

Bladder metastasis from cutaneous melanoma during adjuvant immunotherapy: A case report and literature review

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Abstract. Cutaneous melanoma is among the most common malignancies in the United States and accounts for ~5% of all cancers. Melanoma preferentially metastasizes to lymph nodes, lungs, liver and brain, while bladder involvement is rare and associated with poor prognosis. The present study reports a 79-year-old woman with stage III, operable, *BRAF* wild-type melanoma of the back, treated with surgical excision and adjuvant immunotherapy. During adjuvant pembrolizumab treatment, a first solitary pulmonary relapse was observed. The metastasis was amenable to surgical resection, and the patient continued immunotherapy. Subsequently, recurrent haematuria led to the identification of a bladder lesion, which was removed via transurethral resection and the pathological evaluation confirmed metastatic melanoma. Following this second relapse, restaging imaging documented systemic disease progression involving lymph nodes, liver and bone.

The patient then initiated first-line treatment with nivolumab and ipilimumab, achieving an ongoing clinical and radiological partial response. This study highlights several clinically relevant aspects: The potential role of local treatment strategies for oligoprogressive disease in prolonging the benefit of immunotherapy, the rare occurrence of bladder metastasis during adjuvant pembrolizumab, and the activity of combined cytotoxic T-lymphocyte-associated protein 4/programmed cell death protein 1 (PD-1) blockade even after progression on prior anti-PD-1 therapy. Early recognition of atypical metastatic sites and multidisciplinary management may contribute to prolonged disease control in selected patients with metastatic melanoma.

Introduction

Cutaneous melanoma is an aggressive malignancy arising from melanocytes and represents one of the most common cancers in the United States, ranking in the top five malignancies in both men and women (1). Its incidence has risen faster than any other cancer worldwide among white populations, particularly those with fair skin and excessive sun exposure (2). The development of cutaneous melanoma results from a complex interplay between genetic susceptibility, phenotypic characteristics, and environmental exposures. Approximately 90% of melanoma cases are sporadic and arise from the accumulation of somatic mutations, largely driven by ultraviolet (UV) radiation exposure and age-related genetic alterations (3,4). Familial melanoma accounts for 7-15% of cases, whereas highly penetrant germline mutations are identified in only approximately 2% of patients (5,6). Cutaneous melanoma typically presents as a new or evolving pigmented lesion, often characterized by changes in size, shape, or colour and occasionally accompanied by pruritus, bleeding, or ulceration. Diagnosis is established by histopathological examination of a

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Abbreviations: TURBT, transurethral resection bladder tumour; CT, computed tomography; (18F)FDG PET, 18F-fluoro-2-deoxy-D-glucose positron emission tomography; ICI, immune checkpoint inhibitor; H&E, haematoxylin and eosin; BCG, Bacillus Calmette-Guérin

Key words: cutaneous melanoma, bladder metastasis, case report, rare metastasis, immunotherapy

biopsy specimen. Disease staging is based on key prognostic factors, including Breslow thickness, ulceration, lymph node involvement, and the presence of distant metastases. Prognosis is strongly stage-dependent, with excellent outcomes in localized disease following surgical excision and significantly poorer survival in advanced stages due to the high metastatic potential of melanoma (7). Over the past decade, the therapeutic landscape of advanced melanoma has been revolutionized by the introduction of immune checkpoint inhibitors, including anti-PD-1 agents (pembrolizumab and nivolumab), anti-CTLA-4 therapy (ipilimumab), and anti-LAG-3 therapy (relatlimab), as well as BRAF- and MEK-targeted therapies, resulting in significant improvements in patient survival (8). Nevertheless, metastatic melanoma remains a highly aggressive and clinically heterogeneous disease characterized by a marked propensity for distant spread. It most frequently involves regional lymph nodes, lungs, liver, and brain (9). Although melanoma can metastasize to virtually any organ, urinary bladder involvement is exceedingly rare in clinical practice despite being more frequently reported in autopsy series (10). Here, we report a case of cutaneous melanoma metastasizing to the urinary tract during adjuvant treatment with the anti-PD-1 monoclonal antibody pembrolizumab.

