Recurrent transitional cell carcinoma of the bladder: A mixed nested variant case report and literature review

Ettore De Berardinis, MD; Gian Maria Busetto, MD; Riccardo Giovannone, MD; Gabriele Antonini, MD; Mariarosaria Di Placido, MD; Vincenzo Gentile, MD

Sapienza Rome University, Policlinico Umberto I, Rome, Italy

Cite as: *Can Urol Assoc J* 2012;6(2):e57-60. http://dx.doi.org/10.5489/cuaj.11094

Abstract

Nested variant of urothelial cell carcinoma (NVUC) is a rare histological entity, with about 80 reported cases. It has a deceptively benign appearance with an aspect characterized by confluent small nest or urothelial's cell tubules. This tumour often resembles inverted papilloma, von Brunn's nests (VBNs), cystitis cystica, nephrogenic metaplasia and sometimes usual transitional cell cancer. It is very important to be able to distinguish between benign lesions and nested variant bladder cancer because, in spite of its bland morphology, there is evidence that it behaves aggressively.

A 70-year-old man with hematuria underwent ultrasound examination and cystoscopy that revealed the presence of a bladder cancer. The trans-uretheral resection of the tumour revealed a solitary high-grade cancer with lamina propria involvement (T1G3). Five months after the operation and after an adjuvant endovesical treatment with Bacillus Calmette-Guérin (BCG), a follow-up cystoscopy revealed a recurrent tumour that was resected. Pathological staging and microscopic examination revealed a high-grade (G3) nested variant transitional cell carcinoma (TCC) with a deep lamina propria involvement (T1b). The tumour was characterized by high expression of the tumour suppressor gene p53 and by immunoreactivity for proliferation marker Ki-67. The patient was then submitted to radical cystectomy and a diagnosis of mixed urothelial nested variant tumour at stage pT2a and grade G3 with a linfatic involvement was made. Twelve months after the first diagnosis of bladder cancer, the patient underwent a cycle of intravenous gemcitabine along with cisplatin.

The aggressive behaviour of this neoplasm suggests that the correct indication should be early radical cystectomy with extended lymph adenectomy to avoid the progression into the bladder wall or the metastatic spread.

Nested variant of urothelial cell carcinoma (NVUC) is a rare histological entity that was described for the first time in 1989 by Talbert and Young.[1] This variant of urothelial cancer is often not recognized and its clinical and pathological characteristics are not completely defined. At present, correct management is still not defined, as well as its relationship with conventional TCC. Solitary nested variant tumours have been observed, as well as cases synchronous with urothelial bladder cancer.[2] Furthermore, there are cases with ureter involvement in association or not with the urinary bladder.[3] About 80 cases are reported and the largest series (30 cases) is described by Wasco and colleagues.[4] Nested variant lesions have a deceptively benign appearance with an aspect characterized by confluent small nest or urothelial's cell tubules infiltrating lamina propria and/or muscular layer. There are urothelial cells with mild pleomorphism, slightly increased nuclear/cytoplasmic ratio and occasionally prominent nucleoli.[5]

This variant of urothelial bladder cancer often resembles clinical and histological features of inverted papilloma, von Brunn's nests (VBNs), cystitis cystica, nephrogenic metaplasia and sometimes usual TCC. It is very important to be able to distinguish between benign lesions and nested variant bladder cancer because, despite its bland morphology, there is evidence of its aggressive behaviour and its capacity to progress to muscle invasive and metastatic disease.

A 70-year-old man, a smoker and with no occupational risk factors, consulted the urology department for hematuria and dysuria characterized by increased voiding frequency and nocturia. He underwent a bladder and kidney ultrasound examination and provide three samples for urinary cytology. Both exams revealed suspected bladder cancer, which was confirmed by the cystoscopic detection of a single right-lateral and trigone wall lesion of about 2 cm in diameter. The patient underwent transurethral resection of the bladder tumour (TUR-B) and random biopsies of suspect areas were performed. The pathological evaluation carried out at the pathology department revealed a high-grade

