CASE REPORT

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Primary malignant melanoma of the bladder – case report and literature overview

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Abstract
Malignant melanoma is one of the common skin cancers but as a primary cancer localized in urinary bladder is a very rare clinical entity, 0.2% of all melanomas. We report the very rare case of primary malignant melanoma of the bladder in an 80-year-old man. According with our knowledge is the first case of primary malignant melanoma reported in Romania. Only a few percent of malignant melanoma have origin outside the skin. Less than 30 cases of primary bladder melanoma have been reported in the literature. The most common metastasis in urinary bladder comes from breast carcinoma and skin melanoma The tissue examination presents the same futures does not matter if is a primary or secondary malignant melanoma. The ancillary tests like immunohistochemistry help us to do an accurate diagnostic but to discriminate primary *vs.* metastatic tumor remain an important issue. Usually, the bladder melanoma has an aggressive lethal behavior. Histopathological examination, immunohistochemistry, clinical history, and endoscopic evaluation can provide certain diagnostic features.

Keywords: malignant melanoma, bladder tumors, cystoscopy, macroscopic hematuria, transurethral surgery.

Introduction

Ninety-five percent of bladder tumors are primary urothelial carcinomas, other primary carcinoma types include adenocarcinomas, squamous cell tumors, and small cell tumors [1, 2]. The bladder is also the origin for rare primary cancers like sarcomas, gastrointestinal stromal tumors (GISTs), lymphoma and neuroendocrine tumors [1, 3–5].

Two percent of bladder tumors are metastases from other primary sites. Most bladder metastases have colorectal, ovarian or uterine origin [6].

Malignant melanoma of the bladder is a very rare clinical entity [3]. Barillaro *et al.* published an article where are counted only 28 cases of primary melanomas of urinary bladder [7, 8]. Rather than being a primary tumor, malignant melanoma of the bladder is mostly a metastatic tumor. Primary malignant melanoma of urinary bladder account for 0.2% of all melanomas with no gender preferences [4, 8–10].

While the penis and urethra are the most common urinary tract localizations and often the primary sites of malignant melanoma, the prostate, ureter, renal pelvis and urinary bladder are more often secondary sites of localization [11, 12]. Although a variety of therapeutic alternatives exist for malignant melanoma with bladder localization, prognosis remains reserved.

The malignant melanoma metastasis and the primary melanomas present the similar histological appearance and rise and issue regarding the diagnosis.

We present a case of primary bladder melanoma, which, according to our knowledge, would be the first case diagnosed in Romania.

Case presentation

An 80-year-old man presented to the Department of Urology (September 2011) for lumbar pain, obstructive syndrome and bladder irritation. Imagistic studies and laboratory analysis were performed to establish the diagnostic.

Ultrasound (US) revealed non-obstructive cortical cysts in the right kidney, bladder wall thickening and intravesical prostatic protrusion. Alpha-blocker and anti-inflammatory treatment was initiated and a 30-day re-evaluation was recommended to assess therapeutic response.

Over the next four years, the patient was treated for multiple associated conditions: cutaneous eczematides, megaloblastic anemia, atrophic gastritis, sigmoid diverticulosis, chronic duodenal ulcer, hiatal hernia, hypertension, heart failure. Patient history was significant at that time for prostate adenoma but without clinical suspicion of malignancy based on rectal examination. US showed an enlarged prostatic median lobe near the bladder neck.

The patient was admitted later (September 2015) to

the Department of Urology for macroscopic hematuria with clots and elevated prostate specific antigen (PSA) levels (6.68 ng/mL). We plan to perform an extended resection cystoscopy.

Cystoscopy demonstrated two tumor lesions in the prostatic urethra (Figure 1) and alongside the left wall of the bladder (Figure 2). The lesions appeared infiltrative with a brownish black pigment, an atypical presentation for bladder tumors. Extended resection of the tumors for biopsy (Figure 3) was performed endoscopically under spinal anesthesia using a standard monopolar CHR-26 resectoscope.

