T4 urothelial carcinoma in undiagnosed closed bladder exstrophy in a post-menopausal female

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It is rare to see an adult presenting with exstrophy of the bladder. Malignant conversion in exstrophy occurs in 4%, with adenocarcinoma as the most common histopathology. We report the first case of metastatic high grade urothelial carcinoma with squamous and sarcomatoid differentiation arising from undiagnosed, closed bladder exstrophy in a female at advanced age with associated bilateral deep vein thrombosis and clot retention. The patient developed clinical progression of disease despite neoadjuvant gemcitabine-cisplatin and salvage (or palliative) radiotherapy. To the best of our knowledge, this is the first reported case of a primary urothelial malignancy in occult bladder exstrophy.

Key Words: closed bladder exstrophy, urothelial carcinoma, unreconstructed bladder exstrophy, congenital anomaly

Introduction

Exstrophy of the bladder is a rare congenital anomaly which is typically diagnosed and repaired in the neonatal period. The incidence in adults is unknown. It is well recognized that exstrophy is associated with an increased risk of malignant conversion (4%); 95% of which are adenocarcinoma and 3%-5% are squamous cell carcinoma.[1] Here we present a rare case of urothelial carcinoma arising in an undiagnosed exstrophy patient in her sixth decade of life.

Case report

A 52-year-old Hispanic female was referred from outside institution with several month history of progressive hematuria, with passage of clot and debris refractory to hand and continuous bladder irrigation. She had associated worsening of urinary urgency and frequency with new onset mixed urinary incontinence. She had also developed bilateral lower extremity edema over this time. The patient's only medication was coumadin, which was initiated at the referring institution for concomitant diagnosis of bilateral deep vein thrombosis prior to her transfer to our care. Otherwise, she denied any prior medical history. Her only prior procedure was a cystoscopic evaluation with bladder mass biopsy at the referring institution prior to her transfer. The biopsy results showed undifferentiated urothelial cells, but were otherwise non-diagnostic. She denied any personal or familial history of genitourinary disease. She denied any lifetime tobacco, alcohol, or illicit drug use and denied any known allergies. She has been sexually abstinent to this point in her life noting, "I've always been told I'm different than everyone else."

Clinical findings

At presentation, her vital signs were significant for sinus tachycardia, confirmed with electrocardiogram. She was alert, oriented, and diaphoretic; in mild

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distress associated with intermittent bladder spasms. On exam of the inferior abdomen, a protuberant, firm, irregular and mildly tender mass was appreciated. The overlaying skin was thinned, yet intact without ulceration or desquamation. The umbilicus was absent. The groin exam revealed firm, fixed bilateral inguinal lymphadenopathy, the largest of which measured 3 cm on the left. The genital exam was significant for multiple vaginal septations, bifid clitoris and poorly fused labia. The patient was having active bladder spasms with witnessed incontinence of hematuria, mixed with clots and tissue debris.

Diagnostics and management

Serum analysis revealed microcytic anemia (Hgb 9.8 g/dL, MCV 70 fL), with elevated WBC (20.6 k/uL) and normal renal function (Cr 0.7 mg/dL). She had a supratherapeutic INR (16). Urinalysis confirmed hematuria with loaded RBCs with no bacteria seen. A contrast enhanced CT examination revealed large heterogeneously enhancing mass filling the bladder, extending into the anterior abdominal wall with paucity of the anterior rectus musculature and absence of the symphysis pubis with large necrotic pelvic and inguinal lymphadenopathy, Figure 1.

The patient's urinary symptoms were mitigated with bilateral percutaneous nephrostomies. The patient underwent repeat cystoscopic examination with removal of bilateral ureteral stents to complete the supravesical urinary diversion. Repeat bladder mass biopsies were obtained at that time which revealed carcinoma in situ and invasive urothelial carcinoma with squamous and sarcomatoid differentiation, Figure 2. As she was a poor surgical candidate, the patient was referred for chemotherapy. The patient had a poor response to gemcitabine-cisplatin with clinical and radiographic progression; and was transitioned to palliative radiotherapy. Despite these efforts, she had complete progression through the abdominal wall and was subsequently referred to palliative care where she succumbed to her disease.