Case report

A 79-year-old woman, a former smoker with no family history of malignancy, was diagnosed in July 2023 with a superficial spreading melanoma of the back. Histopathological examination revealed a Clark level IV lesion with a Breslow thickness of 4.3 mm (pT4b), a mitotic rate of 9/mm², and evidence of lymphovascular invasion. Surgical margins were narrow, and a wider excision with sentinel lymph node biopsy was performed. The definitive pathological stage was pT4b N2a. Tumour PD-L1 analysis demonstrated negative expression. BRAF mutational status was assessed on representative formalin-fixed, paraffin-embedded tumour tissue by real-time polymerase chain reaction using TaqMan probes and the BRAF Mutation Detection Kit (EntroGen, Tarzana, CA, USA), after selection of tumour-enriched areas on haematoxylin and eosin-stained sections. The assay investigated clinically relevant BRAF hotspot mutations, including codon 600 alterations, according to the manufacturer's protocol. No BRAF mutation was detected, and the tumour was classified as BRAF wild-type. No next-generation sequencing or conventional sequencing was performed. Initial staging assessment with computed tomography (CT) scan and 18F-fluoro-2-deoxy-D-glucose positron emission tomography [(18F)FDG PET] showed no evidence of metastatic disease. The patient subsequently initiated adjuvant immunotherapy with pembrolizumab at a fixed dose of 200 mg every 21 days, scheduled for one year. In April 2024, restaging with CT and FDG-PET imaging revealed a newly developed right lower-lobe pulmonary nodule measuring approximately 1 cm, with a maximum standardized uptake value (SUV_{max}) of 2 (Fig. 1). Given the absence of additional metastatic sites, after multidisciplinary discussion, the patient underwent surgical excision of the lung nodule, and pathological evaluation confirmed the metastatic nature of the lesion. Pembrolizumab adjuvant therapy was continued until August 2024, when the patient presented with recurrent

haematuria. Prompt urological evaluation led to the identification, on cystoscopic exam, of an 8 mm bladder lesion. The lesion was highly suspicious for malignancy; therefore, transurethral resection bladder tumour (TURBT) was performed. An accurate histopathological analysis demonstrated the presence of metastatic cells from melanoma involving the bladder wall, with a molecular profile characterized by PD-L1 negativity and BRAF wild-type status (Fig. 2). Histological and immunohistochemical analyses were performed on formalin-fixed, paraffin-embedded tissue obtained from the transurethral resection of the bladder lesion. Four-micrometre-thick sections were prepared for haematoxylin and eosin staining and immunohistochemistry. The immunohistochemical panel included dual staining for pan-cytokeratin/SOX-10 and GATA3/HMB45. The following ready-to-use primary antibodies were used according to the manufacturers' protocols: anti-pan cytokeratin AE1/AE3/PCK26, mouse monoclonal antibody cocktail, Roche Diagnostics/Ventana, REF 760-2595; SOX-10, clone SP267, rabbit monoclonal primary antibody, Cell Marque/Roche Diagnostics, Roche no. 07560389001; GATA3, clone L50-823, mouse monoclonal primary antibody, Cell Marque/Roche Diagnostics, Roche no. 07107749001; and CONFIRM anti-Melanosome HMB45, clone HMB45, mouse monoclonal primary antibody, Roche Diagnostics/Ventana, REF 790-4366. The antibodies were used as prediluted automated-platform reagents. Slides were evaluated by light microscopy using a Zeiss Axio Imager 2 microscope equipped with a digital camera system, Carl Zeiss Microscopy GmbH, Jena, Germany, and representative photomicrographs were acquired at x10 and x20 magnification. The patient continued immunotherapy until December 2024. Restaging imaging performed in January 2025 revealed systemic disease progression with involvement of the lymph nodes, liver, and bone (Fig. 3). Consequently, in February 2025, the patient initiated first-line systemic therapy for metastatic disease with a combination of nivolumab and ipilimumab, completing three of the four planned cycles due to the onset of transient thyrotoxicosis, which resolved spontaneously after discontinuation of ipilimumab. The patient achieved an initial partial response to treatment followed by stable disease at subsequent imaging assessments. The patient is currently receiving nivolumab with no additional immune-related adverse events. As of March 2026, her disease remains clinically and radiologically stable. A summary of the patient's clinical course and treatment timeline is reported in Fig. 4.

Discussion

Although nearly all cancers have the potential to metastasize to the bladder, secondary bladder neoplasms account for only 2-3% of all malignant bladder tumours, most commonly originating from adjacent organs such as the colon, prostate, rectum, or cervix (10). In rare cases, the primary sites include the stomach (4.3%), skin (3.9%), lung (2.8%), and breast (2.5%) (11-13). The most common histological type of secondary bladder neoplasm is adenocarcinoma, whereas malignant melanoma is considerably rarer (10). Primary melanoma of the bladder is exceedingly rare, representing just 0.2% of all melanomas. Melanoma metastases to the urinary bladder are rare in clinical practice, with approximately thirty cases reported in the

