Primary Urethral Melanoma: A Case Report and Literature Review

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Patients with localized urethral melanoma have a high risk of recurrence and poor disease-specific survival. Multi-disciplinary approach including surgery, radiation therapy, and chemotherapy/immunotherapy is needed to maximize survival. Current research efforts include investigation of novel tyrosine kinases as well as the combination of targeted therapies with immunotherapies in this population. Combinations may provide a synergistic effect to overcome various obstacles to disease response. UROLOGY 126: 1–4, 2019. © 2018 Elsevier Inc.

CASE

A 73-year-old female with a past medical history significant for hypertension, diabetes mellitus II, and past smoking history presented to her Gynecologist for vaginal pain and hematuria that had been persistent for 1-month. Physical exam revealed a 3 cm urethral mass palpable along the anterior vaginal wall. Office biopsy was taken which revealed malignant spindle cell neoplasm. She was then referred to Urology for further management.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of urethral masses in women may also include benign causes such as urethral polyps, leiomyoma, or urethral diverticulum. The differential diagnosis of primary urethral cancer includes urothelial carcinoma, squamous cell carcinoma, and adenocarcinoma. More rare histologic subtypes of urethral cancers could also be considered including melanoma. Other malignant lesions to consider include spindle cell carcinoma, small cell carcinoma, sarcomas, and lymphomas.[1-4]

DIAGNOSTIC ASSESSMENT, MANAGEMENT, AND OUTCOME

Full laboratory evaluation was performed which included complete blood count, liver, and kidney functions, and serum electrolytes. All laboratory tests were normal. The patient was also sent for imaging studies for evaluation of local extent of the tumor as well as metastatic work up which included chest X-ray (CXR), computed tomography (CT) scan abdomen, and pelvis with contrast, and magnetic resonance imaging (MRI) of the pelvis. CXR was normal. CT of abdomen and pelvis with contrast showed heterogeneous enhancement in anterior vaginal wall invading the urethra. MRI of the pelvis with contrast revealed a heterogeneous mass centered around the vaginal introitus and encasing the distal urethra and urethral meatus (Fig. 1). The mass did not appear to invade surrounding structures including the perineal body or anal canal. There were also no signs of distant spread as well as no pelvic or inguinal lymphadenopathy.

After discussing the case in our multidisciplinary tumor board, she underwent surgical treatment with a robotic anterior pelvic exenteration with total vaginectomy and ileal conduit urinary diversion. A lymph node dissection was not performed as she did not have palpable lymph nodes on physical exam and the imaging did not show any enlarged or suspicious pelvic or inguinal nodes. The surgery was uncomplicated with no intraoperative issues encountered during her surgery. She had an uneventful postoperative course and was discharged home on postop day 6.

Her final pathology revealed 4.9 cm primary urethral melanoma with involvement of the vaginal mucosa (Figs. 2 and 3). The surgical margins were negative. Lymphovascular invasion was present. She was once again discussed in our multidisciplinary tumor board, involving our melanoma medical oncology colleagues in the planning of her future management, and a conclusion of her high risk for recurrence was made with recommendation to offer her adjuvant immunotherapy. However, the patient declined adjuvant therapy and elected for close active surveillance.

Approximately 5 months after her surgery, the patient started to notice a perineal bulge. She was immediately evaluated by the urology and medical oncology teams. Repeat imaging with pelvic MRI with contrast showed multiple

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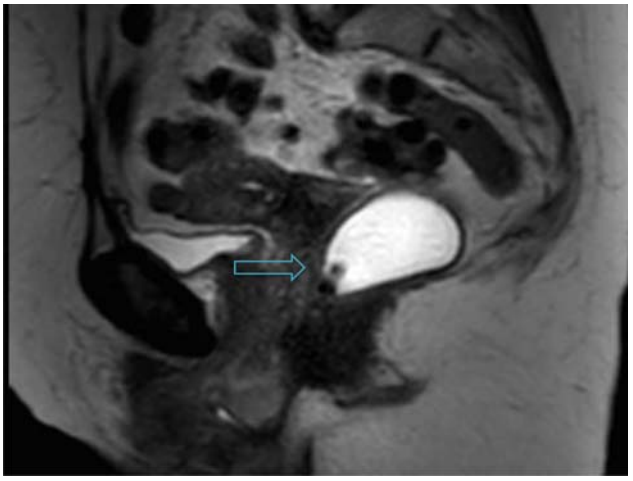

Figure 1. Sagittal view of pelvic MRI showing a heterogenous mass encasing the distal urethra. (Color version available online.)

