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Primary melanoma of the bladder: a case report and review of the literature

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Abstract. – OBJECTIVE: Primary bladder melanomas are rare and aggressive neoplasms. We herein described a new case and performed a review of the literature.

PATIENTS AND METHODS: We present the case of a 81-year-old woman with a primary mucosal melanoma of the bladder after a history of acral melanoma (KRAS mutated) and lentigo maligna of the forehead. Using PubMed, we found that in literature 38 cases were described.

RESULTS: In our patients, during a transurethral resection (TURBT), two bladder lesions were detected. The histologic exam revealed a malignant melanoma, Mib1/ki67: 10-12%, PDL1 <1%. No BRAF, NRAS or KRAS mutations were detected. She subsequently underwent a transurethral revision of the trigone and a partial cystectomy of the dome with bilateral pelvic lymph node dissection. Microscopical findings showed a residual 5 mm non-muscle-invasive melanoma of the bladder, with negativity of the surgical margins and of the 17 pelvic lymph nodes. No adjuvant treatment was proposed. To date the patient is disease-free.

CONCLUSIONS: Primary bladder melanoma carries a poor prognosis and poses a therapeutic challenge to clinicians who manage patients with this rare condition. In our experience the multidisciplinary approach for the diagnosis and management of this rare cancer is mandatory.

Key Words:
Bladder cancer, KRAS mutation, Melanoma, Molecular status, Prognosis.

Introduction

Primary mucosal melanoma includes, in order of frequency, head and neck, anorectal, vulvovaginal and urinary tract melanomas[1,2]. Mucosal melanomas are rare conditions associated with a poorer prognosis than cutaneous presentations with a 5-year Overall Survival (OS) of 34% and 89%, respectively[3]. Penis and urethra, are the most common sites of primary melanoma localization in the male urogenital tract, while prostate, ureter, renal pelvis and urinary bladder are usually affected by secondary disease[4]. Melanomas arise from melanocytes that are pigmented dendritic-like cells located in various anatomic sites, as the base of epidermis, eye, epithelia of the nasal cavity, oropharynx, anus, vagina and urinary tract[5]. While the role of skin and eye melanocytes is the well-known protection against UV radiations, in the mucosa they seem to have antimicrobial and immunological roles[6].

Primary malignant melanoma of the bladder is an extremely rare condition representing the 0.2% of all melanomas. The median age at diagnosis is 61 years (range 34-84)[5].

The histogenesis of malignant melanoma in the urinary tract, and especially in the bladder, is still unclear[7].Two hypotheses are the most accredited. The first one supposes that, during the embryogenesis, melanoblasts migrating from neural cusps into mesenchyme may localize in the urinary tract, as ectopic tissue. These cells remain inactive for a long time and may transform into malignant cells under the influence of local factors. The second hypothesis supports the idea that urothelial cells deriving from stem cells may differentiate in neoplastic melanocytes.

The etiology and risk factors are unknown and the lack of association with UV radiations is the

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most important factor that differentiates this tumor from cutaneous melanoma. The great majority of bladder melanomas consist in metastases, not in primary neoplastic forms.

The updated recommendations on locoregional and metastatic melanoma have been recently published; nevertheless, no indications on acral/rare melanomas are specified[8,9].

We herein present the case of a 81-year-old woman treated at our centre for primary bladder melanoma. Full informed consent was obtained from the patient. Using PubMed, a review of the literature was also performed.

Case Report

The patient suffered from blood hypertension and presented a family history of melanoma (mother). In December 2009, she removed a nailbed lesion of the second finger of the right hand. The histologic exam described "a nodular melanoma, with epithelial and spindle, poorly pigmented cells, in radial and vertical growth phase, with extension to the deep dermis, maximum thickness of 5 mm, 3 mitoses/mm^2, level of Clark IV (Figure 1A)". She subsequently underwent a surgical radicalization and a sentinel lymph node biopsy. The histological specimens revealed a nodal metastasis that led to a subsequent right axillary lymphadenectomy (the 7 lymph nodes removed were negative for metastasis). Considering the absence of distant metastasis evaluated by CT-scan, the final pathological stage was pT4bpN1pM0 (stage IIIB according to the 8th Edition of the American Joint Committee on Cancer). No *BRAF* or *NRAS* mutations were reported, while a mutation in the *KRAS* gene (*A146X*) was shown. After a tumor board discussion, adjuvant therapy with interferon-alpha was performed for a total of two years. After the completion of adjuvant treatment periodic follow-up was started.

In June 2016 a pigmented skin lesion on the forehead was excised. The histological exam diagnosed "*lentigo maligna"* (Tis) (Figure 1B). After radicalization, no mutation of *BRAF, NRAS* or *KRAS* were reported.

