

Potential contribution of benzodiazepine abuse in the development of a bladder sarcomatoid carcinoma: A case report

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Abstract. Invasive urothelial carcinoma has a propensity for disparate differentiation and presentation of morphological variants. Sarcomatoid carcinoma (SaC) of the bladder is an extremely uncommon and aggressive variant of bladder cancer. An accurate diagnosis for this variant is necessary, but at times difficult. Immunohistochemistry can increase the diagnostic accuracy for SaC. The therapeutic approaches currently adopted for the treatment of SaC are similar to those used for the urothelial variant: Surgery, chemotherapy and radiation therapy. To date, however, there exists no standard treatment due to the lack of knowledge regarding the pathogenesis of SaC. Future research is required to focus on this rare histological tumor subtype in order to identify more effective treatment strategies. The present study reported an unusual case of bladder SaC in a woman aged 48 years, who was a non-smoker with a long history of benzodiazepine abuse. Although saving the patient's life was a priority, it was also essential to consider her subsequent quality of life. For that reason, the patient underwent a cystectomy with orthotopic neobladder reconstruction using ileum, followed by chemotherapy. At the 7 month follow-up, the patient was still alive, in complete remission and had normal bladder function. The present case report shows the potential contribution of benzodiazepine abuse in the development of a bladder sarcomatoid carcinoma, a rare variant of BC, whose early detection and accurate diagnosis are key to attaining satisfactory treatment outcomes and a favorable prognosis for patients.

Introduction

Given that bladder cancer (BC) is the most frequent form of genitourinary tract cancer and taking into account the serious

nature of the presenting symptoms, treatment is urgent, due to the high recurrence and treatment-related morbidity associated with the disease (1). Smoking is the main risk factor for BC, accounting for 50-65% of new cases in men and 20-30% in women (2). Occupational exposure to formaldehydes, polycyclic aromatic hydrocarbons and other solvents is also considered to be a significant risk factor (3). A third identified risk factor is the application of a vesical catheter which, over a long period of time, can lead to chronic irritation of the vesical mucosa. Untreated vesical lithiasis and cystitis, as a result of *Schistosoma hematobium* infection, have been found to be causally linked to the onset of bladder squamous cell carcinoma. Urothelial carcinoma (UC), sometimes referred to as transitional cell carcinoma, is an occurring form of BC. However, UC has a propensity for disparate differentiation and presentation of morphological variants, including the sarcomatoid subtype. This variant has historically been given different names, such as sarcomatoid carcinoma (SaC), pseudosarcoma, malignant mixed mesodermal/Müllerian tumor, metaplastic carcinoma and spindle cell carcinoma. Accounting for ~0.3% of all primary urinary BC cases (1), SaC has similar epidemiological characteristics to those of UC, although they differ in terms of behavior and prognosis (4). As a rare malignant neoplasm of the urinary bladder, SaC is a high-grade biphasic neoplasm. Bladder SaC comprises two different components, one malignant epithelial component and one sarcomatoid component of mesenchymal origin. The latter component often manifests itself as a high-grade spindle cell neoplasm, while the former component may manifest itself as UC, squamous cell carcinoma, adenocarcinoma, small cell carcinoma or overlying carcinoma *in situ*. It frequently occurs in older patients, normally those in their sixth or seventh decade of life, and is three times more common in men than in women (5). A survey by the Mayo Clinic conducted between 1936 and 1995 showed that its frequency was higher in men aged 72 years, who had a history of smoking (6). The precise etiology of SaC has not yet been established, but radiation therapy and intravesical cyclophosphamide chemotherapy have been reported to enhance the risk of SaC and smoking has been identified as a major risk factor (5). In addition, the definite histogenesis of SaC is disputed. According to some studies, SaC is the result of the ability of undifferentiated, totipotent neoplastic cells to form multiple pathways of terminal differentiation in histologically recognized mesenchymal and epithelial elements.

