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Primary malignant melanoma of the female urethra: A case report

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ABSTRACT

Primary malignant melanoma of a female urethra is extremely rare. A 71-year-old female was referred to our hospital with bleeding from the urethral meatus. Magnetic resonance imaging revealed a mass of 25 mm in diameter at the external urethral meatus. She underwent anterior pelvic exenteration and ileal conduit diversion. Histopathological findings were urethral malignant melanoma, pT3apN0M0 (stage IIA). Nine months after surgery, computed tomography revealed a local recurrence in the pelvis, the patient was treated with immunotherapy using combined nivolumab and ipilimumab; however, she did not respond to treatment and died 22 months following diagnosis.

Introduction

Melanomas are malignant tumors arising from melanocyte pigment cells. Melanomas are mostly of cutaneous origin; however, they can also occur in various extracutaneous sites where pigment cells are present. Primary mucosal melanomas are rare but aggressive tumors.[1] The immune checkpoint inhibitors approved in recent years have a low response rate to mucosal melanoma.[2]

We report a case of female urethral melanoma. The patient experienced recurrence nine months after surgical resection. She was treated with immunotherapy using combined nivolumab and ipilimumab. However, she did not respond to the treatment and died 22 months following diagnosis.

Case report

In April 2018, a 71-year-old woman was referred to our hospital with external urethral bleeding. A tumor 25 mm in diameter was found around the urethral meatus (Fig. 1). Black pigmentations on the vulva and anterior wall of the vagina were observed. Cystoscopy showed no abnormal findings in the bladder except for pigmentation of the urethral mucosa and pigment spots of the bladder neck (Fig. 1). Magnetic resonance imaging (MRI) findings showed a 25-mm mass that extended to the vagina around the external urethral meatus (Fig. 2). Computed tomography (CT) showed no apparent lymph node or distant metastases. She was clinically diagnosed as having urethral malignant melanoma, T3aN0M0 (stage IIA), based on visual inspection, CT, and MRI findings. Because the present case was a large lesion extending to the entire urethra, bladder neck, the vulva and anterior wall of the vagina and excisional biopsy was difficult, radical surgery was performed concurrent with excisional biopsy. In June 2018, she underwent anterior pelvic exenteration and ileal conduit diversion.

Histopathological findings were urethral malignant melanoma, polypoid and nodular malignant melanoma in the urothelial epithelium and squamous epithelial transition, and slight submucosal infiltration, pT3apN0M0 (stage IIA) (Fig. 3). The tumor cells infiltrated in lymph vessels. It was confirmed that melanosis was present in the background of the tumor. BRAF gene mutation was negative.

In March 2019, CT revealed local recurrence in the pelvis. The patient was treated with immunotherapy using combined nivolumab (1 mg/kg) and ipilimumab (3 mg/kg). In May 2019, CT after four courses of nivolumab and ipilimumab showed tumor recurrence had increased in the pelvis with bone and multiple liver metastases. After radiation therapy (30 Gy/10 fr) for painful ischial metastases, the patient was treated with nivolumab (240 mg/body) monotherapy. In July 2019, CT after three courses of nivolumab therapy showed that the irradiation

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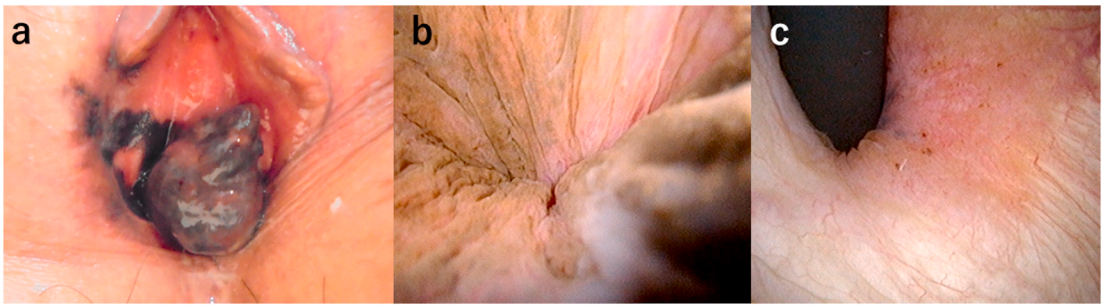

Fig. 1. Macroscopic findings.
A tumor around the urethral meatus (a). Cystoscopy shows no abnormal findings in the bladder except for pigmentation on urethral mucosa (b) and pigment spots on the bladder neck (c).