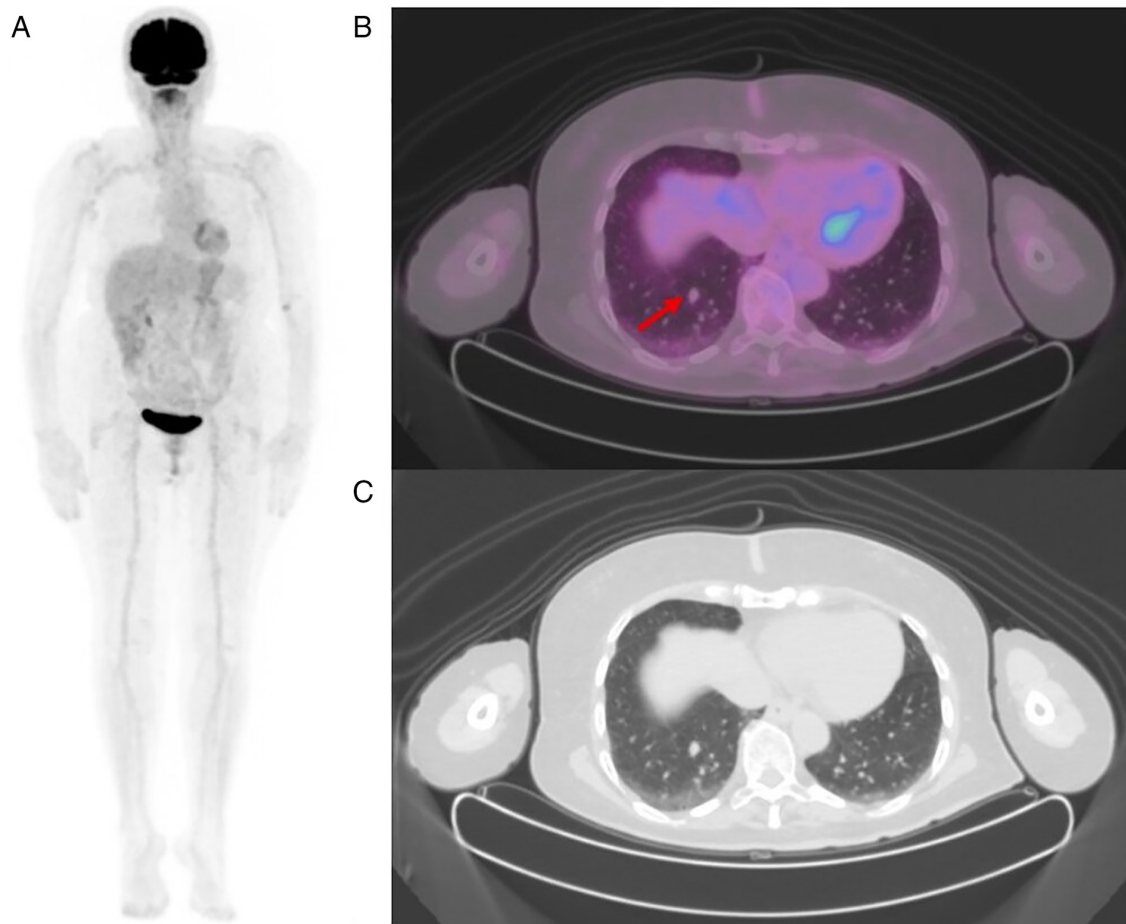


Figure 1. Detection of pulmonary metastasis from melanoma on (18F)FDG PET/CT imaging. (A) (18F)FDG PET maximum intensity projection of April 2024 negative for active disease, with the appearance of a subcentimetric suspicious right lung nodule resulted histologically positive for melanoma localizations. Axial (B) (18F)FDG PET and (C) CT indicative of the appearance of a subcentimetric suspicious right lung nodule (maximum standardized uptake value 2) resulted in histologically positive for melanoma localizations. The red arrow indicates the pulmonary nodule. (18F)FDG PET, 18F-fluoro-2-deoxy-D-glucose positron emission tomography.

