Case Series

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Melanoma Management

Primary malignant melanoma of the genitourinary tract: case series of a rare form of primary mucosal melanoma

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Practice points

- Primary malignant melanoma of the genitourinary tract is a rare, aggressive form of melanoma with a variable clinical presentation, ambiguous pathological features and a uniformly poor prognosis.
- Due to a lack of consensus guidelines, current treatment strategies include protocols from bladder cancers and cutaneous melanomas, respectively, with immunotherapy emerging as a novel therapeutic approach.
- Two elderly Caucasian females presenting with lower urinary tract symptoms were unexpectedly diagnosed with primary bladder melanoma as confirmed by histopathologic evaluation and immunohistochemical staining.
- Urinary bladder melanoma has been characterized by positive expression of S-100, HMB45, SOX10, MART-1 and Melan-A but its variable morphologic presentation can hinder prompt diagnosis.
- Current mutational understanding of cutaneous melanomas and immunotherapy approaches have shown limited applications to mucosal melanomas.
- However, recent investigations of pembrolizumab's efficacy and use of a neoadjuvant-adjuvant treatment approach in mucosal melanoma treatment show promise in improving its dismal overall survival rate.
- Further reporting of the clinical presentations and pathologic features of primary urinary tract melanoma can add to its limited literature and hopefully lead to an improved prognosis in the future.

Primary malignant melanoma of the genitourinary tract is extremely rare. We present two such cases in elderly Caucasian females. An 81-year-old female with urinary retention and polypoid urinary bladder mass and a 72-year-old female with gross hematuria and urethral caruncle. After thorough evaluation, they were both eventually diagnosed with primary urogenital melanoma (SOX10 and MART1-positive in tumor cells). In both cases, the presence of melanoma-*in-situ* and absence of primary melanoma in other sites were consistent with primary urogenital melanoma. Immunotherapy with PD-1 inhibitors and use of neoadjuvant and adjuvant treatment are promising, as treatment guidelines remain unclear and overall survival is low. Additional clinical reporting of primary urogenital melanomas can help in better understanding and ultimately treating it.

Plain language summary: Primary melanomas of the bladder and urinary tract are rare and usually deadly. They represent only 0.2% of all melanomas, including melanomas of skin. They can be difficult to diagnose and treat due to how rare they are and the lack of clear treatment guidelines. We present two cases of elderly Caucasian women who were unexpectedly diagnosed with primary melanoma cancers of the bladder and urinary tract after having surgery and analyzing tissue that was removed. Both tissue samples had features specific to melanoma and there was no cancer in any other organ, thus making them primary melanomas of the bladder and urinary tract. Current treatment approaches with surgery and chemotherapy have not improved the survival outcomes and prognosis associated with this disease, but treatment before and after surgery as well as cancer treatments that harness the person's own immune system are promising. By reporting additional clinical experiences of this often fatal disease, we hope it can be better understood and appropriately managed in the future.

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Tweetable abstract: Primary malignant melanoma of genitourinary tract is rare and underreported. We present two cases that were histopathologically confirmed at our institution. Our reporting can benefit its understanding and management.

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Keywords: immunotherapy • malignant melanoma • melanoma *in-situ* • mucosal melanoma • neoadjuvant-adjuvant treatment • oncology • pembrolizumab • primary malignant melanoma of the genitourinary tract • primary mucosal melanoma • rare melanoma • urogenital tract melanoma

Primary mucosal melanomas are uncommon but typically aggressive malignancies associated with a poor prognosis, with a 5-year overall survival (OS) of 34% as compared with 89% for cutaneous melanoma [1]. Primary malignant melanoma of the genitourinary tract is an extremely rare lesion, representing 0.2% of all melanomas [2], with less than 50 cases documented in the literature.

The prevalence of melanoma in the USA has steadily increased over the past 30 years. Over a million Americans are living with melanoma and nearly 20 Americans die from melanoma daily [3]. A vast majority of melanomas are cutaneous and only 4–5% of melanomas are extracutaneous.

