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Diagnosis and treatment of primary urethral melanoma with regional lymphatic metastasis in an elderly woman: a case report and review of available therapies

Juan Camilo Alvarez Restrepo[1,2*], Juan Felipe Alvarez Restrepo[3], Daniel S Maya Giraldo[1,2], Jhonatan S Santafé Galvis[4], Carlos Andres Riveros[5], Andres Felipe Puentes Bernal[2,1] and Otto Manrique[2,4]

Abstract

Background Mucosal melanomas account for 17% of melanomas, and less than 1% affect the urogenital tract. Primary urethral melanoma is extremely rare; less than 200 cases have been reported so far since it was first described. The clinical presentation is usually delayed, and the prognosis is generally poor.

Case presentation.

An 86-year-old female was referred to urology due to the presence of a three-month-old violaceous mass in the urethral meatus protruding through the vagina. On physical examination, a pedunculated, hyperpigmented, friable, and tender lesion was seen in the urethral meatus bulging between the labia minora. After initial diagnostic studies, the patient was taken to surgical resection of the lesion. The pathology report identified the lesion as a malignant melanoma of the urethra, and staging studies revealed regional lymph node metastases. After discussing the treatment options with the patient, palliative therapy with nivolumab was started. In follow-up at 26 months, the patient had evidence of extensive lymph node involvement, but a conserved performance status and no visceral metastases.

Conclusion Primary melanoma of the female urethra is an uncommon disease with a poor prognosis. Despite the deficiency in literature regarding its management, it is important to consider patient expectations and preferences when treating this rare disease.

Keywords Urethral neoplasm, Mucosal melanoma, Immunotherapy, Lymphatic metastases, Genitourinary melanoma, Case report

*Correspondence:
Juan Camilo Alvarez Restrepo
juancalvarezr92@hotmail.com
Full list of author information is available at the end of the article

1 Background

Urethral melanoma is one of the mucosal melanomas affecting the urogenital tract. Its diagnosis is usually late and based on histopathology. It is rare, accounting for 4% of urethral neoplasms. The low prevalence has limited the study of its behavior and treatment options. Diagnosis, staging, and management are extrapolated from knowledge about cutaneous melanoma and other mucosal melanomas [1]. The current guidelines and the standard of care are based on expert recommendations and small case series. Despite its low frequency, it is an aggressive disease with poor prognosis [2]. The aims of this case report were to highlight a lesson learned and to document treatment success after immunotherapy for urethral melanoma.

2 Case presentation

An 86-year-old female patient was referred to the urology outpatient service by her gynecologist due to the presence of a painful three-month-old violaceous mass attached to the urethral meatus. Besides dysuria, the patient denied any other symptoms. Past medical history included arterial hypertension, chronic kidney disease, tobacco exposure, and hysterosalpingectomy due to abnormal uterine bleeding. There was no relevant family history.

In the urological evaluation, a hyperpigmented violaceous lesion of approximately 4×3x3 cm was documented. It was pedunculated with its base on the urethral meatus and protruding through the labia minora, being friable and tender on palpation (Fig. 1a). On inguinal evaluation, there was hard, fixed, and tender lymphadenopathy in the left groin. The largest lymph node was greater than 2 cm. Vaginal exam revealed no lesions on the vaginal walls.

The patient had a urinalysis that revealed microhematuria without evidence of inflammation. Complete blood count, along with renal and hepatic function studies, showed no abnormalities. As malignancy was high in our differential, contrast-enhanced computed tomography (CT) of the chest, abdomen and pelvis were performed for staging purposes. Inguinal lymphadenopathy measuring 17×15 mm and lymph nodes with thick calcifications in the mediastinum were documented without meeting criteria for adenomegaly.

