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Squamous cell carcinoma in bladder exstrophy: a rare entity

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ABSTRACT Carcinomas arising from an exstrophic urinary bladder are rare entities, and only seven such cases have been reported in the literature. We present the eighth case of advanced squamous cell carcinoma arising from an exstrophic bladder, with a pertinent review of the literature. The mean age of the patients was 54.9 years, with a male to female ratio of 3:1. The average duration of symptoms was 18.6 months. The appearance of a new growth was the most common symptom. Three patients had stage I disease, one patient each had stage II and III disease, two patients had stage IV disease, and the disease stage was not known in one patient. Five out of these eight patients underwent surgery. Four patients in the treatment group remained disease-free, with a mean survival period of 30 months. In conclusion, regular surveillance with cystoscopy is advised in all cases that had primary closure of the exstrophic bladder.

Keywords: carcinoma, exstrophic urinary bladder, squamous cell carcinoma of exstrophy bladder
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INTRODUCTION

Carcinomas arising from an exstrophic urinary bladder are known entities and this was first reported in 1895 by Bergenhem.[1] A variety of malignancies have been identified in bladder exstrophy, such as adenocarcinoma,[1-3] squamous cell carcinoma (SCC),[1,4,5] epithelioma,[1] transitional cell carcinoma,[1] polymorphic carcinoma,[1] poorly differentiated carcinoma[2] and sarcoma botryoides.[6] We present a case of advanced SCC arising from an exstrophic bladder in a 34-year-old Indian man, with a pertinent review of the literature. The current patient represents the fourth such case in Asia and is the youngest among the previously reported cases.

CASE REPORT

A 34-year-old Indian man who had never sought medical attention presented with a polypoid friable mass arising from an exstrophic urinary bladder, with a foul-smelling, purulent discharge, swelling in both groins and a right groin ulcer (Fig. 1). Physical examination revealed complete exstrophy of the urinary bladder with epispadias and symphysis pubis diastases. A 10 cm × 12 cm friable polypoid growth covered the entire surface of the mucosa of the urinary bladder. The right ureteral opening could not be identified but the left ureteral opening was seen, with clear urine exiting. Bilateral superficial, hard and fixed inguinal lymph nodes measuring 3 cm × 3 cm were palpable. A 3 cm × 4 cm ulcer with a necrotic floor, everted margins and a hard, fixed base was present over the right inguinal lymph node mass. The ulcer was in continuity with the bladder growth. The phallus was poorly developed, yet both testes were normally descended. On rectal examination, a hard growth was felt along the anterior and lateral walls. Proctoscopy revealed a normal rectal mucosa. Secondary sexual characteristics were poorly developed.

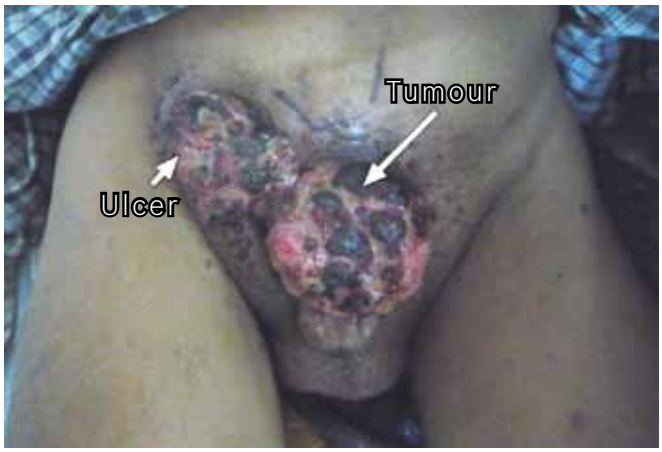

Fig. 1 Photograph shows the exstrophic bladder with squamous cell carcinoma (arrow) and ulcerated right inguinal lymph nodes (arrowhead).

Routine laboratory investigations were within normal limits. An echocardiogram revealed tricuspid regurgitation, severe pulmonary hypertension, mild mitral regurgitation, diastolic dysfunction of the left ventricle, and an ejection fraction of 30%. Contrast-enhanced computed tomography (CECT) of the abdomen and pelvis revealed a large polypoid mass, measuring 7 cm × 6.8 cm × 6 cm, that completely replaced the urinary bladder. The mass showed heterogeneous enhancement and extended laterally to involve the skin, soft tissue of the hypogastrium, and the frenulum and root of the penis. There was invasion of the levator muscle and rectum posteriorly (Fig. 3). Right hydroureter and hydronephrosis were evident although the left kidney was normal. There was no evidence of additional

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visceral involvement, retroperitoneal lymphadenopathy, ascites or pneumoperitoneum. Distant metastatic workup was negative. Biopsies of the bladder mass (Fig. 2a) and ulcer edge (Fig. 2b) revealed moderately differentiated SCC. Althoug pelvic exenteration was considered, it was rejected due to extensive growth, and high surgical and anaesthetic risks. Radiotherapy was advised, but the patient refused any intervention and left the hospital against medical advice. No further follow-up was available.

