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Evaluation of the response chemotherapy for penile metastasis of bladder cancer using 18F-fluorodeoxyglucose-PET/CT

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ABSTRACT

BACKGROUND: Metachronous penile metastasis of bladder cancer occurs very rarely. The clinical management of the disease involves complex problems, and the disease is associated with a poor prognosis. The common mode of spread to the penis is by the retrograde venous route.

PATIENTS AND METHODS: A 68-year-old patient who was diagnosed with invasive bladder cancer underwent ^{18}F-fluorodeoxyglucose (FDG)-positron-emission tomography/computed tomography (PET/CT) for staging purposes. An 18 mm intracavernosal metastatic lesion was detected in the penis with a SUV_{max} of 12.9.

RESULTS: After the administration of gemcitabine + cisplatin-based chemotherapy, remission was observed in the metastatic penile lesion according to EORTC criteria (12 mm, SUV_{max}: 9), and second line chemotherapy program was planned.

CONCLUSION: Penile metastasis from bladder cancer is an indicator of poor prognosis. The patients with penile metastasis poorly respond to therapy, despite the use of effective systemic chemotherapy. The researchers of the current study achieved a partial response to chemotherapy in the current case of penile metastasis. The disease-specific life expectancy is less than one year in these patients. Radical ablative surgery does not contribute to survival; however, it offers an alternative method in symptomatic patients.

1. Introduction

Bladder cancer ranks ninth throughout the world with 380,000 new cases occurring every year [1]. 10–15% of the patients have metastatic disease at the time of diagnosis. Despite the administration of radical therapies, 50% of the patients with muscular invasive bladder cancer develop metastatic lesions within two years. The patients died of these metastases [2]. Unusual metastatic sites for urothelial carcinoma are documented. These sites include cardiac tissues, small bowel, and salivary glands [3–5]. The first penile metastasis was reported by Eberth et al. in a patient with rectal adenocarcinoma in 1870 [6]. The first documented case of penile metastasis from primary bladder cancer was reported by Neumann in 1882 [7]. The failure of conventional methods in the clinical staging of bladder cancer is the most important obstacle to predict survival and planning of additional treatment protocols. Clinical staging using bimanual palpation, CT, or MRI may often result in over- and under-staging and have a staging accuracy of only 70% [8,9]. This poses a more significant problem in the presence of atypical metastases. In the present case, penile metastasis could not be detected with CT scans. It is well-known that metastasis can occur in normal-sized lymph nodes and tissue with normal appearance. PET/CT scans that combine anatomic and functional images provide more sensitive data in the detection of these lymph nodes and metastatic foci. Furthermore, there is a great demand for a diagnostic test offering high sensitivity and specificity in predicting residual disease and monitoring response to treatment in these patients after chemotherapy. ^{18}FDG-PET/CT is the gold standard diagnostic modality in the planning of second line chemotherapy programs using RECIST, PERCIST, and EORTC. In this case, PET/CT was used to evaluate the response of penile metastasis to chemotherapy. The importance of PET/CT has been emphasized in the follow-up of atypical metastases.

2. Case report

A 69-year-old male patient presented complaining of penile pain due to muscle-invasive bladder carcinoma (TCCa, high grade).

Abbreviations: FDG-PET/CT, ^{18}F-fluorodeoxyglucose-positron-emission tomography/computed tomography; SUV, standard uptake value; EORTC, European Organisation for Research and Treatment of Cancer; PERCIST, the PET response criteria in solid tumors; RECIST, response evaluation criteria in solid tumors; MRI, magnetic resonance imaging; CT, computed tomography; CTx, chemotherapy; RTx, radiotherapy; FNAC, fine needle aspiration cytology; TCCa, transitional cell carcinoma; MIP, maximum intensity projection.