Given the findings on imaging, the working diagnosis before surgery was malignancy. Given the pain associated with the mass, along with patient preference, she was taken to the operating room for urethrocystoscopy, followed by surgical resection of the lesion. Transurethral cystoscopy revealed a healthy urethra and bladder, without other pathological findings. Macroscopic residual lesion was not observed in the resection bed with 5-mm margins (Fig. 1b). After histopathological examination, the pathologist reported the lesion as an infiltrating malignant melanoma with ulceration, tumor thickness of 4 mm, Ki-67 cell proliferation index of 80%, and positive microscopic margins for tumor involvement.

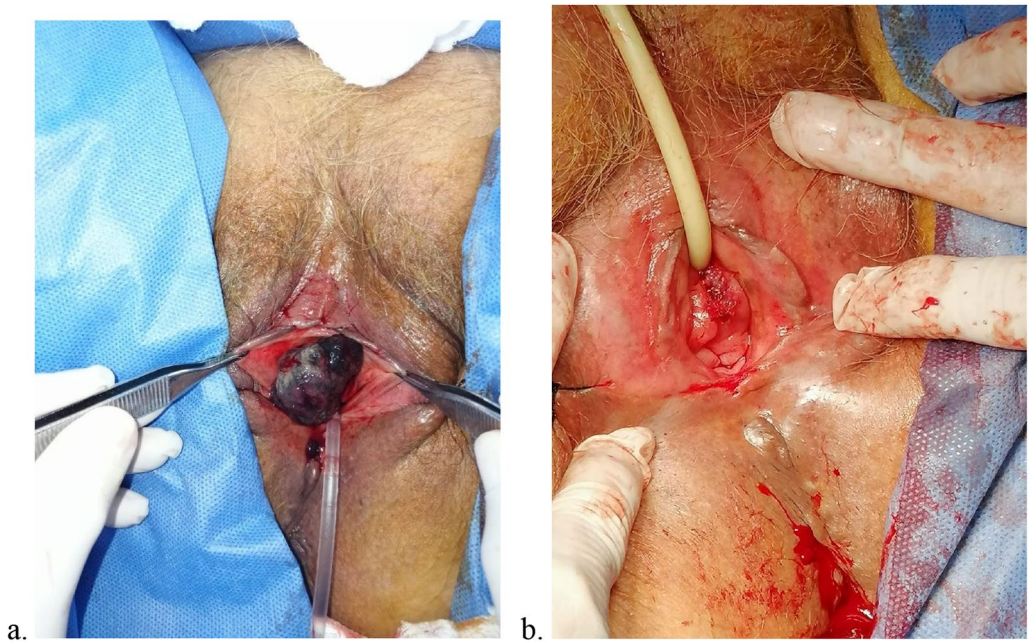

Fig. 1 **a** Pedunculated violaceous lesion in the vaginal introitus, approximately 4×3×3 cm. **b** Resection bed after tumoral excision

Immunohistochemistry was positive for Melan A, HMB45, CK7, CK20, p53, uroplakin, and negative for p16.

Six weeks after resection of the lesion, positron emission tomography (PET) scan showed hypermetabolic left inguinal lymphadenopathy suggestive of metastases (Fig. 2), along with three indeterminate pulmonary nodules, and a region of increased tracer uptake in the distal urethra. During a follow-up visit, the pathology and the possibility of palliative radiation were discussed with the patient. It was concluded that radiation would only negatively affect the patient's quality of life. She was referred to medical oncology and palliative therapy with nivolumab was started two months after the index surgery. The patient received twelve cycles of nivolumab without serious adverse events. At our last follow-up, 26 months after surgery, the patient still had a good performance status, but repeat PET-CT showed growth and a greater number of hypermetabolic pelvic lymph nodes, along with retroperitoneal lymphadenopathy, without evidence of visceral metastases.

3 Discussion

Primary malignant melanoma of the urethra constitutes 1% of melanomas and 4% of urethral neoplasms. It is more common in females than in males, with a ratio of 3:1. In women, this pathology represents 0.2% of malignant melanomas [1]. Its usual age of presentation is between 30 and 80 years [3]. It has an unfavorable prognosis, with a 5-year survival rate of 25% if left untreated [2].