During periodic follow-up, in December 2019, an abdominal ultrasound revealed a centimetric bladder lesion. The subsequent cystoscopy showed two lesions: the bigger of the dome and the smaller of the bladder trigone (possible expression of seeding from the major lesion).

In January 2020 the patient underwent a transurethral resection (TURBT) of the two bladder lesions, which were separately collected. The endoscopic appearance was of high-grade solid bladder cancer without melanocytic aspect. The histologic exam described a malignant melanoma (Figure 2A), MART-1/Melan A+ (Figure 2B), SOX 10+ (Figure 2C) with muscular involvement in the dome and superficial features in the trigone. PDL1 expression was negative and the proliferation index, evaluated with Mib1/Ki67, was 10-12%. The molecular exam did not reveal *BRAF, NRAS* or *KRAS* mutations.

No evidence of metastatic disease was observed on a following whole-body CT scan. Moreover, a dilated eye exam and a dermatological evaluation didn't reveal pathological findings. Considering the location and the pathological characteristics of the bladder tumors, a transurethral revision of the trigone and an open partial cystectomy of the dome with bilateral pelvic lymph node dissection was performed. The histological findings showed a 5-mm residual malignant melanoma superficially involving the urothelium of the bladder dome. No residual disease was identified in the trigone, thus confirming the initial impression of seeding from the major bladder lesion.

All surgical margins were negative, as well as the 17 pelvic lymph nodes removed.

Considering the triple malignant melanomas and the family history for melanoma, genetic counseling with a serological evaluation of *CDKN2A* and *CDK4* genes was performed with no mutations revealed. Imaging and endoscopic follow-up at 14 months did not show evidence of local or distant recurrence of the disease.

Discussion

Primary bladder melanomas are an extremely rare malignancy, with only 38 cases reported in literature (Table I) with 81% of patients over 50 years old[4,5,10-38]. Twenty-two of the 38 reported patients were male and the median age at diagnosis was 61 years (range, 7-87). The clinical outcome of patients with primary bladder melanoma is very poor and two-thirds of cases develop a metastatic neoplasm within 3 years from diagnosis. Prognostic features include type of melanoma, stage and mitotic rate[3]

The pathogenesis is largely unknown and defining whether a bladder melanoma is a primary or a secondary tumor is still a challenge.

Considering the non-specific presentation symptoms (mainly haematuria), the diagnosis is

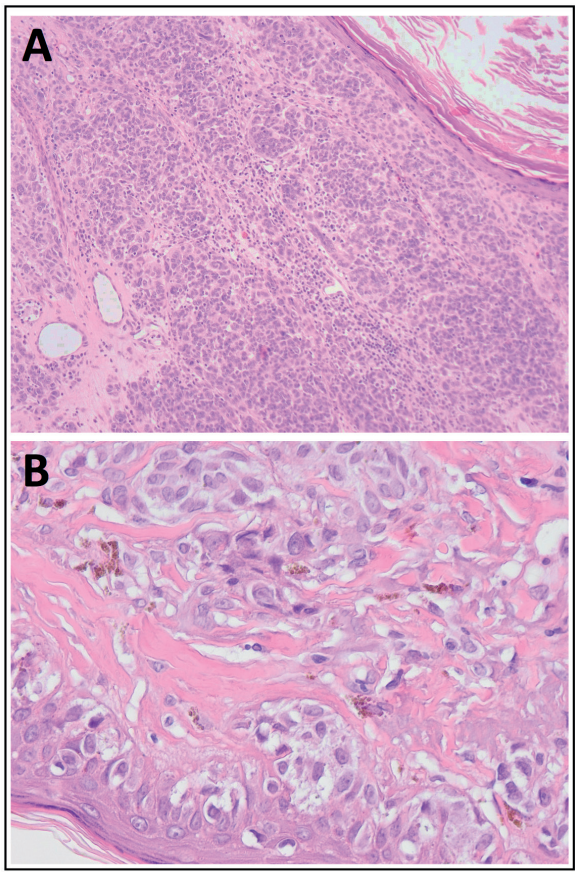

Figure 1. A, Histologic image of the nailbed nodular melanoma composed of epithelial and spindle, poorly pigmented cells (haematoxylin-eosin staining; original magnification: X100). **B,** Histologic image of the forehead *lentigo maligna* characterized by nests of atypical melanocytes and rare cytoplasmic retraction (haematoxylin-eosin staining; original magnification: X200).

based on endoscopic examination and biopsy. All doubt bladder lesions should be biopsied.

