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Case Report

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Non-schistosomal verrucous carcinoma of the bladder

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ABSTRACT

Verrucous carcinoma (VC) of the bladder is a malignant neoplasm associated with schistosomal infection. Non-schistosomal VC of the bladder is highly unusual; to the best of our knowledge, only 16 such cases have been reported to date. We report a case of non-schistosomal VC of the bladder, also review the literature and discuss the possible causes, management, and treatment of this unusual and malignant neoplasm.

1. Introduction

Verrucous carcinoma (VC) is a well-differentiated form of squamous cell carcinoma (SCC) that generally occurs in the oral cavity, larynx, vagina, penis, or perianal regions (Hassan et al., 2016). VC of the bladder is rare and has been linked to schistosomal infection (Lewin et al., 2004). Non-schistosomal VC of the bladder is a highly unusual malignant neoplasm; to the best of our knowledge, only 16 such cases have been reported to date in the English-language literature. In contrast to other bladder carcinomas, VC does not metastasize, and therefore complete local excision is curative. However, VC is locally aggressive and is therefore regarded as malignant (Hassan et al., 2016). We report a case of non-schistosomal VC of the bladder and review the current literature.

2. Case report

A 60-year-old male smoker (20 cigarettes per day) presented with severe dysuria, pollakiuria, and urinary urgency. No macroscopic hematuria was reported. The patient had received various treatments involving antibiotics, alpha blockers, antimuscarinic agents, and combinations thereof, but had failed to benefit from them. The physical examination, prostate-specific antigen, and serum biochemistry values

were normal. Microscopic hematuria was present at complete urinalysis. The bladder ultrasound showed no pathology. Flexible cystoscopy revealed a 7 x 5 mm solitary exophytic mass between the bladder neck and trigone.

Transurethral resection (TUR) of the mass was performed, and all visible lesions were completely removed. Macroscopic examination of the resection material revealed gray-white necrotic and flaky lesions. Microscopic examination revealed a well-differentiated malignant tumoral formation, which typically arise from squamous epithelial islands exhibiting acanthosis and papillomatosis and exophytic growth toward the surface (Fig.1). The tumor cells were large, consisting of squamous cells, moderately chromatin-rich nuclei, abundant eosinophilic cytoplasm, and minimal nuclear and structural atypia, with keratin pearls forming in some areas (Fig. 2).

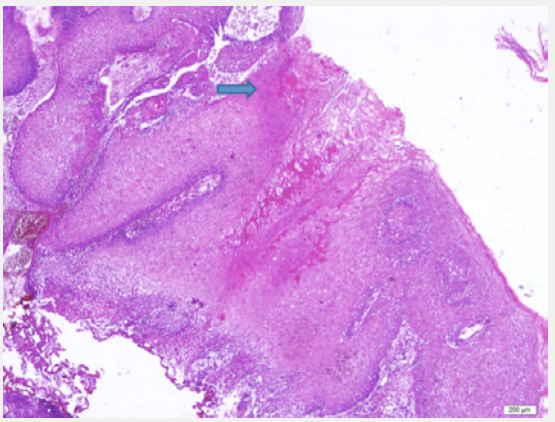

Fig. 1. H&E section (x 40). Tumoral structure consisting of epithelial acanthosis, papillomatosis (blue arrow), and minimal nuclear atypia, the main features of verrucous carcinoma.

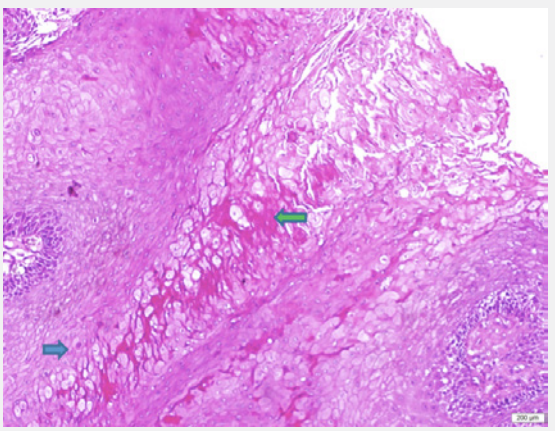

Fig. 2. H&E section (x 200). Squamous pearl (green arrow) formation in epithelial cells and minimal atypia (blue arrow).

Non-schistosomal VC of the bladder was diagnosed. A tumor invading the subepithelial connective tissue (pT1) was detected, but not schistosoma eggs. The surgical margins exhibited no signs of neoplasm. No complication occurred in the early or late postoperative periods, and abdominal computed tomography imaging scans revealed no pathology. The patient received no adjuvant therapy. Control cystoscopy at the third month postoperative also revealed no pathology, and the patient was placed under close clinical follow-up. Subsequent cystoscopy was repeated every three months for a period of one year. No recurrence was observed after the surgery.