tumour with lamina propria involvement (T1G3) and wide consensual phlogosis. A second-look TUR-B was performed 6 weeks after the first one and confirmed the prior diagnosis without muscular-layer spread. The patient started endovesical adjuvant immunotherapy with induction BCG, oncee weekly for 6 weeks; 45 days after endovesical treatment, he had a follow-up cystoscopy that revealed a new transition small lesion (less than 1 cm) that was resected. Pathological evaluation confirmed, again, high-grade a urothelial bladder cancer (G3) confined to lamina propria (T1). The patient repeated endovesical treatment with BCG and, after 5 months, a diagnosis of a recurrent tumour was made. The appearance of the tumour, located on the right wall, 2.5 cm in diameter, in the same area of the first resected lesion, was unusual since it was characterized by a mix of papillary cancer and another part resembling benign morphology, similar to inverted papilloma. Computed tomography (CT) scans showed thickened right bladder wall and neither pelvic lymph nodes swelling nor hydronephrosis were described. An endoscopic resection of the tumour, extended to the muscular layer, was performed. Pathological staging and microscopic examination revealed a high-grade (G3) nested variant TCC with a deep lamina propria involvement (T1b), without muscularis mucosae infiltration (Fig. 1). The tumour was characterized by high expression of the tumour suppressor gene p53 (Fig. 2) and by immunoreactivity for proliferation marker Ki-67 (Fig. 3). Both markers, pathological evaluation and high recurrence rate confirmed the high aggressiveness of this cancer; due to this, the patient was submitted to radical cystectomy with extended lymph nodes dissection. After the surgery, the bladder was studied and superficial muscularis mucosae involvement was observed (pT2a); moreover, 3 of 20 resected lymph nodes were positive for metastasis. Twelve months after the first diagnosis of bladder cancer, the patient was referred to the oncology department and a cycle of intravenous gemcitabine along with cisplatin was started.

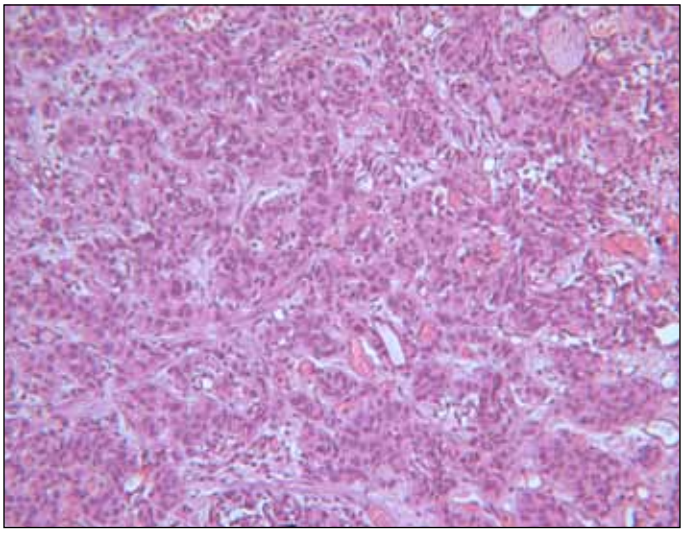

Fig. 1. Transitional cell bladder cancer mixed with nests of urothelial cells.

Discussion

Nested variant bladder cancer is a rare entity,[6] Before its original description by Talber and Young,[1] it was usually described as benign in appearance. Most bladder carcinomas do not represent a diagnostic problem in contrast to transitional cell nested variant histotype that often is similar to lesion of a bland morphology. This is confirmed by the difficult differential diagnosis between these histological appearance and lesions, such as inverted papilloma, VBNs, cystitis cystica and nephrogenic metaplasia.[7] Nest-like structures are the cardinal lesion of both benign and malignant entities that can be misdiagnosed as nested variant bladder carcinoma. In this variant of urothelial carcinoma, the nests must be well-defined and distinguished from the von Brunn ones. Futhermore, when we have limited histological specimens and/or there are no urothelium surface abnormalities, such as carcinoma in situ (CIS), a distinction might be more difficult. The nests of nested urothelial carcinoma are closely packed, with irregular borders, in contrast to VBNs, which are closely packed at the centre of the focus and may be scattered at the peripheral sides. Moreover, hyperplastic nests are usually of relatively uniform size and shape and are not associated with intense edematous or desmoplastic stromal response. In addition, urothelial nests of VBNs and cystitis glandularis are larger. The neoplastic cells of nested carcinoma are medium-sized, round to polygonal in shape, with abundant dense and slightly granular cytoplasm. The nuclei lacked significant nuclear atypia, where, at most, occasional scattered slightly enlarged, hyperchromatic nuclei with small-indistinct nucleoli were noted. The median mitotic count was 1.5/10 high-power fields.

