

Obesity and Nested Urothelial Carcinoma of the Bladder: Falsely Bland Tumor in Young Man. A Rare Case Report and Literature Review

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ABSTRACT

Background: Nested urothelial carcinoma of the bladder is an invasive histological variant that differs from classical urothelial carcinoma. It is a rare cancer, particularly among young people, with a prevalence of 0.3%; its bland histological character makes it less recognized, delays the diagnosis and compromises its prognosis. Causal link of this cancer and obesity is not usual in young subjects. About a case and review of the literature, we define its aggressiveness and its care dilemma especially for young people.

Case Presentation: He was a 38-year-old obese man who was consulted for hematuria preceded by dysuria for six months. Ultrasound revealed a bladder tumor and moderate left uretero-hydronephrosis. On cystoscopy, the papillary tumor extended towards the left ureteral meatus. The patient underwent transurethral resection of the bladder tumor and histological findings were in favor of nested variant urothelial carcinoma of the bladder. On the extension assessment by thoraco-abdomino-pelvic CT scan, the tumor was at an advanced stage with the presence of pulmonary and spinal metastases. The evolution was unfavorable: the tumor did not regress in size under chemotherapy with Gemcitabine and Cisplatin.

Conclusion: Imbricated variant carcinoma of the bladder is underdiagnosed and rare, particularly in young people. The cause and effect between this cancer and obesity deserves further investigation. It remains a public health problem and poses a major challenge in diagnosis, late treatment and often unfavorable prognosis.

Keywords: Nested Variant, Obese Young Man, Bladder, Bland Appearing, Diagnostic Challenges, Von Brunn's Islets

Introduction

Bladder cancer is among the top ten most common cancer types in the world: one in every five people will develop it before the age of 75 years and nearly 10 million die from it every year [1,2]. Several studies show that bladder tumors are very rare in subjects under 40 years of age; their prevalence is 0.4 to 1% of all diagnosed bladder tumors [3]. Despite the clinic reminiscent of conventional carcinoma, it is often diagnosed late because it is difficult to be detected before the stage of muscle infiltration. In addition, some cases are overlooked due to its bland appearance which mimics the benign lesion of Von Brunn's islets, thus implying the prognosis [4]. Hence the attention of practitioners

(urologists, pathologists, etc.) in the face of any bladder tumor whose clinical evolution is not very promising and/or invasive, particularly at the first diagnosis. According to the literature, few cases related to this type of cancer and obesity are studied.

Through a case report and literature review, we discuss the aggressiveness of this rare variant, the diagnostic and therapeutic challenges as well as the cause and effect of obesity.

Case Presentation

This was a 38-year-old man who presented with dysuria for six months complicated by hematuria. Physical examination noted a body mass index (BMI) of 31 kg/m². He had no other particular history. A remodeled ultrasound was performed and showed thickening of the bladder responsible for moderate left

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hydronephrosis. Blood and urine tests were within normal limits. A diagnostic exploration of the tumors was decided. Cystoscopy showed a large papillary tumor infiltrating the left ureteral meatus and occupying the left anterolateral wall, the pericervical and the lower bladder fundus. The tumor is resected; and the histopathological results concluded to a nested urothelial carcinoma of the bladder (Figure 1). CT scan of extension showed a 22.9 x 35.4 mm bladder tumor on the left posterolateral wall invading the left ureteral meatus with upstream uretero-

hydronephrosis, involvement of the left seminal vesicle and base of the prostate, presence of two internal obturator adenopathies, large nodules of the pulmonary parenchyma and suspicious lesion of D5 (Figure 2). The pathological stage was pT4aN2M1. The patient received chemotherapy (Gemzar / Platinol) given the advanced stage of the disease and due to its lower toxicity. The half-year evolution was unfavorable; only lung nodules decreased in size on CT (bladder tumor: 33 x 42 mm vs 22.9 x 35.4 mm) (Figure 3).