DISCUSSION

A comprehensive English and non-English search for all articles relevant to SCC of the exstrophic bladder was conducted using PubMed, a search engine provided by the US National Library of Medicine and the National Institutes of Health. Keywords searched included: squamous cell carcinoma, urinary bladder, exstrophy bladder with malignancy, and squamous cell carcinoma of exstrophic bladder. Cases identified were analysed in relation to the age and gender of the patients, corrective surgery, duration of symptoms, tumour size, treatment and outcome. Patients were staged according to the 7th edition of the American Joint Committee on Cancer's staging for cancer of the urinary bladder.[7] Collected data was tabulated and calculations were performed using Microsoft Excel® statistical functions.

Including the current case, eight cases of SCC of exstrophic bladder have been reported in the literature. The mean age at diagnosis was 54.9 (range 3–74) years, with a male to female ratio of 3:1. The average duration of symptoms was 18.6 (range 4–60) months. The appearance of new growth over the exposed mucosa was the most commonly reported symptom (87.5%). Three out of eight (37.5%) patients had stage I disease, one (12.5%) patient had stage II disease, one (12.5%) patient had stage III disease, two (25%) patients had stage IV disease, and in one patient, the disease stage was not known. Two (25%) patients had metastases to the inguinal lymph nodes, but no patients had systemic metastases. Five out of eight (62.5%) patients had surgery. Of these five patients, one had neoadjuvant chemotherapy, and another one had radiotherapy and chemotherapy following surgery. Three out of eight (37.5%) patients did not receive any therapy. Four patients in the treatment group were reported to remain disease-free, with a mean survival of 30 (range 18–36) months. The two patients who died of the disease did not receive any therapy, and another two patients were not available for follow-up.

Exstrophy of the urinary bladder is a rare anomaly of the urogenital tract, frequently occurring in males, with an incidence of one in every 10,000–40,000 births. Exstrophy is caused by the incomplete closure of the inferior part of the anterior abdominal wall due to the failure of mesenchymal cells to migrate between the ectoderm and endoderm of the abdominal wall. This basic defect involves the absence of the inferior part of the rectus muscles, with deficient external and internal oblique and transverse abdominal muscles. Exposure of the mucosal surface of the posterior wall, trigone and ureteral orifices is characteristic of this anomaly. Epispadias with the wide separation of the pubic bones is often seen with complete exstrophy. In some cases, there is complete nonunion of the two halves of the penis and scrotum.[8]

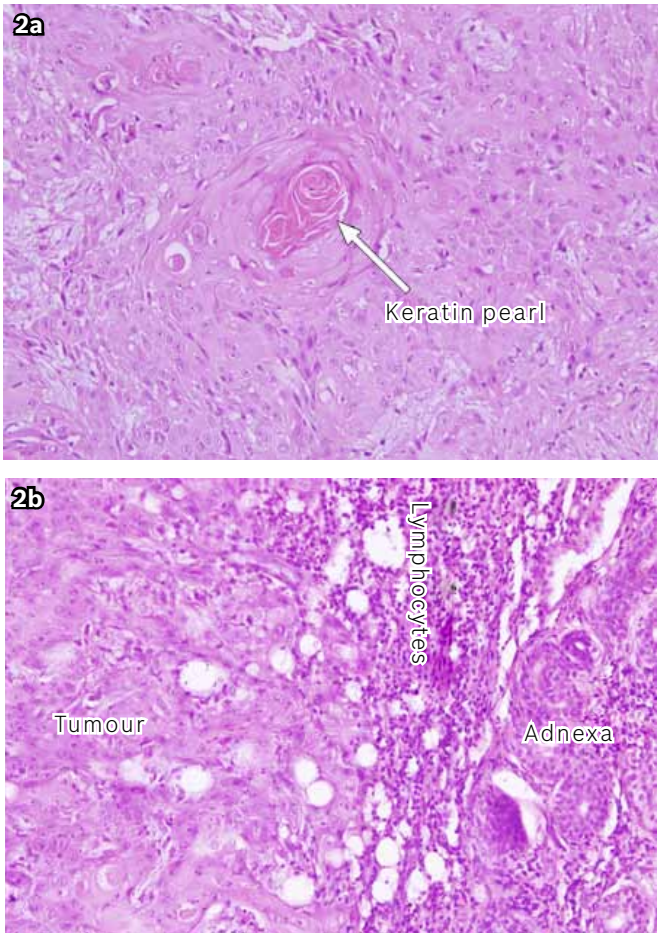

Fig. 2 Photomicrographs show moderately differentiated squamous cell carcinoma with keratin pearl formation in biopsies from (a) the tumour; and (b) the ulcer (Haematoxylin & eosin, × 20).