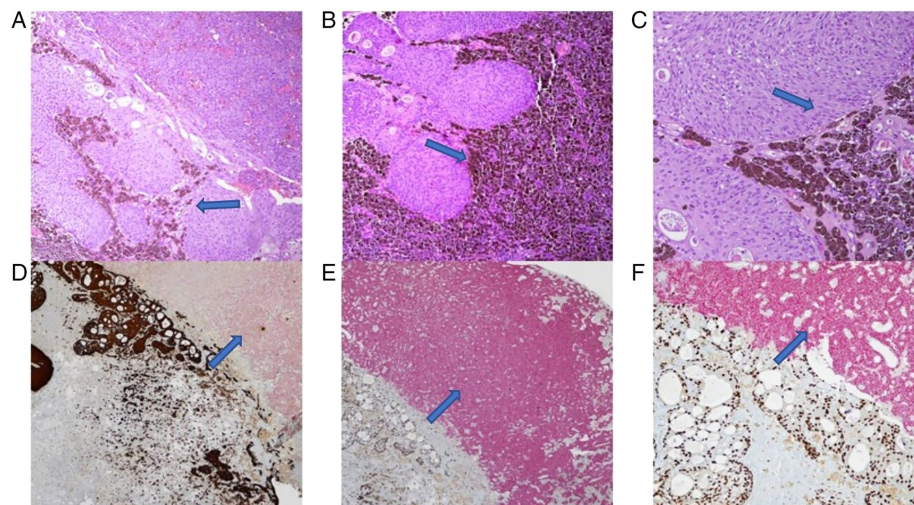


Figure 2. Bladder metastasis from melanoma: Histopathological and immunohistochemical findings consistent with metastatic melanoma. Histopathological examination demonstrates mucosal involvement of the urinary bladder by metastatic melanoma. (A) Low-power view of the bladder mucosa/urothelium showing a compact atypical epithelioid proliferation with frequent erythrocyte extravasation (H&E; magnification, x10); (B) a distinct mucosal area showing marked stromal melanosis (H&E; magnification, x10); (C) higher-magnification highlighting abundant coarse brown melanin pigment within the stroma (H&E; magnification, x20); (D) dual immunostaining (pan-cytokeratin/SOX10) demonstrating a sharp interface between cytokeratin-positive urothelium and SOX10-positive atypical melanocytic cells (magnification, x10); (E) dual immunostaining for GATA3/HMB45 further supports the diagnosis of metastatic melanoma, demonstrating a biphasic pattern composed of GATA3-positive urothelial cells and HMB45-positive atypical melanocytic component (magnification, x10), shown at higher magnification in (F) (magnification, x20). The arrows indicate representative foci of the metastatic melanoma component. H&E, haematoxylin and eosin.

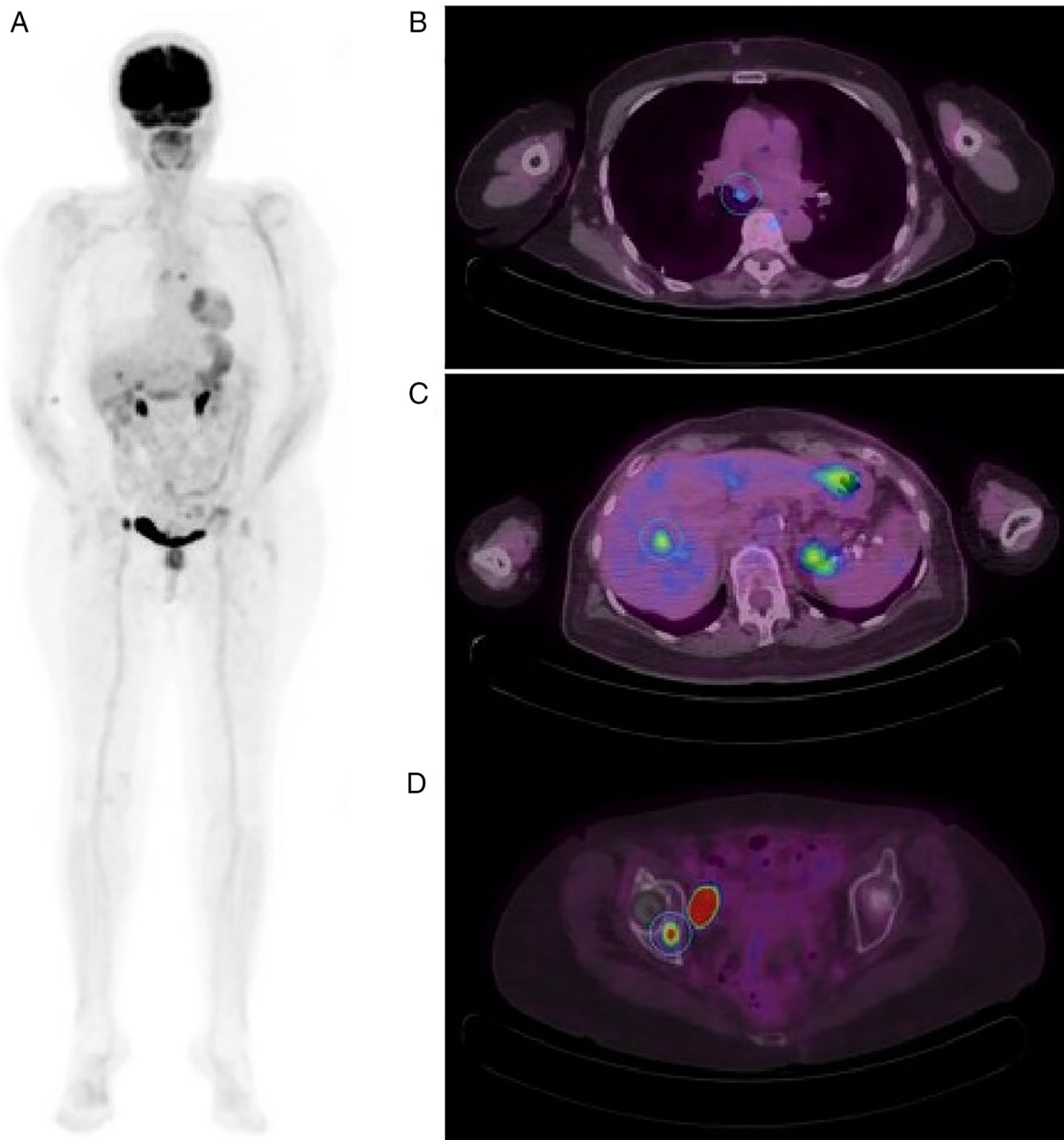


Figure 3. Systemic disease progression on (18F)FDG PET/CT imaging. (A) (18F)FDG PET maximum intensity projection of January 2025 indicative of the appearance of active disease in lymph nodes, liver and skeletal system; (B) axial (18F)FDG PET/CT in the subcarinal lymph node (SUVmax 4.2) (blue circle); (C) right liver lobe (SUVmax 6.6) (blue circle), and (D) right acetabulus (SUVmax 11.5) (blue circle). SUVmax, maximum standardized uptake value; (18F) FDG PET, 18F-fluoro-2-deoxy-D-glucose positron emission tomography.