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This view is based on the immunoreactivity of epithelial markers [cytokeratin and epithelial membrane antigen (EMA)] in mesenchymal areas. Other studies have suggested that SaC results from the 'collision' of two distinct malignant tumors that are mutually invasive. A third explanation is the possible occurrence of metaplasia of malignant epithelial elements into sarcomatoid elements. This theory is backed by the evidence of positive staining for keratins (AE1/AE3) in the epithelial and mesenchymal components (7,8). The presentation of SaC is similar to that of urothelial carcinoma, with symptoms such as gross hematuria, dysuria, pollakiuria and urinary infection. Macroscopically, these tumors present as large exophytic polyps (5-7 cm in diameter on average) with areas of necrosis and ulceration (7). However, the histopathological diagnosis of SaC can be challenging and it may be preferable for it to be combined with immunohistochemistry. Evidence in support of histological diagnosis includes H&E and immunohistochemical staining results [positive staining for cytokeratins in the epithelial component and vimentin, desmin HHF-35, smooth muscle actin (SMA) or S100 calcium binding protein B in the mesenchymal component, respectively] (7,9,10). This positive staining can differentiate this variant from other types of sarcoma (11). In effect, differential diagnosis of SaC with primary sarcomas, primary carcinomas with stromal metaplasia, carcinomas with pseudosarcomatous stroma, sarcomas associated with pseudoepitheliomatous hyperplasia, teratomas and prostate carcinomas with extension into the bladder is recommended. Considering that the incidence of divergent differentiation in cystectomy specimens is as high as 33%, the fourth edition of the World Health Organization (WHO) classification of tumors of the urothelial tract provided a contemporary review of the morphology of urothelial neoplasms, including SaC, within the group of invasive urothelial tumors (12). For this reason, according to the fourth edition of the 2016 WHO Classification of Tumors of the urinary System and Male Genital Organs, it is recommended that pathologists report the divergent histologies in their report (12). The clinical results of SaC are poorer than those of typical UC, usually including liver, lung and distant lymph node metastases and a postdiagnosis survival of 6 months. In effect, SaC is frequently diagnosed at an advanced local stage exhibiting nodal or distant metastasis. This rules out treatment approaches such as transurethral resection of bladder tumor or partial cystectomy; for all these reasons, the identification of this histological variant is clinically crucial and may require a multimodal approach (radical cystectomy plus adjuvant chemotherapy) for its treatment (5,13). The present study reported a rare example of bladder SaC in a 48-year-old woman without the commonly recognized risk factors of the variant.

Case report

A 48-year-old woman was admitted to our Urology Department after undergoing a transurethral bladder resection at another hospital. Histopathology of the resected Transurethral Resection of Bladder Tumor chips revealed a pT2 high-grade tumor. The physical examination and biochemical parameter investigation came back normal. The patient was not a smoker but had an almost 20-year history of benzodiazepine (BZD) abuse originally prescribed for treating anxiety and depression.

