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Case Report

Metastatic Melanoma of the Urinary Bladder in the Era of Targeted Therapy

Luke L Wang*[1] MBBS, BMedSci; Matthew KH Hong[1] MBBS, PhD; Sree Appu[1] MBBS, FRACS (Urol); James G Huang[1] MBBS, FRACS (Urol)

[1]*Department of Urology, Monash Health, 865-823 Centre Road, Bentleigh East, Victoria, 3165, Australia*

**Corresponding author:* *Dr. Luke Wang, 823-865 Centre Road, Bentleigh East, Victoria, 3165, Australia,*

Tel: +61 411843415; Fax: (03) 9928 8278; Email: drlukewang@gmail.com

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Abstract

Metastasis of malignant melanoma to the urinary bladder is a rare clinical entity. Here we present the case of a 78 year-old man with metastatic melanoma in his bladder found on surveillance cystoscopy for previous bladder urothelial carcinoma, in the context of concurrent BRAF and MEK inhibitor therapy for melanoma metastasis to other sites. The bladder lesions were histologically confirmed to be melanoma, but despite lower urinary tract symptoms he was managed expectantly and succumbed to his disease some months later. This is only the second case in the English literature reporting bladder metastases from malignant melanoma with concurrent treatment of targeted therapy. There has been recent promise of longer survival amongst patients with metastatic melanoma afforded by these new therapies, and accordingly we may see a rise in incidence of stable metastases to rarer sites of spread and a need for improved local control of metastatic sites. Although we did not treat our patient's bladder metastasis more aggressively due to his guarded prognosis, this case highlights the potential for metastasis to rarer sites in the context of increased survival from new therapies and the lack of relevant targeted intravesical treatments for bladder metastases.

Keywords: Melanoma; Metastases; Bladder; Urology; Cystoscopy

Introduction

Since 1953, only approximately 24 cases over the duration of 52 years have been reported making metastatic melanoma to the urinary bladder a rare clinical entity[1]. These tumours typically present with painless macroscopic haematuria but are otherwise more frequently discovered at autopsy [1,2]. This suggests that in the majority of cases, treatment would only be expectant due to the very limited survival of this patient cohort. The discovery of PD-1 inhibitors and the use of targeted therapies such BRAF and MEK inhibitors have shown great promise in enhancing survival. Here we present the case of a 78 year-old man with deposits of metastatic melanoma within his bladder found on surveillance cystoscopy for previous bladder urothelial carcinoma 25 years following excision of the primary lesion. This occurred in the context of treatment with both BRAF and MEK inhibitors for known metastatic melanoma to other systemic sites. To the best of our knowledge, there is only one other report of metastatic melanoma to the urinary bladder in the context of concurrent treatment with targeted therapy in the English literature [3].

Case Report

A 78 year-old man presented for routine annual surveillance cystoscopy for previously diagnosed low-grade non-invasive papillary urothelial carcinoma four years prior. Previous surveillance had revealed no recurrence following initial endoscopic resection of his bladder malignancy. Other medical history included near total pancreaticoduodenectomy for intraductal papillary mucinous neoplasm of the pancreas, type 2 diabetes mellitus, atrial fibrillation, hypertension, and melanoma. He had a smoking history. In the few months leading up to his presentation he had been experiencing urinary frequency and nocturia, but no haematuria. Urine cytology was unremarkable.

The patient's primary malignant melanoma was initially excised from the scalp 25 years prior and histology showed a nodular subtype with 4mm Breslow thickness, Clark level IV and with no lymphovascular or perineural invasion. Metastatic melanoma had been diagnosed 5 months prior to his presentation to our service with positron emission tomography (PET) avid lesions found in the occiput, mediastinum and right lung. A combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib was commenced as part of a clinical trial at another institution. There was minimal response to this therapy on follow-up computed tomography (CT) scans at the time of his presentation.

At flexible cystoscopy, multiple small raised black-pigmented lesions were scattered throughout the bladder (Figure 1). Subsequent biopsies of these lesions at rigid cystoscopy confirmed metastatic melanoma with the presence of malignant epithelioid melanocytes staining strongly for Melan A immunoperoxidase (Figure 2).

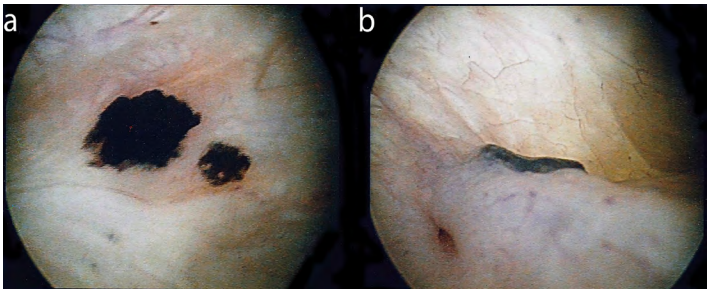

Figure 1. Multiple raised black pigmented lesions seen on flexible cystoscopy (a); lesion near the right ureteric orifice (b).

