

Primary malignant melanoma of the bladder collides with high-grade non-invasive urothelial papillary carcinoma: A case report

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Abstract. The present study reported a case of primary malignant melanoma of the bladder colliding with high-grade non-invasive urothelial papillary carcinoma with clinical, pathologic and immunohistochemical analysis, and reviewed the relevant literature. A 74-year-old male presented with hematuria; B ultrasound and computed tomography revealed a solid mass in the bladder and transurethral resection of the bladder lesion was performed. Microscopically, the tumors were composed of morphologically diverse malignant melanomas (95%) and high-grade non-invasive urothelial papillary carcinoma (5%), with no closely related or transitional regions. Immunohistochemistry indicated that malignant melanoma cells expressed HMB45, Melan-A and S-100, whereas they did not express any epithelial markers. The urothelial carcinomas expressed broad-spectrum cytokeratin and GATA3, and were negative for melanoma markers. The diagnosis of collision tumor between primary malignant melanoma of bladder and high-grade non-invasive urothelial papillary carcinoma depends on clinical and pathological examinations; this pathology is prone to recurrence and metastasis and has a poor prognosis.

Introduction

Urothelial carcinoma is the most common type of malignant tumor of the bladder, but collision tumors of the bladder are rare; they may include urothelial carcinoma and squamous carcinoma collision, urothelial carcinoma and small cell

carcinoma collision, and urothelial carcinoma and lymphoma collision (1-3). Certain studies have reported on primary malignant melanoma of the bladder (4-7), but to the best of our knowledge, there has been no previous report of collision between malignant melanoma of the bladder and high-grade non-invasive urothelial papillary carcinoma. The clinical manifestations of collision tumor of the bladder include gross hematuria, urinary tract irritation symptoms, dysuria and urinary tract infection (1). Ultrasonography, CT and cystoscopy may be used to reveal space-occupying lesions in the bladder. Pathology may indicate different histological morphology and immunohistochemical expression results. Among them, malignant melanoma of the bladder is composed of diffuse infiltrating heterotypes of cells, such as large cell epithelioid, small cell, spindle, clear cell, rhabdoid or mixed type (4-6). The cytoplasm mostly contains obvious pigmentation, while certain cases may have no pigmentation. Urothelial carcinoma may feature high- or low-grade changes. Immunohistochemistry may indicate that S-100, Melan-A and HMB45 are expressed in melanomas. Urothelial carcinoma expresses cytokeratin (CK)pan and GATA3. In the present study, a case of primary malignant melanoma of the bladder colliding with high-grade non-invasive urothelial papillary carcinoma was reported. The clinicopathological characteristics, immunohistochemistry and treatment prognosis were provided.

Case report

A 74-year-old male patient was admitted to the First People's Hospital in Xiaoshan District (Hangzhou, China) in May 2018 due to 'gross hematuria for 3 months and aggravation for 1 week'. The patient reported to have intermittent gross hematuria without any obvious inducement for 3 months and the hematuria had aggravated significantly in the past week, occasionally accompanied by blood clots, but there was no obvious increased frequency of urination, pain or fever when urinating. There was no history of malignant melanoma or cellular nevus in the skin or mucous membranes of other organs, including the penis and urethra. B ultrasound indicated a substantial mass in the bladder with a size of 3.1x2.4x2.1 cm; the blood flow signal was rich and the prostate was enlarged with intense light spots. Contrast-enhanced urological CT indicated focal thickening of

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the left posterior wall of the bladder and a cauliflower-shaped soft-tissue density shadow protrusive into the bladder was observed. On the contrast-enhanced scan, the lesion was mild to moderately enhanced, with space-occupying lesions in the bladder, which was considered bladder cancer. At three days after the first presentation, electrosurgical transurethral resection of bladder injury was performed and cauterization was used to stop the bleeding. During the operation, the cauliflower-shaped tumor was found 1 cm lateral to the left ureteral opening in the bladder, with a scope of ~3.0x2.0x2.0 cm, which was locally solid and broad, and the tumor easily bled when touched.