3. Discussion

VC is a well-differentiated squamous cell carcinoma of the bladder. It is a rare, clinically inert form of bladder cancer that is primarily linked to schistosomal infection, but it can also occur without such infection (Park et al., 2019). Non-schistosomal VC of bladder is a highly unusual tumor, with only 16 cases having been reported in the English-language medical literature (Table 1). The mean age of these 16 patients (nine women and seven men) was 61.18 (range, 33-83) years.

The pathognomonic symptom of bladder tumors is macroscopic hematuria. This was observed in only three patients (Cases 2, 13, 15) (Holck and Jorgensen, 1983; Lewin et al., 2004; Flores et al., 2009). One patient (Case 1) presented with lumbar pain, and the others presented with irritative lower urinary tract symptoms (LUTS) (Wyatt and Craig, 1980). The reason for admission in our case was LUTS that was resistant to medical treatment.

The etiology of non-schistosomal VC of the bladder is unknown. However, various risk factors have been associated with this disease, such as smoking (Cases 8 and 12), urinary tract infection (Cases 9 and 10), condyloma acuminatum (Cases 3 and 6), urinary stones (Case 11 and 14), and interstitial cystitis (Case 12) (Walther et al., 1986; Batta et al., 1990; Blackmore et al., 1995; Ellsworth et al., 1995; Hamm et al., 1997; Oida et al., 1997; Sohn et al., 1997; Usta et al., 2006). All of these diseases feature chronic inflammation, and thus we think that non-schistosomal VC of the bladder can develop in association with chronic inflammation.
VC of the bladder is not metastatic, but malignant, since it is locally invasive (Hassan et al., 2016). Wide, aggressive resection or partial cystectomy with wide margins is sufficient for treatment. Total cystectomy was performed in 11 of the previously reported cases (Cases 1, 3, 6 – 13, and 15) (Wyatt and Craig, 1980; Walther et al., 1986; Batta et al., 1990; Horner et al., 1991; Blackmore et al., 1995; Ellsworth et al., 1995; Hamm et al., 1997; Oida et al., 1997; Sohn et al., 1997; Lewin et al., 2004; Flores et al., 2009). Four different patients (Cases 1, 3, 6, and 15) initially underwent

Table 1. Summary of non- schistosomal verrucoz carsinoma of bladder cases in the literature.

Case no.	Author, reference	Date	Age/ Sex	Plaint	Risk factor	Tumour size	Treatment	Recurrence	Adjuvanttherapy	Follow-up (Months)	Outcome
1	Wyatt&Craig	1980	73/M	Pain	-	VL	TUR	Yes	TC	24	Survived
2	Holck&Jørgen-sen	1983	75/M	H	-	VL	PC	Yes	PC	3	Survived
3	Walther et al.	1986	43/F	LUTS	CA	VL	TUR	Yes	TC	30	Survived
4	Boileau et al.	1986	83/M	LUTS	-	15 x 10 mm	RT	No	-	3	Died (Uremia)
5	Pierangeli et al.	1989	48/F	LUTS	-	VL	PC	Yes	TUR	6	Survived
6	Batta et al.	1990	43/F	LUTS	CA	VL	TUR	Yes	TC	12	Survived
7	Horner et al.	1991	68/F	LUTS	-	VL	TC	No data	-	No data	No data
8	Ellsworth et al.	1995	58/F	LUTS	Smoking	VL	TC	No	-	36	Survived
9	Blackmore et al.	1995	58/F	LUTS	UTI	VL	TC	No	-	24	Survived
10	Oida et al.	1997	66/F	LUTS	UTI	110 x 80 mm	TC	No	-	23	Survived
11	Sohn et al.	1997	69/F	LUTS	Urinary stone	VL	TC	No	-	12	Survived
12	Hamm et al.	1997	66/F	LUTS	IC	VL	TC	No	-	No data	Survived
13	Lewin et al.	2004	64/M	H	Smoking	VL	TC	No	-	3	Died (Unknown)
14	Usta et al.	2006	54/M	LUTS	Urinary stone	Small	TUR	Yes	TUR	3	Survived
15	Flores et al.	2009	33/M	H	-	VL	PC	Yes	TC	36	Survived
16	Hassan et al.	2016	78/M	LUTS	-	30 x 20 mm	TUR	Yes	TUR I-MMC	3	Survived
17	Present case	2019	60/M	LUTS	Smoking	7 x 5 mm	TUR	No	-	12	Survived