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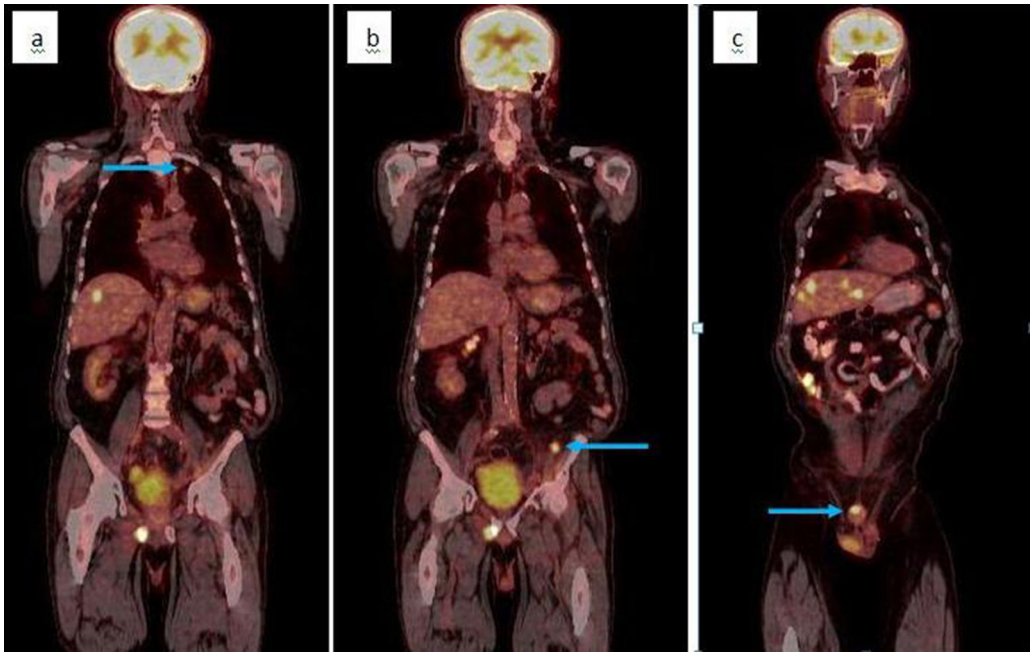

Fig. 1. PET/CT Imaging(pre-chemotherapy). (a) The coronal 18FDG-PET/CT scans show, (arrow: left lung metastasis), SUVmax: 10.9. (b) The coronal ^{18}FDG-PET/CT scans show, (arrow: pelvic lymph node metastasis), SUV_{max}: 9.9. (c) The coronal ^{18}FDG-PET/CT scans show, (arrow: penile metastasis, 18 mm), SUV_{max}: 12.6.

The bimanual physical examination revealed normal findings. The penile examination revealed a 2 cm painful mass in the right corpus cavernosum. Biochemical analyses were as follows: glucose, 151 mg/dL; creatinine, 0.9 mg/dL; urea, 45 mg/dL; aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and gamma glutamyl transferase levels were within normal ranges; white blood cells, $7.42 \times 10^3/\mu L$; hemoglobin, 12.9 g/dL; sodium, 137 mmol/L; potassium, 4.3 mmol/L; chloride, 102 mEq/L; and calcium, 8.9 mg/dL. The patient's medical history was remarkable for diabetes mellitus and the patient was using oral anti-diabetic agents. The patient was a nonsmoker. ^{18}FDG-PET/CT was performed for staging purposes and revealed metastasis in the right supraclavicular lymph node, multiple lung metastases, external iliac lymph node metastasis, and penile metastasis. Fine needle aspiration cytology (FNAC) of the penile swelling revealed metastatic transitional cell carcinoma (Figs. 1 and 2).

After administration of gemcitabine + cisplatin-based chemotherapy, the patient was re-evaluated with repeat ^{18}FDG-PET/CT scan. A partial response to therapy was obtained according to the response criteria of European Organization for Research and Treatment of Cancer (EORTC) (Fig. 3). The patient developed multiple liver metastases despite the administration of chemotherapy. PET/CT findings of the patient are summarized in Table 1.

Table 1
PET/CT findings in this study (pre-chemotherapy and post-chemotherapy).

PET/CT findings	Metastatic focus	Size (mm)	SUV_{max}
Pre-CTx	Supraclavicular lymph node	10	2.7
	Lung	20 and 26	10.9 and 10.6
	Pelvic lymph node	16 and 31	9.9 and 20.4
	Penile	18	12.6
Post-CTx	Supraclavicular lymph node	0	0
	Lung	23 and 34	15.2 and 8.9
	Pelvic lymph node	24 and 61	14.8 and 19.7
	Penile	12	9.0

3. Discussion

It is still unknown, why the penile metastasis is infrequent despite the fact that penis has got rich vascularazition and intensive venous communication with neighboring organs. There are around 500 case reports in the literature. The primary tumor foci were pelvic cancers in 70% of these cases. Metastasis from the bladder (28.6%), prostate (27.9%), and rectosigmoid (12.2%) tumors are the most commonly encountered metastases [6]. In a review of 372 patients by Cherian et al., prostate, bladder, rectosigmoid and rectum, and kidney were the most common sites for primary tumor

