

CASE REPORT

The Nested Variant of Urothelial Carcinoma: an Aggressive Tumor Closely Simulating Benign Lesions

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The "nested" variant is a rare form of urothelial carcinoma and its biologic behavior is highly aggressive. Herein two new cases of nested variant of urothelial carcinoma with immunohistochemical examination are presented. In one of the cases, the tumor extended through the bladder wall into the perivesicular soft tissue, prostatic urethra and left vesicula seminalis,

and metastasized to obturator lymph nodes. In the other case, invasion of muscular layer was observed and three recurrences were developed during a follow-up period of 23 months. Both tumors of our study demonstrated high p53 and Ki-67 indices, supporting the aggressive nature of such tumors. (Pathology Oncology Research Vol 12, No 2, 105–107)

Key words: urothelial carcinoma, nested variant

Introduction

The nested variant is a rare but important form of urothelial carcinoma, which was first described by Talbert and Young in 1989.¹ Until now, approximately 80 cases have been reported in the English literature. The nested variant of urothelial carcinoma (NV-UC) is characterized by foci of small nests and tubules of urothelial cells with low-grade nuclear features, infiltrating the lamina propria and muscularis propria of the bladder. Despite its innocuous appearance, the clinical course of NV-UC is generally highly aggressive,²⁻⁶ and to date, the optimal treatment procedure has not been well established due to the rarity of the tumor. We report two new cases of NV-UC with their immunohistochemical features.

Case reports

Case 1

A 78-year-old man presented with urinary urgency, increased frequency, and nocturia for a one year period and one episode of gross hematuria. Ultrasonographic examination revealed a polypoid mass 5 cm in diameter in the left posterolateral wall of the bladder. The mass located at the

close proximity to the left ureteric orifice, and hydronephrosis was observed in the left kidney. A transurethral resection was performed to bladder and prostatic urethra. Pathologic examination revealed small, closely packed nests of epithelial cells infiltrating the lamina propria and muscularis propria in the bladder wall (*Figure 1*). The tumor cells were uniform with only focal moderate atypia. Tumoral invasion was also seen in prostatic urethra. CT scans of abdomen and thorax and scintigraphic examination demonstrated no metastatic disease. Radical cystoprostatectomy was performed. Microscopically, the tumor extended through the bladder wall into the perivesicular soft tissue, prostatic urethra and left vesicula seminalis. The neoplastic cells were characterized by pale, eosinophilic or clear cytoplasm and rounded nuclei with inconspicuous nucleoli. The cells showed generally mildly atypical features, but occasionally, large atypical cells were present in the deeply infiltrated areas (*Figure 2*). Extensive perineural invasion was noted. Two out of 14 and 2 out of 11 right and left obturator lymph nodes were positive for the tumor, respectively. Iliac lymph nodes were negative for the tumor. The patient was operated on recently, and systemic chemotherapy is planned.

Case 2

The case was a 56-year-old man who had been followed since 1996 for WHO grade 2 papillary urothelial carcinoma located towards the left lateral wall of the urinary bladder. At

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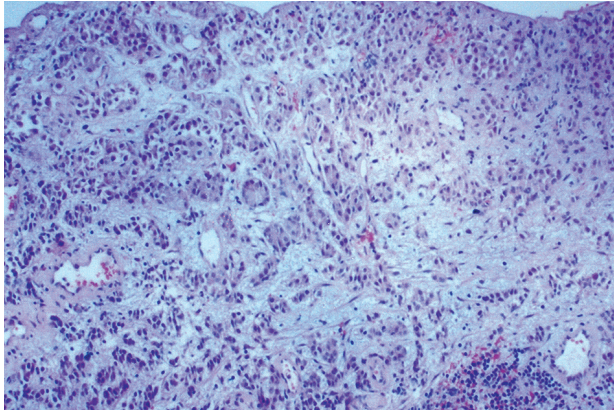


Figure 1. Small, closely packed nests and tubules of epithelial cells infiltrating the lamina propria (HE, x40).

