QMJ
A peer reviewed journal
QATAR MEDICAL JOURNAL

RESEARCH ARTICLE

Primary amelanotic melanoma of the male urethra: A rare entity and diagnostic challenge

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http://dx.doi.org/10.5339/qmj.2020.11
Submitted: 14 June 2019
Accepted: 1 December 2019

Cite this article as: Zeighami S, Soltani M, Khajeh F, Ariafar A, Jahanabadi Z, Miladpour B, Naghdi-sede N. Primary amelanotic melanoma of the male urethra: A rare entity and diagnostic challenge, Qatar Medical Journal 2020:11 http://dx.doi.org/10.5339/qmj.2020.11

كيوسايتس
QSCIENCE
دار جامعة حمد بن خليفة للنشر
HAMAD BIN KHALIFA UNIVERSITY PRESS

ABSTRACT

Malignant melanoma (melanoma) is a tumor of melanocytes that usually presents as cutaneous lesions. While melanoma can infrequently appear as a primary tumor elsewhere in the body, it is extremely rare in the urethra and even rarer as amelanotic malignant melanoma. We report the case of a 66-year-old male who presented with painless gross hematuria and lower urinary tract obstructive symptoms in the recent 2 weeks prior to his visit to our clinic. History and physical examination, including external genital examination, abdominopelvic sonography, and urine culture, were not conclusive. Cystourethroscopy revealed a creamy pink fragile mass located in the anterior proximal urethra that extended to the mid portion. Pathological examination of this lesion confirmed the diagnosis of amelanotic malignant melanoma using immunohistochemistry. Radical cystourethrectomy with ileal conduit was subsequently conducted. Although this tumor is extremely rare, urologists and pathologists should consider malignant melanoma as a diagnosis in patients with urethral tumor because of the likelihood of early metastasis and, consequently, poor prognosis. Complete surgical removal of the tumor and use of effective therapies can improve outcomes in these patients.

Keywords: malignant melanoma, melanoma, urethra, amelanotic, male urethra

BACKGROUND

Malignant melanoma, also known simply as melanoma, is a neoplasm of pigment-producing cells known as melanocytes. The tumor is mainly diagnosed as a cutaneous lesion and found most commonly on the back, legs, and arms. While

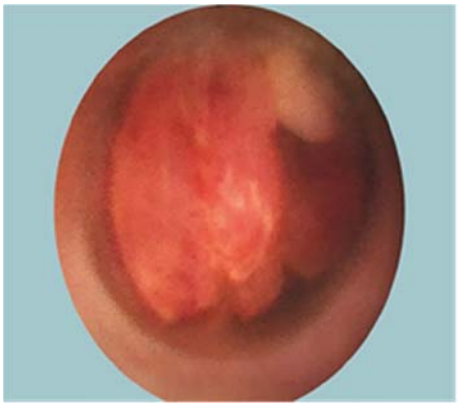

Figure 1. Urethral amelanotic melanoma, cystoscopy photo.

melanoma of the urethra is an extremely rare tumor, amelanotic melanoma is an even rarer entity.[1,2] Early diagnosis and use of effective therapies after tumor removal can remarkably improve patient outcomes.

CASE PRESENTATION

A 66-year-old male was referred to our clinic; the patient complained of painless gross hematuria and severe lower urinary tract obstructive symptoms in the recent 2 weeks prior to his visit. The results of penile, scrotal, and inguinal region examination were normal. Sonography of the abdomen and pelvis was inconclusive. No evidence of urinary tract infection was seen in urinalysis and urine microbial culture.

Cystourethroscopy revealed a creamy pink fragile mass measuring 5 cm × 0.7 cm × 0.5 cm located in the anterior part of the proximal urethra extending to the middle portion and causing severe luminal stenosis. No other abnormality was seen within the bladder. Transurethral biopsy of the mass lesion was conducted, and the specimen was sent to the pathology laboratory (Figure 1).