On the other side, inverted papilloma consists of thin anastomizing cords and nests of normal urothelium, with peripheral palisading of basal cells and central streaming.[8,9]

Cytological urine evaluation is not a good indicator of the disease because the cellular atypia is mild and not always present, particularly in non-muscle invasive lesions; moreover, the bland cytomorphologic features of NVUC generate diagnostic problems with urinary cytology specimens. This is an important difference, since urinary cytology is fundamental in the detection of urothelial carcinoma with a high sensitivity (up to 79%) and a high specificity (90%), especially for high-grade lesions. Another difference is with CIS, which tends to shed cells in the urine and is sometimes absent on biopsies.[10] Most patients affected by bladder cancer with confluent nests are male with a mean age >60 years (similar to conventional bladder cancer). The tumour is persistent and often tends to progress; the histology usually confirms

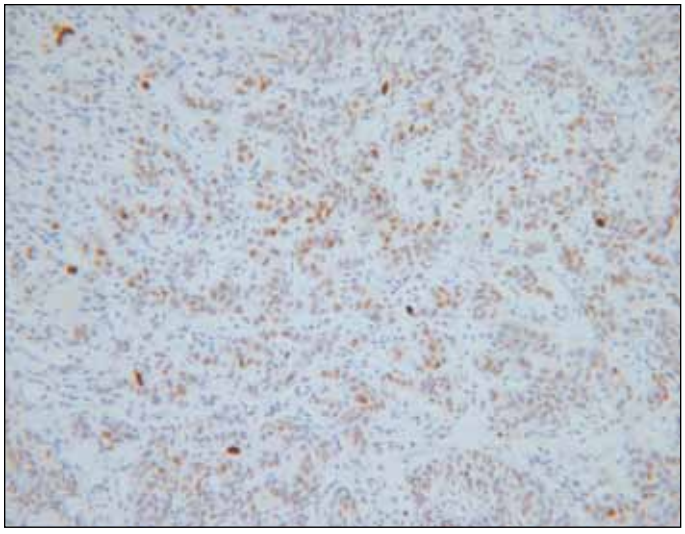

Fig. 2. Tumour cells are strongly positive for p53 in some tumour cell nuclei.

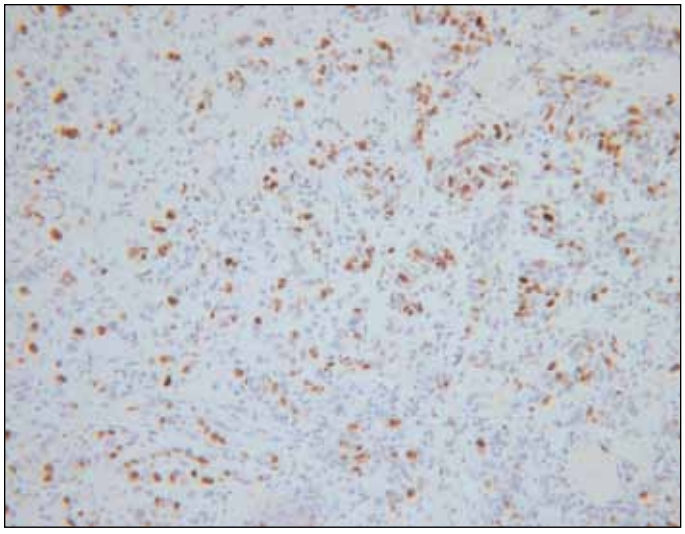

Fig. 3. Immunoperoxidase staining for Ki-67, showing nuclear expression within tumour.

T1/T2 stage.[11] The most common presenting symptom is hematuria, often associated with dysuria characterized by increased urinary frequency and nocturia depending on bladder irritation.[12] There is also one case of renal pelvis and ureter nested variant urothelial tumour, synchronous with high-grade urothelial papillary carcinoma.[13] Furthermore, Lau presented patient with an isolated case of a pelvic tumour with nested differentiation and locally advanced disease at the time of nephroureterectomy. Although rare, these variants of urothelial carcinomas may occur at particular sites and are not to be confused with other pathologic lesions of the renal pelvis.[14] Concerning the cell-cycle regulation, an overexpression of tumour suppressor protein p53 (associated with high cellular proliferative activity) and the loss of cyclin-dependent kinase inhibitor p21 that has the capability to stop the cell-cycle at G1 phase were found after pathological evaluation of the resected tumour. Sten and colleagues confirmed the role of overexpression of p53 in association with a lack of p21 as a negative prognostic factor.[15] The evaluation of the proliferation Ki-67 marker, associated with high recurrence and progression rate in conventional transitional bladder cancer,[16] reported with MIB-1 antibody application, is highly positive in confirming the aggressive behaviour of the neoplasm.