Ainsworth *et al.* initially established diagnostic criteria for primary bladder melanoma in 1976 which includes the absence of any previous cutaneous lesion, regressed cutaneous malignant melanoma, or primary visceral melanoma, a recurrence pattern consistent with the primary tumor site and atypical melanocytes at the tumor margin on microscopic evaluation [4].

The histopathogenesis of malignant melanoma in the urinary tract is not well defined and is currently theorized via two mechanisms [2]. The first mechanism proposes melanoblast migration during embryogenesis with migration into the mesenchyme and localization in the urinary tract as ectopic tissue. Malignant transformation subsequently occurs in the future due to local triggers and factors. Namita *et al.* reiterated this, proposing that malignant melanoma stems from melanoblasts which differentiated from neural crest neuroectodermal cells; that later differentiate to melanocytes in the skin, nasal mucosa, oral mucosa and vulva; therefore melanoma can occur in these regions [5]. The second mechanism suggests that stem cell-derived urothelial cells differentiate into neoplastic melanocytes under certain exposures or stresses.

Overall, metastasis is the most common form of melanoma in the urinary tract. Ultimately, the clinical outcome of patients with primary bladder melanoma is uniformly poor, with two-thirds of patients developing metastatic disease within 3 years from diagnosis [2].

There are no established guidelines for the treatment of primary bladder melanoma. The current therapeutic approach is based on treatment protocols using outcomes data from bladder cancers and cutaneous melanomas, respectively [2]. As feasible, urologic intervention with transurethral resection versus partial or radical cystectomy is pursued, with a goal of margin-free outcome as well as a lymph node evaluation. Radiotherapy, chemotherapy and immunotherapy can all be considered with assessment of the patient's co-morbidities and life expectancy. Molecular analyses for the use of targeted therapies are also warranted [6]. Immunotherapy with PD-1/PD-L1 inhibitors such as Nivolumab and Pembrolizumab or CTLA-4 inhibitors, such as ipilimumab, well-established in metastatic cutaneous melanoma treatment, offer feasible but not well-studied treatment options in bladder melanoma [7]. Furthermore, the use of surgical treatment alone versus in conjunction with chemo- or immunotherapy is not clearly delineated.

Thus, we present two cases of elderly Caucasian females who both had rapid clinical progression following an unexpected diagnosis of primary bladder melanoma. Our objective is to provide additional clinical reporting of this rare malignancy to add to the limited current literature as well as demonstrate additional demographic and clinicopathologic factors associated with its presentation and clinical course.

Informed consent for publication of patients' clinical details and images was obtained. Verbal consent, rather than written, was obtained and deemed appropriate as direct patient access was not feasible due to geographic distance from our institution; no prospective data was included. Furthermore, the study meets IRB criteria for only minimal risk research with no direct involvement of human participants and no significant risk that data will be able to definitively identify individuals.

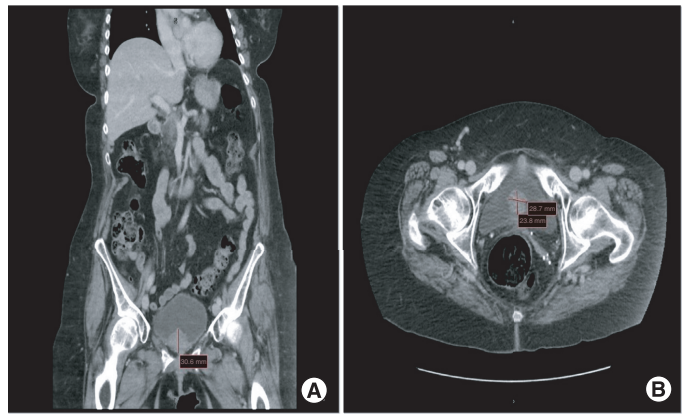

Figure 1. CT intravenous pyelogram (coronal and axial views) of polypoid urinary bladder mass. (A & B) CT intravenous pyelogram (coronal and axial views) showing polypoid soft tissue mass at the lower aspect of the urinary bladder measuring 3.3 × 3.1 × 2.4 cm compatible with the biopsy-proven malignant melanoma.

