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Mucosal Melanoma of the Male Urethra: A Case Report

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ABSTRACT

This is a rare case of a mucosal melanoma, located in the urethra of a 59-year-old male. Malignant melanomas of the genitourinary tract are rare, representing <1% of malignancies in the genitourinary tract, and <0.1% of all melanomas. In the male genitourinary tract, the most affected sites are the glans penis and the distal urethra in the fossa navicularis. Urethral melanomas comprise 4% of all urethral cancers.

Key words: mucosal melanoma, urethra, genitourinary, urethral melanoma

ISSN 2507-8364 (Online)
Printed in the Philippines.

Received: 22 November 2023.
Accepted: 20 December 2023.
Published online first: 28 December 2023.
https://doi.org/10.21141/PJP.2023.14

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CASE

A 59-year-old Filipino male sought consult with a chief complaint of severe dysuria with accompanying symptoms of gross hematuria and urinary retention. Symptoms started nine (9) months (February 2022) prior to consult, when the patient complained of episodes of gross hematuria with blood clots and slight dysuria. Two (2) months (September 2022) prior to consultation, he was seen at the emergency room (ER) due to severe dysuria, gross hematuria and urinary retention. At the time of the ER consult, he was described to be frail-looking and had difficulty doing daily activities of living. A Foley catheter was inserted and CT urogram was performed which shows a non-enhancing exophytic cortical cystic focus measuring 1.4 x 1.3 cm at the right upper pole cortex. A slight enhancing iso to hypodense solid mass measuring 3.0 x 3.2 x 3.0 cm is seen in the middle pole calyx. Magnetic resonance imaging (MRI) of the abdomen and pelvis revealed an enlarged prostate, under-distended urinary bladder with diffuse wall thickening, irregular mucosal thickening with focal areas of restricted diffusion noted in the superior wall, kidneys with mild to moderately dilated right renal pelvis and mid to lower pole calyces, likely representing hemorrhagic or high proteinaceous content.

Submitted to our institution for slide review and immunohistochemical staining studies was a urethral mass biopsy specimen. Microsections of the mass disclosed atypical round cells arranged in nests and sheets. These atypical cells exhibited hyperchromatic nuclei with scant cytoplasm with inconspicuous nucleoli (Figure 1).

The case was initially signed out as a round-cell malignancy. Primary considerations included poorly differentiated urothelial carcinoma, lymphoma, metastatic prostatic adenocarcinoma, and melanoma. Thus, immunohistochemical staining with Cytokeratin (CK), Leucocyte Common Antigen (LCA), p63, p40, GATA-3, Prostate Specific Antigen (PSA), S100, Melan A, and HMB-45 were requested.

Cytokeratin, LCA, p63, p40, GATA-3 and PSA all stained negative. S100 and HMB-45, stained positive and Melan-A was focally positive (Figures 2-4). The immunohistochemical staining results, in correlation with cytomorphology,

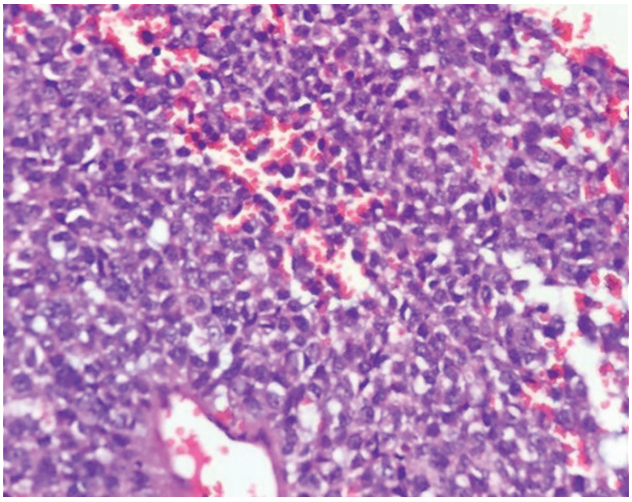

Figure 1. Atypical cells show hyperchromatic nuclei with scant cytoplasm with inconspicuous nucleoli (H&E, 200x).

support the diagnosis of high-grade round cell malignancy. The primary consideration was non-cutaneous / mucosal melanoma. Additional immunohistochemical staining with SOX10, Smooth Muscle Actin (SMA) and Desmin was recommended for a more definitive diagnosis. However, the additional stains requested were no longer performed, and the patient was admitted for urethrectomy with cystoprostatectomy. The urinary bladder, prostate, bilateral ureters, and urethra were submitted for processing. Upon gross inspection, there was a dark brown, soft tissue mass arranged in an excrescence-like pattern, occupying 12.8 cm of the length of the urethra. The mass is seen 1.8 cm and 0.3 cm away from the urethral portion of the prostate and urethral resection margin, respectively. Sections from the specimen were submitted for study.