In particular, the patient was receiving alprazolam at a dose of 1 mg twice daily in combination with a selective serotonin reuptake inhibitor (SSRI). However, she reported that, depending on the severity of her depression, she often exceeded the dosage recommended by the specialist. Furthermore, upon analyzing her clinical history, it emerged that the patient had undergone sleep treatment in adolescence. She had no family history of bladder neoplasms; furthermore, no additional urological and gynecological symptoms or diseases were identified. The computed tomography (CT) scan of the chest, abdomen and pelvis revealed that a huge mass was occupying almost the entire bladder without metastatic lesions. The mass exhibited enhancement upon the intravenous administration of contrast material. After signing written informed consent, the patient underwent radical cystectomy with bilateral extended pelvic lymphadenectomy, with neobladder reconstruction performed for urinary diversion. The most effective surgical technique for muscle-invasive BC is radical cystectomy which, in female patients, includes the removal of the uterus and parts of the ventral vagina, thus resulting in sterility (14). The patient underwent a total cystectomy with lymph node dissection, a total abdominal hysterectomy, as well as a bilateral salpingo-oophorectomy. During the surgery, ureters were exposed and split as close as possible to the urinary bladder; the urinary bladder was then resected and the uterus and both ovaries were removed. The urethra was carefully mobilized and exposed for subsequent neobladder anastomosis. Intraoperative pathology sections of the urethra and both ureters showed that they were tumor-free. Lymphatic tissue around the external iliac and internal iliac vessels and obturator nerve was dissected. The terminal ileum was identified and 45 cm of the ileum was isolated for the reconstruction of an orthotopic neobladder. The ureters were placed underneath the bowel in the orthotopic position. The neobladder remained intact, showing no leaks when filled with 180 ml sodium chloride. A total of two ureteral stents and an indwelling catheter were placed intraoperatively. The follow-up was uneventful. The surgical specimen revealed an ulcerated polypoid mass with a 6,5 cm diameter, which involved almost the entire bladder; this mass presented a histopathological pattern of a high-grade muscle-invasive tumor with heterogeneous sarcomatoid elements, which consisted of elongated spindle cells (Fig. 1). Immunohistochemistry showed that these elements were positive for GATA binding protein 3, vimentin (Fig. 2), cytokeratin AE1/AE3 (Fig. 3) and EMA. The diagnosis reached was that of SaC. In addition, the proliferation index, which was assessed with anti-Ki67 staining, was high (60%), indicating the malignant nature of the lesion (Fig. 4). The TNM pathological stage was pT3a N2 M0 (G3, R0) (15). Therefore, adjuvant chemotherapy was deemed necessary. At the 6-month follow-up, the patient was alive and in complete remission, according to CT scans. Urodynamic testing and post-void residual urine investigation results showed that normal bladder function had been preserved. Table I summarizes the clinical and histopathological features of the patient and the treatment data.

Discussion

UC is one of the most common types of urinary BC, accounting for ~90% of tumors of this anatomic region. UC is known for

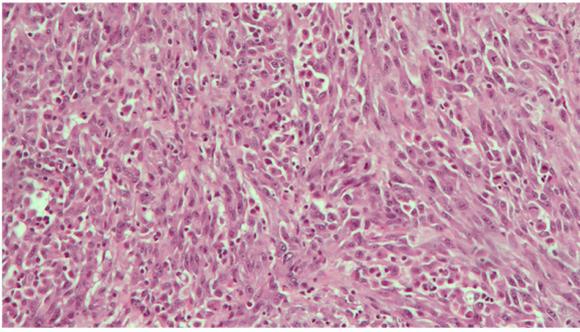


Figure 1. Presentation of UC with sarcomatoid changes (magnification, x10). Microscopically, the conventional urothelial component was mixed with the predominantly sarcomatous areas, which consisted of elongated spindled cells with vesicular, pleomorphic nuclei and conspicuous mitotic figures on a myxomatous background exhibiting a vaguely fascicular growth pattern. In this figure, obtained by hematoxylin-eosin staining, the nuclei appear colored as violet while the cytoplasm takes on a pink color.

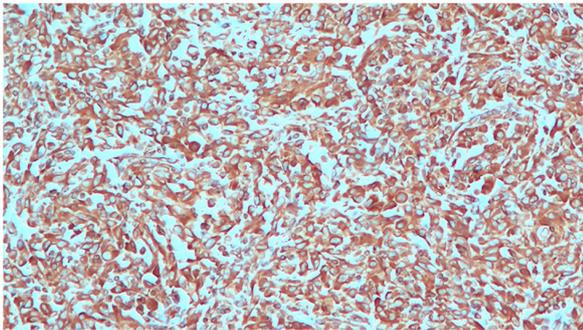


Figure 2. Tumor cells positive for vimentin expression. Vimentin is used as a marker of mesoderm-derived tissues and, for this reason, it is an immunohistochemical marker for sarcomas. This figure shows the positivity of bladder sarcomatoid cancer cells for vimentin expression (magnification, x10). Immunohistochemical staining for vimentin indicates cytoplasmatic positivity. The antigen-antibody immune reaction is revealed by a secondary antibody conjugated to a catalyst enzyme that reacts with a substrate, which forms a brown stain. While nuclei stain blue with hematoxylin.

its propensity towards disparate differentiation and presentation of morphological variants. The most frequent variant is the squamous variant, followed by the glandular variant (4). As bladder SaC is a rare and aggressive subtype of BC (16), there is a lack of data regarding its clinical outcomes and no effective treatments for the disease. Following a search of The Surveillance, Epidemiology and End Results database between 1988 and 2001, only 301 reported bladder SaC cases were identified out of 182,283 BC cases. This represented a mere 0.16% of all BC cases, highlighting the rarity of this condition. However, despite its rarity, this variant is a much more aggressive form of BC.