Gross pathological examination indicated a mass of gray and white broken tissue with a volume of 3.0x2.0x2.0 cm. Certain sections had a solid structure with a medium-firm texture, accompanied by clots. The tissue was fixed in 4% neutral formalin (24 h at 25°C) and embedded in paraffin, and 4- μ m serial sections were prepared and subjected to hematoxylin-eosin staining (according to a standard protocol) and Envision immunohistochemical staining (Beijing Jinqiao Zhongshan Biological Co. Ltd.) according to the standard protocol, as well as fluorescence quantitative PCR assay.

At low magnification, the tumor was observed to consist of two components with no tightly linked or translocated regions (Fig. 1A). At high magnification, one of the major tumor components was solid and had lamellar structures. The tumor cells were medium in size and round or oval in shape, with obvious atypia. Most had a small amount of cytoplasm, a high nucleoplasmic ratio, hyperchromatic nuclei and mitosis was obvious. In certain cells of different sizes, the nuclei were signet-ring cell-like and the cytoplasm had red staining. Pigmentation was present in the focal area, clear cytoplasm was observed in the cell and a small number of scattered aberrant multinucleated giant cells were present, accompanied by a small amount of necrotic cells. There were obvious apoptotic bodies in the region, thin-walled or fibrous vessels in the interstitium, and tumor infiltration into the muscularis propria (Fig. 1B-F). A small fraction of the tumors exhibited a typical noninvasive high-grade papillary urothelial carcinoma structure (Fig. 1G), with a papillary fibrous vascular axis covered by multiple layers of urothelial cells with atypia, nucleoli and mitotic figures. Focally, urothelial carcinoma *in situ* was observed (Fig. 1H).

Immunohistochemistry performed with reagents purchased from Beijing Jinqiao Zhongshan Biological Co. Ltd. (pre-diluted working solutions unless otherwise indicated) indicated the following: Mesenchymal tumor cells: HMB45+ (cat. no. 21065615), Melan-A+ (cat. no. 2106160275b), S-100+ (cat. no. 2012240585C8) (Fig. 2A-C), CD56+ (cat. no. 21082702), Ki-67 positive index, 60% (1:200 dilution; cat. no. 21030436), CKpan- (cat. no. 21061509), leukocyte common antigen- (cat. no. 0385), Desmin- (cat. no. 20092713), P504S- (cat. no. 2101200546 a), synaptophysin- (cat. no. 2105130742 c), Chromogranin A- (cat. no. 21060816); urothelial carcinoma: CKpan+ (cat. no. 21061509), CK20+ (cat. no. 20083095), GATA3+ (cat. no. 19122616). DAB staining solution (polymer method; KIT-0014; Beijing Jinqiao Zhongshan Biological Co. Ltd.) was applied at 25°C for 20 min.

The fluorescence quantitative PCR assay performed by Shanghai Keyi Lianchuang Medical Laboratory, Co., Ltd. according to a standard protocol indicated that BRAF V600E was negative (V600E forward primer, 5'-GGACCCACTCCA

TCGAGATTACT-3' and reverse primer, 5'-TGTTTTCCCTTTA CTTACTACACCTCAGA-3'; the probe: FAM-5'-CTGTGAGGTCTTCATGAA-3'-MGB).

The pathological diagnosis was as follows: Primary malignant melanoma of bladder colliding with high-grade non-invasive urothelial papillary carcinoma; malignant melanoma involving muscularis. The patient underwent total cystectomy at an external hospital without any chemotherapy, immunization or gene therapy. The patient died of systemic metastasis 31 months after the first operation.

Discussion

Collision tumors are rare neoplasms consisting of two or more distinct cell populations that maintain clear boundaries. They may be composed of two benign tumors, one benign and one malignant tumor or two malignant tumors (8). The collision of urothelial carcinoma with squamous cell carcinoma or adenocarcinoma is relatively common in literature reports, including reports of urothelial carcinoma with small cell carcinoma or lymphoma (1-3). Among them, malignant melanoma occurring in the bladder is also rare (4-7), accounting for <1% of primary melanoma. The present study reported, for the first time, a case of collision tumor between malignant melanoma of the bladder and urothelial carcinoma, and reviewed the literature in order to deepen the understanding of this disease.

