CASE REPORT

A case report of primary malignant melanoma of male urethra with distinct appearance in multiple regions

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Abstract A 66-year-old man presented with macrohematuria. Cystoscope examination found a 5 mm nodular tumor at external urethral orifice and multiple papillary tumors at fossa navicularis of urethra; those are non-black colored. Transurethral resection of the urethra tumor was performed, and pathologically diagnosed as malignant melanoma. Image examinations showed no lymphadenopathy and metastasis. Accordingly, total penectomy was conducted to remove the remaining tumors, resulting in surgically curative resection. After the operation, monthly interferon- β injection into inguinal region has been administered as adjuvant therapy, resulting in no recurrence at 6 months after penectomy.

Keywords Male urethra · Malignant melanoma · Penectomy · Interferon

Introduction

Primary malignant melanomas of the male urethra are extremely rare, where secondary melanomas are more common than primary melanomas. Therefore, urethral melanomas are difficult to be diagnosed initially, which

may lead to a delay in diagnosis and poor prognosis, where histopathological examination is the mainstay of diagnosis. To describe the characteristics of this rare disease, we here present the case of a 66-year-old man with primary malignant melanoma of the male urethra.

Case report

A 66-year-old man consulted an urologist with macrohematuria, and urine cytology was diagnosed as class V. Accordingly, he was referred to our institution in June 2015. Urine cytology in our institute was diagnosed as class IIIb although laboratory tests showed no abnormal values. Cystoscope examination found a 5 mm grossly amelanotic nodular tumor at external urethral orifice and grossly amelanotic multiple papillary tumors at fossa navicularis of urethra (Fig. 1a, b). Then, transurethral resection of urethral tumor was performed. In histopathological examination, the specimens showed numerous atypical melanocytic cells with large hyperchromatic nucleus or vesicular nucleus with prominent nucleoli and abundant eosinophilic cytoplasm or large multinucleated giant cells, accompanied by melanin pigments, often arranged in nests and in trabecular pattern (Fig. 1c). The tumor cells were positive for HMB-45 staining (Fig. 1d) and Melan-A staining, and pathologically diagnosed as malignant melanoma. CT scan and ¹⁸F-FDG PET showed no abnormal finding in upper urinary tract as well as no lymphadenopathy and metastasis. However, follow-up cystoscopy suggested the remaining tumorous region with multiple flat black spots around distal urethra in mid-shaft (Fig. 2a), while there was no abnormal finding in proximal urethra as well as urinary bladder. Accordingly, total penectomy without lympho-node dissection was performed without intraoperative pathological examination on August 2015. Grossly, there are black spots

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Fig. 1 Urethral tumors at initial diagnosis. **a** Macroscopic finding showed a 5 mm nodular tumor at external urethral orifice. **b** Cystoscope finding showed multiple papillary tumors at fossa navicularis of urethra. **c** Microscopic finding showed numerous atypical

melanocytic cells (hematoxylin and eosin staining; original magnification $\times 200$). **d** Microscopic finding showed tumor cells strongly positive for HMB-45 (HMB-45 staining; original magnification $\times 200$)

where we performed transurethral resection of urethral tumor before and pale black spots around distal urethra in mid-shaft (Fig. 2b), which was diagnosed histologically as remaining malignant melanoma in distal urethra apart from the region removed in transurethral resection, invading the epithelial connective tissue, but with negative surgical margin where tumor edge was about 2 cm apart from proximal margin (Fig. 2b, c). After the operation, monthly interferon (IFN)- β injection into inguinal region has been administered as adjuvant therapy, resulting in no recurrence at 6 months after penectomy.

Discussion

Cutaneous malignant melanoma is the fifth most common cancer in male [1]. However, primary malignant melanomas of the genitourinary tract are rare. Especially, primary

malignant melanoma of the male urethra is extremely rare and its incidence accounts for only about 1 % among all malignant melanomas [1]. Until 2014, 150 cases with primary urethral melanoma have been reported, among which 60 cases of melanoma in male urethra occurred [2].

Primary urethral melanoma affects female threefold more frequently [2], which may be due to higher concentration of melanocytes in the mucocutaneous tissue of vulva [3]. The symptoms of urethral melanoma are hematuria, urethrorrhagia, dysuria, strangury, and palpable tumor [4], as well as a peak age of onset is around 65 years old [2], consistently with this case. Prognostic prediction in cutaneous malignant melanoma is based mainly on tumor thickness and ulceration as well as disease extension to adjacent structure and metastasis to regional lymph nodes and distant organs, which may be prognostic also in malignant melanoma of the male urethra [5, 6].

