Primary malignant melanoma of the urinary bladder and ureter

Munad Khan, MD,[1] Dermot O'Kane, MD,[1] Justin Du Plessis, MD,[2]
Nathan Hoag, MD,[1] Nathan Lawrentschuk, MD[1,3,4]

[1]Department of Surgery, University of Melbourne, Austin Hospital, Melbourne, Victoria, Australia
[2]Department of Anatomical Pathology, Austin Pathology, Austin Hospital, Victoria, Australia
[3]Olivia Newton-John Cancer Research Institute, Austin Hospital, Victoria, Australia
[4]Department of Surgical Oncology, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

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Primary malignant melanoma of the urinary bladder is a rare lesion. We report the case of a 78-year-old male with no previous history of cutaneous melanoma who presented with hematuria. Further investigation with imaging and cystoscopy raised suspicion of a primary bladder and ureteric melanoma, which had subsequently metastasized. This was confirmed with histological assessment and a thorough search for alternative primary lesions. Unfortunately, our patient passed away prior to receiving any oncological treatment for his metastatic melanoma, underscoring both the high mortality of this lesion and the need for a consensus on definitive treatment.

Key Words: malignant melanoma, urinary bladder, non-cutaneous malignant melanoma

Introduction

Primary malignant melanoma of the genitourinary tract is a rarely encountered clinical entity. It accounts for 0.2% of all primary melanomas.[1] The most frequent sites in the urinary tract to be affected are the penis and urethra.[2] Primary malignant melanoma of the urinary bladder and ureter make up a smaller proportion of primary genitourinary melanoma. To date, there are less than 50 reported cases in the literature of primary bladder melanoma[3,4] and even fewer instances of primary ureteric melanoma.[5] However, the genitourinary tract is not an uncommon site of metastasis of malignant melanoma. It has been reported that at post mortem, as many as 18% of patients who have died as a result of metastatic melanoma will have metastatic spread to the urinary bladder.[2] As such, it becomes important to distinguish primary from secondary malignant melanoma in organs such as the bladder, although this remains difficult. Despite advances in radiological and surgical techniques, melanoma of the urinary bladder and/or ureter presents diagnostic and management dilemmas as these lesions tend to present insidiously and have usually metastasized by the time of presentation. To date, there is no consensus on definitive treatment, and survival from melanoma of the urinary bladder or ureter is dismal.[1]

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Address correspondence to Dr. Munad Khan, Department of Surgery, Austin Hospital, Suite 5, 210 Burgundy Street, Melbourne, Victoria Australia 3084

Case presentation

A 78-year-old Caucasian male was referred to the urology outpatient clinic with macroscopic hematuria. He had no previous history of urological pathology, and had no history of cutaneous melanoma or skin malignancy. There were no other genitourinary symptoms. The patient's medical history included paroxysmal atrial fibrillation, congestive cardiac failure, hypertension, type 2 diabetes mellitus and hypercholesterolaemia. The patient had no known family history of melanoma, and no obvious environmental exposures. Physical examination was unremarkable. Routine blood and urine tests were normal. A computed tomography intravenous pyelogram (CTIVP) demonstrated multiple bladder wall masses, a filling defect in the distal left ureter and numerous soft tissue nodules scattered throughout the peritoneum and retroperitoneum, which were concerning for metastatic malignancy, Figure 1. Given the radiological evidence for malignancy, the patient did not undergo cytological examination of the urine.

Following discussion at our urology unit meeting, a rigid cystoscopy and left ureteroscopy with retrograde