The pathogenesis of bladder collision tumor may be the result of a variety of pathogenic factors, which have been reported to include chronic stimulation, smoking and germline radiotherapy (1). Regarding their histogenesis, scholars have proposed that the reasonable explanation is pluripotent stem cells derived from normal urothelium (9), which also explains the presence of melanoma and urothelial carcinoma components in the current case. Histological origins of bladder malignant melanomas are thought to be melanocyte remnants, agrophilic cells in normal urothelium or metaplasia of urothelium (10). At the same time, detailed general examination and review of the patient's history are required to exclude metastasis of malignant melanoma in the skin and other parts of the internal organs. The diagnosis of primary collision bladder tumor (malignant melanoma and urothelial carcinoma) was established after the exclusion of systemic pigmentotic lesions in the present case.

The clinical manifestations include gross hematuria, urinary tract irritation symptoms, dysuria and urinary tract infection (1). Imaging examinations such as B-mode ultrasound and CT may indicate space-occupying lesions in the bladder, as well as the presence or absence of invasive changes outside the bladder. Cystoscopy may indicate single or multiple lesions, a broad-based cauliflower-shaped mass, papillary or microprotuberant structures and invasive growth. Non-invasive urine cytology may reveal the presence of tumor cells and a definite diagnosis may be made only when combined with certain immunohistochemistry features (11). The pathological characteristics of bladder collision tumor are different histological morphology and immunohistochemical expression results according to different components. Among them, bladder malignant melanoma is composed of diffuse infiltrating malignant tumor cells, such as large cell epithelioid, small cell, spindle, clear cell, rhabdoid or mixed type (4-6). Most of them contain obvious pigment in the cytoplasm, while certain cases have no pigmentation. Cell atypia