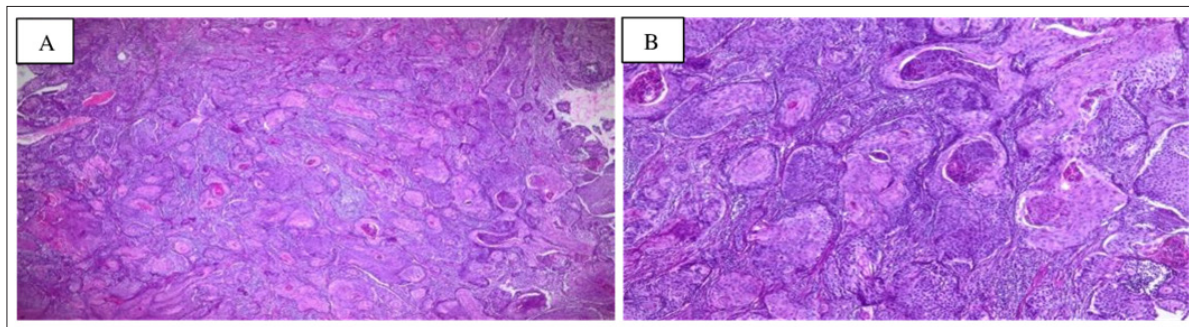


Figure 1: High-grade papillary urothelial carcinoma that infiltrates the lamina propria and detrusor muscle as nests (A) and tumor cells with moderate to marked cytonuclear atypia associated with foci of squamous inflection (B).

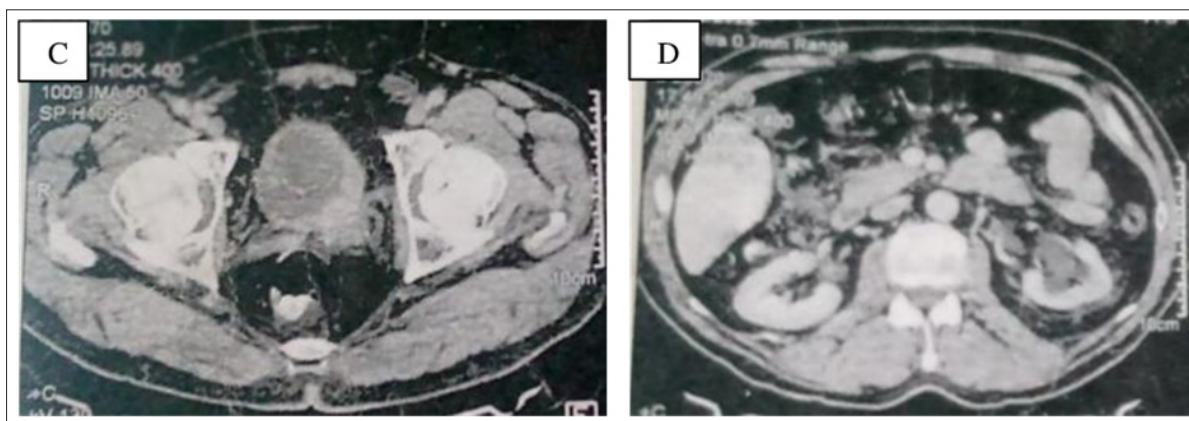


Figure 2: Before chemotherapy: an injected thoraco-abdomino-pelvic CT scan showing a tumor of the left anterolateral wall of the bladder measuring 22.9 x 35.4 mm in size (C) and responsible for a moderate left ureterohydronephrosis (D).

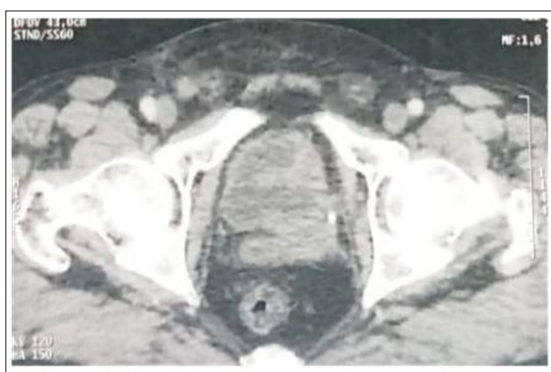


Figure 3: On the follow-up CT scan, the left anterolateral bladder tumor increased in size: 33 x 42 mm vs 22.9 x 35.4 mm.