Conclusion

It is important to bear in mind that Ki-67 expression that is low in benign lesions and high in nested variant bladder cancer can be considered a good method to distinguish between the two entities. Although NVUC of the urinary tract is very rare, it is important to be aware of its existence to avoid delays in treatment and to orient the surgical strategy. The aggressive behaviour of this neoplasm suggests that the correct indication should be early radical cystectomy with extended lymph adenectomy to avoid the progression into the bladder wall or the metastatic spread. The response to conventional chemotherapy and to radiation therapy has not been shown as significantly beneficial.[17]

Competing interests: None declared.

This paper has been peer-reviewed.

References

1. Talbert ML, Young RH. Carcinomas of the urinary bladder with deceptively benign-appearing foci. A report of three cases. *Am J Surg Pathol* 1989;13:374-81. http://dx.doi.org/10.1097/00000478-198905000-00004
2. Drew PA, Furman J, Civantos F, et al. The nested variant of transitional cell carcinoma: an aggressive neoplasm with innocuous histology. *Mod Pathol* 1996;9:989-94.
3. Ooi SM, Vivian J, Sinniah R, et al. Nested variant of urothelial carcinoma: a rare presentation. *Urology* 2006;67:843-5. http://dx.doi.org/10.1016/j.urology.2005.10.002
4. Wasco MJ, Daignault S, Bradley D, et al. Nested variant of urothelial carcinoma: a clinicopathologic and immunohistochemical study of 30 pure and mixed cases. *Human Pathol* 2010;41:163-71. http://dx.doi.org/10.1016/j.humpath.2009.07.015
5. Lin O, Cardillo M, Dalbagni G, et al. Nested Variant of Urothelial Carcinoma: A Clinicopathologic and Immunohistochemical Study of 12 Cases. *Mod Pathol* 2003;16:1289-98. http://dx.doi.org/10.1097/01.MP.0000094091.04541.FC
6. Marti Mestre J, Cañis Sánchez D, El Boutaibi A, et al. Nested variant of urothelial carcinoma. A rare histological variant [in Spanish]. *Actas Urol Esp* 2009;33:90-2.
7. Dhall D, Al-Ahmadie H, Olgac S. Nested variant of urothelial carcinoma. *Arch Pathol Lab Med* 2007;131:1725-7.
8. Patriarca C, Colecchia M, Lopez-Beltran A, et al. Nest-Like Features in Bladder, Simulating the Nested Variant of Urothelial Carcinoma. *Int J Surg Pathol* 2011;19:11-9.
9. Cox R, Epstein JI. Large nested variant of urothelial carcinoma: 23 cases mimicking von brunn nests and inverted growth pattern of noninvasive papillary urothelial carcinoma. *Am J Surg Pathol* 2011;35:1337-42. http://dx.doi.org/10.1097/PAS.0b013e318222a653

10. Cardillo M, Reuter VE, Lin O. Cytologic features of the nested variant of urothelial carcinoma: a study of seven cases. *Cancer* 2003;99:23-7. http://dx.doi.org/10.1002/cncr.10955
11. Drew PA, Furman J, Civantos F, et al. The nested variant of transitional cell carcinoma: an agressive neoplasm with innocuous histology. *Mod Pathol* 1996;20:1448-54.
12. Murphy WM, Beckwith JB, Farrow GM. Tumor of the kidney, bladder and related urinary structures. In: *Atlas of tumor pathology*. 3rd series, fascicle II. Washington DC: Armed Forces Institute of Pathology; 1994:233:4-5.
13. Pusztaszeri M, Hauser J, Iselin C, et al. Urothelial carcinoma "nested variant" of renal pelvis and ureter. *Urology* 2007;4:778.
14. Lau SK. Nested variant of urothelial carcinoma of the renal pelvis. *Pathol Res Pract* 2009;205:508-12. http://dx.doi.org/10.1016/j.prp.2008.12.006
15. Stein JP, Ginsberg DA, Grossfeld GD, et al. Effect of p21WAF1/CIP1 expression on tumor progression in bladder cancer. *J Natl Cancer Inst* 1998;90:1072-9. http://dx.doi.org/10.1093/jnci/90.14.1072
16. Asakura T, Takano Y, Iki M, et al. Prognostic value of Ki-67 for recurrence and progression of superficial bladder cancer. *J Urol* 1997;158:385-8. http://dx.doi.org/10.1016/S0022-5347(01)64485-9
17. Xiao GQ, Savage SJ, Gribetz ME, et al. The nested variant of urothelial carcinoma: clinicopathology of 2 cases. *Arch Pathol Lab Med* 2003;127:333-6.

Correspondence: Dr. Ettore De Berardinis Sapienza University of Rome, Viale Regina Elena, 324, 00161, Rome, Italy; ettore.deberardinis@uniroma1.it