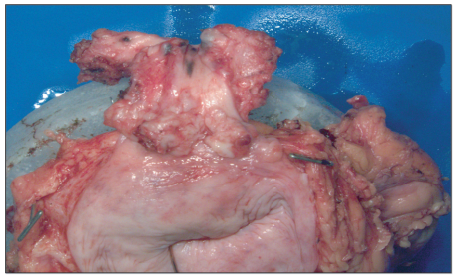

Figure 2. Gross image of 4.0 × 3.0 × 2.5 cm polypoid inferior bladder mass with proximal urethral involvement and multifocal melanosis.

Case series

Case 1

An 81-year-old female presented to her local urologist following an episode of acute-onset urinary retention requiring Foley catheter placement. In-office urinalysis was notable for microscopic hematuria; ultrasound was notable for an incidental inferior bladder mass. The patient was noted to have a remote cigarette smoking history but no active use in over 20 years; her husband, however, was a daily heavy smoker.

She subsequently underwent cystoscopy a month later, with the identification and excision of a large 6–7 cm inferior urethral mass suspected to be a benign caruncle. Post-cystoscopy course was notable for intermittent gross hematuria but no other significant symptoms. However, CT intravenous pyelogram (Figure 1A & B) and PET CT demonstrated a polypoid urinary bladder mass. The urethral mass was biopsied and the patient subsequently underwent a robotic-assisted laparoscopic radical cystectomy and total urethrectomy with the creation of an ileal conduit for urinary diversion 4 months later.

Gross image of the resection specimen from the cystourethrectomy revealed multiple detached masses in the urinary bladder, with a 4.0 × 3.0 × 2.5 cm polypoid mass in the inferior bladder and proximal urethra (Figure 2). Histopathologic evaluation showed nodular and invasive proliferation of pleomorphic epithelioid cells with prominent nucleoli, numerous atypical mitosis, and associated brown pigment (Figure 3A & B). Final histopathology unexpectedly revealed malignant melanoma of the distal bladder/urethral mucosa (Figure 4A & B) with multiple polypoid growths, multifocal melanosis with cytologic atypia involving the urothelial and vaginal mucosa in the distal bladder and urethra, and detached nodules of melanoma in the bladder lumen. In addition, melanoma *in situ* of the urinary bladder/urethral mucosa was identified (Figure 5A & B). The tumor thickness was approximately 7 mm in the polypoid areas, and there was lamina propria invasion, but no downward invasion of the detrusor muscle was seen. Immunohistochemical stains for SOX10 and MART1 were performed on selected blocks to help evaluate the extent of invasive and *in situ* melanoma. MART1 was also performed on selected lymph nodes for additional evaluation. All controls stained appropriately. The neoplastic cells demonstrated positivity for SOX10 (Figures 3B, 4B & 5B) and MART1, consistent with melanoma. The tumor displayed a high mitotic rate, up to 19 per square mm.

No previous or concurrent diagnosis of cutaneous melanoma was documented. A subsequent PET scan did not reveal any other site of malignancy. The presence of melanoma *in situ* and the absence of other known primary sites of melanoma are consistent with primary malignant melanoma of the urinary bladder and/or urethra. It appears

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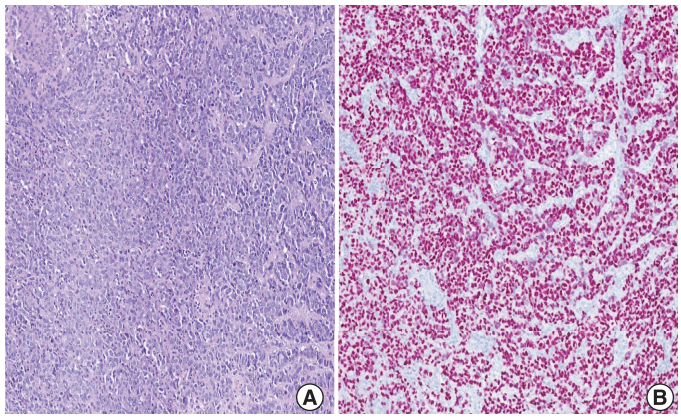

Figure 3. Robotic-assisted laparascopic cystourethrectomy of urinary bladder showing sheets of highly atypical melanoma cells. (A & B) Robotic-assisted laparoscopic radical cystourethrectomy showing sheets of highly atypical dyscohesive melanoma cells in the urinary bladder 10× (left), tumor cells demonstrate positivity for SOX10 (right).