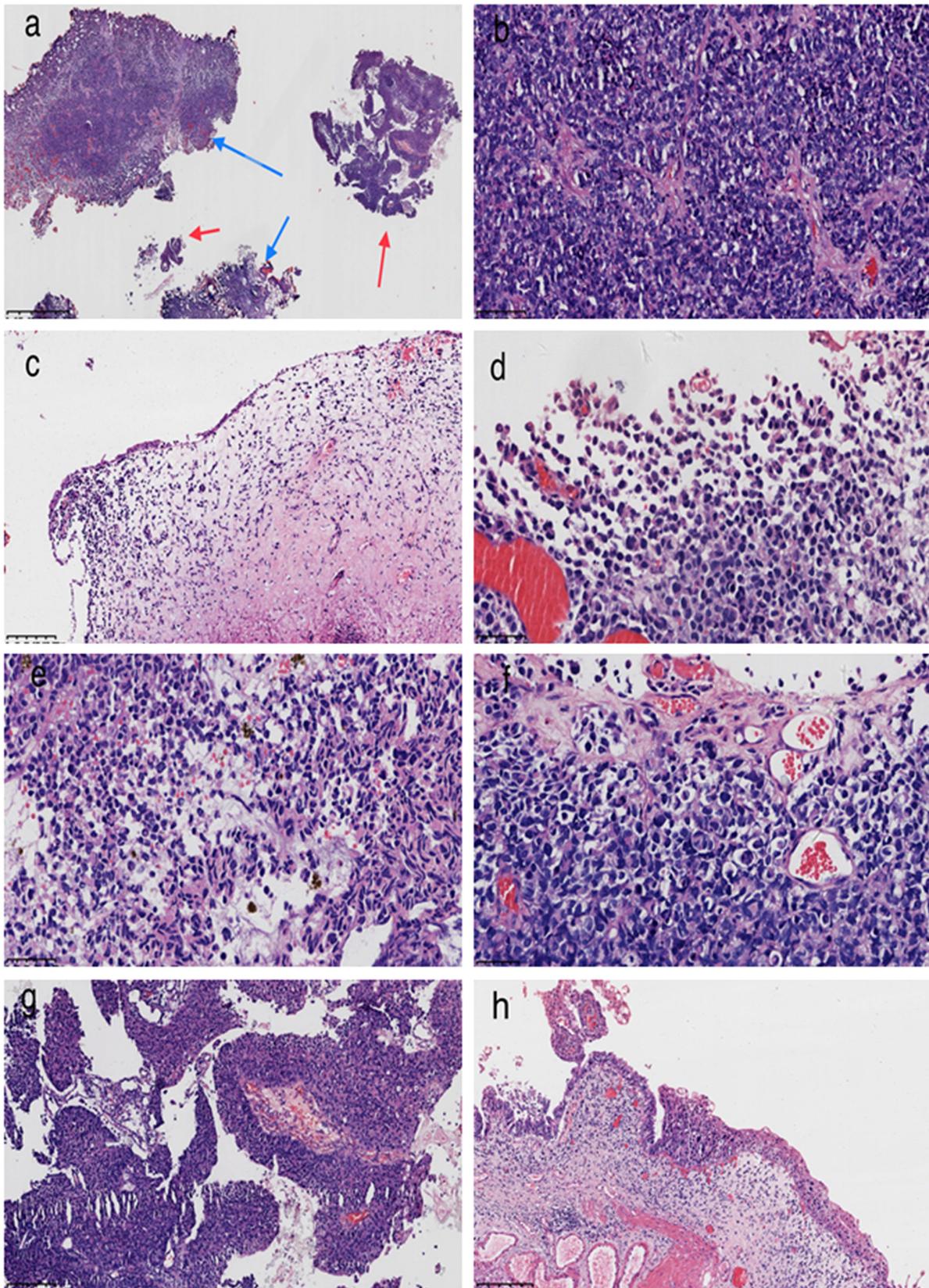


Figure 1. Tumor histology. (a) The two tumor components were not closely related or migrated into each other (blue arrows indicate malignant melanoma and red arrows carcinoma; magnification, x1.25; scale bar, 16,000 μm ; H&E staining). (b) Solid growth area of malignant melanoma with round and oval cells and hyperchromatic nuclei (magnification, x200; scale bar, 100 μm ; H&E staining). (c) Malignant melanoma tumor cells are located below the atrophic urothelium; the cells are round and a small number of scattered multinucleated giant cells are present (magnification, x100; scale bar, 200 μm ; H&E staining). (d) Malignant melanoma cells of different sizes, nuclear deviation, signet-ring cell-like appearance, cytoplasmic red staining (magnification, x400; scale bar, 50 μm ; H&E staining). (e) Melanin was found in the cytoplasm of certain tumor cells (magnification, x400; scale bar, 50 μm ; H&E staining). (f) Certain malignant melanoma cells have clear cytoplasm (magnification, x400; scale bar, 50 μm ; H&E staining). (g) Urothelial papillary carcinoma; the papillary structure is surrounded by multiple layers of atypical urothelial cells, the stroma is a component of the fibrous blood vessels (magnification, x100; scale bar, 200 μm ; H&E staining). (h) Focally, urothelial carcinoma *in situ* was observed (magnification, x100; scale bar, 200 μm ; H&E staining).

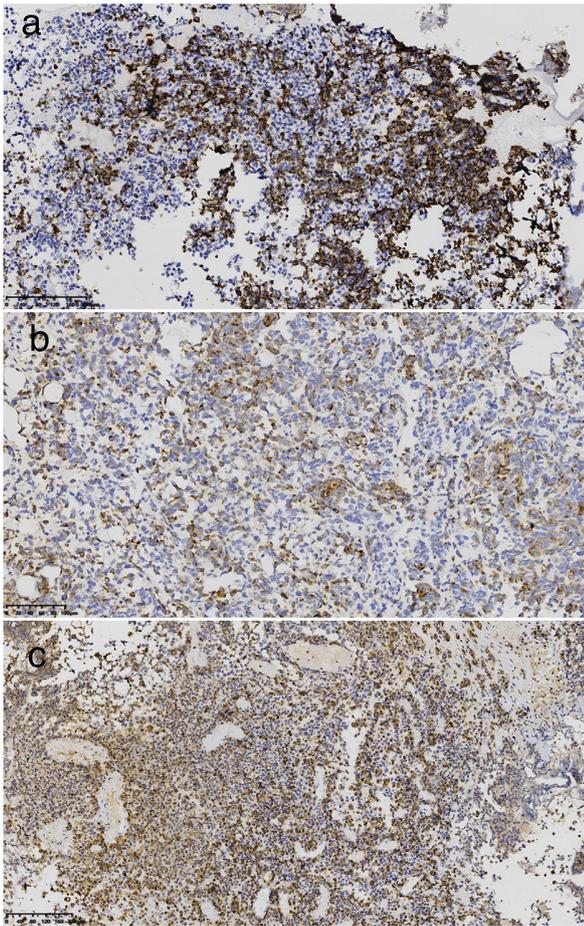


Figure 2. Immunohistochemistry. (a) Staining for HMB45 in malignant melanoma cells was positive (magnification, x100; scale bar, 200 μ m). (b) Staining for Melan-A in malignant melanoma cells was positive (magnification, x200; scale bar, 100 μ m). (c) Staining for S-100 in malignant melanoma cells was positive (magnification, x100; scale bar, 200 μ m).