Microsections from the urethral mass disclose atypical round cells arranged in nests and sheets, like the ones in the initial biopsy specimen, now seen invading but limited

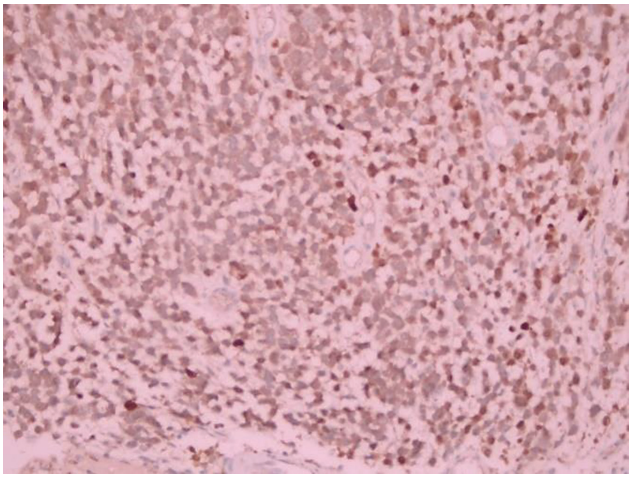

Figure 2. Cytoplasmic and nuclear immunohistochemical staining for S-100 was observed in neoplastic cells (S-100, 200x).

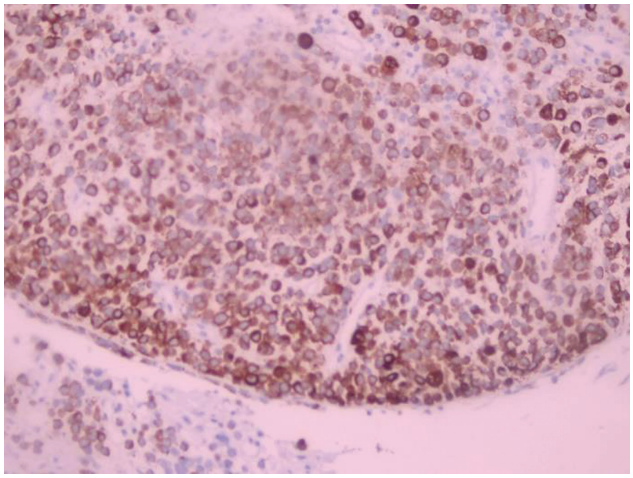

Figure 4. Cytoplasmic immunohistochemical staining for HMB-45 was observed in neoplastic cells (HMB-45, 200x).

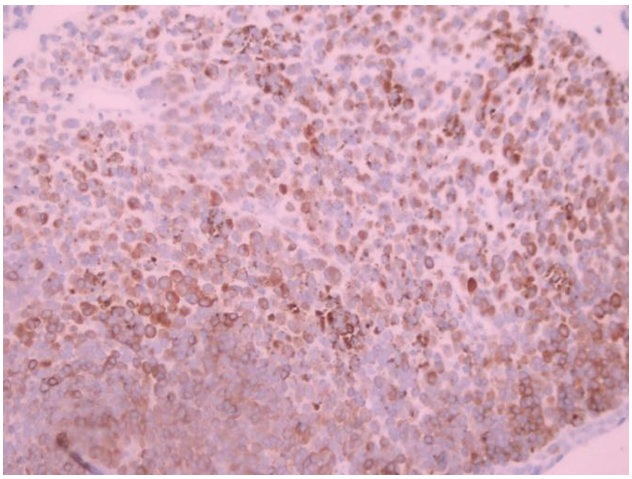

Figure 3. Focal cytoplasmic and nuclear immunohistochemical staining for Melan-A observed in neoplastic cells (Melan-A, 200x).

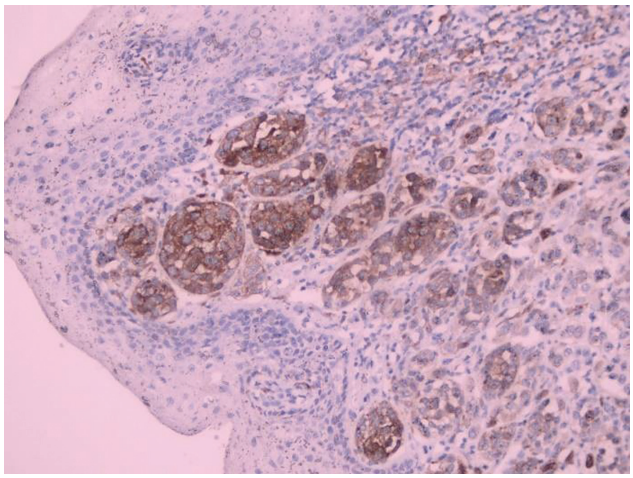

Figure 5. Complete and partial membranous immunohistochemical staining for PDL-1 was observed in 30% of neoplastic cells (PD-L1, 200x).

to the muscularis propria of the urethra. The atypical cells show hyperchromatic nuclei with scant cytoplasm with inconspicuous nucleoli. Additional immunohistochemical staining with PD-L1 and CD 117 (KIT) was requested which showed positivity for 30% (Figure 5) and 40% of the tumor cells, respectively. The case was signed out as mucosal (non-cutaneous) melanoma.