The clinical presentation is usually delayed, with local lymphatic involvement in most cases [4]. The main symptoms are a bulging sensation, vulvar pain, and mild bleeding. Other described symptoms are painless hematuria, irritative urinary symptoms, purulent urethral discharge, split voiding stream, and bad odor in case of ulceration [5, 6]. The study of metastatic involvement is based on a review of systems, considering that spread occurs via the lymphatic pathway to the vulva, vagina, and inguinal lymph nodes, and with a hematogenous predilection to the liver and lungs. Its appearance can be confused with other types of lesions such as urethral polyps, myrtiform caruncles, mucosal prolapse, or chancre [3].

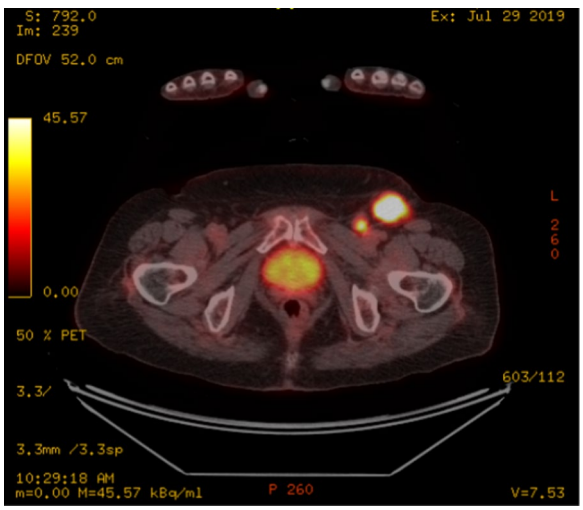

Fig. 2 Hypermetabolic left inguinal lymphadenopathy

Risk factors for the development of mucosal melanomas have not been clearly identified [7]. Several studies have found no association between the pathogenesis of mucosal melanoma, and human papillomavirus, human herpes virus, or polyomavirus [8].

Histologically, urethral melanoma is a tumor of melanoblastic origin, derived from neuroectoderm cells [5]. Unlike melanomas, where ultraviolet exposure and the BRAF-V600 mutation are frequent, this mutation has only been found only in 2% of cases of mucosal melanoma (9). On the other hand, mutations in genes related to the MAPK pathway are the most frequently described, especially in c-KIT, being mutated in 25% of these lesions (9). Other molecular pathways such as TP53 and NF1 have been shown to be altered in up to 34% of cases [5, 9, 10]. The study of the compromised molecular pathways has given rise to new therapeutic possibilities.

Given the scarcity of reported cases, there are no specific guidelines for the staging of urethral melanoma. It is extrapolated according to the suggestions of the 2020 ano-urogenital mucosal melanoma UK national guidelines, using the eighth edition of the TNM stage classification of the American Joint Committee for Cancer (AJCC 8) [2]. In 1980, Levine et al. proposed a staging system that takes into account the degree of local growth, along with involvement of the periurethral muscles, vagina, bladder, labia, clitoris, and inguinal lymphatics [11]. Both systems are considered when determining the treatment and prognosis of each patient [6]. In this case, the patient's primary urethral melanoma was initially classified as T3bN2M0 and stage D according to the Levine staging system.

Due to the paucity in evidence and subsequent extrapolation of the management of genital melanomas, surgical management has been the standard of care for localized urethral melanoma. The options include gross lesion resection, partial or radical urethrectomy, pelvic exenteration, with or without inguinal or pelvic lymphadenectomy [2].

The 2020 ano-urogenital mucosal melanoma guidelines have clear recommendations regarding vulvar, vaginal, and penile melanoma, without appropriate

evidence on surgical outcomes in patients with urethral melanoma [2]. A review by Carr et al. found that although the current recommendation is toward radical resections to prevent local recurrences, there is no evidence of better patient outcomes or longer survival [6]. The current recommendation is based on the Levine staging system, stage A calls for a local resection with margins of 2.5 cm, while stage B or C require the same margins plus sentinel lymph node mapping, and lymphadenectomy if positive [6, 7, 12]. Inguinal metastases or large tumors with local invasion are usual contraindications for surgery. However, there are reports of survival for more than five years in surgically treated patients with known distal metastases [7].