literature over the past few decades (10). A summary of available literature (10,14-28) is reported in Table I. However, autopsy studies have shown bladder involvement in 18-37% of patients with disseminated melanoma, highlighting a higher incidence of bladder metastases in this setting (23). These metastases are commonly associated with synchronous lesions in other organs, suggesting an unfavourable prognosis (23,29). The mechanisms underlying bladder metastasis from melanoma remain incompletely understood. Hematogenous dissemination is considered the most likely pathway, owing to the highly vascular nature of melanoma and the rich vascular supply of the bladder. This hypothesis is supported by the frequent coexistence of bladder metastases with synchronous distant metastatic sites, including

lung, liver, bone, and brain involvement (30). Nevertheless, the discrepancy between the relatively high prevalence observed in autopsy studies and the rarity of clinically detected cases suggests that additional biological factors may influence metastatic colonization and tumour outgrowth within the bladder microenvironment (31). Local stromal composition, immune-cell infiltration, endothelial adhesion molecules, and organ-specific chemokine signalling may contribute to the establishment of clinically evident bladder metastases only in selected patients (32). Furthermore, the frequent asymptomatic presentation likely contributes to underdiagnosis during the early phases of dissemination. Symptomatic presentation is uncommon, occurring in only about 15% of cases, with gross haematuria being the most

