In recent years, small cell carcinoma has increasingly been recognized in the urinary bladder. \(^1\) Many of these tumors evolved from high-grade urothelial carcinoma. The spectrum of neuroendocrine tumors reported in the urinary bladder also includes large cell neuroendocrine carcinoma\(^2,3\) and carcinoid tumors.\(^4\)\textendash\(^17\) Carcinoid tumors of the urinary bladder are rare, and widely used textbooks and monographs give scant information about these tumors and do not provide illustrations or describe additional cases.\(^16\)\textendash\(^20\) A critical review of the literature reveals only 4 previously reported pure carcinoid tumors of the urinary bladder in which there was convincing evidence of neuroendocrine differentiation.\(^8,15\)\textendash\(^17\) In this report, we describe the clinical, histopathologic, and immunophenotypic features of 2 additional pure carcinoid tumors of the urinary bladder and review the literature.

**REPORT OF CASES**

**Clinical Findings**

**Case 1.**—A 69-year-old man who smoked cigarettes underwent urologic evaluation for microscopic hematuria. The results of cystoscopy, a renal ultrasound examination, and urine cytology were normal. He continued to smoke cigarettes and 6 years later again had asymptomatic hematuria. Cystoscopy revealed a 3-mm smooth-surfaced sessile polypoid lesion just superior to the prostate at the level of the bladder neck, and some areas of patchy mucosal erythema. The polyp was excised through the cystoscope. The findings on a renal ultrasound examination were normal.

**Case 2.**—A 47-year-old man was admitted to the hospital for hematuria. Cystoscopy showed a 7-mm sessile polypoid mass at the junction of the posterior wall and bladder neck. The tumor was excised through the cystoscope. Initial competing differential diagnoses of the tumor were adenocarcinoma of the bladder and urothelial carcinoma with extensive glandular differentiation.

**Microscopic Findings**

Both tumors were ovoid masses covered by attenuated layers of normal urothelium, which showed foci of cystitis glandularis in case 1. Small cystic spaces were present in the tumor in case 1 (Figure, A). Both tumors were composed of anastomosing cords, acini, and cribriform structures of columnar and cuboidal cells (Figure, B). The neoplastic cells had granular eosinophilic cytoplasm that was most visible below the nuclei at the bases of the cells (Figure, C). The nuclei were round to oval, with finely stippled chromatin and generally inconspicuous nucleoli, although occasional larger nuclei were present in case 2 (Figure, D). Mitotic figures were rare, and there were no foci of necrosis. Nuclear crush artifact was absent. A mucicarmine stain revealed intracytoplasmic mucin in case 1 and intraluminal mucin in both tumors.

**Immunohistochemical Findings**

In both tumors, 80% to 90% of the cells had positive reactions with antibodies to the neuroendocrine markers chromogranin (Figure, E) and synaptophysin (Figure, F). The intracytoplasmic granular positive reactions were particularly evident in the basal poles of the columnar cells, paralleling the polarization of the granular eosinophilic cytoplasm. There was less reactivity with antibodies to other neuroendocrine markers. Antibodies to CD56/NCAM decorated the plasma membranes of 30% of the cells in case 1 and 10% of the cells in case 2. The antibody to serotonin stained 40% of the cells in case 1 and less than 5% of the cells in case 2. The antibody to thyroid transcription factor 1 (Figure, H) was expressed in 20% of the tumor cell nuclei in case 1 (Figure, I) but was not detected in case 2. The results of staining for cytokeratin 20 were negative in both tumors. Staining for cytokeratin 7 was strong in case 1 and present in 80% of the cells, whereas the results of staining for cytokeratin 7 were negative in case 2. Antibodies to prostate-specific antigen, prostatic acid phosphatase, and S100 protein did not react with any of the cells of either tumor.

**MATERIALS AND METHODS**

Both tumors were retrieved from the consultation files of one of the authors (J.N.E.). Tissue specimens from the 2 patients were
fixed in formalin, embedded in paraffin, and stained with hematoxylin-eosin. Immunohistochemical stains were performed using the streptavidin-biotin peroxidase method. The primary antibodies and their final dilutions were cytokeratin 7 (clone K72; Ventana Medical Systems, Inc, Tucson Ariz; dilution provided by manufacturer); cytokeratin 20 (clone Ks20.8; Ventana; dilution provided by manufacturer); chromogranin (clone LK2H10; Ventana; dilution provided by manufacturer); synaptophysin (polyclonal; Ventana; dilution provided by manufacturer); serotonin (clone 5HT-H209; Dako Corporation, Carpinteria, Calif; prediluted by manufacturer); S100 (Ventana; dilution provided by manufacturer); CD56/neural cell adhesion molecule (NCAM) (clone 1B6; Novocastra Laboratories Ltd, Newcastle Upon Tyne, United Kingdom; dilution 1:80); thyroid transcription factor 1 (clone 8G7G3/1; Dako; dilution 1:50); CD99 (O13; Signet, Dedham, Md; dilution 1:40); prostate-specific antigen (Ventana; dilution provided by manufacturer); and prostatic acid phosphatase (Ventana; dilution provided by manufacturer). The nuclei were counterstained with hematoxylin.

COMMENT

Neuroendocrine neoplasms of the urinary bladder are uncommon and consist almost entirely of small cell carcinoma.1,13,14 Two carcinoid tumors have been reported in association with small cell carcinoma.13,14 In one of these, the carcinoid tumor and small cell carcinoma were mingled, and in the other, the small cell carcinoma and carcinoid tumor appear to have been independent. Only 12 cases of primary pure carcinoid tumor of the urinary bladder have been reported.4-12,15-17 A critical review of the descriptions and illustrations of these reports leaves only 4 in which the morphology and evidence of neuroendocrine differentiation provide convincing evidence that the tumors were carcinoid tumors.8,13-17 In 4 of the reports of so-called primary pure carcinoid tumor of the urinary bladder with photomicrographs, 3 show small cell carcinomas,5,7,9 and 1 shows a paraganglioma.5 Photomicrographs were not provided for the tumor reported by Jia,11 but the tumor did not react with argyrophil and argentaffin stains. The tumor described by Murayama et al10 contained argyrophilic granules but behaved more aggressively than would be expected of a carcinoid tumor. The nature of the lesion reported by Feyrter4 in 1951 is uncertain, and it may have been an inverted papilloma with...
argyrophilic cells. The tumor reported by Yang et al in 1985 lacked argyrophilic and argentaffin granules, and ultrastructural micrographs appear to show lysosomes rather than neurosecretory granules.

The remaining 4 previously reported pure carcinoid tumors of the urinary bladder and extramural carcinoma of the urinary bladder. However, differentiation to small cell carcinoma is another manifestation of small cell carcinomas and in small cell carcinomas of the urinary bladder: case report and review of the literature. In conclusion, carcinoid tumors of the urinary bladder are rare neoplasms that occur in both sexes, predominantly during the fifth and sixth decades of life. The tumors present with hematuria, are typically located in the bladder neck or trigone, and are small and usually curable by excision through the cystoscope. Urinary bladder carcinoid tumors typically have a glandular architecture and neuroendocrine differentiation that is readily confirmed by immunohistochemical staining for markers such as chromogranin and synaptophysin.

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References