The patient in the present study and her parents did not have a history of radiation therapy, cyclophosphamide exposure or smoking. However, the patient had an ~20-year history of BZD abuse, originally prescribed for treating anxiety and depression. In particular, after having been prescribed alprazolam at a dosage of 1 mg twice daily in combination with an SSRI by a specialist, the patient reported that she often exceeded the recommended dose, depending on the severity of her depression. BZDs have been prescribed on a

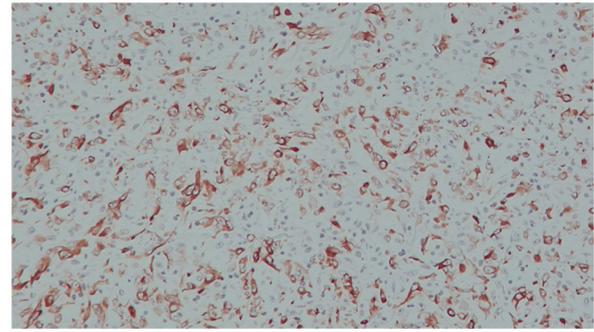


Figure 3. Focal positivity of bladder sarcomatoid cancer cells for high molecular weight cytokeratins. AE1/AE3 is a mixture of two monoclonal antibodies obtained by immunizing mice with human callus keratins, which identifies most human cytokeratins and can be used for positive identification of cells of epithelial origin on immunohistochemical examination (magnification, x10). Immunohistochemical staining for cytokeratins indicates cytoplasmatic positivity. The antigen-antibody immune reaction is revealed by a secondary antibody conjugated to a catalyst enzyme that reacts with a substrate, which forms a brown stain. Nuclei stain blue with hematoxylin.

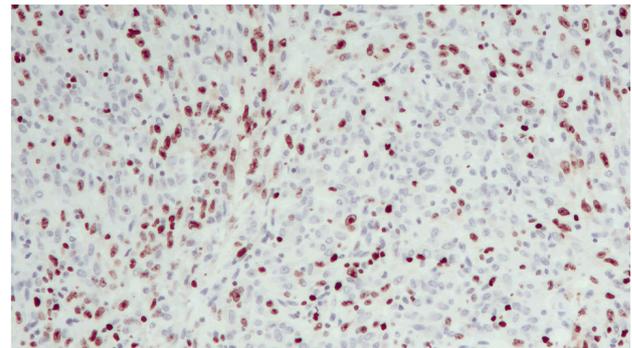


Figure 4. Immunohistochemical staining for Ki-67 expression, showing nuclear positivity, revealed a high proliferation index (magnification, x10). Nuclei of the replicating cells turn brown. Conversely, the nuclei of the cells that are not replicating are colored blue.

global scale for ~50 years, with a consumption rate of 10-42% in the elderly population. An association has been identified between the use of BZDs and a risk of cancer, but further research is required; to date, most studies have focused on cancer in animals exposed to BZDs (17,18). Some of these studies have reported an association between carcinoma risks and the use of BZDs, more specifically between clonazepam and thyroid cancer (19), diazepam and breast cancer (18) and oxazepam and liver cancer (20). Iqbal *et al* (21) identified clonazepam, lorazepam, alprazolam, bromazepam, zolpidem and zopiclone as unsafe BZDs following exposure duration experiments. In particular, the study pointed to the high risk of cancer (15%) associated with the use of clonazepam (21). However, the researchers admitted that this could possibly be an aggregated effect resulting from the combination of BZDs with long-term polypharmacy or metabolic drug use (22). The studies listed the increased risk for the development of various types of cancer as a result of BZDs exposure: Overall cancer risk increased by 21%, brain cancer by 98%, colorectal cancer by 25%, lung cancer by 10%, cancer of the esophagus by 59%, prostate cancer by 36%, BC by 39%, liver cancer by 18%, pancreatic cancer by 41% and other types of cancer