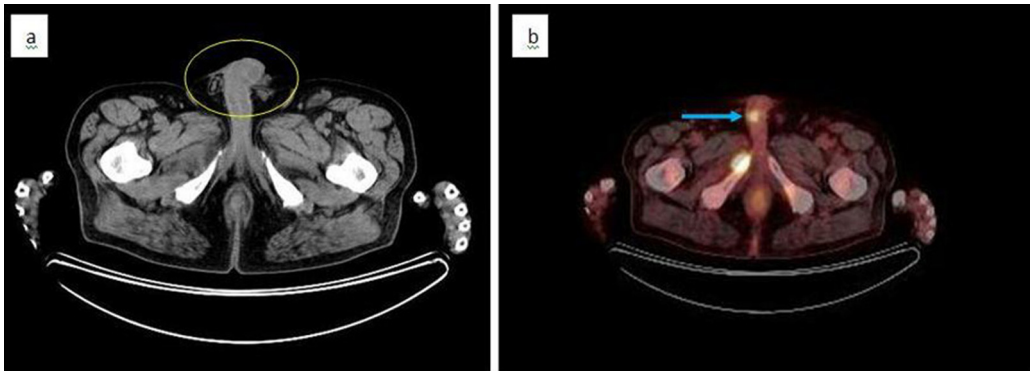

Fig. 2. (a) The axial CT scans show, (Undedectable Penile Metastasis). (b) The axial ^{18}FDG-PET/CT scans show, (arrow: dedectable penile metastasis) SUV_{max}: 12.6.

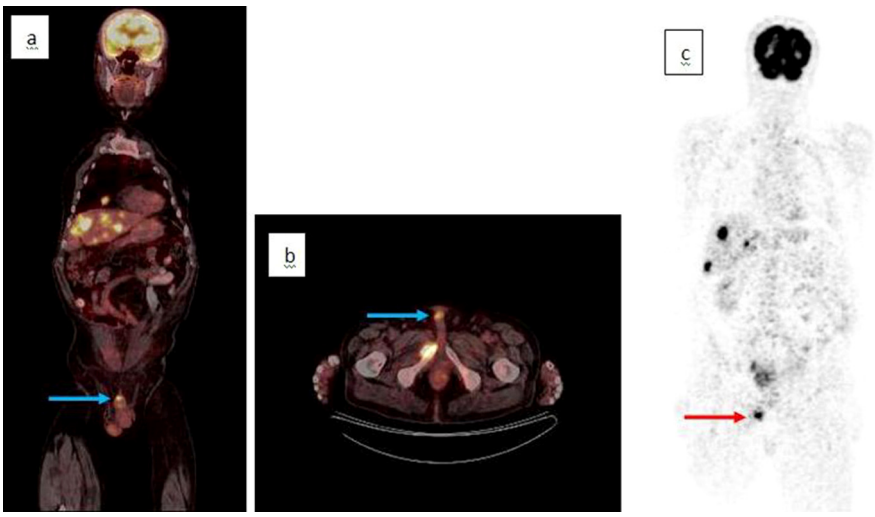

Fig. 3. PET/CT Imaging(post-chemotherapy). (a) The coronal ^{18}FDG-PET/CT scans show, (arrow: penile metastasis, 12 mm), SUV_{max}: 9.0. (b) The axial ^{18}FDG-PET/CT scans show, (arrow: penile metastasis, 12 mm) SUV_{max}: 9.0. (c) Maximum intensity projection (MIP) images, (arrow: penile metastasis).

