Nested Variant of Urothelial Carcinoma, a Rare Diagnosis: Case Report, and Review of the Literature

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Abstract

Nested variant of urothelial carcinoma is an aggressive neoplasm with less than 50 reported cases. This rare pattern of urothelial carcinoma was first described as a tumor with a "deceptively benign" appearance that may closely resemble non-neoplastic tissue, infiltrating the lamina propria or down to muscularis propria. We report the case of an urothelial carcinoma in a 74-year-old man who presented with gross hematuria. Transurethral resection of neck of urinary bladder was performed. Grossly, the specimen consisted of multiple irregular fragments of light tan rubbery tissue. Histologically, the tumor consisted of a proliferation of benign-looking structures involving lamina propria and detrusor muscle, except for an area of less differentiated infiltrative tumor. Immunohistochemical studies were consistent with infiltrating urothelial carcinoma, nested variant.

The neoplastic cells in nested variant of urothelial carcinoma show little atypia, and they are arranged in nests that mimic normal urothelium or Brunn's nests, leading to a possible under-recognition of this tumor. It is important for pathologists, surgeons, and oncologists to be aware of the possibility of this rare variant of infiltrating urothelial carcinoma since accurate identification and recognition of this entity is important in prognosis, adjuvant therapeutic options, and survival.

Introduction

Urothelial carcinoma is the most common malignancy of the urinary tract system. Urothelial carcinomas can also involve the renal pelvis, ureter, or urethra. But their development is far less common than in the urinary bladder. In urothelial carcinoma the histology is variable. Approximately 70% of urothelial carcinomas of the urinary bladder are noninvasive or superficially invasive; they are usually papillary and exhibit different degrees of differentiation; meanwhile, most urothelial carcinomas with muscle invasion are non-papillary and usually exhibit a high-grade of cytomorphology. These types of urothelial carcinomas can be easily diagnosed histologically by the pathologist.

A variety of criteria have been used for grading and classification of urothelial bladder tumors. The World Health Organization (WHO) in collaboration with the International Society of Urological Pathologists (ISUP) developed a classification system for urothelial transitional cell tumors (1998). This classification scheme was subsequently revised by studies carried out after the consensus, validating its clinical significance thus in 2004 it was accepted as the standard classification system.

Urothelial carcinomas, by this classification system, have been classified into (a) low, grade and (b) high grade depending on the degree of nuclear atypia and abnormalities in architecture with the exception of some tumors, such as, tubular or nested/tubular variant.

In 2004, variants of urothelial carcinoas were added to the World Health Organization classification scheme which include sarcomatoid variant, lymphoepithelioma-like cell variant, micropapillary variant, plasmacytoid variant, micropapillary variant, small cell type and nested variant. These have different biological behaviors but small cell carcinoma of the urinary bladder is very aggressive with a poor prognosis. Nested variant of urothelial carcinoma presents an unusual bland morphology that mimics some benign lesions of the urinary bladder but with a clinical behavior that simulates the clinical behavior of high-grade conventional urothelial carcinomas.

Nested variant of urothelial carcinoma was first reported by Stern. The first reported case was interpreted as a benign lesion, but it subsequently recurred. Thereafter, Talbert and Young reported 3 cases of nested variant of urothelial carcinoma in 1969 who described these carcinomas of the urinary bladder with deceptively benign appearing foci. Murphy and Deana in 1992 formulated for this tumor the terminology of nested variant of transitional cell carcinoma, as it resembles von Brunn’s nests. There are reports that reflect an advanced stage at diagnosis and are thus associated with a poor prognosis. There is no general agreement on the optimum management of nested variant of urothelial carcinoma. We present a case of nested variant urothelial carcinoma.

Case Presentation

This is a 74 year old man who presented with gross hematuria. A transurethral resection of the prostate was performed which revealed an invasive tumor with a deceptively benign appearance. Atypical areas involving the muscularis propria were also focally present. This case was consulted to our department with the working diagnosis of benign versus malignant urothelial tumor and after a careful evaluation (including immunohistochemistry) the diagnosis of infiltrating urothelial carcinoma, nested variant, was reached.

Discussion

The nested variant of urothelial carcinoma is one of the variants of urothelial carcinoma that was added to the WHO classification in 2004. This variant reveals a deceptively benign appearing invasion by nests of cells. This rare tumor is composed of irregular and confluent small nests and abortive tubules which consist of urothelial cells infiltrating the lamina propria or muscularis propria, usually without any evidence of tumor in surface epithelium. This variant was first described in 1969 by Talbert and Young who reported the cases of three men aged from 53 to 77 with carcinoma of the urinary bladder characterized by foci with a benign histologic appearance. This feature lead to a significant delay in the establishment of the correct diagnosis in these cases. The resemblance of the infiltrating carcinoma to von Brunn’s nests, cystitis glandularis, cystitis cystica, and nephrogenic adenoma, alone or in combination, resulted in the diagnostic difficulty of these cases. The features that distinguish these small foci from benign processes include an irregular distribution, large number of closely packed epithelial aggregates, cysticologic atypia and the transitions to unequivocal carcinoma.

Nested variant of urothelial carcinoma with a reported incidence of 0.3% of invasive bladder tumors is either rare or underreported. Lin and associates stated that the nested variants of urothelial carcinoma exhibit aggressive behavior despite their bland histologic features. Wassco and associates stated that the clinical outcome of pure or mixed nested variant with usual urothelial carcinoma is similar. This variant at first presentation is often diagnosed in an advanced stage and often involves the ureteric orifices. It may be misinterpreted as benign as these resemble von Brunn nests. The treatment of choice is radical surgical resection and often there is no evidence of a clearly defined tumor.

Conclusion

Nested variant of urothelial carcinoma is a rare tumor with histologic features that must be carefully identified to establish its diagnosis. In spite of benign features suggestive of Brunn’s nests, small islands of urothelium and cystitis glandularis, a careful search will reveal either tumoral infiltration of muscle or less differentiated areas consistent with malignant tumor. It is often diagnosed at an advanced stage and is associated with a poor prognosis. However, results of a recent study revealed no statistically significant difference between the outcome of patients with nested variant of urothelial carcinoma and patients with conventional urothelial carcinoma of similar stages who had undergone cystectomy. Correct and early diagnosis of this tumor is essential in order to provide early treatment and avoid diagnosis at an advanced stage.

References