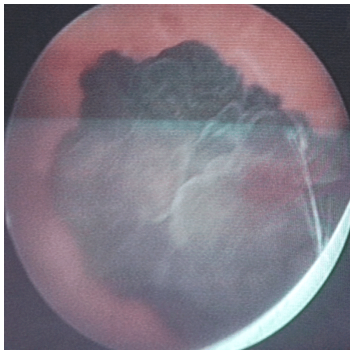

Figure 1 – ***Tumor lesion in the prostatic urethra seen endoscopically.***

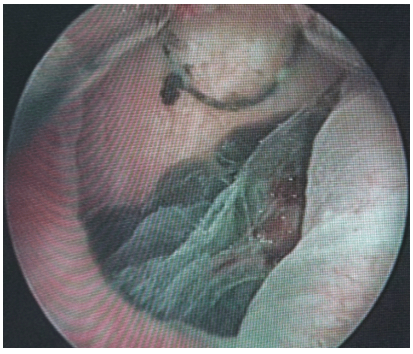

Figure 2 – ***Brown-to-black tumor lesion along the left wall of the bladder seen endoscopically.***

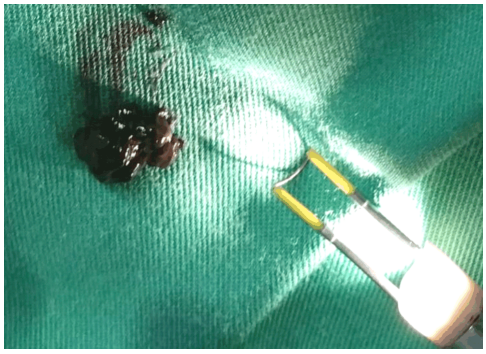

Figure 3 – ***Resected tumor specimen obtained using a standard monopolar CHR-26 resectoscope.***

In order to assess tumor extension, magnetic resonance imaging (MRI) with contrast was performed. Imagistic studies of the tumor spread revealed an asymmetrical bladder wall with irregular contours, with a thickened circumference of 15 mm width infiltrates in the surrounding fatty tissue and seminal vesicles without cleavage plan to the prostate. The prostate was enlarged, non-homogeneous, with maximum axial diameter of 50/56 mm. A 3.5×3.5 cm nodular formation in the right lobe captured the intravenous contrast substance. Several adenopathy with diameters of up to 1.6 cm have been identified, with non-homogeneous structure and central necrosis. No bone metastases and no fluid have been identified in the peritoneal cavity. The findings suggest a diagnosis of infiltrative bladder tumor with involvement of seminal vesicle and perivesical fatty tissue, possibly prostate tumor, necrotic node lymph and, bilateral multicystic kidney.

All tissue fragments from the resection were fixed in 10% buffered formalin (pH 7.4) for up to 24 hours, processed using the paraffin-embedding technique for microscopy analysis. Then, all slides were stained with Hematoxylin–Eosin (HE) and examined with Leica DM 1000 LED microscope.

Microscopic examination in HE-staining revealed alveolar proliferation of large epithelial tumor cells (Figure 4) showing atypical nuclei with large nucleoli and irregular nuclear contour. Abundant cytoplasm present variable amounts of melanosomes up to 3 μm in diameter. The shape and dimensions of the tumor cells were very varied; some cells were round, small in size and contained small amounts of melanic pigment, while others were very large, polyhedral, round or oval, and contained large amounts of melanin pigment (Figure 5). The tumor stroma contained variable amounts of pigment cells that invaded and destruction of the bladder muscle layer.