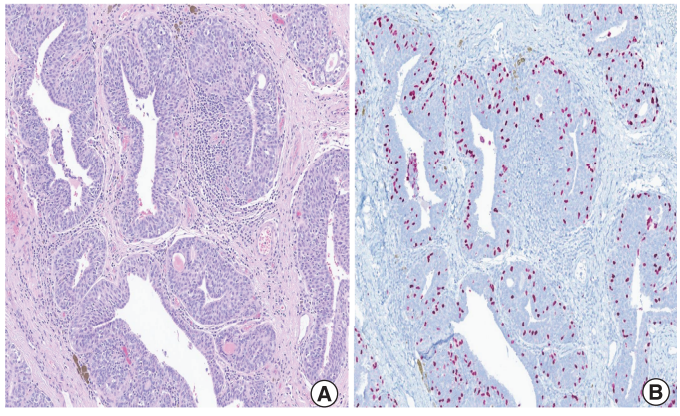

Figure 4. Robotic-assisted laparascopic cystourethrectomy of urinary bladder showing pagetoid spread of melanoma cells. (A & B) Robotic-assisted laparoscopic radical cystourethrectomy showing the pagetoid spread of melanoma to the urethra (left), tumor cells demonstrate positivity for SOX10 (right).

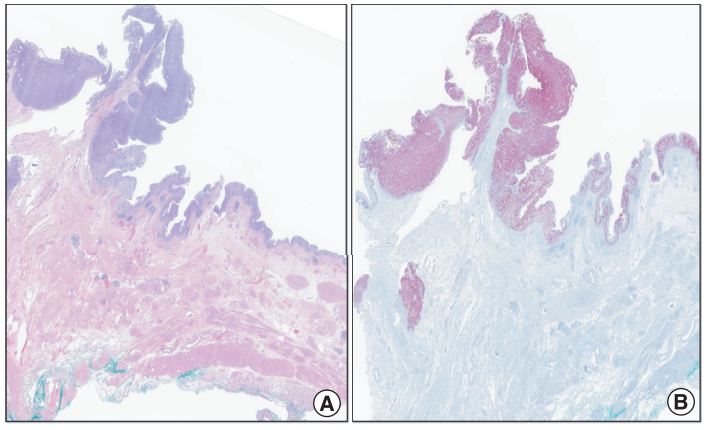

Figure 5. Robotic-assisted laparascopic cystourethrectomy of urinary bladder showing melanoma in situ. (A & B) Robotic-assisted laparoscopic radical cystourethrectomy showing primary malignant melanoma of the urinary bladder with melanoma *in-situ* (left), specimen stains positive for SOX 10 (right).

to arise in a setting of multifocal melanosis of the bladder, urethral and vaginal mucosa. There is no established reporting protocol or staging system for this rare circumstance.

The patient was followed up by the medical oncology team with plans for systemic chemotherapy versus immunotherapy. Unfortunately, the patient passed away from necrotizing fasciitis complicated by new-onset atrial fibrillation and prolonged encephalopathy prior to initiation of treatment.

Case 2

A 72-year-old Caucasian female presented to her local gynecologist with new-onset post-menopausal bleeding. Pelvic exam revealed a new urethral caruncle without other masses. She was subsequently referred to uro-gynecology for further evaluation.