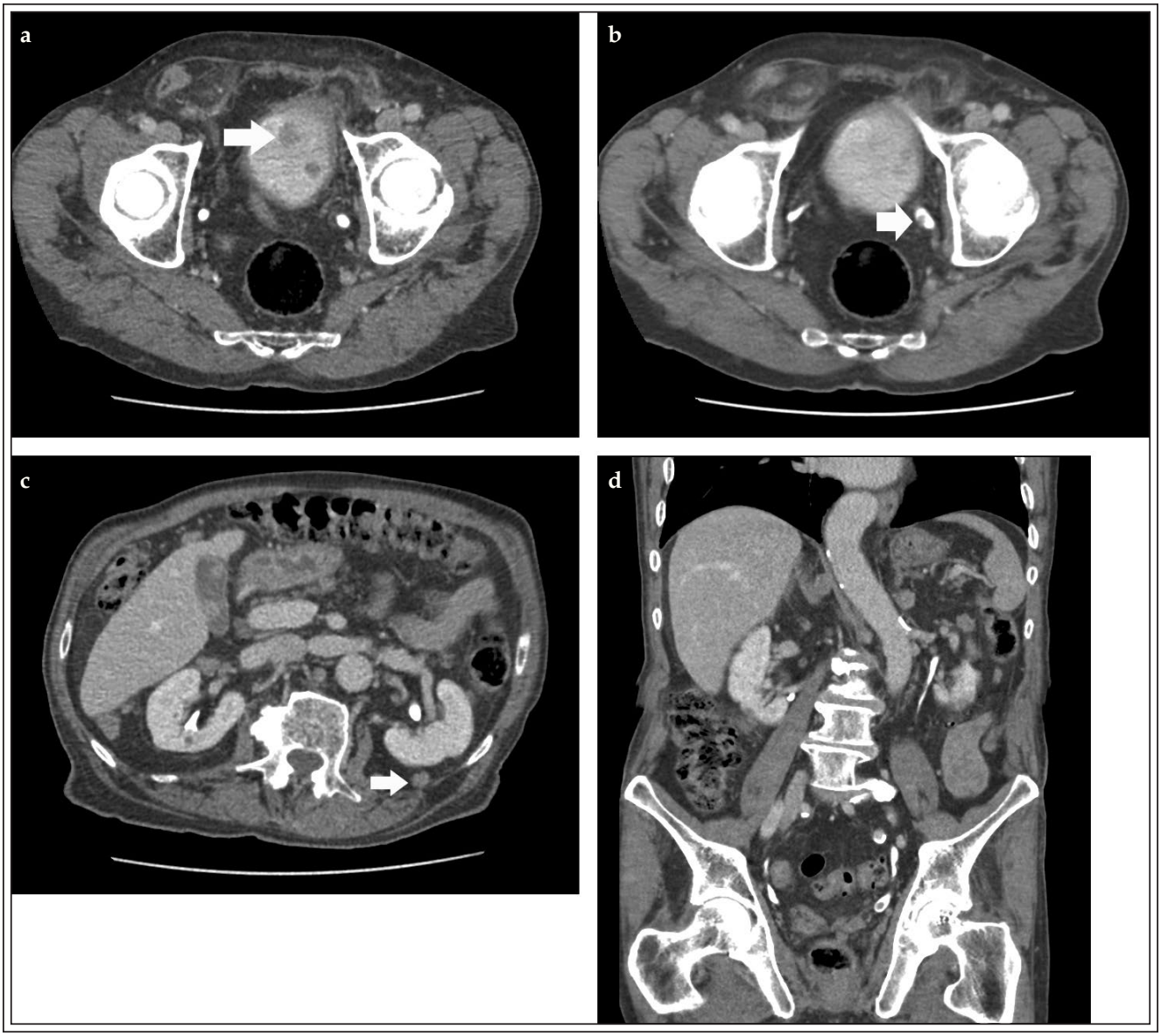

Figure 1. Axial and coronal CTIVP images demonstrating bladder **(a)** and left ureter **(b)** lesions plus retroperitoneal **(c)** and peritoneal **(d)** metastases (examples of lesions indicated by white arrow for reference).