is obvious with large nucleoli and infiltrative growth. Urothelial carcinoma has no specific morphology and may present with high-grade or low-grade changes. Immunohistochemistry may indicate that S-100, Melan-A and HMB45 are expressed in melanoma and CK was also reported to be puncta-positive around the nuclei of the tumor cells (5). Urothelial carcinoma expresses CKpan and GATA3. Molecular examination indicated that B-raf mutation exists in certain melanoma cases (5). In the present case, a collision between a malignant melanoma with a small amount of pigment and a high-grade noninvasive urothelial papillary carcinoma was identified, which was confirmed by clinical and pathological examination.

The differential diagnoses include the following: i) High-grade urothelial carcinoma with malignant melanin differentiation (12): The tumor is rare, and is a high-grade poorly differentiated tumor. The majority of the tumor cells are morphologically and immunohistochemically consistent with melanoma, a minority of cells are positive for urothelial markers and rare cells coexpress both melanocytic and urothelial markers. Cells that express melanocytic markers or urothelial markers are closely admixed together. A minor component of high-grade papillary urothelial carcinoma and carcinoma *in situ* is also present. ii) Small round cell malignant tumors

of the bladder, including lymphoma, primitive neuroectodermal tumor (PNET) and small cell carcinoma. When the tumor cells exhibit diffuse growth of uniform size, immunohistochemical staining is necessary for further differential diagnosis. Immunohistochemistry was positive for lymphoma, PNET or small cell carcinoma, but negative for melanoma markers. iii) Metastatic malignant melanoma of the bladder: The primary lesion may be found mainly by dermoscopy examination of the whole body skin, or CT and magnetic resonance imaging examination of the whole body system. iv) Metastatic renal clear cell carcinoma of the bladder: Primary malignant melanoma of the bladder should be differentiated when it is of the clear cell type. Morphologically, renal clear cell carcinoma has small atypia, clear cytoplasm and round or oval nuclei located in the center of the cell. Immunohistochemistry is positive for Vim, CK and CD10, while melanoma markers are negative.

Regarding treatment and prognosis, different surgical plans may be made according to the different conditions of patients with collision bladder tumor. If the patient's condition is good, complete cystectomy is recommended, and if the condition is generally poor, partial cystectomy is feasible. Whether to receive radiotherapy and chemotherapy after surgery is still a controversial issue, which should be determined according to the pathological type of the collision cancer. Chemotherapy for malignant melanoma and urothelial carcinoma mainly refers to the chemotherapy regimens of cutaneous or mucosal malignant melanoma and urothelial carcinoma. In recent years, breakthrough progress was made in the targeted therapy of advanced malignant melanoma. Schindler *et al* (4) first reported that Ipilimumab was used to treat patients and achieved partial response. However, the survival time of patients with malignant melanoma of the bladder is <3 years (13). The patient of the present study was diagnosed by electrosurgical resection and then received total cystectomy at another hospital without chemotherapy, immunization or gene therapy. The patient died of systemic metastasis 31 months after surgery.

In conclusion, primary malignant melanoma of the bladder with high-grade non-invasive urothelial papillary carcinoma collision is a rare tumor type. The diagnosis depends on clinical and pathological examinations. The degree of malignancy is high and recurrence and metastasis occur easily. In general, comprehensive treatment, mainly surgery, immunotherapy and targeted therapy, may help improve the prognosis of patients, but the prognosis is poor. Due to the small number of reported cases reported to date, the clinical and pathological features, treatment and prognosis require to be further explored.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

BH and XC drafted the manuscript and conceived the study. HL and XC were responsible for the collection and analysis of case data and literature. HG, JY and XC revised the manuscript and interpreted the data. BH and HL confirm the authenticity of all the raw data. All authors agreed on the journal to which the article has been submitted and agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided written informed consent for the case study to be published.

Competing interests

The authors declare that they have no competing interests.

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