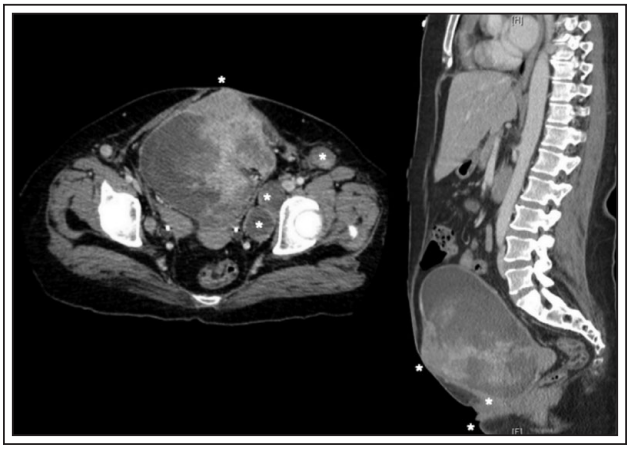

Figure 1. Contrast enhanced CT abdomen and pelvis. There is a large, heterogeneous, enhancing bladder mass extending into the abdominal wall, relative paucity of rectus musculature, absent symphysis pubis and large necrotic pelvic and inguinal lymphadenopathy (up to 3 cm).

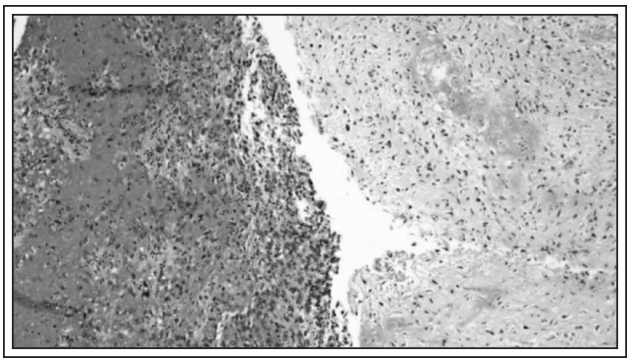

Figure 2. Cystoscopic bladder mass biopsy. Sections show in situ and invasive urothelial carcinoma with squamous and sarcomatoid differentiation displaying elongated, spindle-shaped cells, high cellularity, and cellular atypia (H&E, x400). This also stained positive for keratin.

Discussion

Bladder exstrophy is a rare congenital anomaly that occurs in an estimated 1 in 10,000-50,000 live births.[2] A more recent survey has estimated that the United States showed a weighted national incidence of 2.15 cases per 100,000 live births (205 of 9,452,110 newborns).[3] Males are more commonly affected (male:female, 5:1 to 6:1).[4] The exstrophy-epispadias complex comprises a spectrum of congenital anomalies that includes classic bladder exstrophy, epispadias, cloacal exstrophy along with several variants.[5] This results from failure of mesenchyme to migrate between the ectodermal and endodermal layers of the lower abdominal wall, leading to instability and premature rupture of the cloacal membrane. In this closed-variant case, a thin cloacal membrane was sustained allowing the patient to maintain continence throughout life. Nerli et al describes one series with seven males presenting as adults for reconstruction while Shoukry et al describes another with five males presenting as adults (mean

age 23).[6,7] In general, exstrophy patients presenting as adults are not well represented in the literature and cases of adult females are sparse. Cases of adult females with malignant transformation have not been reported in the literature.

With advances in antenatal high-resolution ultrasound and reconstructive surgical techniques, the associated morbidity and mortality has diminished substantially and quality of life has been drastically improved. Intervention is typically performed in the neonatal period to avoid the physical, functional, social, sexual, and psychological burdens. Thus, exstrophy patients presenting as adults is incredibly rare and the true incidence is not available.

Since 1940, it has been well established that bladder exstrophy engenders a 4% risk of metaplastic transformation. Adenocarcinoma is the most common histopathologic type, accounting for 95% of cases.[8] The etiology is unclear and is thought to be related to chronic inflammation related to bladder exposure. However, this does not explain continued risk associated with closed variants of exstrophy. There are no reported cases of urothelial carcinoma with squamous and sarcomatoid differentiation arising in a bladder exstrophy patient.

Conclusion

To the best of our knowledge, this is the first reported case of metastatic high grade urothelial carcinoma with squamous and sarcomatoid differentiation arising from undiagnosed, closed bladder exstrophy in a female in the sixth decade of life. This highlights the importance of early identification, surgical correction, and education regarding risks of malignant transformation in patients with bladder exstrophy. It further illustrates disparities in access to health care where congenital anomalies remain undiagnosed so late in life. □

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