that exhibited penile metastasis (34%, 30%, 13%, and 8%, respectively) [10]. Lymphomas, lung cancer, gastrointestinal tract tumors, and bone and ureteral tumors rarely metastasize to the penis. The metastasis most commonly occurs to corpus cavernosum. However, the tumors can also metastasize to the glans penis and corpus spongiosum, urethra, and penis skin [11,12]. The mechanisms of penile metastasis were described by Paquin and Roland in 1956 [13]. There are four possible ways of spread to the penis: (a) direct infiltration; (b) during instrumental examination; (c) hematogenous – either through arterioles, retrograde venous stream or as a paradoxical embolism through an atrial septal defect; and (d) through retrograde lymphatic permeation [13]. Mass, induration and nodules are the initial presentation of penile metastasis in 51%, priapism in 27%, urinary symptoms like hemorrage, hematuria, incontinence, and irritative and obstructive symptoms in 27%, pain in 17%, retention in 13% and skin lesions in 11% of the patients [14]. Cherian et al., reported that up to 40% patients with penile metastasis may initially present with priapism, due to compromised penile venous drainage. Pain, hematuria, and obstructive voiding symptoms are rarer presentations [10]. Furthermore, the authors suggest that metastasis must be considered if priapism has been detected in urogenital cancers unless otherwise is proven. In most cases of bladder carcinoma with penile metastases have also other organ metastasis. So that at the time of diagnosis, these patients usually have disseminated disease and prognosis is dismal. Isolated metastases of the penis are exceptionally rare event [15]. Approximately 30% of all penile metastases are detected concomitantly with the primary tumor, whereas remaining 70% present within a mean interval of 18 months after primary tumor detection [16]. The diagnosis must be based on histopathological examination. This is due to the fact that a pagetoid pattern of infiltration is seen, particularly with transitional cell carcinoma of the urinary tract and this should be differentiated from primary Paget's disease of the penis [17]. The disease is differentiated with primary tumors of the penis. The primary tumors of the penis mostly appear as superficial skin lesions, and secondary tumors mostly occur in deeper locations [6]. Some premalignant and malignant primary diseases (Bowen's disease, erythroplasia of queyrat, verrucos carcinoma, squamous cell carcinoma, melanoma, sarcoma), some infectious diseases (tuberculosis, chancroid, syphiloma), and some common benign disorders (Peyroni's disease, nonmalignant priapism) should be taken into consideration in the differential diagnosis of metastasis penile cancers [18]. US is often the first diagnostic method employed and MRI offers a valuable diagnostic tool in confirming the diagnosis and demonstrating the extent of the disease. However, although conventional methods are valuable in the diagnostic workup, they can sometimes fail to detect lesions, as was the case in the current patient. Intracavernosal metastasis without causing any change in penis anatomy in the current patient could not be detected on CT scans; however, the lesion was visualized with FDG accumulation on PET/CT detector. FDG-PET/CT is an important diagnostic tool in the follow-up these foci and monitoring response to therapy after chemotherapy. The treatment options vary depending on the performance status of the patient, local stage of the primary tumor, presence of other metastases, and prevailing symptoms. The treatment options include local excision, partial or radical penectomy, radiotherapy, and chemotherapy [19]. The optimal treatment of penile metastasis requires a multidisciplinary approach that is correlated with the disease extent. The average survival in patients with penile metastasis is 3.9 months from diagnosis and, with extensive surgery and chemotherapy, a survival of 9.2 months has been reported [20]. The surgical treatment of metastatic lesions can be considered in small isolated lesions; however, surgery is complicated in lesions located in proximal part of penis. Penectomy is occasionally indicated after failure of other modalities to palliate intractable pain. Radiotherapy can be given in these cases.

In the study by Zhu et al., comprising eight patients, a painless nodule was the most common symptom (80%), which is different from the literature [21]. The mean time between the diagnosis of primary tumor and the diagnosis of penile metastasis was 26.4 months (1–00). The mean time between the diagnosis of penile metastasis and death was 11.4 months (4–23). This study also recommended radical ablative surgery only in symptomatic patients [21]. The prognosis is poor due to presence of widespread metastases in patients with penile metastasis, and 6-month mortality rate is reported to be around 80%. The survival rate in penile metastasis of bladder cancer is extremely low, with a mean of 47 weeks. However, the studies have reported a survival up to nine years in penile metastasis from prostate cancer. In other words, biological behavior of the primary tumor is more important in terms of prognosis [6,19]. Secondary penile tumors are usually associated with disseminated disease and indicate a poor prognosis. Most of the patients with penile metastasis have advanced disease and survival after the diagnosis is generally short, and 80% of the patients die within six months [15].

4. Conclusion

Penile metastasis from bladder cancer is an indicator of poor prognosis and it is often a part of a systemic disorder. An isolated penile metastasis from bladder cancer is an extremely rare condition. It is difficult to detect atypical metastases of bladder cancer such as penile metastasis using conventional techniques. ^{18}FDG-PET/CT is an important diagnostic tool used in staging of the disease and evaluating response to therapy.

Conflict of interest

The authors declare that they have no competing interests. Financial support has not been received.

Peer-review

Externally peer-reviewed.

Informed consent

Written informed consent was obtained from patient who participated in this case.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Author contribution

The manuscript written by only one author.

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