There are no established guidelines for the treatment of this disease and therapeutic approach is based on data concerning bladder cancers and cutaneous melanomas. If feasible, surgery (transurethral resection, partial or radical cystectomy) is the cornerstone for organ-confined tumors to obtain free margins with a lymph nodal assessment. Radiotherapy, immunotherapy, target therapy, chemotherapy represent different possible approaches in the therapeutic armamentarium. Compared to other localization of mucosal melanomas, there are no data on the feasibility and effectiveness of hadrontherapy[39].

The patient's overall health status and life expectancy are important aspects to be considered when defining the appropriate treatment for each case.

From a pathological point of view, the differential diagnosis includes other primary neoplasms of the bladder, as urothelial carcinoma, sarcomatoid carcinoma and sarcomas. The presence of intramucosal atypical melanocytes is mandatory to confirm the primary bladder origin[39]. The mu-

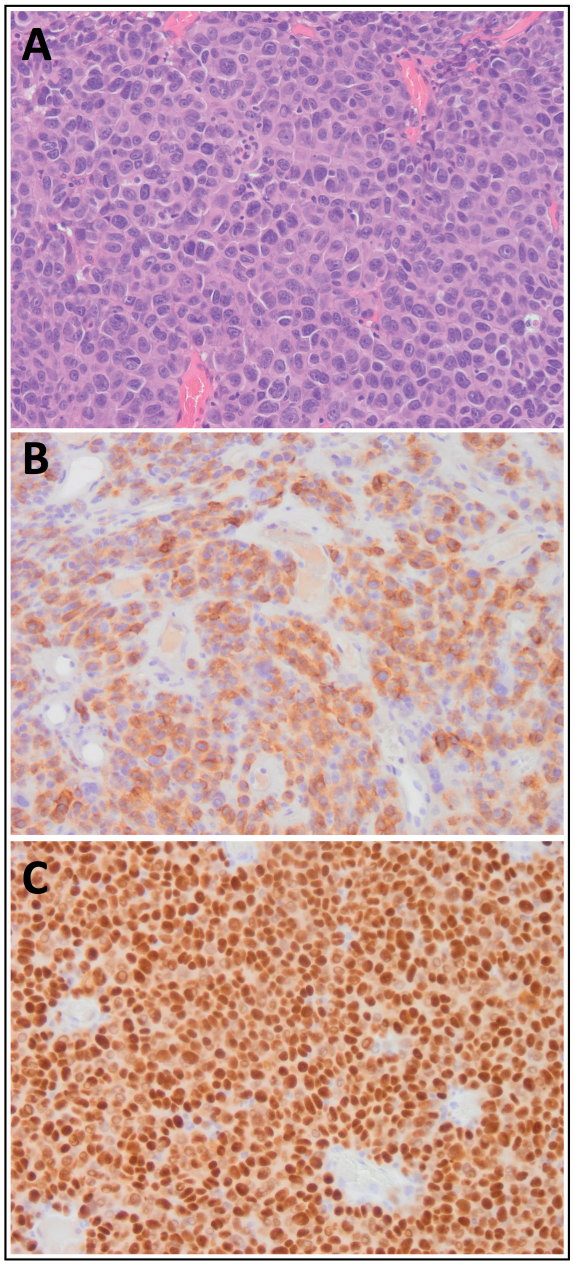

Figure 2. A, Histologic image of the melanoma of the bladder dome composed of highly atypical and pleomorphic epithelioid cells with prominent nucleoli (haematoxylin-eosin staining; original magnification: X200). Note the diffuse cytoplasmic MART-1/Melan A+. **B,** MART-1 immunostaining, original magnification: X200) and nuclear SOX-10. **C,** SOX-10 immunostaining; original magnification: X200) immunoreactivity of the bladder melanoma cells.

Table I. Cases of primary melanoma of the bladder published in literature.