DiMarco et al. has the largest comparative series, a total of 11 women with urethral melanoma undergoing radical or partial urethrectomy, where it was concluded that partial resection could not achieve local control, and instead facilitated local and distal recurrences [13]. Geisler et al. in a series of four cases concluded that vaginal or urethral melanomas in women with > 3 mm of invasion benefited from pelvic exenteration, 75% with a disease-free survival of 31–97 months postoperatively [14]. In the case presented here, a surgical resection was carried out with macroscopic tumor-free margins, but positive margins microscopically.

The systemic treatment of urethral melanoma is controversial, with scarce literature and mostly low-level evidence (see Table 1). Radiotherapy, chemotherapy, and more recently immunotherapy are some of the described adjuncts to the standard surgical management [6, 15]. Neoadjuvant radiotherapy has been described as an option in tumor debulking or palliation, showing little effectiveness in locally advanced disease with lymph node involvement; there are no randomized clinical trials in this setting [12, 15].

Neoadjuvant chemotherapy and immunotherapy do not seem to have a clear role. In a series of six cases by Frumovitz et al., adjuvant radiotherapy decreased the risk of local recurrence, as well as increase the overall survival (OS) from 16.1 months to 29.4 months [16]. In vulvar, vaginal, and urethral involvement, adjuvant radiotherapy has not demonstrated a significant improvement in OS or recurrence-free survival (RFS), reserved for palliative symptomatic management [12, 17]. Adjuvant chemotherapy with dacarbazine or temozolomide appears to show some response. Other schemes based on cisplatin and temozolomide for stage II and III disease show improvement with median OS from 41 to 52 months ($p < 0.01$) and RFS up to 20.8 months ($p < 0.001$), with mild-to-moderate toxicity [18–20].

Immunotherapy in cutaneous primary melanoma has shown remarkable effectiveness, which has led to studies in genitourinary melanoma [6]. Immune checkpoint inhibitors such as nivolumab and pembrolizumab have shown a response rate of up to 37% in urethral melanoma, with adverse events rates between 8.1%, in monotherapy with nivolumab, and 12.5%, in combinations with ipilimumab [21, 22]. Interleukin 2 (IL2) and interferon IFNα2b at high doses have shown a mean RFS of 9.4 months and OS of 40.7 months [20, 23]. For nivolumab and ipilimumab, thAvailability of data ande RFS was 5.9 months and OS was 6.4 months in metastatic or unresectable disease [22, 24]. In phase II studies, tyrosine kinase (TKI) inhibitors such as imatinib and nilotinib have shown overall response rates of 23% and 26%, respectively. OS rates of 14 months for imatinib and 18 months for nilotinib have been reported [25, 26].

In genitourinary melanoma, despite its unique biology, systemic treatment has mirrored the experience with primary cutaneous melanoma. However, the efficacy of novel systemic therapies is still under investigation. There are ongoing clinical trials with

Table 1 Modified from Carr [6]. IFNα2b: Interferon alpha 2 b. IL2: Interleukin 2

Author	Drug	Number of patients	Median response rate (%)	Median global survival (months)
Shoushtari [21]	Pembrolizumab	35	23	12.4
D'angelo [22]	Nivolumab + Ipilimumab	35	37.1	Not reached
	Nivolumab	86	23.3	Not reached
	Ipilimumab	36	8.3	Not reached
Yi [18]	Dacarbazine + Temozolomide	21	26.3	9.2
Lian [20]	Cisplatin + Temozolomide	30	Not reported	48.7
	IFNα2b	34	Not reported	40.4
Harting [23]	IL2	11	36, partial response	10
Guo [25]	Imatinib	11	23	14

camrelizumab (programmed cell death 1 [PD-1] inhibitor) plus apatinib in patients that progress on chemotherapy (NCT039986515) and ipilimumab plus nivolumab in the adjuvant setting (NCT03241186) (6).