The patient tolerated the procedure well, was discharged stable and was referred to the oncology service for definitive management.

DISCUSSION

Incidence

Malignant melanomas of the genitourinary tract are rare, representing <1% of malignancies in the GU tract[1-4] and <0.1% of all melanomas.[1,5-7] The most common sites being affected are the skin and the eyes.[8] In the male genitourinary tract, the most affected sites are glans penis and the distal urethra in the fossa navicularis.[1,8] Urethral melanomas compromise 4% of all urethral cancers.[7] It is more common in older adults, with the mean age at diagnosis being 65 years.[1,7] There is no gender predilection for urethral melanomas.[1]

In a paper published by Altieri et al., they concluded that "although 1% of melanomas occurring in non-Hispanic whites were mucosal, other racial/ethnic groups have higher proportions of mucosal melanomas (15% for Asian/Pacific Islanders, 9% for non-Hispanic blacks, and 4% for Hispanics)."[3]

Clinical presentation

Signs and symptoms are often non-specific and depend on the anatomical location. In the early stage, patients may be asymptomatic.[9] In the later stages, patients with urethral melanoma may present with hematuria, dysuria, frequency, spraying urinary stream or other symptoms related to urinary obstruction.[1,4,9] Hematuria due to ulceration occurs in cases of urethral melanoma.[5] Ulceration is more common in the urethra compared to the glans penis.[5] Diagnosis of cases is often delayed because of their non-specific signs and symptoms.[5] In men, urethral melanoma can present with symptoms similar to chronic prostatitis or prostatic hyperplasia due to urethral discharge and obstructive symptoms and diagnosis is only achieved after failure of treatment for mimicking diseases.[9] In a systematic review conducted by Safadi et al., urethral mass is the most common presenting symptom.[7]

Imaging

According to Rambhia et al., currently, there are no algorithms for the workup of genitourinary melanomas as patients would present in the late stages of the disease and the prognosis is typically poor for these patients.[8] Primary approach to diagnosis would include a thorough physical exam. For men, this includes inspection of the prepuce, glans, scrotum, frenulum and penile shaft for any lesion, such as ulceration, crusting and irregularity. Excision biopsy is confirmatory for histologic diagnosis and imaging studies such as Positron Emission Tomography (PET), CT, MRI, and chest X-rays are performed to rule out metastases.[9]

Histomorphology and immunohistochemical studies

According to the World Health Organization (WHO), macroscopically, urethral melanomas would present as ulcerated, nodular masses, and associated nevus are rarely present.[1] Microscopically, urethral melanoma would present as "sheets or expansile nodules of large pleomorphic epithelioid or (less commonly) spindle-shaped malignant melanocytic cells. Necrosis is uncommon. The nuclei often have vesicular chromatin and prominent nucleoli. Occasionally, small, or nevoid cells may predominate. Melanin production is variable but usually focally present both within melanoma cells and within macrophages. The junctional component is typically characterized by a lentiginous growth of single atypical melanocytes in the basal epithelial layer, sometimes with nests or confluent growth. A subepithelial lymphocytic infiltrate is common. Immunohistochemically, there is usually reactivity of the tumor cells for S100, SOX10, HMB45, and Melan-A (MART1).[1]

Fine-needle aspiration biopsy is used as a rapid, minimally invasive means of diagnosing metastatic melanoma. The regional lymph nodes would generally be the first ones to be affected.[10] In a paper published by Murali et al., smears of the FNAB specimens would show spindle and/or epithelioid cells with malignant cytologic features.[10] Aside from the previously mentioned findings, according to WHO, the smears would also show, isolated giant cells and intranuclear pseudo-inclusions are often present. Cytoplasmic pigment is usually present in a minority of cells. Pigmented macrophages may be seen in the background.[1]