Author, [ref]	Age at diagnosis (years)	Sex	Treatment	Follow-up (months)	Outcome
Su et al[11]	61	F	None	2	Died
Ainsworth et al[12]	65	F	RC	17	Alive
Willis et al[13]	57	F	RC	36	Died
Anichkov et al[14]	48	M	PC	12	Died
Anichkov et al[14]	46	M	RC	3	Alive
Ironside et al[15]	56	M	None	8	Died
Goldschmidt et al[16]	53	F	PC	7	Died
Goldschmidt et al[16]	56	F	None	6	Alive
Philippe et al[17]	77	M	TURB	n.r.	n.r.
Van Ahlen et al[18]	81	M	RC, RT, INN	24	Died
Lund et al[19]	81	F	Local excision, RT, CT	15	Alive
Kojima et al[20]	63	F	CT	18	Died
Lenge-Welker et al[21]	75	M	PC	3	Died
Mourad et al[22]	34	M	RC	12	Alive
Niederberger et al[23]	53	M	RC	18	Alive
De Torres et al[24]	44	M	RC	14	Died
Tainio et al[25]	52	M	TURB	8	Died
Garcia Montes et al[26]	44	F	TURB	144	Alive
Khalbuss et al[27]	82	F	RT, RC	16	Alive
Hsu T. and Hsu Y[28]	73	M	TURB, BCG, Re-TURB	16	Alive
Baudet et al[29]	7	F	PC	84	Alive
Pacella et al[30]	82	M	TURB	9	Died
Sundersingh et al[31]	56	M	RC	10	Alive
El Ammari et al[32]	71	M	TURB	5	Died
Truong et al[33]	84	F	TURB + ipilimumab	n.r.	n.r.
Sayar et al[7]	70	M	TURB	30	Died
Karabulut et al[34]	52	M	RC, LND	60	Alive
Karabulut et al[34]	63	F	RC, LND, vemurafenib	12	Alive
Karabulut et al[34]	76	F	TURB, vemurafenib	15	Alive
Karabulut et al[34]	54	M	TURB	4	Died
Karabulut et al[34]	70	M	Refused treatment	32	Died
Otto et al[35]	52	M	TURB, INN/CT	18	Died
Burela et al[36]	53	F	TURB	9	Died
Barillaro et al[10]	72	M	RC, nivolumab	16	Alive
Chaus et al[37]	27	F	PC, LND, pembrolizumab	24	Alive
Bumbu et al[4]	80	M	TURB, CT	6	Died
Kirigin et al[5]	87	F	TURB	n.r.	Died
Rapisarda et al[38]	74	M	TURB, BCG	6	Alive

Abbreviations: BCG: intravesical Bacillus Calmette-Guerin; CT: chemotherapy; F: female; INN: interferon-alpha; LND: Lymph node dissection; n.r., M: male; not reported; PC: partial cystectomy; RC: radical cystectomy; RT: radiotherapy; TURB, trans-urethral resection of the bladder.

cosal melanoma is characterized by nests of large epithelioid pleomorphic cells with rare spindle cell morphology; macronuclei and prominent nucleoli, as well as intranuclear inclusion are typical microscopical features[39,40]. The surrounding stroma is desmoplastic and usually characterized by melanophage aggregation. Immunohistochemical is mandatory for diagnosis.

S100 and SYR-box10 are the most sensitive but not really specific immunohistochemical markers[41]. MART-1, MITF and/or HMB-45 are used since their higher specificity and adequate sensitivity[6]. In our clinical case the histologic exam revealed a malignant melanoma with MART-1/Melan A+ and SOX 10+.

The absence of an history of ocular or visceral melanoma and the presence of atypical melanocytes at the margins of the tumor are reported criteria for defining bladder melanoma as a primary disease[12]. Regarding the molecular profile, mucosal melanoma is a distinct subtype that is subjected to different selective pressures than cutaneous melanoma during melanomagenesis[42]. *BRAF* mutations are often reported in cutaneous melanoma, while in mucosal melanomas, c-*KIT*, *NF1* or *RAS* mutations[43] are more frequent. In par-

ticular, *RAS* alterations, consisting of *NRAS* and *KRAS* mutations, are the second most frequent mutation type. *KRAS* mutation is an infrequent event identified in only 1.7% of melanomas, representing an early event in carcinogenesis[44]. On the other hand, *in situ* melanoma lesions are rarely characterized by molecular gene alterations. Molecular analyses are warranted also in uro-genital melanomas to drive the use of target agents that should be evaluated in patients with advanced and/or metastatic tumors.

In this case, considering: i) time from the first diagnosis (10 years); ii) results of the restaging exams, which resulted negative for distant metastasis, iii) absence of pelvic lymph nodes involvement, and iv) presence of a different molecular profile compared to the previous tumors, we concluded for a primary melanoma of the bladder. Considering the final histological exam, after a multidisciplinary discussion, no adjuvant treatment was prescribed and the patient started a clinical and instrumental follow-up. To date, 14 months after the diagnosis, the patient is alive and disease-free. She does not have urinary symptoms and the preservation of urinary bladder guarantees an excellent quality of life.

Conclusions

Primary bladder melanoma carries a poor prognosis and poses a therapeutic challenge to clinicians who manage patients with this rare disease. A multidisciplinary evaluation of the cases with urologists, medical and radiation oncologists, dermatologists, ophthalmologists, pathologists and radiologists should be performed to allow a correct diagnosis, a customized therapeutic approach and a proper follow-up. As shown in the presented clinical case, the integration of molecular profile with histological features may be crucial for diagnosis. Considering that mucosal melanoma may hide mutations in molecular pathways under investigation for target therapy, molecular analysis should be performed and patients should be encouraged to participate in clinical trials.

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Conflict of Interest
The Authors declare that they have no conflict of interests.

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