For a positive and differential diagnosis, we performed some immunohistochemical (IHC) determinations on the endoscopic resection material. IHC analysis was performed on 4 μm-thick sections prepared from formalin-fixed paraffin-embedded tissue by using an automated immunostainer (BenchMark GX, Ventana Medical Systems Inc., Tucson, AZ, USA). IHC assays were performed on a Ventana BenchMark GX automated staining instrument, according to the manufacturer's instructions. Slides were deparaffinized using EZ Prep solution (Ventana Medical Systems, Inc.), at 90^0C, and all reagents and incubation times were chosen as directed on antibody package inserts. Slides were developed using the HEP Green Kit (Zytomed System) and counterstained with Mayer's Hematoxylin to distinguish the brown melanin pigmentation from 3,3'-diaminobenzidine (DAB) staining. The following antibodies were used: anti-Ki67 antibody (monoclonal mouse anti-human Ki67, clone MIB-1, 1:50 dilution, Dako); anti-melan A antibody (monoclonal mouse anti-human melan-A, clone A103, 1:50 dilution, Dako); anti-human melanoma black 45 (HMB45) antibody (monoclonal mouse anti-human melanosome, clone HMB45, 1:100 dilution, Dako); anti-S100 antibody (polyclonal rabbit S100, 1:1000 dilution, Dako); anti-MNF116 antibody (monoclonal mouse anti-human cytokeratin, clone MNF116, 1:100 dilution, Dako).

The use of the anti-Ki67 antibody showed that more than 50% of the tumor cells nuclei were positive, demonstrating a very high proliferation index and an increased aggression of the tumor cells (Figure 6). Also, tumor cells showed intense positive reactions to anti-melan A (Figure 7) and anti-HMB45 (Figure 8) antibodies. Both melan-A and HMB45 are two IHC markers of particular value in the positive and differential diagnosis of malignant melanoma. The IHC positive response to anti-S100 antibody, demonstrates that tumor cells have neuroectodermal origin (Figure 9). In contrast to these reactions, the use of anti-MNF116 antibody showed that the tumor cells were negative, and the superficial urothelial cells were intensely stained (Figure 10). This IHC reaction shows that tumor cells do not have epithelial origin.

As can be seen from our images, IHC reactions were positive in younger cells that had lower melanoma content in the cytoplasm.

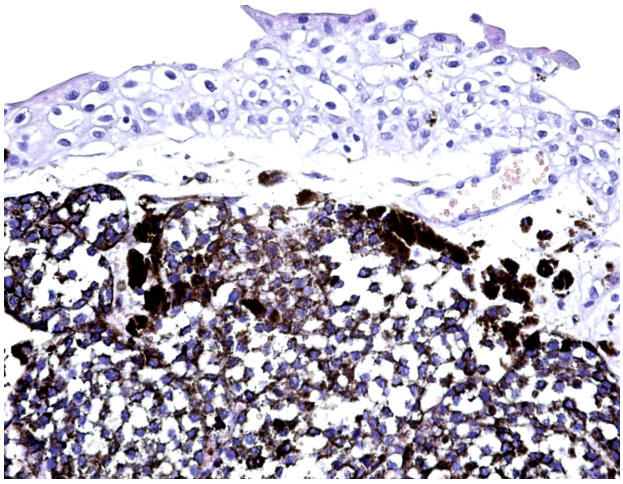

Figure 4 – ***Malignant melanoma cells present in the lamina propria of the urinary bladder mucosa. The epithelium of the surface of the mucosa is not infiltrated with melanocytic cells (HE staining, ×200).***

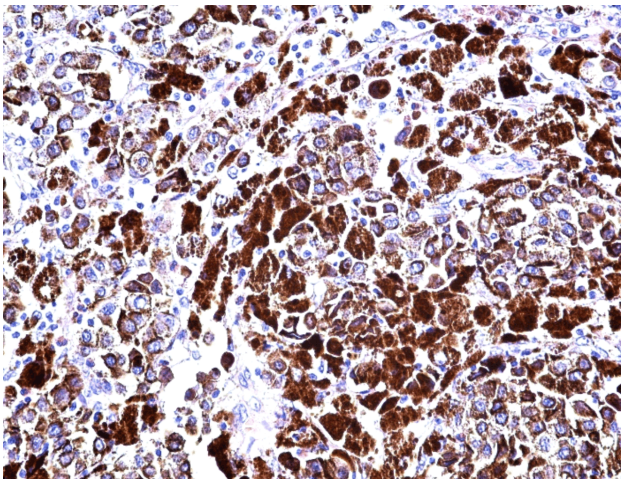

Figure 5 – ***Microscopic aspect of tumor revealed infiltrative growth into the main muscle layer of the bladder (HE staining, ×200).***