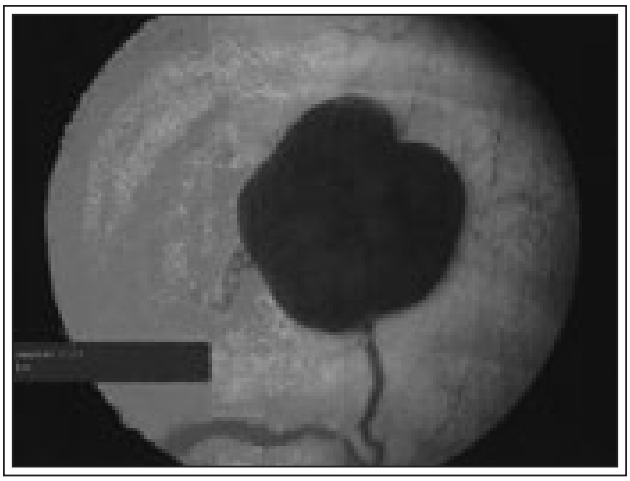

Figure 2. Cystoscopic image displaying a pedunculated, pigmented bladder wall lesion – confirmed histologically as malignant melanoma.

pyelogram (RPG) was performed. Cystoscopy demonstrated multiple pedunculated, pigmented bladder wall lesions, Figure 2, all of which were resected transurethrally and sent for histology. RPG demonstrated the filling defect in the left ureter as seen on the CTIVP. A left ureteroscopy displayed a pigmented ureteric lesion similar in macroscopic appearance to the bladder wall lesions. Biopsies of this lesion were taken.

Histopathological examination of bladder and ureteric lesions demonstrated moderately disrupted polypoid fragments of tumor constituting solid sheets of mitotically active epithelioid cells with prominent rufescent nucleoli and sprinkling of brown cytoplasmic pigment, Figure 3a and3b. Tumor cells extended up to the surface urothelium, which displayed focal melanosis with cytological atypia. No detrusor, perineural or lymphovascular invasion was evident. On immunohistochemical (IHC) staining, tumour cells were positive for S-100 protein, HMB-45 and Melan-A; confirming diagnosis of malignant melanoma, Figure 3c and 3d.

The case was discussed at a multidisciplinary meeting, where consensus was that in light of the extent of disease there was no curative surgical option, and a medical oncology opinion was sought. Immunotherapy was proposed as an option following results of BRAF gene mutation testing and staging CT of the brain and thorax. Dermatology consultation was also arranged and dermatological examination was negative. Sadly, the patient suddenly passed away prior to completion of the remaining staging investigations. The cause of death was deemed to be intracerebral hemorrhage, possibly as a result of intracerebral tumor metastasis. Three months had passed between initial presentation and patient demise. In accordance with the wishes of the family, no autopsy was performed.

Discussion

The etiology of primary melanoma of the urinary bladder and ureter overall is poorly understood. It is suggested that primary melanoma of the urinary bladder occurs due to malignant transformation of ectopic melanocytes within the urothelium of the urinary tract. Melanocytes normally migrate from their origin in the neural crest, through the mesenchyme, to be deposited in skin and hair follicles. During this migration the cells can be deposited in ectopic locations such as the urinary bladder.[4] The pathology of malignant transformation of these cells is not well understood and to date there are no definitive risk factors known for primary melanoma of the urinary bladder/ureter. Melanoma of the urinary bladder appears cystoscopically as raised or sometimes flat, irregular, darkly pigmented lesions of the urothelium. The differential diagnosis of a lesion with this macroscopic appearance within the bladder includes; endometrioma, hemangioma, sarcoma, and benign bladder melanosis.[3] CTIVP is a useful adjunct for diagnosis and staging, particularly in the case of upper tract involvement but definitive diagnosis requires cystoscopy and biopsy, with or without accompanying ureteropyeloscopy.

TABLE 1. **Stein and Ainsworth criteria**

i)	No history of previous cutaneous lesion
ii)	No evidence of regressed cutaneous malignant melanoma
iii)	No evidence of other visceral primary melanoma
iv)	Pattern of recurrence should be consistent with the region of initial malignant melanoma
v)	Margins of bladder lesion should contain atypical melanocytes similar to those seen in the periphery of primary mucous membrane lesions

