described.[15] However, the fact that the neoplasm in question was positive for prostate-specific antigen and prostatic acid phosphatase suggests the possibility of adenocarcinoma with carcinoid-like features.

In the case presented herein, we were able to study both prostatic tumors and the bladder adenocarcinoma for possible neuroendocrine differentiation. The bladder adenocarcinoma was of the conventional type, with no evidence of neuroendocrine differentiation. Regarding the prostatic neoplasms, one, the low-grade neuroendocrine carcinoma (carcinoid tumor), was positive for the neuroendocrine markers (chromogranin and synaptophysin) and also showed positive staining for prostatic acid phosphatase. The tumor cells were negative for prostate-specific antigen. On the other hand, the conventional adenocarcinoma showed negative staining for neuroendocrine markers. Those findings supported the fact that 3 different and independent neoplastic processes in the genitourinary tract were present. Those neoplasms of the prostate were of the low-grade malignancy, whereas one in the bladder was not only of high-grade malignancy but also of advanced clinical stage. The carcinoid tumors in the prostate may

cross-react with prostatic acid phosphatase but not with prostate-specific antigen.

Our findings suggest that low-grade neuroendocrine carcinoma (carcinoid tumor) may pose a diagnostic challenge in a core prostatic biopsy specimen. The finding of such a neoplasm in the prostate does not rule out the possibility of an associated conventional adenocarcinoma. In this setting, serum levels of prostate-specific antigen should be carefully analyzed and correlated with pathologic findings. On the contrary, the presence of a prostatic neoplasm with neuroendocrine features should be evaluated with caution, since conventional adenocarcinomas may show a carcinoid-like growth pattern. In addition, conventional adenocarcinomas may also show positive staining for neuroendocrine markers. The diagnosis of low-grade neuroendocrine carcinoma (carcinoid tumor) should be reserved for those cases in which the histologic findings and the immunostains fit the case. It appears that a true prostatic carcinoid tumor may not show reactivity for prostate-specific antigen, a feature seen in our case, which may be useful in the separation of these neoplasms in more difficult biopsy specimens.

References

1. Young RH, Srigley JR, Amin MB, Ulbright TM, Cubilla AL. *Tumors of the Prostate Gland, Seminal Vesicles, Male Urethra, and Penis*. Washington, DC: Armed Forces Institute of Pathology; 2000. *Atlas of Tumor Pathology*; 3rd series, fascicle 28.
2. Wasserstein PW, Goldman RL. Primary carcinoid of the prostate. *Urology.* 1979;13:318–320.
3. Montasser AY, Ong MG, Metha VT. Carcinoid tumor of the prostate associated with adenocarcinoma. *Cancer.* 1979;44:307–310.
4. Capella C, Usellini L, Buffa R, Frigerio B, Solcia E. The endocrine component of prostatic carcinomas, mixed adenocarcinoma-carcinoid tumours and non-tumour prostate: histochemical and ultrastructural identification of the endocrine cells. *Histopathology.* 1981;5:175–192.
5. Ghali VS, Garcia RL. Prostatic adenocarcinoma with carcinoidal features producing adrenocorticotropic syndrome: immunohistochemical study and review of the literature. *Cancer.* 1984;15:1043–1048.
6. Slater D. Carcinoid tumor of the prostate associated with inappropriate ACTH secretion. *Br J Urol.* 1985;57:591–592.
7. Whelan T, Gatfield CT, Robertson S, et al. Primary carcinoid of the prostate in conjunction with multiple endocrine neoplasia II-b in a child. *J Urol.* 1995; 153:1080–1082.
8. Stratton M, Evans DJ, Lampert IA. Prostatic adenocarcinoma evolving into carcinoid: selective effect of hormonal treatment. *J Clin Pathol.* 1986;39:750–756.
9. Almagro UA, Tieu TM, Remeniuk E, Kueck B, Strupf K. Argyrophilic, "carcinoid-like" prostatic carcinoma: an immunohistochemical study. *Arch Pathol Lab Med.* 1986;110:916–919.
10. Turbat-Herrera EA, Herrera GA, Gore I, Lott RL, Grizzle WE, Bonnin JM. Neuroendocrine differentiation in prostatic carcinomas: a retrospective autopsy study. *Arch Pathol Lab Med.* 1988;112:1100–1105.
11. di Sant'Agnese PA. Neuroendocrine differentiation in human prostatic carcinoma. *Hum Pathol.* 1992;23:287–296.
12. di Sant'Agnese PA, Cockett AT. The prostatic endocrine-paracrine (neuroendocrine) regulatory system and neuroendocrine differentiation in prostatic carcinoma: a review and future directions in basic research. *J Urol.* 1994;152:1927–1931.
13. Schmid KW, Helpap B, Totsch M, Kirchmair R, et al. Immunohistochemical localization of chromogranin A and B and secretogranin II in normal, hyperplastic and neoplastic prostate. *Histopathology.* 1994;24:233–239.
14. di Sant'Agnese PA. Neuroendocrine cells of the prostate and neuroendocrine differentiation in prostatic carcinoma: a review of morphologic aspects. *Urology.* 1998;51:121–124.
15. Azumi N, Shibuya H, Ishikura M. Primary prostatic carcinoid tumor with intracytoplasmic prostatic acid phosphatase and prostate-specific antigen. *Am J Surg Pathol.* 1984;8:545–550.