Given the advanced stage and overall treatment resistance of his disease, a multi-disciplinary team consensus decision was made for no further active management of his bladder metastases. The patient succumbed to respiratory complications of his melanoma three months later.

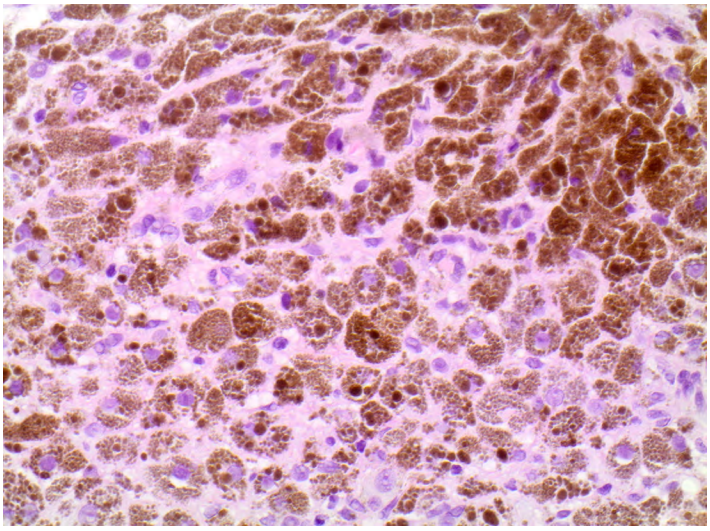

Figure 2. Malignant melanocytes staining strongly for Melan A immunoperoxidase.

Discussion

Secondary tumours of the bladder represent just 2% of all bladder tumours with most due to local invasion commonly by cancers of the colon, prostate, rectum and cervix [4]. Distant metastases to the bladder arise from cancers of the stomach, skin, lung and breast.[4] Although melanoma itself is a common malignancy with an incidence of 15-25 per 100,000, with Australia having the highest incidence in the world[5,6], metastasis to the bladder is rare. Only 24 cases have been reported in the literature over a half century with most involving some form of active treatment (Table 1) [3,7-9]. These tumours can present with painless macroscopic haematuria but they are often asymptomatic and more frequently discovered at autopsy [2].

Management options for bladder metastases include no active treatment, endoscopic resection and systemic therapy, all aimed generally at symptom relief. Radical and partial cystectomy have been reported for select patients with solitary metastasis, but this would be a rare situation [7,9]. Treatment would traditionally account for patient performance status as well as the context of the short 6-12 months median survival of metastatic melanoma [6].

Major advances have been made recently in the treatment of metastatic melanoma and key mutations resulting in alterations in molecular pathways driving melanoma cell proliferation have been identified. Successful treatment with targeted agents such as BRAF and MEK inhibitors have followed, along with immune checkpoint blocking agents, such as antibodies to PD-1 and PD-L1, with an extension in survival beyond 2 years for many patients [6,10]. This success could see symptomatic bladder metastases encountered more frequently and necessitating intervention. In this exciting landscape of promising systemic treatments for metastatic melanoma, the bladder remains unique in that intravesical lesions could be treat-

ed directly with potentially less systemic toxicity if intravesical modes of delivery for these novel agents can be found.

Table 1. Previously reported cases of malignant melanoma to the urianry bladder.

Author	Year	Presenting symptom	Treatment
Amar et al.	1964	Haematuria	Partial cystectomy
Bartone et al.	1964	Haematuria	Partial cystectomy
Weston et al.	1964	Urinary retention	None
Dasgupta et al. Case series of 2	1965	Haematuria	Fulguration
Silverstein et al.	1974	Haematuria	BCG
Meyer et al. Case series of 3	1974	Asymptomatic	Chemotherapy / TURBT
Tolley et al.	1975	Haematuria	Radical cystectomy
Chin et al.	1982	Haematuria	Partial cystectomy
Stein et al.	1984	Haematuria	TURBT and chemotherapy
Arapantoni-Dadioti et al.	1995	Dysuria	Chemotherapy
Ergen et al.	1995	Haematuria and flank pain	None
Demirkesen et al.	2000	Haematuria and LUTS	Chemotherapy
Marthinez-Giron et al.	2008	Haematuria	Unknown
Efesoy et al.	2010	Haematuria	TURBT
Nair et al.	2011	Haematuria	Chemotherapy
Paterson et al.	2012	Incidental	None
Wisenbaugh et al. Case series of 4	2012	Haematuria/ incidental	TURBT
Rishi et al. *	2013	LUTS*	TURBT

** in context of targeted therapy; LUTS – Lower Urinary Tract Symptoms; TURBT – Transurethral Resection of Bladder Tumour; BCG – Bacillus-Calmette-Guerin*

Conclusion

Recent advances in new targeted therapies for the treatment of metastatic melanoma have seen prolonged survival amongst patients with advanced melanoma. This may lead to a rise in incidence of stable metastases to urologic organs requiring treatment for symptomatic relief, and potential intravesical delivery of the targeted agents may be of benefit in these patients.

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