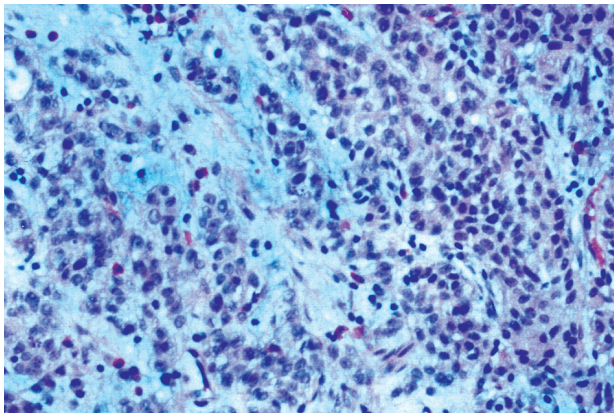


Figure 2. Nests of cells with moderately atypical features in deeply invasive areas (HE, x100).

his routine cystoscopic examination, two small tumor foci in the dome of the bladder were observed, and transurethral resection was performed. No remarkable change was found in left lateral wall. The microscopic features of the neoplasm were markedly different from those of his previous tumor by the infiltration of neoplastic cells, which were arranged in a diffuse pattern of variably sized nests. Invasion of lamina propria and muscular layer were observed. No papillary configuration was seen. The neoplastic cells were characterized by pale to eosinophilic cytoplasm with bland nuclear features. Mitotic activity was low. No perineural invasion was seen. The histopathologic findings were consistent with NV-UC. Radical cystoprostatectomy was planned, but the patient refused the operation. During a follow-up period of 23 months, three recurrences were developed in the form of NV-UC.

Immunohistochemistry

Immunohistochemical studies were performed using monoclonal antibodies to Ki-67, p53, p27^{Kip1}, high-molecular-weight cytokeratin (34bE12), prostate specific anti-

gen (PSA) and low-molecular-weight cytokeratin (AE1). They were applied using a labeled streptavidin-biotin complex (LSAB) kit (DAKO, Carpinteria, USA). Immunohistochemical studies showed that the percentage of cells positive for Ki-67, p53 and p27^{Kip1} was 20%, 40% and 40% in case 1, and 15%, 40% and 50% in case 2, respectively (Figure 3). In both cases, the tumor cells were positive for high-molecular-weight cytokeratin (34βE12), but negative for PSA and low-molecular-weight cytokeratin (AE1).

Discussion

NV-UC is a rare entity with an incidence of less than 0.3% of all invasive bladder tumors.⁵ There is a marked predominance of male patients.²⁻⁶ In four studies, the average age of patients with NV-UC was 67.7 years.^{2,3,5,6} The most common presenting symptom is macroscopic hematuria.^{5,6} At cystoscopy, NV-UC has a widely variable appearance and has been described as a flat tumor, papillary tumor, a submucosal bump, indurated mucosa, or just slightly irregular or hemorrhagic mucosa.⁶ As it was seen in our second case, previous, synchronous and subsequent transitional cell tumors (non-nested type) have been reported in NV-UC cases.⁷

Microscopically, NV-UC is composed of small nests of uniform cells infiltrating the lamina propria and muscularis propria. The neoplastic cells generally exhibit low-grade histologic features. The nuclei are rounded with finely granular chromatin, and the cytoplasm is pale, eosinophilic or clear. Increasing cellular anaplasia with increasing depth of invasion is frequently observed. The nests may be surrounded by stroma that varies from dense and collagenous to loose and edematous. NV-UC must be histologically differentiated from its malignant and benign mimickers. Among the malignant tumors, histologic mimickers of NV-UC include adenocarcinomas of the bladder and prostate. Because of its bland morphology, NV-UC is often confused with benign proliferations, such as von Brunn's nests, cystitis cystica and glandularis, nephrogenic metaplasia, inverted papilloma and paraganglioma but can be differentiated from these by the presence of irregular and confluent nests which may infiltrate deeply into the bladder wall. In addition, tendency towards increasing cellular anaplasia in deeper portion of the lesion is a useful feature in differential diagnosis.

High proliferation index has been reported to occur frequently in NV-UC,^{2,4,6} as in our cases. There are conflicting results about the p53 immunoreactivity in NV-UC. In our study, the neoplastic cells in both cases demonstrated high p53 expression (approximately 40% of neoplastic cells). Lin et al² have shown immunoreactivity for p27^{Kip1} in 11 of 12 cases, and the immunoreactivity was limited to the superficial portion of the tumor in 9 of 11 positive