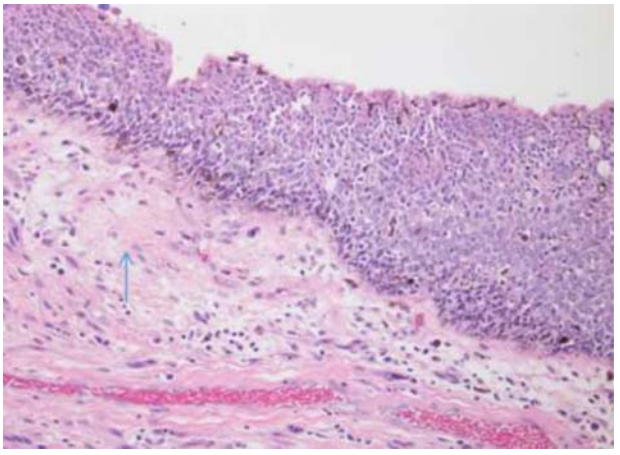

Figure 2. Melanoma insitu involving the urethral urothelium. There are individual melanocytes infiltrating the urothelium in a pagetoid fashion. Of note, brown melanin pigment can be seen in the cytoplasm of the neoplastic melanocytes (arrow). There is no invasion of the neoplastic cells beyond the basement membrane and into the lamina propria. (H&E 10×) (Color version available online.)

enhancing masses within the perineum, extending into the labia, and abutting the anterior rectal wall; consistent with recurrent disease. Metastatic work up was performed including CT chest, abdomen and pelvis, as well as whole body positron emission tomography (PET) scan. Scans were positive for widely metastatic disease with multiple hypermetabolic large abdominopelvic masses and peritoneal deposits compatible with metastases. A palliative course of pelvic radiation therapy was started at that time. After completion of her radiation therapy, she began immunotherapy with pembrolizumab. The patient eventually died of metastatic disease 11 months after surgery.

DISCUSSION

Urethral melanoma is a mucosal melanoma. Mucosal melanomas arise in any mucosal epithelium containing

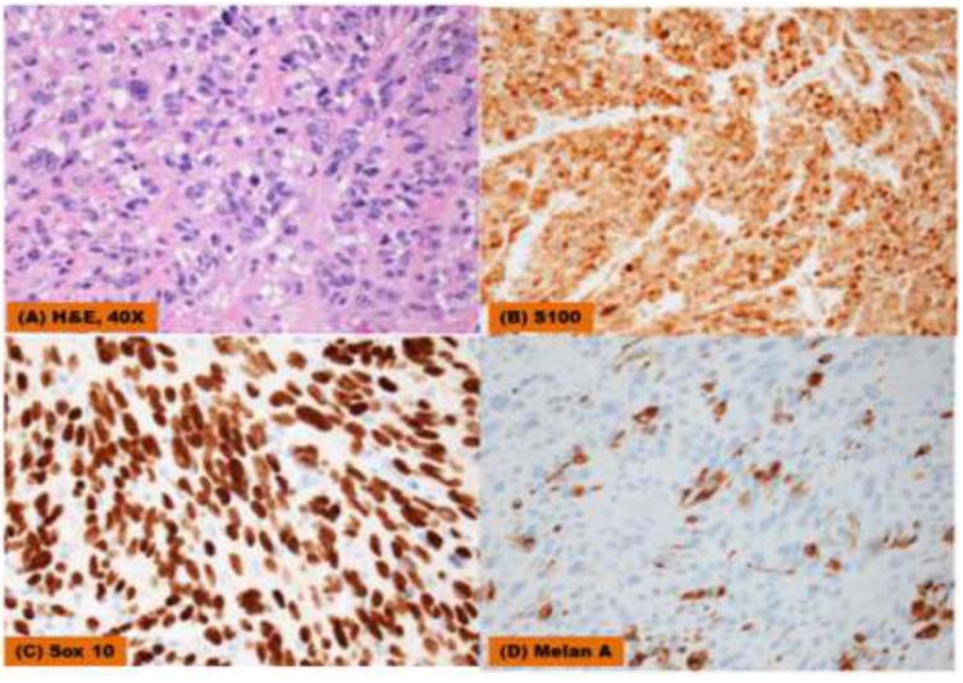

Figure 3. Immunohistochemical staining of urethral lesion (**A**) H&E, 40× magnification showing oval and pleomorphic cells with increased nuclear to cytoplasmic ratio, irregular nuclear contours, hyperchromatic nuclei, and increased mitosis. (**B**) S100 showing both nuclear and cytoplasmic staining. (**C**) SOX-10 showing diffuse and strong nuclear staining. (**D**) Melan A showing scattered positive cells. (Color version available online.)

melanocytes, such as the respiratory, gastrointestinal, and urogenital tracts, including the urethra.[5,6] Urethral melanoma comprises 4% of all urethral cancers. Eighty percent of cases are in the distal urethra and/or urethral meatus.[4,7] In females, it commonly presents as it did in our patient as a painful urethral mass or vaginal bulge. In males, it can present as a mass at the urethral meatus, hematuria, or dysuria.[3,8] Urethral melanoma is 3 times more common in females compared to males.[2]

