

Nested Variant of Urothelial Carcinoma of the Urinary Bladder: Four Case Reports

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Abstract

Nested variant of urothelial carcinoma (NVUC) is a rare histological subtype of urothelial carcinoma. It has a benign appearance with an aspect characterized by confluent small nest or urothelial's cell tubules. However, it shows aggressive clinical course despite the benign-looking histology so it must be differentiated from the benign proliferative lesions. Herein reported are four cases of NVUC. The data was collected from the medical records in the Department of Urology, at the University Hospital Center of Rabat Morocco during the period from January 2014 to December 2017.

Keywords: Nested variant; Urothelial carcinoma; Urinary bladder

Introduction

Urothelial carcinoma of the bladder is the most common malignancy involving the urinary tract system. Nested variant of urothelial carcinoma (NVUC) is one of the morphologic variants of urothelial carcinoma that is characterized by an unusual, bland morphology and a clinical behavior similar to that of high-grade conventional urothelial carcinomas [1]. Although rare, with a reported prevalence of 0.3%, it is more often under recognized as its clinic pathologic spectrum is not well defined [2]. There is no consensus opinion regarding the optimum management of this entity. Herein reported are four cases with a review of the literature on nested variant of urothelial carcinoma.

Methods

Four cases of urothelial carcinoma with the morphologic characteristics of nested variant of urothelial carcinoma were identified from the files of Urology department at the Ibn Sina University Hospital Center of Rabat from January 2014 to December 2017. All patients were treated and followed at the same institution. Age at diagnosis, clinical presentation, pathological stage, and follow-up were extracted from the medical charts.

Discussion

Nested variant of urothelial carcinoma is one of the variants of urothelial carcinoma that was added to the WHO classification in 2004. This tumor was first reported by Stern in 1979 [3], as a benign lesion, but this lesion subsequently recurred. In 1989, Talbert and Young [4] reported 3 cases of nested variant of urothelial carcinoma

which they described as the carcinomas of the urinary bladder with deceptively benign-appearing foci. Murphy and Deana in 1992 [5] coined for this tumor the terminology of nested variant of transitional cell carcinoma, as it resembles von Brunn's nests.

Nested variant of urothelial carcinoma usually occurs in men who are older than 60 years which is similar to the occurrence of classic urothelial carcinoma [6]. It has been reported in patients aged between 42 years and 90 years. Wasco et al. [7] showed that male to female ratio was 2.3: 1.

Clinically, it is a gross hematuria, more rarely a syndrome of obstruction of the upper urinary tract related to a ureteral compression [8]. Often nested variant of urothelial carcinoma at first presentation is diagnosed in an advanced stage and the tumor often involves the ureteric orifices [6]. The clinical outcome of pure or mixed nested variant with usual urothelial carcinoma is similar [7]. In cystoscopy, the lesion found is flat or papillary, moderately indurated, sometimes irregular and hemorrhagic [8]. Urine cytology is of little value [9].

NVUC is histologically characterized by irregular and confluent small nests and abortive tubules composed of urothelial cells infiltrating the lamina propria or muscularis propria, usually without surface involvement [1]. Deep tumour-stroma interface is jagged and infiltrative, and more atypia and focal anaplasia with increasing depth of invasion are one of the features [6]. Typical urothelial is often present [10]. By definition these tumors cannot be high grade nor have overlying surface carcinoma in situ [6].

The cytological features include medium sized round/polygonal cells with abundant, dense, slightly granular basophilic cytoplasm and well-defined cell borders, irregular cell counters, increased nuclear/cytoplasmic ratio, coarse chromatin, and occasional prominent nucleoli [9]. It has been stated that subtle features are not diagnostic themselves.

Immunohistochemical study shows that NVUC is positive for CK7, CK20, p63, Ki-67, and CK903 [11]. The positivity for P53 is variable [6]. Wasco et al. who reported 30 cases, demonstrated that NVUC was positive for CK7 in 93%, CK20 in 68%, and p63 in 92% [7]. However, NVUC stain negatively with Bc12, EGFR, and PSA [6]. Immunohistochemical study may help in differential diagnosis with other malignant tumors. Beltran et al believe that histological features, together with the patient's clinical history and appropriate immunohistochemical studies should help to distinguish NVUC from other closely resembling tumors [12].

Indeed, NVUC must be differentiated from other differential diagnoses such as:

Adenocarcinoma: Colonic differentiation and more prominent atypia [6].

Cystitis cystica/cystitis glandularis: This has no atypia and no invasion [6].

Inverted papilloma: This has no deep invasion [6].

Nephrogenic metaplasia/adenoma: This usually has papillary component, prominent tubular or cystic structures lined by single layer of cuboidal cells, no atypia, and no invasion [6].

Adenocarcinoma of prostate: This is centred in the prostate gland and immunohistochemical stains positively with PSA and PSAP [6].

Urothelial carcinoma with small tubules: This is an invasive carcinoma with small gland-like spaces lined by urothelial cells without intracellular mucin or columnar lining; some authors have considered this as part of nested variant of urothelial carcinoma [13].

Von Brunn's nests: These have no invasion, no prominent atypia, and no focal anaplasia as stated by some authors [8].