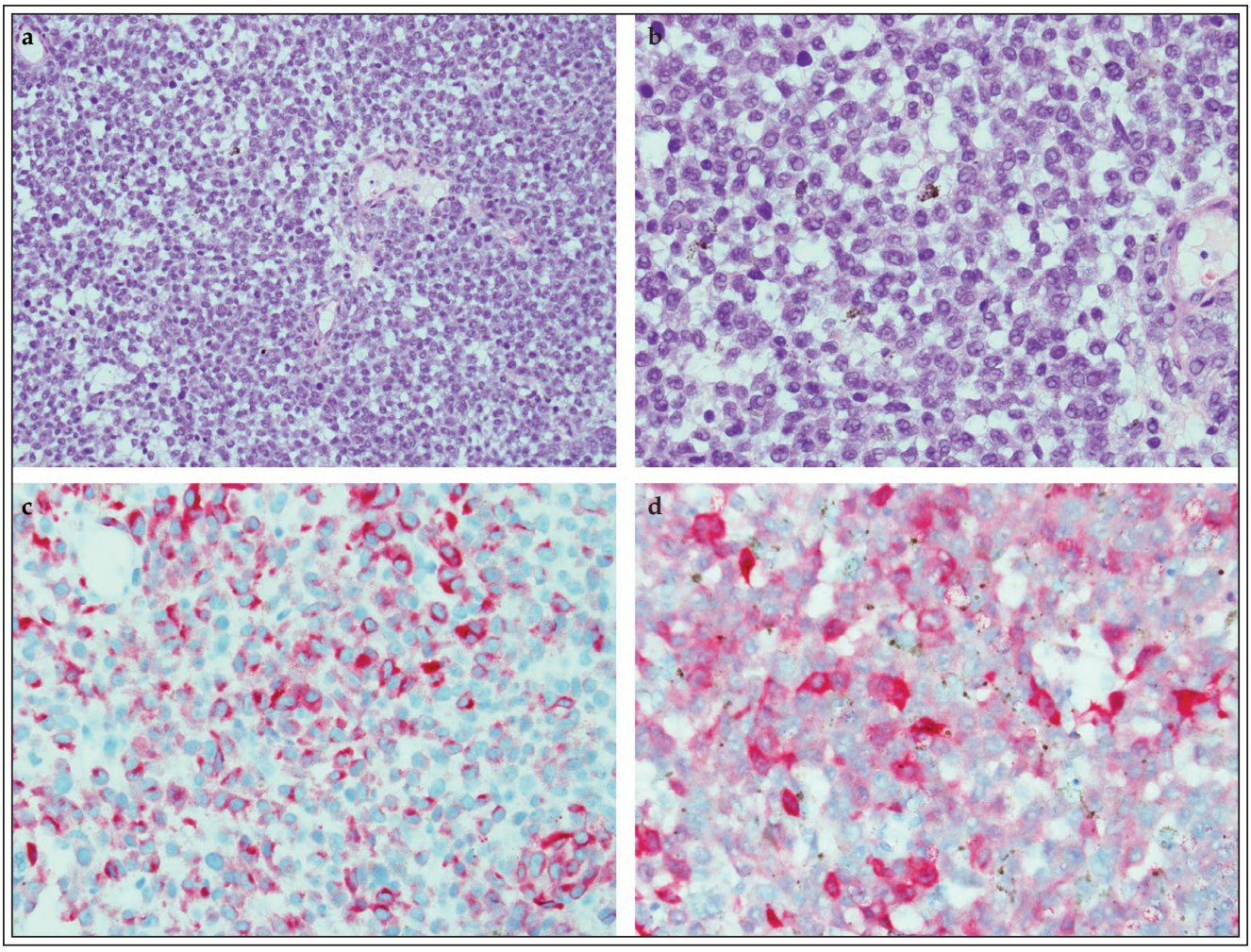

Figure 3. (a) Hematoxylin and eosin (H&E) stain (magnification x200) showing sheets of malignant epithelioid cells. **(b)** Some tumor cells possessed a sprinkling of brown cytoplasmic melanin pigment (H&E, x400 magnification). **(c)** and **(d)** Lesional cells exhibit positivity for Melan-A and S-100 protein immunostains, respectively (IHC, x200 and x400 magnifications). Contrast agent used: Amino-ethylcarbazole (AEC).