Despite variances in histological types, primary urethral melanoma is a rare disease in both males and females and with less than 200 indexed cases in the literature. Optimal treatment for this condition is unclear and prognosis for these patients remains poor. In a recent analysis of survival data for melanoma subtypes, median overall survival for patients with advanced mucosal melanoma, such as urethral melanoma, was only 9.1 months (95% CI, 7.6-9.8). For primary urethral melanoma, recurrence has been cited to be as high as 60%-70% within the first year.[2,9] Three-year survival has been recorded to be 27%, with 5-year survival very low at 11%.[10]

While there may be differences in pathogenesis of the various histologic subtypes, treatment for urethral carcinoma depends on the location and extent of disease. Therefore, prior to surgical planning for primary urethral melanoma, extensive physical examination is necessary to ensure that this is not a metastatic process, and that no obvious cutaneous lesions are missed.[4] Imaging with MRI is very useful as it allows better evaluation of the soft tissue and can determine the extent of invasion into surrounding structures. Furthermore, exam under anesthesia and urethrocystoscopy may provide further information for surgical planning.[11,12] As mentioned previously, a biopsy of the specimen is also required as the management planning may vary based on the histology.

There is a paucity of literature for management of primary urethral melanoma and postsurgical outcomes are unclear with few case series published over the years. The summary of these studies is listed in Table 1.[2,3,8,10]

Based on the limited literature, the initial extent of surgery depends on the mass itself. If the mass is limited to the urethra, a urethrectomy or wide local excision remains an option for these very selective patients, but only if negative margins can be achieved. However, if there is any evidence of local invasion, as there was in this case, more aggressive surgical approach such as a radical cystourethrectomy is the recommended treatment option.[7,11,13] Additionally factors such as tumor size, depth of invasion, presence of lymphadenopathy, or distant metastasis must be considered with surgical planning. Benefits of the surgery must be carefully balanced with the risks and can be considered in a case by case basis.[13,14] Regardless of surgical approach, the recurrence rate for urethral melanoma is as high as 71%.[2]

Therefore, the recent adoption of various immunotherapy regimens has given hope for better survival of patients with urethral melanoma. Recent data has shown that PD-1 inhibitors have efficacy in patients with urethral melanoma, although the rates of response may be somewhat lower compared to other cancers.[6]

Table 1. Summary of studies reporting on urethral melanoma

Author (Year)	Article Type	# of Patients (N)	Male (%)	Average Age (years)	Metastatic at Presentation (%)	% of Patients getting Initial Surgical Treatment	Adjuvant Therapy	Recurrence (%)	Average Time to Recurrence (months)	Prognostic Factors	Overall Survival	Cancer Specific Survival
El-Safadi et al. (2014)	Systematic Review	150	40	64.7	13	69%	20% RT 13.6% Chemotherapy 8 % Immunotherapy	71	12.5	T-Stage (depth of invasion), local recurrence, metastatic disease, ocular melanoma	25% (5 year)	N/A
Sanchez-Ortiz et al. (2005)	Retrospective Review	10	100	52.9	10	100%	12.5% Chemotherapy	40	17.25	T-Stage, clinically positive lymph nodes	60% (5 year)	80% (5 year)
Di Marco et al. (2004)	Retrospective Review	11	0	68	0	100%	Not reported	64	10.4	N/A	27% (3 year)	38% (3 year)
Olivia et al. (2000)	Retrospective Review	15	40	73	13	93%	13.3% RT	67	20.5	Mucosal location & nodular growth	20% (5 year)	N/A

Factors associated with a poorer prognosis include advanced T stage at time of diagnosis, histologic subtype, node positive disease, African American race, Age > 65, tumor size.[11,14-19] Certain studies have shown that T stage and histologic subtype are the most influential factors.[17-19] There are reports that surgery is associated with improved survival for urethral carcinoma, but it is unclear for melanoma. This may be due to the more advanced nature urethral melanoma at time of diagnosis.

Stains that can be used histologically to diagnose cutaneous lesions are helpful including S-100, HMB-45, and manin-A. The pathologist can be helpful in determining how aggressive the lesion is based on other pathologic characteristics including angioinvasion and multicentricity.[12] Genetic makeup of urethral melanomas is unknown. However, certain genes such as BRAF activating mutations and KIT mutations may have some role.[12] However, given the rarity of urethral melanomas, the full genetics of this disease are still unknown.

CONCLUSION

Patients with localized urethral melanoma have a high risk of recurrence and poor disease-specific survival. Multi-disciplinary approach including surgery, radiation therapy, and chemotherapy/ immunotherapy is needed to maximize survival. Current research efforts include investigation of novel tyrosine kinases as well as the combination of targeted therapies with immunotherapies in this population. Combinations may provide a synergistic effect to overcome various obstacles to disease response.

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