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Primary Malignant Urethral Melanoma in a Female: A Case Report

Dr Ahmed Salmaan [a] and Dr Haris Kamran [b*]

[a] *Duty Medical Officer, J&S Aesthetic Care Clinic, Islamabad, 44000, Pakistan*
[b] *Psychiatrist, Healing House Drug Rehab, Rawalpindi, 44000, Pakistan*

A B S T R A C T

Primary malignant melanomas of the female genitourinary tract are extremely rare, accounting for less than 1% of all cases, with only 0.2% of all melanomas occurring in the female urethra. The most common site of occurrence is the urethral meatus or the distal third of the urethra. The rarity of the documented cases makes it very difficult to have a standard protocol for the treatment and management of the disease. As in our case, there is no validated adjuvant path for node negative urethral mucosal malignant melanoma.

Keywords: Malignant Melanoma, Female Urethra, Tumor, Primary Melanoma

1. Introduction

Melanomas are malignant tumors of the skin or the mucosa, arising from the melanoblast cells, and therefore, can occur anywhere in the human anatomy (Gupta, Bhatti, Dinda & Singh, 2007) However, primary malignant melanomas of the female genitourinary tract are extremely rare, accounting for less than 1% of all cases, with only 0.2% of all melanomas occurring in the female urethra (Das et al, 2010). Since 1966, only a little over a hundred cases of malignant urethral melanomas in females have been reported in the indeed literature, most of it as case studies, with the first ever reported by Reed in 1896 (Akbas et al, 2010). The lack of literature, hence, leads to a dearth of treatment and management options. Females are more susceptible to this kind of tumor, with a 3:1 ratio in its prevalence in females and males (DiMarco et al, 2004). The range of presentation of age ranges from 32 to 80 years, with the average of 68 years (Oilva et al, 2000).

The most common site of occurrence is the urethral meatus or the distal third of the urethra (Kim et al, 1993). The usual presentations include the presence of the tumor mass, problems in voiding, bleeding, and discharge or spotting (Alvarez et al, 2000). The survival rate depends upon factors such as the extent of the disease, its anatomical localization, early diagnosis, and the size of the lesion (Gillenwater, 2002). Despite best measures, the prognosis is poor, with a 3-year survival rate of only 38% (Gillenwater, 2002).

This case report presents a case of an elderly woman who was diagnosed with a malignant urethral melanoma, and focuses on the presentation, gross histological and histochemical findings, the radiological findings, and the management plan. It also lays importance on further research into this area for better management plans.

2. Case summary

Our subject, a 72-year-old G6P5 Spanish speaking single lady, nutritionist by profession, was referred for the diagnosis of a pea-sized vaginal bulge that she had been noticing sometimes in the shower for the past 5-6 months, since August 2017, ever since she underwent sigmoid colectomy for diverticulitis. A week prior to presenting to the hospital, she had noticed pink tinged discharge/spotting. She denied any other associated symptoms, such as gross hematuria, incontinence or otherwise dysfunctional voiding, dysuria or pain otherwise, and was not bothered cosmetically by the bugle itself. Therefore, she had been ignoring it previously. On examination, there was a 2-3 cm fleshy mass emanating from her urethra, which was initially thought to be a thrombosed urethral caruncle. Nevertheless, she underwent excisional surgery in February of 2018, and the pathology was found to be positive for malignant melanoma with a depth of at least 1.5cm.

The mass was soft, non-tender, and reducible back into the urethra. The patient was advised to use estrogen cream and do sitz baths. The urine as negative with no growth. She stopped using the estrogen cream after about ten days because it caused itching, for which she was instructed to use a steroid cream for 2 weeks. Over the course of time, there was no change in the size or color of the prolapsed tissue.

The patient had always been in excellent health up until now, with no premorbids. Past medical history was non-significant, and past surgical history included hysterectomy and sigmoidectomy for diverticulitis. There was a non-significant social history with no drug abuse or tobacco use. She was allergic only to codeine which caused her nausea. There were no current facility- administered medications prior to the visit. She denied any weight loss,

decreased appetite, low energy, night sweats, or fever. The systemic review was non-significant, with no associated findings in her HEENT, gastrointestinal, cardiac, respiratory, genitourinary, musculoskeletal, neurologic, or psychiatric evaluation. Her lab results were all within normal ranges.