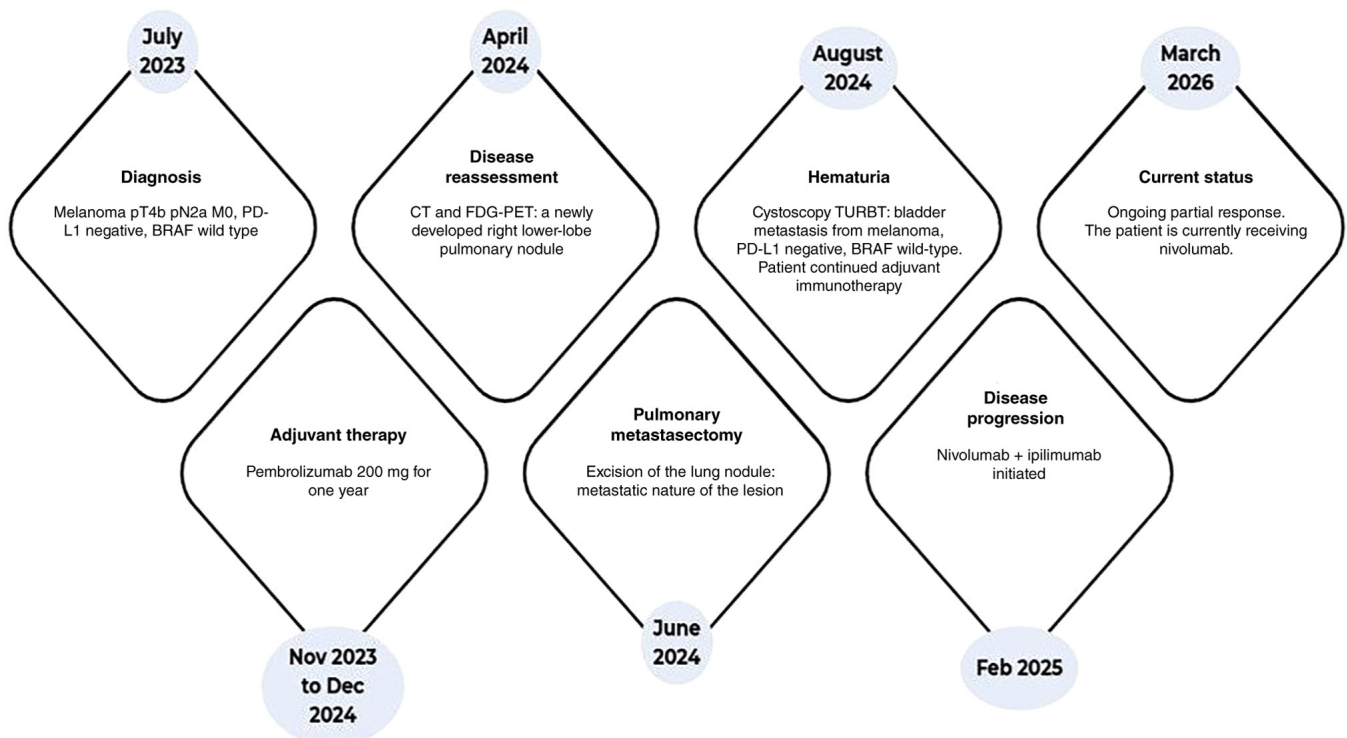


Figure 4. Clinical timeline of disease progression and treatment strategy. Timeline of the patient's clinical course, including diagnosis, adjuvant pembrolizumab treatment, oligoprogressive pulmonary and bladder metastases managed with local therapy, subsequent systemic progression, and initiation of nivolumab plus ipilimumab. CT, computed tomography; (18F)FDG PET, 18F-fluoro-2-deoxy-D-glucose positron emission tomography; TURBT, transurethral resection bladder tumour.

frequent manifestation (19), though urinary retention, dysuria, increased frequency, flank pain, or suprapubic pain may also occur (33). In the majority of cases, patients are asymptomatic, with metastases discovered incidentally on systemic follow-up imaging, including abdominal CT scans (20,23). Radiologically, melanomas, whether primary or metastatic, are hyperintense on T1-weighted magnetic resonance imaging (MRI) in 24-47% of cases, owing to the paramagnetic properties of melanin and its copper, manganese, and zinc content, which shorten T1 relaxation times (34,35). Haemorrhage, present in up to 50% of cases, can further enhance T1 signal, although poorly differentiated lesions may lack this feature (35). Recognition of this pattern is essential, and a T1-hyperintense bladder mass in a patient with known melanoma should prompt high suspicion (25). Histologically, pigmented bladder lesions provide an important diagnostic clue and should be confirmed immunohistochemically, with positive staining for S-100, HMB45, MART-1/Melan-A, tyrosinase, and MITF (29). Treatment of metastatic melanoma to the bladder should be individualized, taking into account the patient's overall condition, extent of metastatic disease, and symptom burden (36). Therapeutic options include TURBT, partial or radical cystectomy, radiotherapy, and systemic therapies. TURBT serves both diagnostic and palliative roles, relieving haematuria and urinary symptoms, although it rarely achieves complete tumour control. Radical cystectomy may be considered in selected patients with isolated lesions and good performance status; however, even in such cases, survival seldom exceeds three years (36,37). The management of bladder metastases from melanoma should follow a multidisciplinary approach, integrating surgical, systemic, and supportive treatments. The

therapeutic landscape of advanced melanoma has dramatically evolved with the introduction of immune checkpoint inhibitors and targeted therapies. In patients harbouring the BRAF V600E mutation, targeted therapies with BRAF and MEK inhibitors, as well as immune checkpoint inhibitors (anti-CTLA-4, anti-PD-1, anti-LAG3), have demonstrated superior overall and progression-free survival compared with conventional chemotherapy or interleukin-2 therapy (38). Immunotherapy has transformed the therapeutic landscape, achieving 5-year overall survival rates of up to 49.5% (23). However, treatment resistance and immune-related adverse events continue to pose significant clinical challenges. In our patient, metastatic dissemination occurred despite adequate local control of the primary melanoma and adjuvant treatment with pembrolizumab. Several high-risk pathological features of the primary lesion, including increased Breslow thickness, lymphovascular invasion, nodal involvement, and elevated mitotic activity, likely contributed to the aggressive biological behaviour of the disease. In contrast to most cases reported in the literature, we performed molecular profiling of the primary melanoma and metastatic sites, to study the evolution of PD-L1 expression and genomic alterations during tumour progression over time. Interestingly, molecular profiling remained substantially consistent across the primary tumour and metastatic sites, with persistent PD-L1 negativity and absence of BRAF alterations, supporting a model of metastatic spread driven by pre-existing resistant clones rather than the acquisition of new driver alterations during progression. This may reflect immune-selective pressure under PD-1 blockade leading to outgrowth of pre-existing resistant clones rather than true genomic evolution of the tumour (39). Another clinically relevant

Table I. Case reports of melanoma metastasis to the bladder.