Molecular studies

Molecular signatures and patterns of chromosomal aberrations in mucosal melanoma have been compared to those in cutaneous melanoma.[9] BRAF mutations in GU melanomas are less common compared to cutaneous melanomas.[9] C-KIT proto-oncogenes receptor tyrosine kinase gene (KIT), which are commonly found in acral melanomas and melanomas arising from chronically sun-exposed skin, have also been described in mucosal melanomas.[9] The downstream targets of KIT include the RAF/MEK/extracellular signal-regulated kinase (ERK) and PI3K/AKT pathways.[9] In a paper published by Omholt et al., there is no association between KIT mutations and a worse prognosis.[11] Activating mutations in the N-ras proto-oncogene (NRAS) are seen in cutaneous melanomas and some cases of mucosal melanoma.[9,12] As reported by Van Engen-van Grunsven et al., NRAS mutations are detected in 20% of urethral melanomas, showing that NRAS mutations are present in significant amounts of GU melanomas but not in the majority.[9,12] Lastly, PD-1, programmed cell death receptor and PD-L1, programmed cell death receptor ligand, have been noted to be expressed in mucosal melanomas in the same amounts as in cutaneous melanomas. Targeted immune checkpoint inhibitors directed against PD-1 receptors were noted to have improved outcomes.[9] Therefore, PD-1 directed immunotherapies in GU melanomas might have a role. In summary, GU melanomas should be tested for BRAF and KIT mutations along with PD-L1 testing if systemic treatment with immunotherapy is being considered.[1]

Staging and prognosis

There are currently no standardized criteria for staging mucosal melanomas of the male GU system.[1,5] Compared to cutaneous melanomas, the prognosis of urothelial primary melanomas is poor with a median survival time being 28 months with a 5-year survival rate of 28%.[1]

Our patient was 58 years old at the time of the presentation of the disease, 7 years younger than the mean age at presentation. He initially presented to his attending physician with the chief complaint of severe dysuria with the accompanying symptoms of gross hematuria and urinary retention, which is a common disease manifestation. However, in our patient's case, the hematuria was not caused by ulceration as gross and microscopic examination of the urethral mass did not show any break in the lining of the epithelium. His imaging studies show no sign of metastasis. A gross examination of the urethral mass showed dark brown, soft tissue mass arranged in an excrescences-like pattern, unlike the usual presentation of ulcerated, nodular masses. Microsections of the urethral mass disclosed atypical round cells arranged in nests and sheets, which is similar to how mucosal melanomas are commonly described (i.e., "sheets or expansile nodules of large pleomorphic epithelioid or [less commonly] spindle-shaped malignant melanocytic cells"). Immunohistochemical staining results were positive for S100 and HMB-45 and Melan A which is compatible with the usual picture. For our patient, PD-L1 and KIT testing expressed positivity for 30% and 40% of the tumor cells, respectively. As such, our patient is considered for targeted immunotherapy with pembrolizumab or kinase inhibitors as options for treatment.

FOLLOW-UP AND OUTCOMES

A few months after the initial diagnosis and surgery of the patient, a Computed tomography (CT) scan of the whole abdomen and chest was performed on two (2) separate occasions. CT scan of the whole abdomen (status post cystoprostatectomy and ileal conduit formation/construction) revealed non-specific punctate pancreatic tail calcification, likely post-inflammatory; splenomegaly; swollen left kidney with decreased nephrogram enhancement and moderate hydronephroureter which may be related to obstructive nephropathy; dilated distal left ureter with lobulated border and surrounding fat stranding densities; bilateral renal cortical cysts with suggestive parapelvic cyst in the right; prominent retroperitoneal lymph nodes; and minimal ascites. The possibility of tumor recurrence was not ruled out. CT scan of the chest revealed fibrotic changes, in both upper lobes; subsegmental atelectasis, right lower lobe; minimal bilateral pleural effusion with passive atelectasis; atherosclerosis, thoracic aorta and coronary arteries; dorsal spondylosis; and vertebral hemangioma, T8.

Unfortunately, no further testing has been performed on the patient as he was reported to have passed away last April 2023, fourteen (14) months after the initial onset of symptoms, shorter than the reported median survival period of patients with urothelial melanoma.

CONCLUSION

We have reported a case of a urethral mucosal melanoma in a 59-year-old male. Malignant melanomas of the genitourinary tract are rare, representing <1% of malignancies in the genitourinary tract, and <0.1% of all melanomas. Survival remains dismal for patients with this disease, underscoring the need for its recognition and diagnosis in the appropriate clinical context, aided by appropriate imaging, histopathological, and immunohistochemical studies.

ACKNOWLEDGMENT

The authors acknowledge Dr. Ralph Albert Patrick C. Uy for his expert contribution to this paper.

ETHICAL CONSIDERATION

Patient consent was obtained before submission of the manuscript.

STATEMENT OF AUTHORSHIP

The authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

The authors declared no conflict of interest.

FUNDING SOURCE

None.

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