CA: Condyloma acuminatum, H: Hematuria, IC: Interstitial cystitis, I-MMC: Intravesical mitomycin, LUTS: Lower urinary tract symptoms, MM: Millimeter, PC: Partial cystectomy, RT: Radiotherapy, TC: Total cystectomy, TUR: Transurethral resection, UTI: Urinary tract infection, VL: Very large (occupying minumum 50% of bladder)

bladder sparing surgery but later received total cystectomy due to recurrence at follow-up (Wyatt and Craig, 1980; Walther et al., 1986; Batta et al., 1990; Flores et al., 2009). Four patients underwent bladder sparing surgery, two with partial cystectomy (Cases 2 and 5) two with TUR (Cases 14 and 16) (Holck and Jorgensen, 1983; Pierangeli et al., 1989; Usta et al., 2006; Hassan et al., 2016). One patient (Case 4) received radiotherapy (Boileau et al., 1986). This patient's general condition was unsuitable for surgery, and mortality occurred due to uremia on the third month postoperative.

The size of tumors in patients in the early years was sufficient to encompass more than 70% of the bladder, although the tumors' dimensions subsequently gradually decreased. This reduction was reflected in the type of treatment administered; treatments in the earlier publications consisted of aggressive surgery, but they were gradually modified to be minimally invasive. The rarity of this cancer and the resulting scarcity of reports and studies make it difficult to define and optimize therapy. We applied TUR in our case due to the small size of the tumor. We observed no recurrence throughout the 12-month follow-up period.

Non-schistosomal VC frequently involves a solitary lesion with an exophytic and filiform appearance. Microscopically, it is characterized by papillary proliferation accompanied by epithelial acanthosis and hyperkeratosis (Park et al., 2019). Histopathologically, since VC bears a close resemblance to lesions such as giant condyloma, verrucous hyperplasia, and SCC, diagnosis may be problematic (Hassan et al., 2016; Park et al., 2019). VC of the bladder must be distinguished from the more common neoplasias, including ordinary SCC and transitional cell carcinoma, with squamous differentiation. The majority of authors recommend that, in the presence of dysplasia in VC or small foci of SCC that resemble VC, patients should be treated as they would for SCC (Patel et al., 2015).

The prognosis for non-schistosomal VC of the bladder is generally good. Mortality was reported in only two cases (Cases 4 and 13) in the 15-patient series (Boileau et al., 1986; Lewin et al., 2004). The first patient (Case 4) was elderly, in poor general condition, and was not indicated for surgery, instead receiving radiotherapy. Mortality occurred due to uremia (Boileau et al., 1986). Mortality in the other patient (Case 13) occurred three months after total cystectomy (Lewin et al., 2004). No cause of death could be determined. No metastasis was observed in any of the 16 patients. Recurrence was identified in all eight patients (Cases 1-3, 5, 6, and 14-16) that underwent bladder sparing surgery at initial treatment (Wyatt and Craig, 1980; Holck and Jorgensen, 1983; Walther et al., 1986; Pierangeli et al., 1989; Batta et al., 1990; Usta et al., 2006; Flores et al., 2009; Hassan et al., 2016). Adjuvant

total cystectomy was performed on four patients (Cases 1, 3, 6, and 15), and adjuvant bladder sparing surgery was performed on four (Wyatt and Craig, 1980, Walther et al., 1986; Batta et al., 1990; Flores et al., 2009). One patient (Case 16) received intravesical mitomycin therapy as well as TUR, but this failed to prevent recurrence (Hassan et al., 2016). No recurrence was observed in our cases during the 12-month follow-up. The tumor in our case was detected incidentally and was very small (7 x 5 mm). In the other cases, tumors represented more than 50% of the bladder. The lack of recurrence over a 12-month follow-up may be due to the size of the tumor.

Due to the rarity of non-schistosomal VC of the bladder, there are no clear guidelines regarding its treatment. Based on a literature review, there is no answer regarding which is the treatment of choice, although it is difficult to recommend a standard therapy. If the tumor has invaded the perivesical tissue or is of a high volume (i.e., occupying at least 50% of the bladder), then radical cystectomy may be required. Radiotherapy can be applied in inoperable cases or with patients for which surgery is not indicated. In cases of low-volume tumors, minimally invasive approaches, such as partial cystectomy or TUR, may be employed if the patient will attend follow-ups, although close surveillance must be recommended due to the risk of recurrence. Subsequent cystoscopy should be repeated every three months, and semiannual or annual surveillance with pelvic CT studies should be recommended to evaluate the perivesical tissue.

To summarize, non-schistosomal VC of the bladder is observed in patients in their 60s, and it is slightly more common in women. It does not metastasize, but it has a very high recurrence rate. Although the etiology is unknown, the most likely cause is chronic inflammation. Further epidemiologic and clinical studies are required to evaluate the need for therapy and potential long-term recurrence in patients with non-schistosomal VC of the bladder.

Informed consent

Written informed consent was obtained from the patient for his clinical data to be published in this article.

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