Author	Year	Age	Gender	Presentation	Timing (Syn/Met)	Other metastatic sites	Treatment	OS	Molecular profile	Primary tumour	(Refs.)
Walsh <i>et al</i>	1966	68	Male	Haematuria	Met	NR	TURBT	NR	NR	Cutaneous melanoma	(14)
deKernion <i>et al</i>	1975	56	Male	Haematuria	Met	Small bowel and liver	Immunotherapy with BCG	11 months	NR	Cutaneous melanoma	(15)
Arapantoni-Dadioti <i>et al</i>	1995	28	Female	Pain and burning during micturition	Met	Skin, lung, brain	Patient refused any further treatment	NR	NR	Melanoma	(16)
Ergen <i>et al</i>	1995	65	Male	Right flank pain and haematuria	Met	Gastroduodenal mucosa	NR	NR	NR	Cutaneous melanoma	(17)
Demirkesen <i>et al</i>	2000	45	Female	Urinary frequency, macroscopic haematuria and right inguinal swelling	Met	Skin, lymph nodes, and meninges	Resection, chemo-immunotherapy protocol that consisted of cisplatin, DTIC, fotomustin and interferon α , followed by immunotherapy protocol of interferon α and interleukin-2	13 months	NR	Melanoma	(18)
Ozan Efesoy <i>et al</i>	2011	60	Female	Gross haematuria and weight loss	Met	Brain, lymph nodes, and lung	Transurethral resection	7 months	NR	Cutaneous melanoma	(19)
Eric S. Wisenbaugh <i>et al</i>	2012	81	Male	Microscopic haematuria Urinary frequency and hesitancy	Met	None	TURBT	NR	NR	Cutaneous melanoma	(20)
Eric S. Wisenbaugh <i>et al</i>	2012	84	Male	Incidental finding	Met	Small bowel	TURBT	4 months	NR	Cutaneous melanoma	(20)
Eric S. Wisenbaugh <i>et al</i>	2012	85	Male	Gross haematuria	Met	Abdominal lymph nodes, stomach, lung	TURBT	4 months	NR	Cutaneous melanoma	(20)
Eric S. Wisenbaugh <i>et al</i>	2012	62	Female	Incidental on restaging CT	Met	NR	TURBT	5 months	NR	Uveal melanoma	(20)
Arvind Rishi <i>et al</i>	2014	61	Female	Gross haematuria	Met	Subcutaneous tissue, brain, lungs	TURBT	2 months	BRAF V600E mutation	Cutaneous melanoma	(21)
Rahoui Moez <i>et al</i>	2020	31	Male	Haematuria and low urinary tract signs	Met	Lymph nodes	Monopolar loop electrocautery followed by chemotherapy	NR	NR	Cutaneous melanoma	(22)
Raj A. Kumar <i>et al</i>	2021	78	Female	Haematuria	Met	Lung and meninges	Ipilimumab/nivolumab combination immunotherapy	NR	BRAF V600E mutation	Cutaneous melanoma	(23)

Table I. Continued.

Author	Year	Age	Gender	Presentation	Timing (Syn/Met)	Other metastatic sites	Treatment	OS	Molecular profile	Primary tumour	(Refs.)
Jesús Machuca-Aguado <i>et al</i>	2022	78	Male	Haematuria	Met	Lung, liver, lymph nodes and bone	2015 haemostatic radiotherapy and 2017 TURBT	36 months	NR	Uveal melanoma	(24)
Jesús Machuca-Aguado <i>et al</i>	2022	56	Male	Incidental finding	Met	NR	NR	NR	NR	Uveal melanoma	(24)
Duarte Vieira e Brito <i>et al</i>	2022	73	Male	Haematuria	Met	Suspected pulmonary and peritoneal metastasis	TURBT	NR	NR	Uveal melanoma	(9)
Maria Clara Fernandes <i>et al</i>	2022	47	Female	Lower urinary tract symptoms and haematuria	Met	Left inguinal nodes, spleen, lungs, brain and endometrium	TURBT	NR	NR	Cutaneous melanoma	(25)
Takashi Ueno <i>et al</i>	2024	86	Male	Incidental finding	Met	Liver	TURBT followed by best supportive care	NR	BRAF wild-type	Uveal melanoma	(10)
Takashi Ueno <i>et al</i>	2024	57	Male	Right abdominal discomfort	Met	None	TURBT	22 years	NR	Cutaneous melanoma	(10)
Takashi Ueno <i>et al</i>	2024	79	Female	Haematuria	Met	Lung, lymph nodes, adrenal glands, suspected peritoneal nodule	TURBT followed by pembrolizumab	NR	NR	Cutaneous melanoma	(10)
Abdelmounim Boughaleb <i>et al</i>	2024	75	Female	Haematuria	Met	Breast, liver, lymph nodes, bone, and multifocal subcutaneous and muscular lesions	TURBT followed by continuation of immunotherapy with nivolumab and ipilimumab	NR	NR	Cutaneous melanoma	(26)
Tu Anh Do <i>et al</i>	2024	53	Female	Incidental finding	Met	Lymph nodes	Chemotherapy with dacarbazine	10 months	BRAF wild-type	Cutaneous melanoma	(27)
Marwin Anandratil <i>et al</i>	2024	71	Female	Haematuria	Met	None	Surgery followed by immunotherapy	NR	NR	Cutaneous melanoma	(28)
Mariapia Marafioti <i>et al</i>	2026	79	Female	Haematuria	Met	Lung, lymph nodes, liver, bone	Adjuvant immunotherapy with pembrolizumab for one year; first-line systemic therapy with a combination of nivolumab and ipilimumab	Patient alive	Negative PD-L1 expression, BRAF wild-type	Cutaneous melanoma	