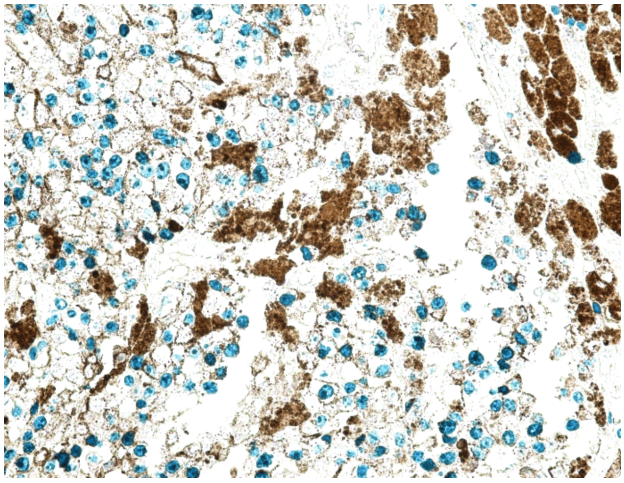

Figure 6 – ***An intense positive reaction of tumor cells (green color) to the anti-Ki67 antibody; it can be seen that more than 50% of the tumor cells nuclei are positive (Immunostaining with anti-Ki67 antibody, ×200).***

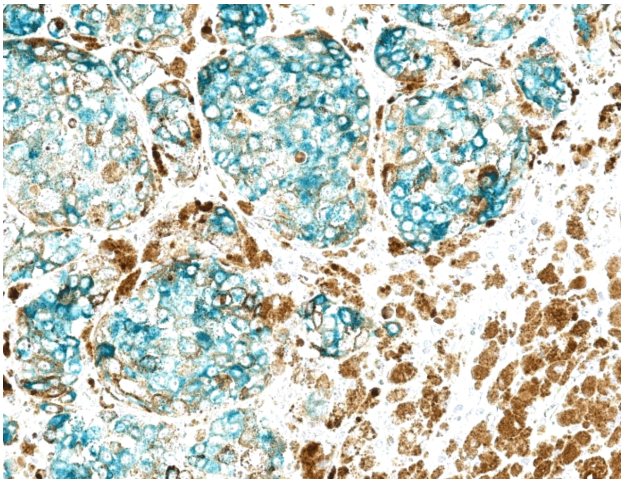

Figure 7 – ***Intense positive reaction of young tumor cells (green color) to anti-melan A antibody (Immunostaining with anti-melan A antibody, ×200).***

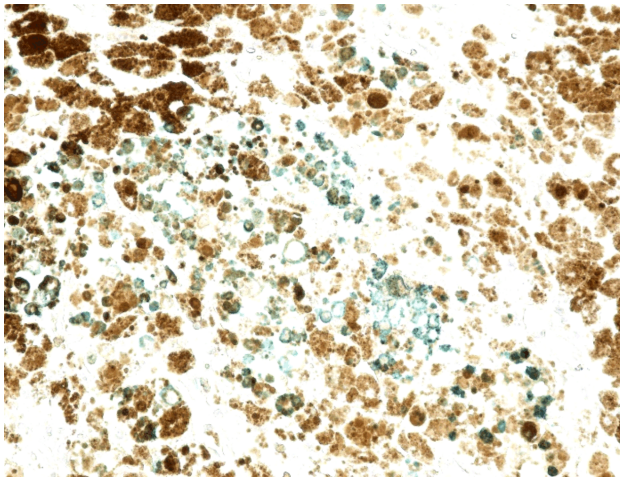

Figure 8 – ***Moderately positive tumor cell response to the anti-HMB45 antibody (Immunostaining with anti-HMB45 antibody, ×200). HMB45: Human melanoma black 45.***