Following biopsy, immunohistochemical examination is performed to confirm the diagnosis of malignant melanoma. Melanoma cells typically stain positive for S-100 protein, Melan-A and HMB-45. A positive result with these stains in combination confirms malignant melanoma with a high degree of sensitivity and specificity. Two additional stains (MITF-1 and tyrosinase) are being developed to improve diagnostic accuracy for certain subtypes of malignant melanoma.[6]

Primary melanoma of the urinary bladder or ureter remains a diagnostic dilemma. Hematuria is often the only symptom, and often presents when the disease is already advanced.[1] Ureteric involvement can present with symptoms of renal colic.[5] Unfortunately, both hematuria and renal colic are very common symptoms in urology patients and in the vast majority of cases reflect an alternative underlying diagnosis.[7] At the time of diagnosis of primary bladder/ureteric melanoma most of these lesions have already metastasized, and this also confounds the diagnosis of primary versus secondary disease. Although secondary melanoma involving the bladder and ureter is far more common, diagnosing primary bladder/ureteric melanoma remains important, as this has major implications for treatment options. In the absence of known risk factors, the criteria proposed by Stein and Ainsworth remains the only guideline to aid in the diagnosis of primary disease, Table 1.[8] When applied to the present case, all criteria have been fulfilled for primary melanoma of the urinary bladder. The only caveat in our case

is the difficulty in determining whether the primary lesion involved the bladder or ureter, or whether this represents two distinct primary lesions. Overall, the adaptation of these criteria in the literature remains variable.[1] Without quantifiable parameters defining what is needed to exclude criterion number ii) and iii) there may be discrepancies in the diagnosis of primary melanoma of the urinary bladder.

The presence of widespread metastasis in this case, along with comorbid medical conditions, rendered the option of radical surgery untenable. Metastatic spread from a primary bladder melanoma is a poor prognostic factor, and the treatment options are limited. However, if primary bladder melanoma is detected at an early stage, several surgical treatment options are available. As previously mentioned there has been no consensus to date on definitive surgical management of primary bladder melanoma. Previous case reports have discussed a variety of surgical approaches including; radical cystoprostatectomy, cystectomy, partial cystectomy, and transurethral resection.[1] A treatment algorithm for melanoma involving the ureter has been proposed by Gakis et al although this remains in the context of metastatic disease.[9] Adjuvant treatments include radiotherapy, and chemotherapy including interferon therapy, none of which have shown satisfactory improvements in outcome. Unfortunately, even with early detection and treatment, there are very few reported cases who survive beyond 3 years.[1,3] To maximize therapeutic options, it is important such cases are discussed early in a multidisciplinary setting.[10]

Our case is consistent with the aggressive, rapidly progressive nature of other primary bladder melanoma reported in the literature. What is slightly unusual though is the occurrence of melanoma in the ureter along with the bladder. One instance of bladder and ureteric involvement has been reported in the literature, with the authors defining the case as primary malignant melanoma of the genitourinary system with concomitant upper and lower tract involvement.[5] In that particular case, both ureters were involved. In contrast, our case reflected unilateral ureteric involvement. Although concomitant upper and lower tract involvement is a possibility, given only one ureter was involved, it is also possible that the primary lesion developed in the ureter and subsequently spread to the bladder or vice versa. Unfortunately, given the nature of our patient's presentation, we were unable to determine the exact sequence of melanoma progression.

Primary melanoma of the urinary bladder/ureter is a rare condition with a very high mortality rate. This case highlights a typical late presentation, and the aggressive nature of this disease. To improve the ongoing management of patients in this setting, it is essential to ensure early cystoscopy in any patient presenting with unexplained macroscopic hematuria. This should include some form of ureteric imaging or visualization to ensure that there is no ureteric involvement. Furthermore, centralized management of patients with primary bladder/ureteric melanoma in specialist units will potentially provide the best chance for definitive treatment. Despite potential improvements in radiological and surgical techniques further research is required in this area to understand the etiology and pathology of primary melanoma of the urinary bladder and ureter if outcomes for these patients are to be improved. □

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