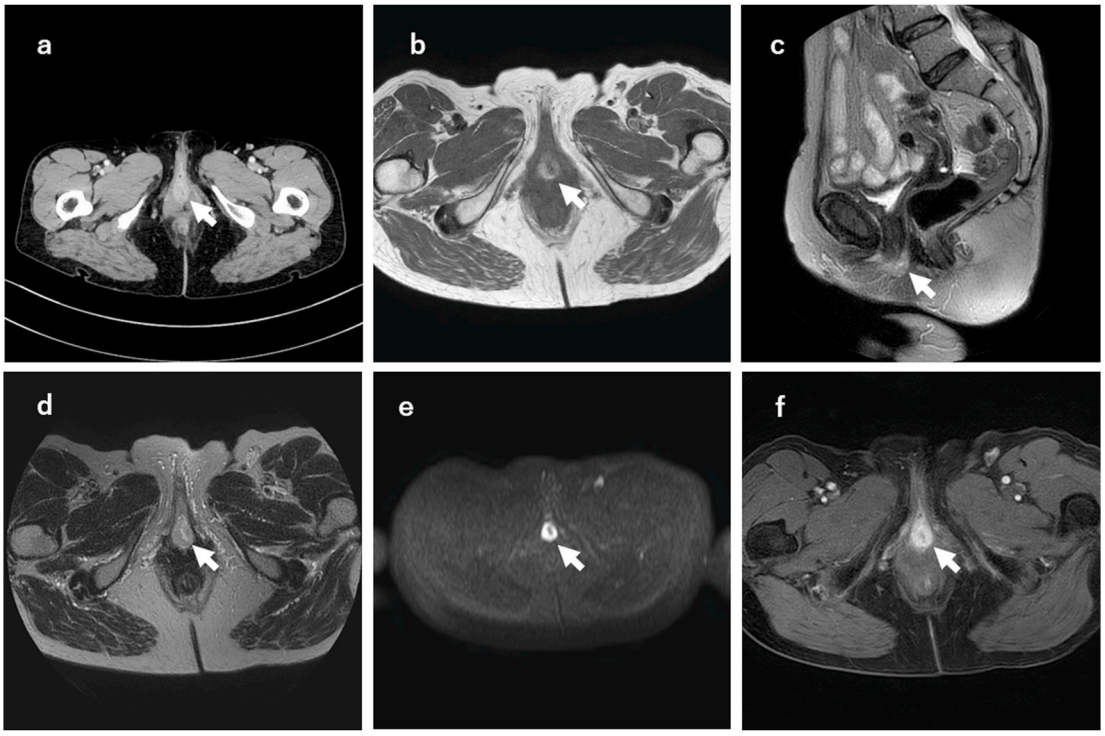

Fig. 2. Imaging findings.
Pelvic CT shows a contrast enhanced tumor, 25 mm in diameter, surrounding the urethral meatus. Pelvic MRI shows a tumor at the vulva that extends into the urethra and anterior vaginal wall. MRI revealed a high signal intensity on T1-weighted imaging (b: arrow), a high signal intensity on T2-weighted imaging (c: axial, d: coronal image, arrow), a high signal intensity on diffusion-weighted imaging (e: arrow), and early enhancement after the administration of gadolinium in dynamic contrast-enhanced imaging (f: arrow).

field tumor was partially reduced; however, the other metastatic sites had increased. In October 2019, after six courses of nivolumab therapy, the patient complained of abdominal pain and vomiting. CT showed worsening metastatic lesions and ileus, and she died in February 2020.

Discussion

Mucosal melanoma is an extremely rare variant of cutaneous melanoma.[1] Mucosal melanomas occur in the head, the neck, and the anorectal and genitourinary tract. Mucosal melanomas such as urethral melanoma are often aggressive and associated with a worse prognosis than those arising from the skin.[1] Malignant melanomas of the genitourinary tract account for a quarter of mucosal melanomas.[1] Although the urethra is considered to be the most frequent site of primary melanoma of the urinary tract, primary urethral melanoma is rare. It accounts for less than 1% of all melanoma and about 4% of urethral cancer.[3] The distal urethra is the most common site of occurrence of melanoma in the urinary tract. In the present patient, the tumor originated from the distal urethra.

As melanocytes, which are the origin of melanoma, do not usually exist in the mucous membrane, melanosis is necessary in the background to develop melanoma in the mucous membrane. It was confirmed that melanosis was present in the background of the tumor in the present patient (Fig. 3).

Guidelines for the clinical course of mucosal melanoma have not been established due to the rarity of the disease. Surgery is still the primary therapeutic intervention for mucosal melanoma.[1] The standard surgical procedure for primary melanoma of the urethra has not yet been established. In female urethral melanoma, total or partial urethral resection in addition to total cystectomy and vulvar resection are performed. However, postoperative quality of life may be reduced by radical resection depending on the site of occurrence. Whether there is an advantage for the prognosis of urethral resection with cystectomy over bladder-sparing urethral resection is unknown. According to a