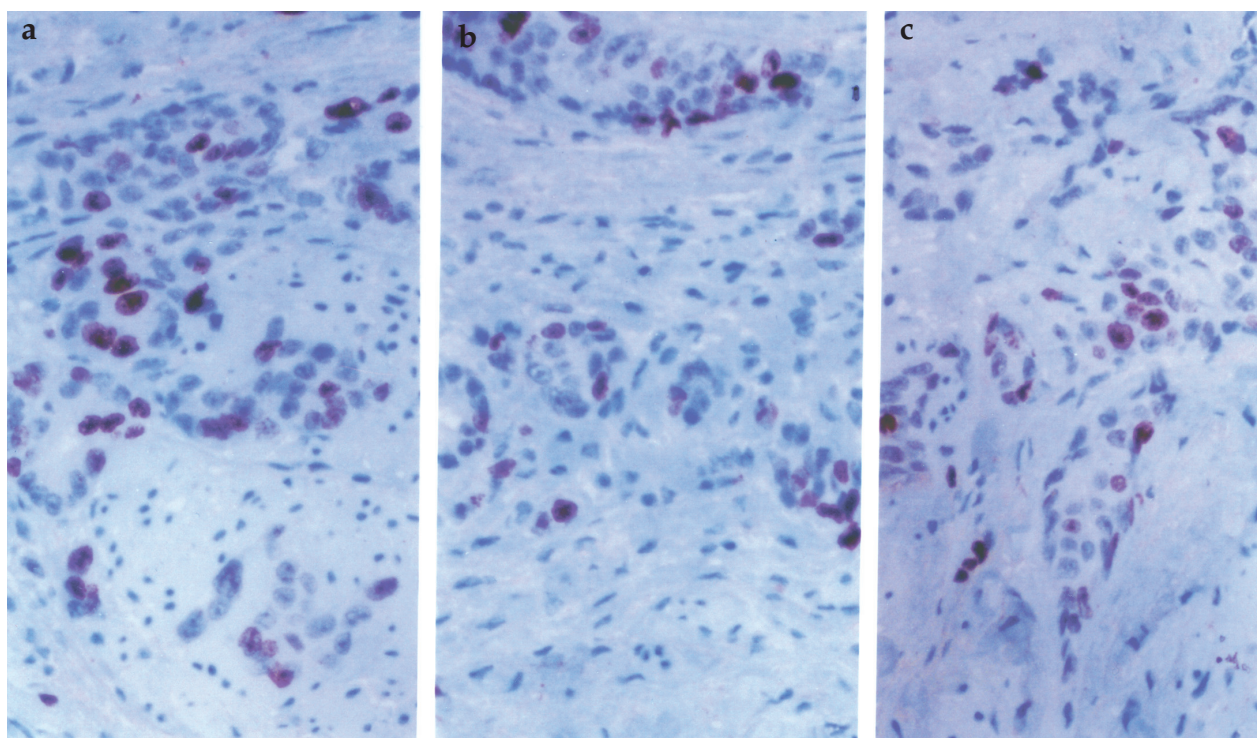


Figure 3. (a) Immunoperoxidase staining for Ki-67, showing nuclear expression within tumor cells (x200). (b) Tumor cells are strongly positive for p53 in some tumor cell nuclei (x200). (c) Positivity of tumor cells for p27^{Kip1} (x200).

cases. The authors stated that the low or absent p27^{Kip1} expression in the deeper component of the tumors in association with high proliferation index might represent common tumorigenic pathways in NV-UC. However, in our cases, there was no significant reduction in the expression of p27^{Kip1}, and no significant staining difference between superficial and deep portions of the tumor was noted.

The clinical course of NV-UC is generally highly aggressive. In the series of Holmang and Johansson,⁵ seven of ten patients treated with locoregional therapy died of disease or treatment complications 4-40 months after diagnosis. Drew et al⁷ reported 55% to 60% of the tumors to show aggressive behavior, with mortality rates similar to high-grade conventional urothelial carcinoma. In the present study, in one of the cases, the tumor extended through the bladder wall into the perivesicular soft tissue, prostatic urethra and left vesicula seminalis, and metastasized to obturator lymph nodes. In the other case, invasion of muscular layer was observed, and three recurrences were developed during a follow-up period of 23 months.

Although radical cystectomy seems the best choice, the optimal treatment procedure has not been well established to date in NV-UC, due to the rarity of tumor and the absence of randomized studies. Postoperative adjuvant chemotherapy and radiation therapy have not been shown to be significantly beneficial in reported cases.^{4,5}

In summary, the NV-UC is a rare but important variant of urothelial carcinoma. Since confusion with benign lesions has led to delay in diagnosis and subsequent treatment, NV-UC should be considered in differential diagnosis of the lesions showing nested type growing pattern in the urinary bladder.

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