4 Conclusions

The case reported herein represents the typical presentation of a rare pathology and a response in accordance with the current evidence. Standard surgical management was performed as advised, and once the histopathology of the tumor was confirmed, palliative immunotherapy was administered due to the metastatic stage of the disease. At the time of this report, the patient still had a good functional status with minimal symptoms, despite extensive lymph node involvement in PET-CT.

Abbreviations

CT	Computed tomography
PET	Positron emission tomography
AJCC	American Joint Committee for Cancer
OS	Overall survival
RFS	Recurrence-free survival
IFNα2b	Interferon alpha 2 b
IL-2	Interleukin 2
PD-1	Programmed cell death 1

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Author contributions
JCAR involved in conception, design, supervision, materials, data collection and processing, analysis and interpretation, literature review, writing, and critical review. JFAR involved in data collection and processing, analysis and interpretation, and literature review. DSMG involved in data collection and processing, analysis and interpretation, and literature review. JSGG involved in data collection and processing, analysis and interpretation, and literature review. CAR involved in writing, editing, and critical review. AFPB involved in supervision and critical review. OM involved in supervision and critical review. All authors read and approved the final manuscript.

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Availability of data and materials
Data sharing is not applicable to this article as no datasets were generated oranalyzed during the current study.

Declarations

Ethics approval and consent to participate
The Hospital Mayor Mederi (Bogotá, Colombia) approved this study on February 12, 2020. Written consent was obtained from the patient to publish the case report.

Consent for publication
Written consent for publication was obtained from the patient.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Department of Urology, School of Medicine, Universidad Nacional de Colombia, Carrera 30 No. 45-03, Edificio 471, Bogotá, Colombia. [2]Urology Research and Innovation Group, Universidad Nacional de Colombia, Bogotá, Colombia. [3]Department of Urology, School of Medicine, Universidad de Antioquia, Medellín, Colombia. [4]Department of Urology, School of Medicine, Fundación Universitaria Sanitas, Bogotá, Colombia. [5]School of Medicine, Universidad Nacional de Colombia, Bogotá, Colombia.