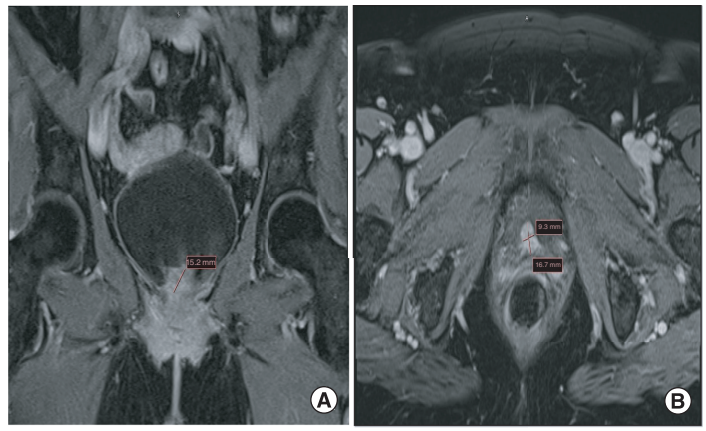

Figure 6. MRI pelvis (coronal and axial views) of nodular enhancing urinary bladder mass. (A & B) MRI pelvis (coronal and axial views) showing nodular enhancing soft tissue mass at the posterior segment of the urethra and urinary bladder base measuring 1.7 × 1.5 × 0.9 cm compatible with the biopsy-proven malignant melanoma.

She subsequently underwent cystoscopy, D&C and complete urethral mass excision 2 months later. Operative findings noted a mobile, firm and friable 2.5 × 3.0 cm mass at the urethral meatus with right-sided paraurethral involvement. Surgical pathology of the urethral mass unexpectedly revealed poorly differentiated malignancy consistent with malignant melanoma. Histopathology showed pleomorphic malignant cells with amphophilic cytoplasm and prominent nucleoli. Immunohistochemistry revealed tumor cells were diffusely positive for SOX10, S-100 and MART-1 while negative for pan-cytokeratin (CKAE1/AE3) and CD45 and p63. The patient was then urgently referred to uro-oncology as well as dermatology with concerns for primary versus metastatic disease. No personal or family history of skin cancer was noted.

Staging imaging was subsequently performed. A 1.7 cm nodular enhancing soft tissue focus in the inferior bladder and posterior urethra without associated lymphadenopathy concerning for malignancy was found on MRI pelvis (Figure 6A & B); whole-body PET-CT demonstrated focal urethral FDG uptake without evidence of metastatic disease. The patient then underwent cystourethroscopy with TURBT for further investigation of the residual intravesically protruding bladder neck mass seen on MRI. Three solid bladder masses ranging from 2 to 5 cm were noted at the bladder trigone near the bladder neck and ureteral orifices. Ensuing histopathology of all three masses were consistent with malignant melanoma. Immunohistochemistry demonstrated the tumor cells were diffusely positive for SOX10, S-100 and MART-1 while negative for pan-cytokeratin (CKAE1/AE3) and GATA3.

The patient was then evaluated by medical oncology and uro-oncology; with a diagnosis of suspected primary malignant melanoma of the urethra and bladder. BRAF mutation status on the resected bladder specimens was found to be V600E wild-type; next-generation sequencing was ordered. A tentative plan for adjuvant immunotherapy with Ipilimumab and Nivolumab was made. A comprehensive workup was then completed which revealed no extra-genitourinary melanoma. MRI brain was performed and negative. Ophthalmic evaluation was negative for iris/choroidal nevi or ocular melanoma. ENT evaluation was negative for mucosal melanoma. Colonoscopy was performed with biopsies revealing tubular adenoma only.

The decision was made to pursue anterior pelvic exenteration with bilateral pelvic lymphadenectomy and ileal conduit urinary diversion, followed by dual immune checkpoint inhibitor therapy. The patient then underwent open radical cystectomy with ileal conduit. Histopathology revealed malignant melanoma involving the urethral meatus (Figure 7A & B), bilateral ureteral orifices and extending to the bladder neck posteriorly (Figure 8A & B). Melanoma involved the submucosa and muscularis propria, but the corresponding urothelium was not involved (Figure 9A & B). The tumor cells were again positive for SOX10 (Figures 7B, 8B & 9B), S-100 and MART-1 by immunohistochemistry. The peritoneum, uterus, bilateral ovaries, fallopian tubes and cervix were uninvolved. All 22 examined bilateral pelvic lymph nodes were negative for malignancy.

She commenced Ipilimumab and Nivolumab once every three weeks with her local oncologist. At the time of writing this report, she remains stable, functionally active and without evidence of new malignancy, constitutional or localized genitourinary symptoms.