Fig. 2 Urethral tumors when total penectomy was performed. **a** Cystoscope finding showed the remaining tumors with multiple *black spots* in distal urethra from external orifice to close to urethral bulb. **b** Macroscopic finding showed *black area* where we performed transurethral resection of urethra tumor before and *pale black spots* on

the nearer pendulum of the urethra. *Arrow* indicates malignant region closest to proximal surgical margin. **c** Microscopic finding showed the residual tumors in distal urethra (hematoxylin and eosin staining; original magnification $\times 200$)

So far, malignant melanomas in several sites of the genitourinary tract have been reported including ureter [7], bladder [8], prostate [9], urethra and penis [4]. Among them, the distal urethra including urethral bulb and urethral meatus is the most common location of melanomas in the genitourinary tract [10]. The prognosis of malignant melanoma of the urethra is poor (2- and 5-year survival are about 63 and 31 %, respectively) [5]. This case showed multiple regions affected with malignant melanoma of the male urethra, which presented with distinct appearance of tumors in each region. Although several cases with multiple regions have previously been reported from Japan [11–13], this is the first case presented with distinct appearance of tumors including nodular tumor at outer orifice, papillary tumors at fossa navicularis of urethra and flat tumor at distal urethra close to bulb. Also, since

multiple tumors can occur in urinary tract, careful attention for other urinary tracts should be paid. In this case, there was no abnormal finding in urinary bladder on cystoscopy and upper urinary tract on CT scan.

Initially, Bracken et al. have developed staging system, as follows; stage I, confined to the penis; stage II, being metastatic to the regional lymph nodes; stage III; representing disseminated disease [14]. Alternatively, Levine et al. have developed more common staging system as follows: stage A, tumor confined to the submucosa; stage B, tumor infiltrating the corpus spongiosum in men and the periurethral muscle in women; stage C, tumor extending beyond the corpus spongiosum in men or periurethral invasion including vagina, bladder, labia, or clitoris in women; and stage D, tumor with metastasis to lymph nodes [15]. According to this criterion, this case

was staged as stage I/A. For stage I/A melanomas located in the distal urethra, wide local excision with adequate margins has been the mainstay of treatment and thought to be sufficient [1, 5]. In addition, similar to cutaneous melanoma, in stage I mucosal melanoma, routine lymph node dissection has been thought to be contraindicated because there is no evidence of survival benefit and it carries considerable morbidity [4, 16]. Although sentinel node biopsy may be utilized for staging in cutaneous malignant melanoma, this procedure is not established and technically challenging in urethral malignant melanoma, which should be developed in the future. Accordingly, in this case, total amputation of the penis without lymph node dissection was chosen since the tumors located in distal urethra close to urethral bulb, making partial resection challenging. Intraoperative examination would be required if surgical margin is suspicious. However, since we could resect with enough margin in this case, we did not perform pathological examination intraoperatively.

The effective systemic therapy specific for genitourinary melanoma has not been established so far. Therefore, most therapeutic strategy usually determined according to standard care of cutaneous malignant melanoma. So far, chemotherapy and radiotherapy were utilized as adjuvant therapy for urethral melanoma although their efficacy has been limited [4]. Previously, it has been reported that adjuvant IFN for patients with high-risk stage II/III cutaneous melanoma reduced the risk of disease recurrence and prolonged disease-free survival [17]. Accordingly, we chose monthly IFN injection into inguinal region as adjuvant therapy in this case. Recently, novel combination therapy using BRAF inhibitor dabrafenib and MAPK kinase (MEK) inhibitor trametinib [18] as well as anti-CTLA-4 antibody ipilimumab and nitrosourea antineoplastic agent fotemustine [19] has shown promising anticancer effects to advanced cutaneous malignant melanoma in clinical trials. In addition, immune checkpoint inhibitors such as anti-PD-1 antibody and anti-CTLA-4 antibody currently investigated in clinical trials may lead to changing landscape of adjuvant therapy for malignant melanoma, which may also benefit patients with primary malignant melanoma of the genitourinary tracts.

In conclusion, we experienced a case of primary malignant melanoma of the male urethra. Primary malignant melanoma of the urethra should be bore in mind as differential diagnosis of urethral tumors.

Compliance with ethical standards

Conflicts of interest All authors declare no potential conflict of interest to disclose.

Research involving Human Participants All procedures performed in studies involving human participants were in accordance with the ethical standards of the national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the individual included in the study.

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