After the primary diagnosis of melanoma, we performed thoracic and abdominopelvic computed tomography scanning, which did not reveal any sign of metastasis. Considering the rarity of urethral malignant melanomas, especially the amelanotic variant, we examined the patient thoroughly and found no other lesion. The patient had no past history of skin lesion or biopsy elsewhere in the body. Thus, we confirmed the diagnosis of primary melanoma of the urethra. Radical cystourethrectomy with ileal conduit was carried out, and the specimen was sent to the pathology ward. The patient was also administered immunotherapy of 240 mg of nivolumab

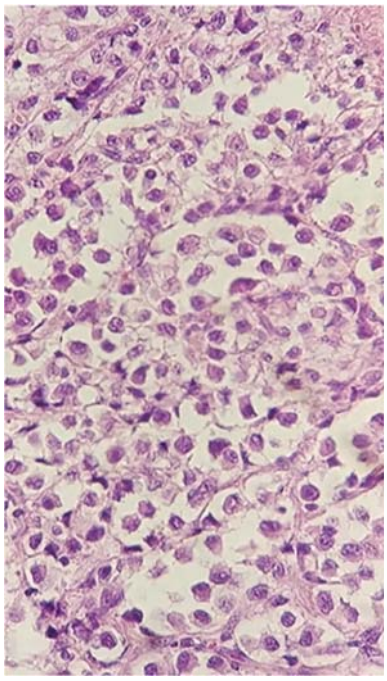

Figure 2. Urethral amelanotic melanoma: note nesting pattern, clear cytoplasm and small oval nucleus with mild atypia and inconspicuous nucleolus, H&E staining ×100.

once every 2 weeks. We noted no issues at the patient's 6-month follow-up. However, the patient progressed to metastatic lesions despite receiving standard systemic treatment and expired due to progressive disease 18 months later.

Microscopically, the tumor resembled a urothelial carcinoma but showed a dominant nesting pattern. Individual tumor cells had a clear halo cytoplasm and ovoid, small, and uniform nucleus with an inconspicuous nucleolus. Mitosis was rarely seen, but cellular atypia was not evident.

Necrosis was present focally. No melanin pigment was seen. The histological image suggested possible malignant tumors, including malignant melanoma and urothelial carcinoma (Figure 2). Finally, immunohistochemistry (IHC) confirmed the diagnosis of malignant melanoma (Figure 3).

DISCUSSION AND CONCLUSION

Non-urothelial malignant neoplasms of the urinary tract are very uncommon. Malignant melanomas of the urinary tract and urethra respectively constitute 1% and 0.2% of all melanoma cases.[1–3] Melanoma of the urethra is three times more common in females than in males.[4,5] Amelanotic melanoma makes up approximately 20% of all melanoma cases. Diagnosis

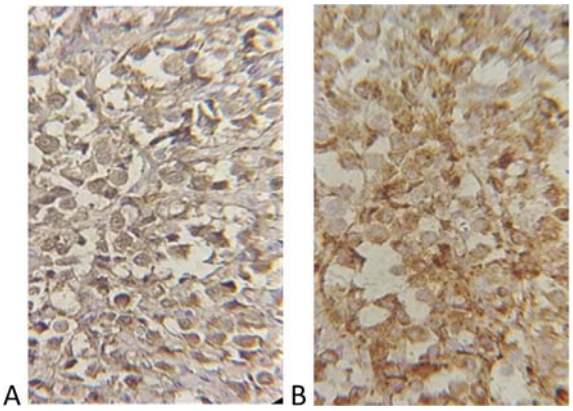

Figure 3. Positive tumoral cells for HMB-45(A) and S-100(B) Antigen in melanoma, IHC staining.

of urethral melanoma is usually delayed until a later stage or may be missed entirely because of the rarity of the disease and its similarity of clinical presentation to other tumors of the urinary tract.[6] Patients with urethral melanoma usually present with hematuria, dysuria, and voiding dysfunction. Rapid tumor growth, surface ulceration, and necrotic foci are common. Lesions can cause urethral lumen stenosis and even obstruction. Among these presentations, hematuria is the most common. Melanuria, which is defined as a dark brown or black pigment in the urine and the dark blue, brown, or black pigmentation of the tumor itself, may provide diagnostic clues in some patients.[6,7] However, melanuria is not a common finding; indeed, some melanomas are amelanotic, such as in our case. The difficulty of early diagnosis and rapid vertical tumor growth may place patients in a higher stage group with poorer prognosis at the time of diagnosis compared with patients with cutaneous melanoma.[8]