The patient's CT abdomen/pelvis w/ contrast was unremarkable, other than reporting evidence of sigmoidectomy, scattered diverticula in the descending colon, and incidental horseshoe kidney. Opportunistic screening for osteoporosis was performed, showing lumbar vertebral body trabecular CT-attenuation of HU 106, putting her at an increased risk for fragility fractures. CT head without contrast showed no acute pathology, only age appropriate parenchymal, skeletal, and soft tissue findings, and mild cavernous calcifications. MR brain w/wo contrast showed no evidence for metastatic disease, only age related changes. PT PET/CT FDG whole body showed nonspecific hypermetabolic activity within the region of the urethra, and no evidence of metastatic disease. A 1.5 cm coarse calcification in the posterior right lobe of the liver was observed, and was reported dystrophic and of doubtful clinical significance. The Guardant360 (test) did not detect somatic alterations in the circulating cell-free DNA isolated from the patient's blood specimen. It should be noted here that the absence of a detected genomic alteration does not necessarily mean that there would be no clinical benefit of a medication or treatment plan.

Two specimens were sent for pathology during excisional biopsy. The lab reported the specimens as fragments of tan-purple soft tissue measuring 4x1.5x1.1 cm and 1.5x1.5x0.5 cm. They were unoriented and appeared to have surface disruption. They were inked black and then serially sectioned to reveal tan-brown cut surfaces with a lobular architecture. Microscopically, both specimens exhibited a malignant neoplasm composed of large, polygonal cells with large nuclei, nuclear hyperchromasia, and abundant melanin pigment production. Immunoperoxidase studies showed the tumor cells to react with antibodies to HMB45 and Melan-A, but showed no reactivity with S100, cytokeratin AE1/AE3, and smooth muscle actin or desmin. In one specimen, the tumor invaded to a depth of at least 1.5cm, but the complete depth in both the specimens could not be measured as it extended to the deep surface of the specimen. The surface of the masses was covered by a moderate quantity of hyperkeratotic squamous mucosa, and within the masses were a number of periurethral ducts. Both the surface epithelium and the perurethral ducts showed rare foci of pagetoid extension of melanoma cells into the epithelium. The mitotic rate was estimated at 3-5 per mm^2.

The patient was, hence, labeled as a patient of urethral malignant melanoma.

Another suspicious lesion was found on the vagina. The biopsy was taken and sent for pathology.

Due to a dearth of literature on the subject, we had two management options. First was re- excision of the area of lesion on the urethra. The lesion had a deep positive margin. Standard resection would likely have resulted in functional impairment. There would also have been a moderate risk of both local and distant recurrence. The other option was neoadjuvant immune therapy. The rationale was that since mucosal melanoma does respond to immune modulation, if the standard resection is too morbid or there is additional disease (pending biopsy) _as was in our case_ treatment with ipi/nivo can be a consideration. We would not have considered this truly neoadjuvant as the intent was curative and avoiding the need for surgery. If, down the line, there was gross progression, then surgery could be performed at that point. The ipi/nivo regime that was reviewed with the patient was of 4 doses every three weeks and the usual irAEs.

It was decided that the plan would be to complete the evaluation with the pending XRT consult, and once the pathology was back from the vaginal biopsy, the patient would make her final decision regarding immunotherapy vs surgery vs radiation.

3. Discussion

Malignant melanoma arises from the pathological proliferation of melanoblast cells, originating from the neuroectodermal neural crest cells, and differentiating into melanocytes of the skin and the mucosa, particularly the oral, nasal, vulvar mucosa (Gupta, Bhatti, Dinda & Singh, 2007). The incidence of this tumor in skin accounts for the majority of the cases, that is, 81% of the total cases, with only 17% occurring in the mucosa (Das et al, 2010). When it occurs in the mucosa, it is usually in the eyelid and eyeball. Less than 1% of these occur in the female genitourinary tract, with only 0.2% occurring in the urethra (Akbas et al, 2010).

