Primary melanoma of the female urethra

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ABSTRACT

Introduction: Of all melanoma cases, approximately 0.2% occur in the female urethra. Although cutaneous melanoma is considerably more prevalent, there are a few reports of primary melanoma of the urethra. We report a rare case of primary melanoma arising from the female urethra as well as the management of this individual with a novel immunologic based therapy. Case Report: A 78-year-old Caucasian female presented to urology clinic for further evaluation related to her previous urethral tumor resection. Histopathologic evaluation of the resected tumor showed melanoma involving the urethral mucosa and lamina propria, with extensive ulceration and focal invasion into lymphovascular structures. Tumor margins were positive on microscopy. Metastatic survey with positive emission tomography scan of body was negative. Repeat cystoscopy showed persistent mass, approximately 1-2 cm distal to the urethral sphincter. Surgical resection would have required full urethrectomy and cystectomy to achieve a negative margin. The patient was presented with two alternative therapeutic options: radical surgical extirpation or systemic immunotherapy in combination with local radiation. Ultimately, the patient pursued a treatment paradigm of systemic therapy with anti-PD-1 antibody- based immunotherapy (pembrolizumab) and radiation. Conclusion: In the recent years, immunotherapy has become a promising therapeutic option for urethral melanoma. Primary female urethral melanoma is a rare occurrence without clear guidelines for optimal surgical and medical management.

Keywords: Anti-PD-1 Antibody, Immunotherapy, Melanoma, Urethral neoplasm

INTRODUCTION

Melanocytes are pigment-producing cells found in various anatomic locations, including the epidermis, eye, and epithelia of the respiratory, gastrointestinal, and genitourinary tract. Due to environmental stress and genetic factors, these cells can become malignant developing into melanomas [1]. In 2018, there were over 36,000 new cases of melanoma among females in the United States [2]. Of all melanoma cases, only 0.2% of them were located in the female urethra [3]. A rare urethral malignancy, melanoma of the female urethra is not well characterized in literature because of the low incidence rate and paucity of case reports. Frequently, patients with urethral melanoma undergo extensive pelvic surgery and lymph node dissection [4]. Prognosis and survival postoperatively is poor for these individuals [5]. In this case report, we present a rare case of primary melanoma...
of the female urethra as well as the management of this individual with a novel immunologic based therapy.

CASE REPORT

A 78-year-old Caucasian female presented with a “blueberry-like lesion” in her vulva. Her past medical history was significant for hypertension, hyperlipidemia, type 2 diabetes mellitus, and mild dementia. The lesion was present for four months. She denied pain, bleeding, or pruritus. Family and social history were noncontributory. Inspection of the genitourinary region revealed a pedunculated purple mass at the urethral meatus and anterior vagina. No inguinal lymphadenopathy was noted on physical examination. The patient was diagnosed with clinical stage IIC melanoma of the vulva and urethral meatus. At that time, cystoscopy was performed and was negative for bladder or proximal urethral involvement. Subsequently, she underwent gross total excision of the lesion. Histopathologic evaluation of the lesion showed an extensively ulcerated and partially necrotic nodular tumor composed of malignant-appearing polygonal and epithelioid cells (Figure 1A). The tumor invaded to a depth of nine mm, and focal invasion of lymphovascular structures was present (Figure 1B). Many of the cells demonstrated cytoplasmic melanin pigment, consistent with melanoma. Immunohistochemical stains were positive for S-100 and MART-1 (Figure 2A, 2B), and negative for pancytokeratin, synaptophysin, chromogranin, and CD56, supporting that interpretation. Molecular testing was negative for BRAF mutation. While evaluation of mucosa was limited by extensive ulceration, a focus of intramucosal melanoma was identified within transitional-type epithelium (Figure 3). Given this finding and the absence of a source of metastasis from the skin, a diagnosis of primary urethral melanoma was rendered. Tumor margins were positive on microscopy. Metastatic survey with positive emission tomography scan of body was negative.

The patient was referred to urologic oncology for further evaluation. In clinic, repeat cystoscopy showed a persistent pigmented mass, approximately 1-2 cm distal to the urethral sphincter, in the absence of bladder involvement. Since the tumor was adjacent to the urethral sphincter and histology showed local invasion to deeper tissue, resection would have required full urethrectomy and cystectomy to achieve a negative margin, with a possibility of permanent incontinence. The patient was presented with two alternative therapeutic options: radical surgical extirpation or systemic immunotherapy in combination with local radiation. Ultimately, the patient pursued a treatment paradigm of systemic therapy with anti-PD-1 antibody- based immunotherapy (pembrolizumab) and radiation. Patient has a follow up period of 5.5 months.