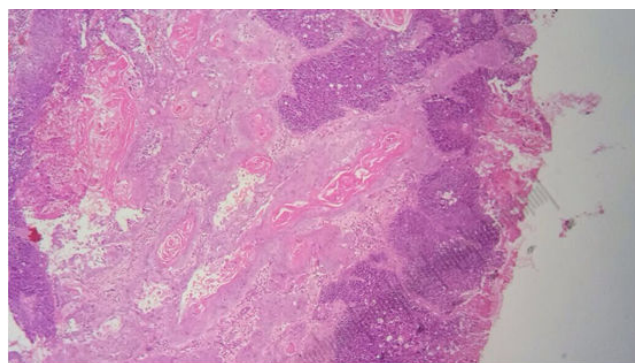
Treatment depends on the behavior of the tumor that is, whether it is indolent or very aggressive. Dhall et al. [1] suggested that NVUC should be considered a high-grade aggressive disease and treated immediately by cystectomy. Mally et al. [14] showed that although NVUC may be diagnosed at a later stage, there was no statistical evidence of the tumor being more aggressive than the typical urothelial carcinoma, when matched for stage. However, they suggested that early cystectomy was beneficial in patients with a clinical stage T1 on restaging biopsy, due to a higher risk of developing nodal metastatic disease. Only stages less than cT1 could be treated conservatively. Linder et al. [15] evaluated the oncologic outcomes after cystectomy in patients with NVUC compared to those with pure forms of urothelial carcinoma. No significant differences were observed in terms of cancer-specific survival or local recurrence-free survival between the two. Some studies have reported a positive outcome for multimodal therapy, while others found this type of cancer to be chemo-radio resistant [16].

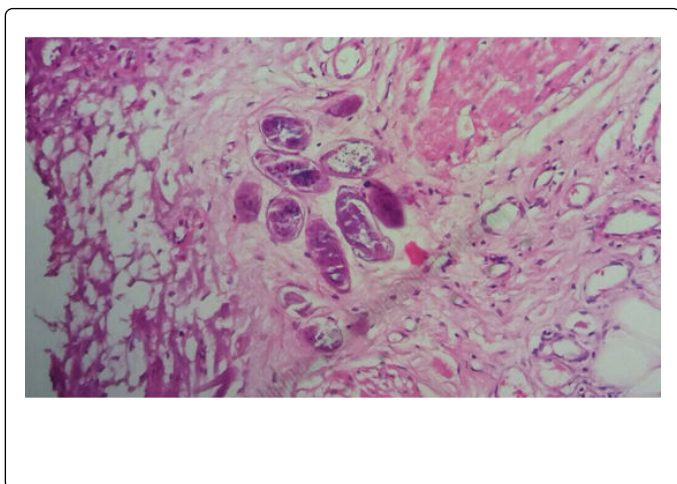
When compared to pure high-grade urothelial carcinoma in transurethral resection of the bladder specimens, NVUC is more often associated with muscular invasion (31 vs. 70%), extra-vesical pathology at cystectomy (33 vs. 83%), and metastatic disease (19 vs. 67%) [7]. The mortality rate for NVUC 40 months after diagnosis is 70%, irrespective of the therapeutic approach [17]. In a recent study, Comperat et al. [18] emphasized that despite the benign cytological appearance and misleading pattern of invasion, NVUC is potentially malignant, with metastatic spread and tumor-related deaths reported.

Studies on NVUC have focused more on its histological features showing that although the tumor presented with innocent cytological features, it seemed to be associated with aggressive tumor behavior, and questions still remain regarding its therapeutic management. A correct and early diagnosis seems to be the only way to improve the survival rates of patients with under-diagnosed tumors for which a consensus regarding the treatment does not exist.

Results

The patients in this series were all male ranging in age from 36 to 78 years old (mean=63 years). All patients presented with hematuria, one of them with obstructive symptoms and another one with acute obstructive renal failure requiring urinary diversion with bilateral nephrostomy. Cystoscopy revealed two tumors located in lateral or anterior wall, 1 case involving the ureteral orifices and trigone, and a multifocal tumor in one case. Transurethral resection of bladder tumor (TUR-BT) was performed in all cases. Histologically, all lesions were composed of small and well-delineated nests of urothelial carcinoma cells infiltrating the lamina propria and muscularis propria (Figures 1 and 2). The carcinoma cells had hyper chromatic and enlarged nuclei. Nested variant of urothelial carcinoma was the only variant of urothelial carcinoma present in all patients associated to papillary carcinoma. Pathologic stage was at least pT2 after TUR-BT in all cases. No patient had neoadjuvant chemotherapy. Two patients underwent cystectomy only, one patient received adjuvant chemotherapy after cystectomy and the last one received chemotherapy because of distant metastases (lymph node and lung). Two patients were alive with a decline of 12 months. One cancer progressed under chemotherapy and the patient died 8 months later, and the evaluation could not be done for one patient.





Conclusion

Nested variant of urothelial carcinoma is an important variant of bladder cancer that has a diagnostic, prognostic, and therapeutic significance. Correct and early diagnosis of this tumor is essential in order to provide early curative treatment and to avoid diagnosis at an advanced stage. There is a need for a multicentre trial to validate the recent finding and to identify treatment protocols.

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