The pathologist plays an important role in the diagnosis of primary melanoma, especially amelanotic ones. The histopathologic pattern of melanoma ranges from diffuse to nesting, fascicular, storiform, or pleomorphic. While the presence of a prominent eosinophilic nucleolus may be adequate to obtain a diagnosis in some cases, the most valuable and common tool for diagnosis is IHC staining. We used two markers, namely, S-100 antigen and human melanocyte black-45 antigen (HMB-45 Ag), to diagnose the patient. S-100 antigen is a sensitive, whereas HMB-45 Ag is a specific marker for melanocyte differentiation.[9]

The first case of urethral melanoma was reported by Reed et al. as primary urethral melanocytic sarcoma in 1896.[10] In our case, although the tumor was amelanotic, we were able to diagnose melanoma versus other common urothelial tumors accurately using the characteristics below.

1. Nesting pattern in melanoma versus papillary pattern in urothelial tumors
2. Clear cytoplasm in melanoma versus amphophilic cytoplasm in urothelial tumors
3. Small oval basophilic nucleus in melanoma versus elongated oval nucleus with an occasional longitudinal groove in urothelial tumors
4. High mitotic rate despite the absence of other morphological features of high-grade urothelial tumors, such as severe cellular atypia and pleomorphism.

The diagnosis of melanoma should be tested using IHC markers to confirm the microscopic suggestion of melanocytic differentiation. To date, only Nakamoto et al.[11] has reported one case of amelanotic melanoma of the female urethra that was also confirmed by IHC.

Survival of melanoma depends on the tumor stage, location, and size at the time of diagnosis. The American TNM staging system of the American Joint Committee on Cancer (AJCC) provides useful and practical staging guidelines for this tumor.[12]

Because of the rarity of primary urethral melanoma, no common consensus for its treatment is yet available. Most authors recommend complete tumor removal and even radical surgery when no evidence of metastasis is present. Some authors do not recommend, and even discourage, lymph node dissection in the case of inguinal lymph node metastasis.[12] We cannot draw definitive conclusions regarding the optimal treatment approach because of the limited number of patients. Radical surgical resection with postoperative adjuvant chemotherapy or immunotherapy is recommended, but the existing clinical experience supporting adjuvant treatment is limited. Different regimens of adjuvant immunotherapy with interferon alpha or interferon beta have been described, including nivolumab with or without dacarbazine chemotherapy; however, reports have recommended combination chemotherapy with cisplatin, vinblastine, and bleomycin, which is possibly associated with a better response than single-agent dacarbazine[12]. In the present case, radical cystourethrectomy was performed followed by adjuvant immunotherapy with nivolumab. The patient

remained well at his 6-month follow-up but progressed to metastatic lesions despite receiving standard systemic treatment. The patient expired due to progressive disease 18 months later.

In conclusion, improved awareness of urethral melanoma could result in earlier diagnosis. An early diagnosis allows urologists and oncologists to develop optimal treatment plans featuring effective advanced-modality treatment options and procedures to achieve favorable outcomes. We believe that outcomes may be improved by considering the diagnostic characteristics of suspected tumors described above and IHC markers.

LIST OF ABBREVIATIONS

IHC, Immunohistochemistry; HMB-45 Ag, Human melanocyte black-45 antigen; AJCC, American Joint Committee on Cancer

DECLARATIONS

Ethical approval and consent to participate

Ethical approval relevant to our case report was not necessary. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Consent for publication

A copy of the written consent provided by the patient for publication of the necessary data, images, and/or videos is available for review by the Editor-in-Chief of this journal.

Availability of data and materials

All of the data and materials are available in our clinic and laboratory.

Conflict of interests

The authors declare that they have no competing interests.

Funding

The authors declare that they have not received any funding for this work.

Authorship contributions

All of the authors contributed to the writing of this report. Dr. SH. Zeighami, Dr. Z. Jahanabadi, Dr. A. Ariafar, and Dr. MR. Soltani collected the data and visited the patient. Dr. SH. Zeighami was the main surgeon responsible for all operations and clinical management of the patient. Dr. F. Khajeh was the pathologist and diagnosed the case. Dr. B. Miladpour assisted in the diagnosis and design of the patient's IHC profile. All authors have read and approve of the final manuscript.

Acknowledgment

We are grateful to Prof. A. Safaei and the staff of the molecular pathology laboratory of Faghihi Hospital for their professional help in the IHC study of this case.

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