DISCUSSION

Neural crest cells migrate and differentiate into melanocytes. Environmental and genetic factors can alter the genomic composition of melanocytes leading to the development of melanoma. Although the most common location for melanoma is the epidermis, malignant melanoma can develop on mucosal regions, including the oropharynx, nasal cavity, vulva, and urinary epithelium [6]. In fact, only 0.2% of all malignant melanomas arise from the mucosal lining of the urethra, and urethral melanoma accounts for 4% of all urethral cancers [3]. Primary malignant melanoma of the urethra typically affects the meatus and distal urethra and is three times more common in females than males. Men (62.9 years) present at an earlier age compared to women (66.7 years).
Urethral melanoma may be clinically confused with urethral carcinoma, transitional cell carcinoma, sarcomatoid carcinoma, or sarcoma [6]. Urethral melanomas have an array of histological patterns, including diffuse, nested, fascicular, and/or storiform growth of pleomorphic cells [7]. Immunohistochemistry is often crucial to accurately diagnose melanoma. S-100 antibody has a 90% sensitivity for melanoma, though this protein can also be present in other cell lineages such as chondrocytes, schwann cells, adipocytes, and myoepithelial cells [8]. A transmembrane protein present in normal melanocytes and highly upregulated in malignant melanoma, MART-1 also has a high sensitivity and specificity for melanoma, providing diagnostic value [9]. In this case, the tumor cells demonstrated areas of melanin production, and showed positive staining for both S-100 and MART-1, supporting the diagnosis of malignant melanoma.

In comparison to cutaneous melanoma, risk factors for melanoma of the urethra are poorly understood. The genitourinary tract is not readily exposed to ultraviolet radiation, a prominent risk factor for development of cutaneous melanoma. On the other hand, persistent inflammatory states, microbial infections, and chemical irritants have been associated with the development of genitourinary melanomas [6]. Metastasis often occurs early in female urethral melanoma, spreading through the superficial lymphatics to the vulva and vagina, through the deep lymphatics to the inguinal lymph nodes, or to distant body sites through hematogenous spread [10]. Compared to the cutaneous form, urethral melanoma has a worse prognosis because of the frequent findings of deep invasion and lymph node involvement on presentation, due in part to delayed diagnosis [11]. Even with proper recognition and diagnosis, patients with urethral melanoma have a poor prognosis because of inadequate surgical resection due to the anatomic location of the tumor [10]. Melanoma in the urinary tract have a 5-year survival rate of 18% [12].

Treatment of urethral melanoma ranges from local resection with or without radiation therapy to more extensive surgery, including vaginectomy, vulvectomy, cystourethrectomy, and lymph node dissection [13]. For relatively small and superficial distal urethral tumors, local resection is a sufficient treatment option. Furthermore, in males, penile amputation is a possible option for individuals with distal urethral or meatus lesions [14]. However, local excision may not adequately manage more proximal and advanced urethral tumors. DiMarco et al. demonstrated that partial urethrectomy did not adequately control urethral melanomas; 71 percent of their cohort failed this treatment option. Radical urethrectomy with bladder preservation may be a viable option for individuals with more aggressive urethral melanomas. In this type of resection, the bladder neck, periureteral tissues, anterior vagina, and labia are resected to acquire 2.5 cm surgical margins [10]. Radiation and chemotherapy have been shown to be ineffective options for melanoma in the urethra; in the recent years, immunotherapy has been utilized more frequently to manage mucosal melanoma [10]. In the D'Angelo et al. study, the combination of nivolumab, a programmed death-1 checkpoint inhibitor, and ipilimumab, a cytotoxic T-lymphocyte antigen-4 checkpoint inhibitor, was efficacious in the treatment of mucosal melanomas with an objective response rate of 37.1% [15]. Similarly, patients with mucosal melanoma treated with pembrolizumab had an objective response rate of 23% and median progression-free survival of 3.9 months [16].

Female urethral melanoma is a rare tumor, thus limiting definitive management of this disease. Prognosis is generally poor for patients because of advanced disease upon presentation and rapid metastasis to vagina, vulva, bladder, or pelvic lymph nodes. Moreover, recent data has demonstrated specific criteria, such as the presence of melanotic cells in the peripheral blood and ulceration, to correlate with overall survival [17]. Nevertheless, more studies are required to better develop an optimal surgical and/or medical treatment plan for patients with urethral melanomas.

CONCLUSION

Urethral melanoma is generally managed with surgical intervention. Given the poor prognosis and survival outcomes, more studies are clearly necessary to better develop an optimal management plan for patients with urethral melanomas and the role of immunotherapy in these individuals.

REFERENCES

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Authors declare no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.

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