Discussion

Primary malignant melanoma of the urinary bladder is a rare and aggressive form of mucosal melanoma with a poor prognosis and often delayed presentation. Nonspecific urinary complaints as well as hematuria are often the

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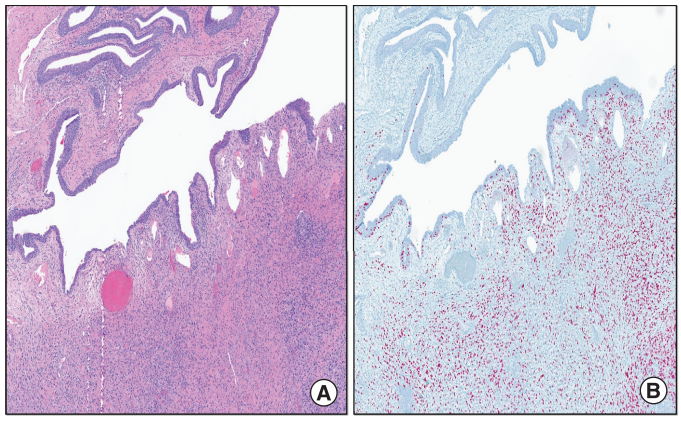

Figure 7. Radical cystourethrectomy showing pagetoid spread to the distal urethral margin. (A & B) Radical cystourethrectomy showing atypical melanoma cells of the urinary bladder with pagetoid spread of melanoma to the distal urethral margin.5× (left), tumor cells demonstrate positivity for SOX10 (right).

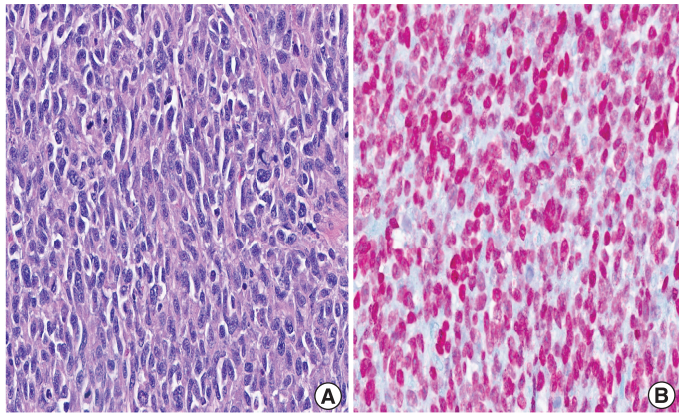

Figure 8. Radical cystourethrectomy showing highly atypical epithelioid melanoma cells. (A & B) Radical cystourethrectomy showing highly atypical epithelioid melanoma cells of the urinary bladder 40× (left), tumor cells demonstrate positivity for SOX10 (right).

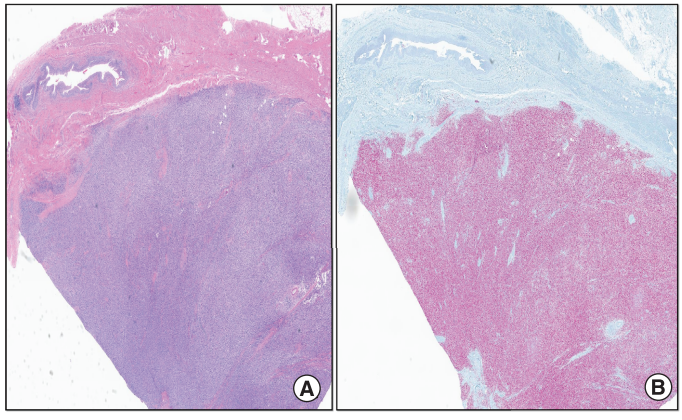

Figure 9. Radical cystourethrectomy showing atypical melanoma cells. (A & B) Radical cystourethrectomy showing atypical melanoma cells in the urinary bladder diffusely involving the submucosa and muscularis propria with corresponding urothelium uninvolved 1× (left), tumor cells demonstrate positivity for SOX10 (right).

only presenting complaints [8]. In contrast to cutaneous melanomas and the development of aberrant melanocyte alterations with direct UV radiation exposure, the etiology and histopathogenesis remain unclear [4].

