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# Primary urethral melanoma treated sucessfully with wide excision and combination immunotherapy: Case report and review of literature

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ABSTRACT

We report the rare case of a primary malignant melanoma of the urethra. An 89-year-old African American woman who was referred to our urology clinic for intermittent gross hematuria and a palpable vaginal mass of two months duration. Cystoscopy revealed a 3 cm mass in the distal urethra and urethral meatus that was surgically resected by wide local excision. The histopathologic diagnosis was primary malignant melanoma of the urethra. The patient was subsequently treated with adjuvant EBRT and immunotherapy with nivolumab and ipilimumab. Post-treatment PET-CT showed good response to treatment and patient remained in remission at eight month follow up.

## 1. Introduction

Primary malignant urethral melanoma is a rare tumor that has been traditionally associated with poor overall prognosis due to unique challenges of diagnosis and treatment. There are currently no management guidelines for primary urethral melanoma. Consequently, there is a high recurrence and cancer-specific mortality rate associated with current reported treatment strategies.

In this article, we present the case of an 89 year old female African American woman diagnosed with primary melanoma of the distal urethra with treatment response to surgery, adjuvant external beam radiation therapy (EBRT) and combination immunotherapy. Only two previous reports using current immunotherapy strategies have been reported: one case used nivolumab (PD-1 inhibitor) in primary urethral carcinoma and yielded recurrent free survival at 20 months post treatment,[1] the other case used pembrolizumab (PD-1 inhibitor) for diffusely metastatic urethral melanoma with poor response to treatment.[2] This is the first reported case of primary urethral melanoma with lymph node metastasis treated with wide local excision, EBRT, and adjuvant combination immunotherapy, nivolumab (PD-1 inhibitor) and ipilumimab (CTLA-4), who had good response to treatment.

## 2. Case presentation

An 89 year old African American female with past medical history of hypertension presented to the with the Urologist chief complaint of intermittent gross hematuria and a palpable vaginal mass for two months. The patient denied history of dysuria, frequency, urgency, fevers, chills or associated weight loss. Physical examination revealed a palpable 3 cm mass protruding from the urethral meatus; the mass was pedunculated, friable, with areas of ulcerations and spots of dark pigmentation (Fig. 1A–B). Cystoscopy revealed the mass was isolated to the distal urethra/meatus without involvement of proximal urethra, bladder or ureteral orifices.

Pathologic analysis and immunohistochemical staining of biopsy specimens identified the specimen as primary malignant melanoma (Fig. 2A–E). Thorough skin examination any ruled out any additional sites of disease. A full body PET CT scan done one month prior to surgery showed increased hypermetabolic activity at the opening of the vagina and in a 1.5 × 1cm left inguinal node without additional sites of hypermetabolic activity elsewhere (Fig. 3). For local and symptom control, the patient subsequently underwent distal urethrectomy and wide local excision of distal urethral mass. Pathology confirmed the 3 cm mass to represent a subepithelial high grade malignant neoplasm, consistent with melanoma. Based on these findings, the patient was diagnosed with primary urethral melanoma, Stage T3N1M0.

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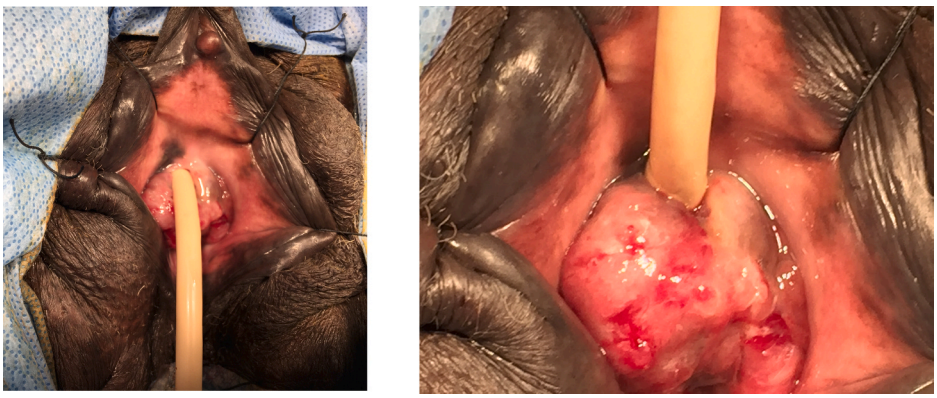

**Fig. 1. Gross appearance of urethral mass on physical exam**. A. Mass protruding from urethral meatus with areas of pink mucosal tissue and ulcerations present. B. Localized dark-brown pigmentation (white square) seen on gross inspection. . (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