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References

1. Safadi A, Schwalb S, Ben-Shachar I, Katz R (2017) Primary malignant urethral melanoma resembling a urethral caruncle. Urol Case Rep 15:28–29
2. Smith HG, Bagwan I, Board RE, Capper S, Coupland SE, Glen J et al (2020) Ano-uro-genital mucosal melanoma UK national guidelines. Eur J Cancer 135:22–30
3. Bhutani N, Kajal P, Pawar D (2017) Primary malignant melanoma of the female urethra: report of a rare neoplasm of the urinary tract. Int J Surg Case Rep 41:319–322
4. Oliva E, Quinn TR, Amin MB, Eble JN, Epstein JI, Srigley JR et al (2000) Primary malignant melanoma of the urethra: a clinicopathologic analysis of 15 cases. Am J Surg Pathol 24(6):785–796
5. El-Safadi S, Estel R, Mayser P, Muenstedt K (2014) Primary malignant melanoma of the urethra: a systematic analysis of the current literature. Arch Gynecol Obstet 289(5):935–943
6. Carr MJ, Sun J, Spiess PE, Zager JS (2019) Advances in the management of genitourinary melanomas. AME Med J 4
7. Papes D, Altarac S (2013) Melanoma of the female urethra. Med Oncol 30(1):329
8. Alvarez Kindelan J, Merchan Garcia JA, Olmo Cerezo I, Moreno Rodriguez MM, Gonzalez Arlanzon MM (2000) [Primary malignant melanoma of the female urethra. Report of a case]. Actas Urol Esp 24(6): 488–90
9. Yde SS, Sjoegren P, Heje M, Stolle LB (2018) Mucosal melanoma: a literature review. Curr Oncol Rep 20(3):28
10. Zarei S, Voss JS, Jin L, Jenkins SM, Bryce AH, Erickson LA et al (2020) Mutational profile in vulvar, vaginal, and urethral melanomas: review of 37 cases with focus on primary tumor site. Int J Gynecol Pathol 39(6):587–594
11. Levine RL (1980) Urethral cancer. Cancer 45(7 Suppl):1965–1972
12. Piura B (2008) Management of primary melanoma of the female urogenital tract. Lancet Oncol 9(10):973–981
13. DiMarco DS, DiMarco CS, Zincke H, Webb MJ, Keeney GL, Bass S et al (2004) Outcome of surgical treatment for primary malignant melanoma of the female urethra. J Urol 171(2 Pt 1):765–767
14. Geisler JP, Look KY, Moore DA, Sutton GP (1995) Pelvic exenteration for malignant melanomas of the vagina or urethra with over 3 mm of invasion. Gynecol Oncol 59(3):338–341
15. Scott JF, Gerstenblith MR, (eds) (2018) Noncutaneous melanoma. Brisbane (AU)
16. Frumovitz M, Etchepareborda M, Sun CC, Soliman PT, Eifel PJ, Levenback CF et al (2010) Primary malignant melanoma of the vagina. Obstet Gynecol 116(6):1358–1365
17. Janco JM, Markovic SN, Weaver AL, Cliby WA (2013) Vulvar and vaginal melanoma: case series and review of current management options including neoadjuvant chemotherapy. Gynecol Oncol 129(3):533–537
18. Yi JH, Yi SY, Lee HR, Lee SI, Lim DH, Kim JH et al (2011) Dacarbazine-based chemotherapy as first-line treatment in noncutaneous metastatic melanoma: multicenter, retrospective analysis in Asia. Melanoma Res 21(3):223–227
19. Ruschi Bechara G, Barros de Santos Schwindt A, Ornellas AA, Abreu da Silva DE, Monnerat Lott F, Santos de Campos F (2013) Penile primary melanoma: analysis of 6 patients treated at Brazilian national cancer institute in the last eight years. Int Braz J Urol 39(6)
20. Lian B, Si L, Cui C, Chi Z, Sheng X, Mao L et al (2013) Phase II randomized trial comparing high-dose IFN-alpha2b with temozolomide plus cisplatin as systemic adjuvant therapy for resected mucosal melanoma. Clin Cancer Res 19(16):4488–4498
21. Shoushtari AN, Munhoz RR, Kuk D, Ott PA, Johnson DB, Tsai KK et al (2016) The efficacy of anti-PD-1 agents in acral and mucosal melanoma. Cancer 122(21):3354–3362

22. D'Angelo SP, Larkin J, Sosman JA, Lebbe C, Brady B, Neyns B et al (2017) Efficacy and safety of nivolumab alone or in combination with ipilimumab in patients with mucosal melanoma: a pooled analysis. J Clin Oncol 35(2):226–235
23. Harting MS, Kim KB (2004) Biochemotherapy in patients with advanced vulvovaginal mucosal melanoma. Melanoma Res 14(6):517–520
24. Postow MA, Luke JJ, Bluth MJ, Ramaiya N, Panageas KS, Lawrence DP et al (2013) Ipilimumab for patients with advanced mucosal melanoma. Oncologist 18(6):726–732
25. Guo J, Si L, Kong Y, Flaherty KT, Xu X, Zhu Y et al (2011) Phase II, open-label, single-arm trial of imatinib mesylate in patients with metastatic melanoma harboring c-Kit mutation or amplification. J Clin Oncol 29(21):2904–2909
26. Guo J, Carvajal RD, Dummer R, Hauschild A, Daud A, Bastian BC et al (2017) Efficacy and safety of nilotinib in patients with KIT-mutated metastatic or inoperable melanoma: final results from the global, single-arm, phase II TEAM trial. Ann Oncol 28(6):1380–1387

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