Urogenital tract melanoma is more commonly seen in Caucasian females in about 90% of cases. They typically develop in the vagina, vulva, cervix, urinary bladder and urethra. The female genital tract accounts for 18% of mucosal melanomas and 3% of those of the urinary tract; the most common site is usually the vulva (76.7%) followed by the vagina (19.8%), with cervical melanoma being the least common. Commonly associated symptoms include bleeding, masses or lumps in the vulva area, itching, pain or irritation, dyspareunia, discomfort and discharge [9]. Pain, mass lesions and vaginal bleeding are the most typical presenting symptoms. Macroscopically, it appears as a variety of often fragile pigmented lesions that bleed easily and are ulcerated in half of the cases. Melanoma of the cervix is extremely rare and typically appears as a pigmented or amelanotic exophytic cervical mass. Melanoma of the urethra accounts for about 4% of all urethral malignancies and commonly affects elderly

women in the distal urethral tract. In about 20% of cases, malignant melanoma of the urethra is amelanotic with a polypoid growth pattern; therefore, it is often mistaken for a urethral polyp, mucosal prolapse or urothelial tumor [10]. Urethral melanomas are frequently misdiagnosed clinically, which leads to a delayed diagnosis and poor prognosis. Grossly, the tumor may be easily confused with a caruncle as in case 1 [5].

Only 20 cases of melanoma of the urinary bladder are currently reported, underlying the rarity of this neoplasm. Common clinical manifestations include hematuria and dysuria, and it is often locally advanced at diagnosis [10]. To differentiate metastatic melanoma to the bladder from primary melanoma of the bladder and/or urethra, a detailed history is essential to rule out cutaneous, regressed or visceral melanoma; and a recurrence pattern consistent with the primary origin of melanoma as well as systemic imaging for distant involvement. Histology can be helpful in confirming the diagnosis of primary melanoma, but due to its highly variable morphological appearance, relying exclusively on these methods may not be definitive. A review of cases has demonstrated that positive expression of S-100, HMB-45, SOX-10, MART-1 and Melan-A in tumor cells can help identify bladder melanoma. Melanosis, which is an abnormal or excessive deposition of melanin pigment in cells and/or tissues, while common in the skin and oral mucosa, is a very infrequent finding in melanoma of the urinary bladder with only a handful of cases reported [11]. Further investigation and characterization of its morphological variability and cellular or architectural patterns (nested, spindle cell and small cell variants) may be helpful to further characterize the lesion and exclude common mimics [12].

Although criteria have been established to differentiate primary from metastatic bladder melanoma, a lack of consistent early screening, variable clinical findings along with ambiguous pathological features can delay early recognition and diagnosis [2]. Thus, although most patients present with clinically localized disease, this is often discovered at an advanced stage. Furthermore, previous reports have outlined a relapsing course with local recurrence preceding near universal development of distant disease and eventual death. In addition to often presenting at an advanced stage, its rarity to clinicians and a lack of consensus guidelines for best treatment regimens can lead to both surgical and medical oncology providers lacking clear guidance for management, especially regarding interventions and continuity of care. Adequate resection is the recommended first step in local control and prevention of recurrence and metastasis. Adjuvant therapy is often required [13]. Pelvic exenteration may be beneficial for vaginal melanoma and female urethral melanoma with a thickness of more than 3 mm [14].

The mutational landscape of mucosal melanomas includes mutations of *BRAF*, *NRAS*, and mutations in the *c-KIT/CD117* gene in 50% of patients (*KIT/CD117* gene aberrations predominate in mucosal melanomas as opposed to cutaneous melanomas), thus limiting therapeutic interventions to immunotherapy. In a study conducted by Zarei *et al.*; where they investigated the mutational status of invasive melanomas arising from various anatomic sites in the female lower urogenital tract (vulvar skin, glabrous skin, vagina, and urethra) in a group of 37 patients. Tumor analysis was performed using a DNA-targeted next-generation sequencing panel covering 21 of the most common genes and mutation hotspots in melanomas. It was found that the most common genetic alterations in invasive melanomas of the lower female genital tract are *KIT* (32%), *TP53* (22%) and *NF1* (19%). Additionally, pathogenic alteration in at least one of the *MAPK* pathway genes was seen in 66% (21/32) of cases [15]. Clinical studies have shown less responsiveness to immunotherapy as compared with cutaneous melanomas, therefore novel therapeutic strategies targeting new molecules are needed to improve the overall survival of patients with mucosal melanomas [10]. Although early surgical resection is the cornerstone of treatment, the use of neoadjuvant or adjuvant treatments including systemic or targeted therapies has not been well established and limits the development of further therapeutic modalities. Moreover, for those with poor responses, the effectiveness of alternatives is sparse [16].