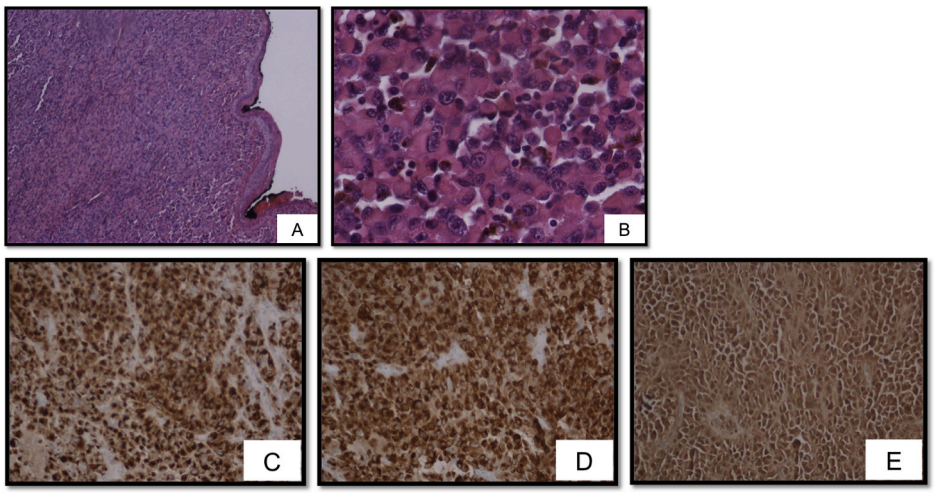


**Fig. 2. Low and High Power images as well as immunohistochemical (IHC) stains of urethral mass**
A. Sub-epithelial pleomorphic atypical cells seen in low power field (H&E stain). B. Diffuse infiltration of large magenta colored pleomorphic, epithelioid, spindle shaped cells with prominent nucleoli and scant cytoplasm. High coarsely granular melanocytic pigment seen between cells. (H&E). C. HMB-45 positive cells. D. Melan-A positive cells on IHC. E. S-100 stain positive for melanoma cells.

The patient was started on adjuvant immunotherapy with nivolumab and ipilimumab one month after surgery with good tolerance and no major side effects. She was referred by her oncologist for radiation therapy one month after starting immunotherapy for control of vaginal bleeding and as an additional adjuvant treatment. The patient, thus, completed a course of pelvic EBRT for 41 days from October 1, 2019 to November 11, 2019.

Follow up PET CT done at eight-months postoperatively showed a decrease in previously seen uptake in the lower gynecologic tract and decrease in size of the previously seen dominant suspicious left inguinal lymph node. The patient is currently alive and in remission eight months postoperatively.

## 3. Discussion

Primary melanoma of the urethra accounts for 4% of urethral malignancies and 0.1–0.2% of all melanoma, making it truly a rare finding. The most commonly observed locations of primay urethral melanoma are the distal urethra and the urethral meatus (80%).[2] It is more commonly diagnosed in Caucasians (85%) than African Americans (7%)[2,3],[4] Presentation is more common in the 6th to 7th decade of life with average age at diagnosis of 65 years (range 32–96 years).[3] The most common symptoms described in the literature are: palpable vaginal mass, vaginal bleeding, hematuria, dysuria, decreased urinary stream.[3]

There is no consensus in terms of optimal surgical treatment for primary urethral melanoma. Surgical management varies in the literature, from local excision to more radical procedures such as anterior pelvic exenteration, and cystourethrectomy with vaginectomy and vulvectomy for patients without evidence of metastasis. The role of radical surgery as primary treatment for urethral melanoma remains controversial due to poor progrnosis as well as high morbidity and mortality.[1] Previous case reports, instead, favor wide local excision with a 2.5cm marging as an adequate option for localized disease. Bilateral lymph node dissection has been previously shown to have high morbidity with limited long-term benefit to patients. In our case, the patient's mass was limited to the distal urethra; therefore, wide local excision was an appropriate surgical management option.