Discussion

Nested variant urothelial carcinoma (NVUC) is an aggressive entity that accounts for only 0.3 % of all invasive bladder carcinomas of approximately 15-25 % [5,6]. Deceptively “bland” in appearance, it was first described as a benign lesion by Stern

in 1979 [7]. Clinically, there is no evidence that NVUC behaves differently from conventional carcinoma. However, despite the “benign” morphological characteristic, it may be associated with an aggressive clinical course [8,9]. The tumor often affects men over the age of 60 years with tobacco as the main exposure, like classic urothelial carcinoma. Macroscopic hematuria is the main sign of consultation; hematuria is frequently attributed to infection, delaying diagnosis and therefore making the cancer worse [10,11]. However, we rarely note these cases of cancer at a young age like our 38-year-old patient [12]. In their retrospective study on the histology of variant urothelial carcinoma of the bladder, Saouli et al. observed a male predominance of 92 % (36 cases out of 39), 77 % smokers and an average age of 62 years [13]. Throughout the literature, only a few cases have ruled on the famous obesity-bladder cancer relationship, even less the NVUC. Overweight and obesity are defined by the World Health Organization (WHO) as an abnormal or excessive accumulation of fat with a BMI greater than 25 and 30 kg/m² respectively [14]. According to available data, obesity confers, in decreasing order, an increased risk of kidney, bladder and prostate cancer

(20-82%, 10-19% and 6-14% respectively) [12]. The biological mechanisms of excess body weight in the genesis of urological cancer include the insulin-like growth factor axis, chronic inflammation and oxidative stress, abnormal adipocytokine secretion, and ectopic fat deposits.

Unlike the other variants, NVUC is often discovered at an advanced stage because it is difficult to confirm it before the stage of muscle infiltration; it requires some experience [13].

The tumor is usually papillary or flat on cystoscopy. Its bladder topography is not specific but it often involves the ureteral meatus with or without impact on the upper tract [10]. In our case, the papillary tumor infiltrated the left ureteral meatus and caused moderate left uretero-hydronephrosis. NVUC is fortuitously characterized by an aggressive course and metastases are not uncommon from the first diagnosis. In a series of 30 cases comparing high-grade urothelial carcinoma to NVUC, the latter was associated with a higher prevalence of muscle invasion during trans-urethral resection of bladder tumor, extra-vesical extension at cystectomy and metastatic disease [15]. In the report by Wasco et al. on 30 cases of NVUC, 4 % of them were at the stage of muscular involvement and 17 % had already invaded the adjacent organs [16]. Our patient already presented with damage to the seminal vesicle and the base of the prostate at the first diagnosis as well as pulmonary and spinal metastases.

Histologically, the NVUC shows a characteristic growth pattern that is deceptively bland. It reflects nest proliferation, urothelial cells with unremarkable cytology, irregular tumor-stroma interface, and minimal desmoplastic response in the superficial compartment; this complicates diagnosis further if the muscle is not resected [8]. This variant can be misidentified because it invariably shares overlapping morphological features with other entities such as proliferative cystitis, von Brunn's nest hyperplasia, nephrogenic adenoma or inverted papilloma [4]. In some cases, the immunohistochemical study helps the diagnosis favorably [15]. Strict monitoring should characterize practitioners (urologists, pathologists, oncologists, etc.) when the tumor is not clinically promising or becomes quickly invasive.

The treatment of NVUC remains controversial because of its rarity; the available therapeutic strategies are extrapolated from the classic urothelial carcinoma model [5]. There is consensus among bladder cancer experts for immediate decision of cystectomy to any T1 tumor with variant histology. Unfortunately, NVUC is often diagnosed at the muscle-invasive stage; this involves management and prognosis in advanced pT2-4 disease [17]. Only limited cases of stage lower than cT1 are treated conservatively. Cystectomy remains the first choice; the radio-chemotherapy is less effective compared to conventional urothelial carcinoma [10]. The gemcitabine (Gemzar) and cisplatin (Platinol) combination is the standard treatment for most patients due to its lower toxicity [18]. The invasive nested variant has always a poor prognosis like conventional high-grade carcinoma [10,16]. In all cases, optimal management of bladder cancer requires an accurate, standardised and timely pathological diagnosis, and close communication between surgeons and pathologists [19]. Crucial questions remain about early diagnosis through the literature to limit the damage associated with late management of this rare variant.

Conclusion

The prevalence of nested cancer remains underestimated. A healthy lifestyle would reduce the risk of its development. Diagnosis is difficult and often late, which compromises the prognosis. Therapeutic strategies are extrapolated in models of urothelial carcinoma due to its rarity. In-depth clinical trials are essential to optimize treatment at the early stage of the disease.

Author Contribution

All authors have contributed to this work and have read and approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare no conflict of interest.

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