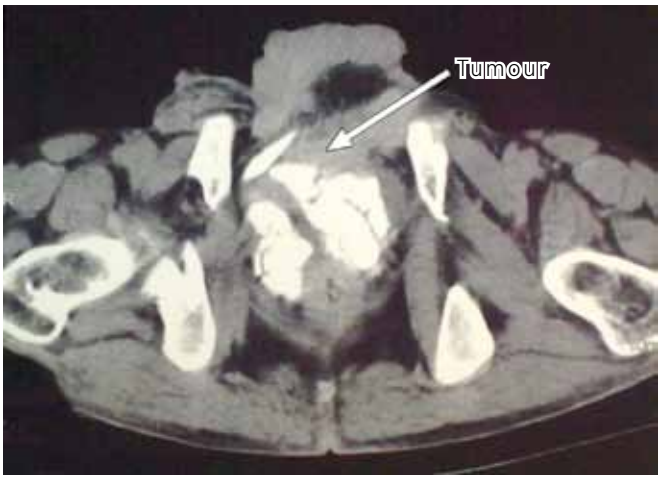

Fig. 3 Contrast-enhanced CT image of the abdomen and pelvis reveals a large polypoid mass measuring 7 cm × 6.8 cm × 6 cm in the region of the urinary bladder, completely replacing the urinary bladder. The tumour shows heterogeneous enhancement, extending laterally to involve the skin, soft tissue of the hypogastrium, and the frenulum and root of the penis. There was posterior invasion of the levator ani and rectum.

Table I. Summary of all published cases of squamous cell carcinoma in bladder exstrophy.

Study, year	Age (yrs)/ gender	Primary surgery for exstrophy	Symptoms/ duration (mths)	Tumour size (cm)	Metastases	Stage	Treatment	Follow-up/ duration (mths)†
Lampe, 1905*	NM/ M	Nil	Mass/ NM	NM	Nil	I	S	LOF
Lacene, 1912*	57/ F	Nil	Mass/ NM	NM	Nil	I	NT	DOD
Gupta, 1976[11]	48/ M	Nil	Mass/ 6	NM	Nil	I	S	DF/ 36
Sahai, 2004[5]	47/ M	Primary closure, 6 mths augmentation cystoplasty with a catheterisable stoma	Difficult catheterisation/ 11	NM	Inguinal LN	IV	S	DF
Ribeiro, 2005[12]	71/ M	Nil	Mass, renal failure/ 60	20	NK	NK	NT	DOD/ 1
Rieder, 2006[4]	53/ F	Nil	Mass/ NM	NM	Nil	II	S + RT + CH	DF/18
Haji, 2008[13]	74/ M	Nil	Mass, bleeding/ 12	11	Nil	III	CH +S	DF/ 36
Current case	34/ M	Nil	Mass, foul-smelling discharge/ 4	7	Inguinal LN	IV	NT	LOF

*As reported in Okane et al's paper.[1] †Follow-up was from the time of diagnosis.
NM: not mentioned; M: male; F: female; LN: lymph node; S: surgery; NK: not known; NT: no treatment given; RT: radiotherapy; CH: chemotherapy; LOF: lost to follow-up; DOD: died of disease; DF: disease-free

Exstrophy increases the risk of developing a bladder tumour by 694 times as compared to the general population.[2] Although squamous metaplasia has been found in 80% of cases, SCC arising from an exstrophic bladder is a very rare entity.[3] To date, only eight such cases have been reported, including the current case (Table I). The precise cause of carcinogenesis in exstrophy is unknown. However, various hypotheses have been offered, including recurrent infections, environmental exposure or genitourinary secretions. Although the presence of carcinogens in urine may predispose one towards the development of carcinoma in the exstrophic bladder,[9] Vik et al reported the case of a 48-year-old man who developed SCC in the remnant of his urinary bladder, although he had previously undergone cystectomy and ureterosigmoidostomy due to exstrophy at two years of age.[10] Rieder et al have suggested that chronic irritation of the adjacent skin by urogenital secretions is the cause of SCC, with the latter invading the urinary bladder.[4] However, this theory insufficiently explains such a locally advanced disease, as seen in our patient. Moreover, malignancy has previously been reported in a patient who had undergone primary closure of the urinary bladder due to exstrophy at six months of age.[5] Smeulders et al have identified different types of metaplastic epithelial changes in the mucosa of the untreated exstrophic bladder, suggesting a potential intrinsic predisposition to malignant transformation.[2]

Complete removal of the malignant tumour is the only operative option. The role of chemotherapy and radiotherapy in this disease state cannot be assessed due to the small number of patients. It is important to be aware that simple cystectomy may not prevent recurrence, especially in males. In a group of 65 (45 males, 16 females) patients with bladder exstrophy, Smeulders and Woodhouse documented malignancy in the bladder remnants of four male patients after a median follow-up of 34 (range 28–48) years. The authors concluded that the male anatomy may not permit as complete a cystectomy as in females and/or the secretions from the male genital tract may act as carcinogens.[2]

In conclusion, primary repair of bladder exstrophy at an early age is the standard care in developed countries. However, this is not as common in developing nations with limited expertise and access to healthcare. Even when performed, primary repair or cystectomy may not ensure protection from the development of malignancy within an exstrophic bladder. Hence, it is advisable to practise regular surveillance of patients who have undergone primary closure.

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