Previously published cases suggest multimodal therapy for improved overall patient survival. Combination treatments with radiotherapy, immunotherapy and/or chemotherapy have been described for high stage, larger size, and proximal urethral lesions. Systemic chemotherapy and immunotherapy regimens such as dacarbazine, nimustine, vincristine and IFN-beta (DAV-feron) have been used with limited improvement in recurrence rate and overall survival.[1]

Contemporary research has shown the potential of immune checkpoint immunotherapies such as cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death 1 (PD-1) antibody treatment for the management of metastatic melanoma.[5] Two recently published case reports employ the use of immunotherapy for the management of urethral melanoma. One case showed no improvement in survival for palliative pelvic radiation and pembrolizumab immunotherapy given for diffusely metastatic disease after robotic anterior

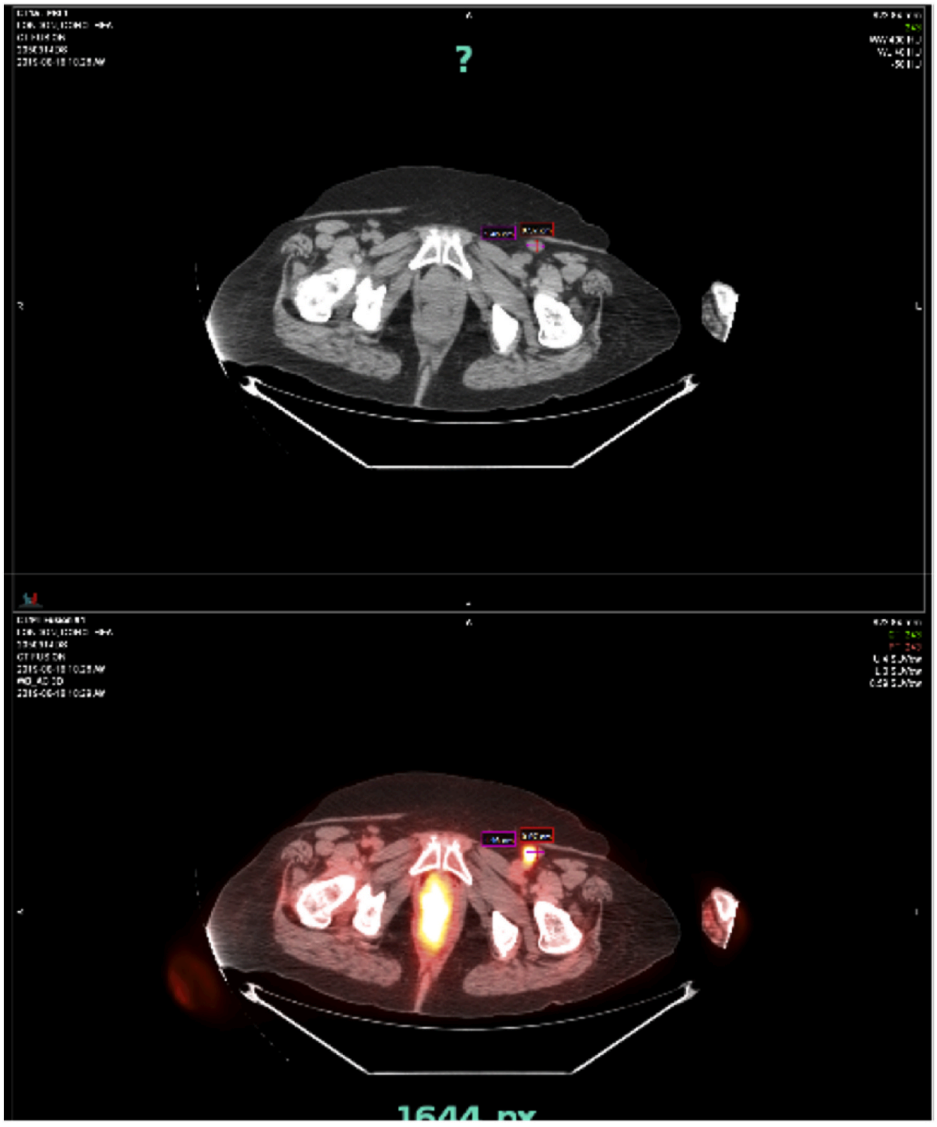

**Fig. 3.** PET-CT images showing increased metabolic activity in the distal vagina and left groin that corresponds to a 1.5 × 1cm left inguinal lymph node.

pelvic exenteration, total vaginectomy, and ileal conduit urinary diversion.[1] The other case had a recurrence free survival of 20 months post nivolumab treatment for systemic metastasis of primary amelanotic melanoma after partial penectomy with amputation of glans and bilateral extended lymphadenectomy followed by DAV-feron chemotherapy. These cases suggest that perhaps early administration of adjuvant immunotherapy could potentially decrease the risk of recurrence and improve overall survival for patients with primary urethral melanoma.

## 4. Conclusion

In conclusion, primary urethral melanoma is a rare malignancy with a high rate of recurrence and generally poor prognosis. Novel immunotherapies targeting mucosal melanomas have emerged and shown promising survival benefits. Further studies comparing surgical techniques and adjuvant therapies with long term follow up are needed to determine the optimal management for this unique disease.

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