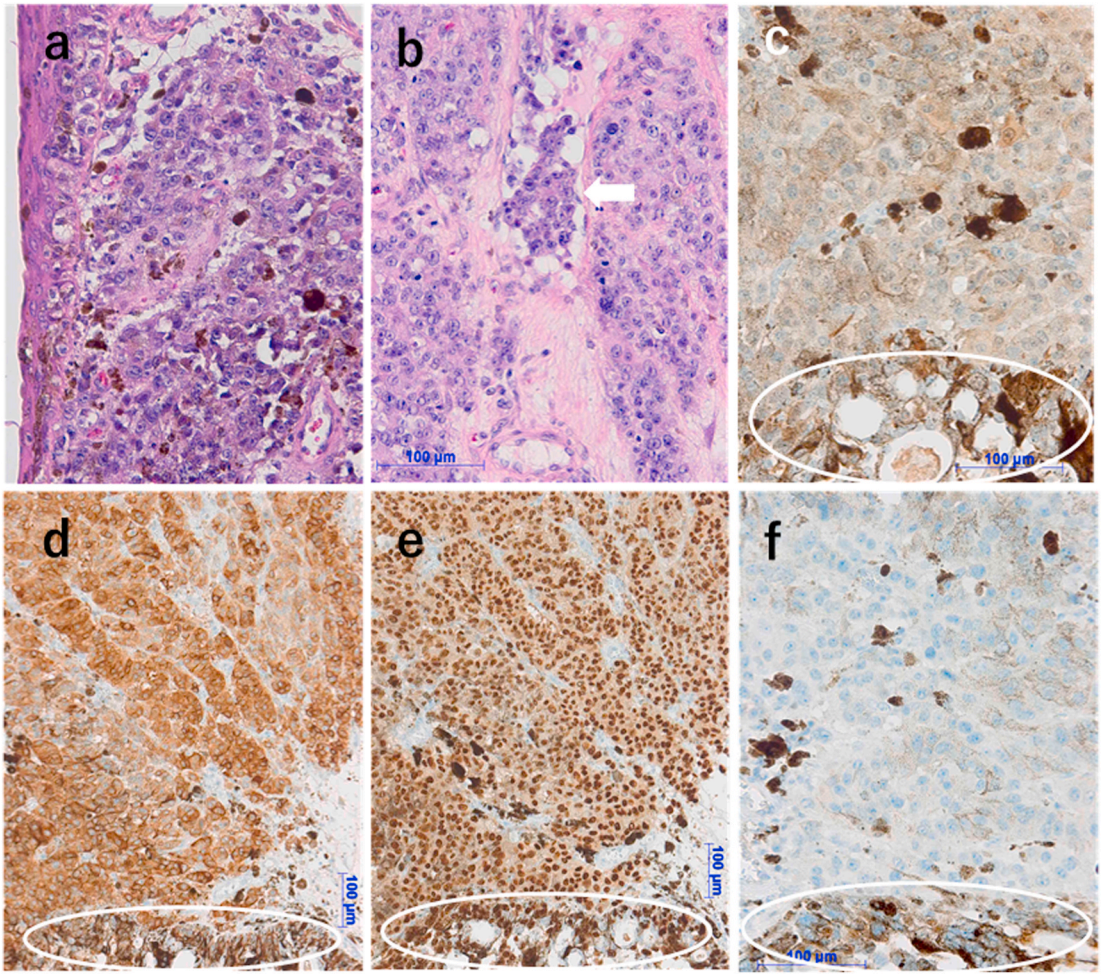

Fig. 3. Pathological findings.
The tumor cells have brown melanin pigments (a: haematoxylin & eosin section, x 20). The tumor cells infiltrated in lymph vessels (b: haematoxylin & eosin section, arrow). The cells are immunoreactive for S-100 (c: cytoplasmic and nuclear regions), Melan A (d: cytoplasmic regions), and SOX 10 (e: nuclear regions), which are typical for melanoma. The tumor cells are negative for GATA3 (f). Melanosis (circle) is present in the background of the tumor and is immunoreactive for S-100 (c: cytoplasmic and nuclear regions), Melan A (d: cytoplasmic regions), SOX 10 (e: nuclear regions), and GATA3 (f: cytoplasmic regions). . (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

report that examined the surgical procedure and treatment results of 11 female urethral melanoma patients, no recurrence was observed in patients without direct invasion of the bladder neck.[4] This suggests that cystectomy may not be essential. In the present case, total urethrectomy in addition to anterior pelvic exenteration was performed because the tumor infiltrated the bladder neck and anterior vaginal wall. The surgical margin was negative.

Systemic treatment of melanoma has markedly advanced since the introduction of ipilimumab in 2011; however, there are no consensus guidelines on the optimal systemic therapy for mucosal melanoma. As a result, systemic therapy regimens are extrapolated from data based on therapies used to treat advanced cutaneous melanoma. Nivolumab combined with ipilimumab has greater efficacy than either agent alone; however, the efficacy was lower in mucosal melanoma.[2] In the present case, the patient was treated with nivolumab combined with ipilimumab without benefit.

While the incidence of mutations in the BRAF oncogene in cutaneous melanoma are the most common with 50–60% prevalence, its prevalence is less than 10% in mucosal melanoma.[5] BRAF gene mutation was negative in the present case.

Urethral melanoma shows a high rate of local recurrence, about 60% at 1 year. Overall survival in a series of 11 women at 3 years was 27%.[4] The present patient exhibited local recurrence, which resulted in distant metastases. She did not respond to treatment and died 22 months following the diagnosis.

Conclusion

Malignant melanoma of the female urethra is an extremely uncommon tumor. It mostly occurs in elderly patients and is more common in females. Urethral melanoma shows a high rate of local recurrence. Surgery is the main treatment option; however, optimal extent of surgery remains to be clarified.

Declaration of competing interest

No conflict of interests exist.

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