In retrospective analyses, objective response rates with immune checkpoint inhibitors range from 17.6 to 20.0% for patients with mucosal melanoma [17]. Post-hoc analysis of the KEYNOTE-001, KEYNOTE-002 and KEYNOTE-006 studies conducted in a global population reported an objective response rate of 19% with pembrolizumab in patients with mucosal melanoma and 33% in patients with non-mucosal melanoma, and median overall survival of 11.3 and 23.5 months, respectively [18]. It appears that tumor stage and mitotic activity can aid in prognosis, with suggestions identifying possible *BRAF*-activating mutations may be beneficial for therapeutic targeting. Recently published results from the SWOG 1801 trial suggest improvement in outcomes (event-free survival) with neoadjuvant-adjuvant immune checkpoint inhibition versus adjuvant therapy alone in stage III/IV cutaneous melanoma. As stated in this report, the response rates of these agents are less studied and understood in patients with mucosal melanoma. Therefore, the potential advantages of considering a neoadjuvant approach in these patients would be *en-vivo* monitoring of disease response, downsizing the primary tumor to potentially lessen the morbidity of surgery, earlier treatment of distant micrometastatic disease in aggressive metastatic histologic

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sub-types and improved long-term outcomes [19]. Immunotherapy with nivolumab after cystectomy have also been suggested. D'Angelo *et al.* analyzed a large dataset for anti-programmed death-1 therapy in urogenital mucosal melanomas and found that Nivolumab when combined with ipilimumab appeared to have superior efficacy than either agent when used alone, also, while activity was lower in mucosal melanoma, the long-term safety was essentially similar [20]. Overall, the best treatment regimen is not yet clearly defined. Furthermore, regardless of the therapy used, the prognosis remains grave and 5-year survival is dismal.

Our patients' courses reflect thesethe multiple factors affecting clinicians in diagnosing and treating primary bladder melanoma. Additionally, the complicated post-operative course shows the morbidity and mortality often associated with this disease entity, besides that stemming from the primary malignancy. Advanced age and co-morbidities added other potential barriers to effective interventions. Thus, despite aggressive surgical intervention and adjuvant therapy, patients would ultimately anticipate having to endure a difficult clinical course.

Conclusion

Primary urogenital tract melanoma remains difficult to treat, due to its rarity, delayed presentation and diagnostic challenges; it is a not-well-understood condition in the current literature with less than 50 cases currently documented. This paper is an important addition to the state of the art, including useful characteristics such as pathologic features and clinical course of this disease. Further research along with thorough analysis of reported cases and potential future clinical trials of therapeutic options are warranted. Early detection and biopsy would be an ideal starting point to address these challenges. By contributing to the presenting characteristics, pathologic features and clinical course of this disease, we hope to add our perspective to this developing and evolving entity to ultimately improve the prognosis of this often fatal lesion.

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The authors have no financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Competing interests disclosure

The authors have no competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Writing disclosure

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained verbal consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

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•• **This reference is of considerable interest as it highlights the current reported response rate for immune checkpoint inhibitors from pooled studies of patients with mucosal melanoma (identification of pembrolizumab as a promising option for mutation-specific target treatment in mucosal melanomas).**

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•• **This reference is of considerable interest as it discusses the current therapeutics and response rates of treatment modalities in the management of melanomas (recent study examining immunotherapy in adjuvant and neoadjuvant-adjuvant settings with findings relevant to potential bladder melanoma treatment).**

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•• **This reference is of considerable interest as it addresses recent therapeutic options in mucosal melanomas which is quite challenging given the lack of consensus guidelines.**

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