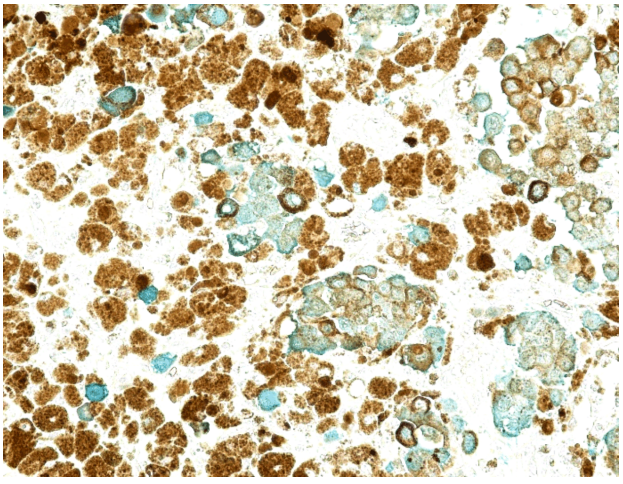

Figure 9 – ***Positive tumor cells to the anti-S100 antibody, demonstrating their neuroectodermal origin (Immunostaining with anti-S100 antibody, ×200).***

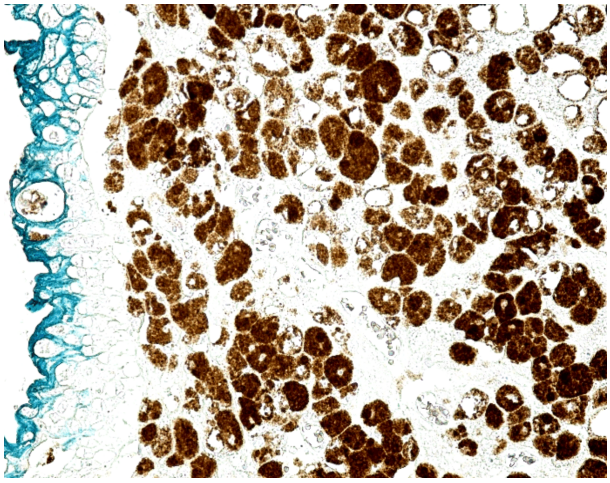

Figure 10 – ***Negative reaction of tumor cells to anti-MNF116 antibody, showing non-epithelial origin; instead, the urothelial superficial cells are highly positive (Immunostaining with anti-MNF116 antibody, ×200).***

Exhaustive imaging and clinical examination of the skin, eyes, gastrointestinal tract, brain and chest was performed without revealing other possible primary sites of melanoma origin. The patient also underwent a positron emission tomography/computed tomography (PET/CT) scan to detect a possible primary melanoma with another location, but the results were negative.

In the absence of a clinical history of melanoma, other lesions with an infiltrative growth pattern were considered.

Our Oncological Committee classified this case as a primary malignant melanoma of the bladder, operated, pT2 N1 M0, and decided to initiate the first chemotherapy course. Due to the overall poor condition of the patient, the multidisciplinary team consensus was against another surgical treatment and prostate biopsy. Over the next six months, the patient deteriorated rapidly towards decease due to fatal complications.

Discussions

Malignant melanoma is an aggressive tumor, with a rapid evolution and extended death [13]. The most frequent localization of the melanoma is the skin, where there were identified about 81% of cases, followed by the eye and certain mucous membranes (oral, valvular, conjunctiva), where there were reported about 17% of the cases [14]. The development of these melanomas in these places is due to the presence of melanocytes, cells that emerge during embryonic life from neural cusps. Under the influence of some harmful factors (especially UV rays), melanocytes acquire malignant properties.

The primary malignant melanoma located in the genital urinary tract is extremely rare, representing less than 1% of all the cases of malignant melanomas [15, 16], while the localization in urinary bladder is only of 0.2% of all the cases of primary melanoma [14, 17]. Approximately 30 cases of primary malignant melanoma of the bladder have been reported, the mean age being 60.6 years old (between 34–82 years old), with is a slight prevalence in male gender (60%) [9].