There are several theories trying to explain the histological pathogenesis of this occurrence, such as the metaplasia of squamous and glandular epithelium into pigment-producing cells, and the transformation of the neural crest elements into melanocytes and nevus cells (Chung, Woodruff & Lewis, 1975). When the female urethral tumors are considered, the occurrence of the various tumors with regards to the histological findings in order from the most occurring to the least, is squamous cell carcinoma (60%), transitional cell carcinoma (20%), adenocarcinoma (10%), undifferentiated tumors and sarcomas (8%), and melanoma (2%) (DiMarco et al, 2004). With only a handful of cases of primary malignant urethral melanomas in females, it is interesting to note that DiMarco reported 11 cases from the Mayo Clinic between 1950 and 1999, making it the most extensive work done on this tumor to date (2004).

The ABCDE is a useful guide for the diagnosis of melanoma: Asymmetry, Border irregular, Color irregular with a loss of skin markings, Diameter >0.5 cm, and Elevation irregular (Nakamoto et al, 2007). It should be noted that the tumor should be diagnosed when it is less than 0.5 cm in diameter (Nakamoto et al, 2007). Also, whereas the loss of skin markings is suggestive of melanoma, the converse, thereof, does not exclude it (Nakamoto et al, 2007). The Glassgow seven-point checklist is another useful guide for the diagnosis (Nakamoto et al, 2007). It is crucial to know that about one-fifth of primary malignant urethral melanomas are amelanotic, and grossly, they can be easily confused with a caruncule; therefore, physicians should be very careful while examining to reach the correct diagnosis (Gunther et al, 2012).

There are limited treatment and management options due to a lack of literature and research concerning primary malignant urethral melanomas. Most of the treatment plans follow the treatment options for melanomas in general (Dasgupta, 1969). The principal surgical treatment is by a wide local excision

with sentinel lymph node dissection (Sugiyama, Chan & Kapp, 2008). When there is no evidence of metastasis, another surgical approach could be partial urethrectomy, radical urethrectomy with a continent urinary diversion or even anterior pelvic exenteration with or without vulvectomy (DiMarco et al, 2004). In case of metastasis, or when the tumor size is too large for surgery, there are the options of adjuvant and neoadjuvant immunotherapy with interferon alpha or interferon beta, with or without dacarbazine, vincristine and cyclophosphamide chemotherapy (Bobin et al, 1983). Radical surgery, of course, is contraindicated in these cases (Dasgupta, 1969).

Generally, primary malignant melanomas have a poor prognosis. The urethral melanomas have a tendency to locally invade the vagina and the vulva via the superficial lymphatics, and metastasis by the deep lymphatics to the inguinal lymph nodes and occasionally to distant sites by the haematogenous route (Chung, Woodruff & Lewis, 1975). They also might be tricky to diagnose, resulting in late detection (Bobin et al, 1983). The survival rate depends upon factors such as the extent of the disease, its anatomical localization, early diagnosis, and the size of the lesion (Gillenwater, 2002). Despite best measures, the prognosis is poor, with a 3-year survival rate of only 38% (DiMarco, 2004). There are only six published cases in the indexed journal with an account of disease survival of over 5 years (Kim et al, 1993). The recurrence rate is about 69%, usually in the first postoperative year (DiMarco, 2004). This can be at the level of lymph nodes, in the lungs, or less frequently, in the liver (Dasgupta, 1969). There are no specific tumor markers for mucosal/urethral melanomas, and none of the prognostic factors of the cutaneous melanomas applies (Oliva et al, 2000).

4. Conclusion

Primary urethral malignant melanomas in females are extremely uncommon tumors. The rarity of the documented cases makes it very difficult to have a standard protocol for the treatment and management of the disease. As in our case, there is no validated adjuvant path for node negative urethral mucosal malignant melanoma.

More research is needed to shed some light on the beneficial outcomes of the various treatment modalities. Currently, surgical, radiological, and immunochemical therapies are used in accordance with the general principles of treating malignant melanomas. In our case, we relied heavily on neoadjuvant chemotherapy, but the patient had yet to decide if she wanted to opt for surgical resection.

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