Table I. Clinical and histopathological features and treatment data.

| Clinicopathological features | Patient |
|--|--|
| Age, years | 48 |
| Sex | Female |
| Usual risk factor (smoking, occupational exposure to solvents and bladder chronic irritation) | None |
| Past history | Benzodiazepine abuse (for 20 years) |
| Tumour-stage and grade after endoscopic bladder resection | T2G3 |
| Tumour-stage and grade after radical treatment (radical cystectomy with lymph node dissection) | T3aN2M0 (G3) |
| State of surgical margins (negative or positive) | Negative (R0) |
| Urinary diversion type | Orthotopic neobladder |
| Adjuvant treatment (yes or not) | Yes (adjuvant chemotherapy) |
| Bladder cancer subtype | Sarcomatoid bladder cancer (positivity for GATA3, Vimentin, Cytokeratin AE1/AE2 and epithelial membrane antigen. |
| Proliferation index (anti-Ki67) | 60% |

by 27% (21). These findings have important implications for BZDs users, particularly considering the frequency of their prescriptions. The findings of Iqbal *et al* were supported by the findings of other studies, such as those of Rosenberg *et al* (23), Kripke and Langer (24) and Cronin-Fenton *et al* (25). BC is the sixth most common type of cancer worldwide, with its incidence rates being considerably high in Taiwan, where BZD usage has been associated with the risk of cancer (21). Studies by Kao *et al* (26) and Coogan *et al* (27) found that BZD use in males was particularly linked to a risk of prostate cancer.

Despite the rarity of this variant and the difficulty in reaching a diagnosis, SaC merits specific investigations, due to its aggressive nature and the poor prognosis associated with the disease (28). The best predictor of survival for SaC is the pathological stage at which it is diagnosed (28). Favorable prognostic characteristics include negative surgical margins and metastatic disease absence at first presentation. At the 2-year stage, the mortality rate is as high as 70%. In the majority of patients, mortality is often caused by local disease or by lymph node, lung, pleura, brain, liver or bone metastasis. Survival prospects are even poorer for sarcomatoid variants than for organ-confined and metastatic UC. Due to the relative rarity of the disease and, consequently, the absence of findings from randomized controlled trials, the experts' opinions with regards to the most effective treatment are divided. Evidence suggests that the overall survival rate is higher following radical cystectomy with pelvic lymphadenectomy (14,29,30). For this reason, it is considered the principal approach; however, patients may develop local recurrence following surgery (16). In an attempt to prevent recurrence and distance metastasis, certain adjuvant treatment approaches, such as radiotherapy or chemotherapy, are often recommended.

In conclusion, SaC is a rare variant of BC, whose early detection and accurate diagnosis are key to attaining satisfactory treatment outcomes and a favorable prognosis for patients. Histopathology and immunohistochemistry are crucial to achieving a timely diagnosis and management of this condition. The present study reported a case of bladder

SaC in a 48-year-old patient, thereby raising awareness for the incidence of this malignancy in a younger population than usually recorded. The present case was noteworthy due to the age of the patient and the total absence of the usual risk factors for SaC. With regards to the causal factors of this disease, several studies cited herein have identified a large number of chemical compounds believed to be carcinogenic. The majority of them are aromatic amines and benzene derivatives; for that reason, there is a very high likelihood that long-term BZD abuse played a fundamental role in tumor development in the reported case.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

RB and NS confirm the authenticity of all the raw data. RB made substantial contributions to conception and design of this case report and to acquisition of data and was the major contributor to the writing of the manuscript. MS, NS and CM analyzed and interpreted the patient data regarding the urological disease. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Signed informed consent was obtained from the patient for publication of this case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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