Most studies state that malignant melanomas located in the urinary tract may be metastases of a skin melanoma. In 2015, Meunier *et al.* [18] identified only 23 cases of metastases of malignant melanoma localized in the urinary bladder, published in *PubMed*. It appears that the number of metastases in the urinary bladder is higher in the patients with skin malignant melanoma, many of them not presenting any clinical symptoms, others being manifested only by painless hematuria. Das Gupta & Brasfield, in 1964, performed 125 autopsies on patients with metastases of malignant melanoma and found that 18% were localized in the urinary bladder [18, 19]. Nevertheless, we have to specify that metastases are also quite rare [20–23].

The histogenesis of malignant melanoma, in the urinary tract, and especially in the bladder, is unclear. At present, there are two theories: one of them supports the idea that melanoblasts migrate during embryogenesis from the neural cusps into the mesenchyme, but they can also migrate in ectopic places, including the developing urinary tract, where they remain inactive for a long time; under the influence of some local factors, they may transform into malignant cells. Another hypothesis supports the idea that urothelial cells derived from the stem cells of the urothelium may differentiate in a direction of neoplastic melanocytes [14, 17, 24].

The case we presented is a primary bladder melanoma, where both the clinical and US examinations did not reveal a possible melanoma localized in a different organ. Also, the study of the data published in *PubMed*, *Medline*, *Google Scholar* and *Google* allowed us to state that this is the first case of primary malignant melanoma localized in the bladder, reported in Romania.

In 1976, Ainsworth *et al.* were the first observers to carefully delineate criteria for defining primary malignant melanoma of the urinary bladder, so an algorithm has been proposed to differentiate malignant melanoma of primary bladder from metastasis [25]. For the diagnostic a detailed patient history, precise dermatological examination and evaluation for other primary sites are necessary to confirm the primary nature of the tumor.

Our cases fulfilled all these criteria; no previous cutaneous lesion history, no evidence of regressed cutaneous malignant melanoma, no evidence of other visceral primary melanoma, the pattern of recurrence should be consistent with the initial lesion and the margining of the bladder lesion should contain atypical melanocytes.

We consider that in establishing a positive and differential diagnosis of the malignant melanoma, together with a clinical examination and imagistics, the histopathological examination plays an essential part.

Clinically, the most of the cases presented hematuria and/or dysuria as initial symptoms [25].

In our study, the tests of immunohistochemistry have helped us for of the final diagnosis. IHC staining of the embedded-paraffin block confirmed that the tumor cells were positive for anti-melan A, anti-S100 and anti-HMB45 antibodies (the most common antibodies for diagnostic of melanoma worldwide). These findings were consistent with malignant melanoma [26]. Tumor cells had no affinity for cytokeratin markers. The markers are negative for melanophages. We used an extra-marker name tyrosinase for accuracy of the melanoma diagnostic. The staining

will be in red to be easily detected from the brown melanin pigment. Usually, in the immunohistochemistry, it is used brown staining with DAB but in this case may interfere with the natural melanin pigment [27–30]. The IHC exams performed by us have demonstrated that tumor cells originate in neural crests simulating other neuroendocrine tumors [28, 31, 32].

Recent studies have shown that the v-Raf murine sarcoma viral oncogene homolog B (*BRAF*)^{V6000E} mutation is present in 50% of malignant melanomas and is associated with a bad prognosis [3] including early onset, reduced survival, and multiple complications [33–35]. Targeted therapies such as *BRAF* inhibitors have been shown to improve response rates, but not durably [36].

Regarding the clinical evolution of the patient, we can observe a fulminant, rapid progressive development with the occurrence of secondary determinations in multiple organs, which in the case of a weakened organism, in an elderly patient; do not allow the appropriate chemotherapeutic treatment recommended by the oncology guidelines [37].

Conclusions

Malignant melanoma of the bladder is a very rare pathology. Histopathological examination, immunohistochemistry, clinical history, and endoscopic evaluation can provide certain diagnostic features. Treatment options include transurethral surgery, systemic chemotherapy, *BRAF* inhibitors or immunotherapy and partial or complete cystectomy had been described. According with various Internet databases, including *PubMed*, *Medline*, *Google Scholar*, and *Google*, this is the first case of primary malignant melanoma in the urinary bladder described in Romania.

Conflict of interests

The authors declare that they have no conflict of interests.

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