NR, not reported; OS, overall survival; Syn, synchronous; Met, metachronous; TURBT, transurethral resection bladder tumour; PD-L1, programmed death ligand 1; PD-1, programmed cell death protein 1; BCG, Bacillus Calmette-Guérin.

aspect of this case is the development of oligoprogression during adjuvant pembrolizumab therapy. Oligoprogression is increasingly recognized as a distinct evolutionary pattern during immune checkpoint inhibition, in which a limited number of metastatic sites acquire resistance while the remaining disease burden remains controlled by systemic therapy. This phenomenon may reflect spatial and temporal heterogeneity in tumour evolution, with resistant subclones emerging under immune-selective pressure (40). In melanoma, acquired resistance to anti-PD-1 therapy has been associated with several mechanisms, including defects in interferon- γ signalling, impaired antigen presentation through alterations in β 2-microglobulin or HLA expression, T-cell exhaustion, compensatory upregulation of alternative inhibitory checkpoints, and development of an immunosuppressive tumour microenvironment enriched in regulatory T cells and myeloid-derived suppressor cells. The persistent PD-L1 negativity observed in both the primary tumour and metastatic lesions in our patient may reflect a poorly inflamed tumour microenvironment, potentially consistent with an immune-desert or non-inflamed phenotype associated with reduced sensitivity to PD-1 blockade (41,42). In our patient, both the isolated pulmonary metastasis and the subsequent solitary bladder lesion were amenable to local treatment while systemic pembrolizumab was maintained. This strategy was supported by the hypothesis that most tumour sites could still remain partially controlled by ongoing immune checkpoint inhibition, whereas locally resistant clones could be eradicated through surgery. Emerging evidence in melanoma and other solid tumours suggests that local ablative approaches, including surgery or radiotherapy, may prolong the duration of benefit from immunotherapy in selected patients with oligoprogression, delaying the need for systemic treatment escalation and preserving quality of life (43). Historically, surgery was primarily palliative-performed to relieve symptoms such as anaemia or urinary obstruction-rather than to extend survival. However, in the era of modern immunotherapy, surgical resection of oligometastatic lesions has been associated with longer overall survival in selected patients (44). Despite these advances, the prognosis of metastatic melanoma remains poor, with a median survival of approximately 12 months and a 5-year survival rate ranging between 5 and 19% (37,45). An additional noteworthy aspect of this case is the durable disease control achieved with nivolumab plus ipilimumab after progression during adjuvant pembrolizumab therapy. Combined CTLA-4 and PD-1 blockade may partially overcome resistance to prior anti-PD-1 monotherapy by enhancing T-cell priming, broadening the repertoire of antitumor T-cell responses, and restoring immune activation within resistant tumour sites (46,47). This observation further supports the biological rationale for sequential and combinatorial immunotherapeutic strategies in metastatic melanoma, even after progression during prior anti-PD-1 treatment. In conclusion, metastatic bladder melanoma carries a particularly poor prognosis and the highest mortality risk among sites of melanoma dissemination. Even with surgical resection and systemic therapy, no patient has been reported to survive beyond three years following bladder metastasis resection (35). Since the advent of ICIs, management has remained primarily palliative, focusing on symptom control and quality-of-life improvement. Nevertheless, this case highlights how modern immunotherapeutic strategies, combined with local treatment

approaches for oligoprogressive disease, may contribute to prolonged disease control even in patients with atypical metastatic sites. Early recognition of unusual metastatic localizations, careful multidisciplinary evaluation, and integration of local and systemic therapies are essential to optimize clinical outcomes in selected patients with metastatic melanoma.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

Conceptualization was conducted by MMA, MMu, ML and MS. Formal analysis and data interpretation were performed by MMA, MMu, GC, MIP and MV. Data acquisition and clinical management were carried out by MMA, MMu, LP, RL, GC, MV, ML and MS. Literature analysis, writing of the original draft, and reviewing and editing of the manuscript was performed by MMA and MMu. Supervision was provided by MIP, ML and MS. Project administration was conducted by MMA and MMu. All authors have read and approved the final version of the manuscript. MS and ML confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

References

1. Siegel RL, Kratzer TB, Wagle NS, Sung H and Jemal A: Cancer statistics, 2026. *CA Cancer J Clin* 76: e70043, 2026.
2. Garbe C, Amaral T, Peris K, Hauschild A, Arenberger P, Basset-Seguin N, Bastholt L, Bataille V, Brochez L, Del Marmol V, *et al*: European consensus-based interdisciplinary guideline for melanoma. Part 1: Diagnostics-update 2024. *Eur J Cancer* 215: 115152, 2025.
3. Jazlyn R, Wadt KAW and Hayward NK: Melanoma genetics. *J Med Genet* 53: 1-14, 2016.
4. Long GV, Swetter SM, Menzies AM, Gershenwald JE and Scolyer RA: Cutaneous melanoma. *Lancet* 402: 485-502, 2023.
5. Pastorino L, Andreotti V, Dalmaso B, Vanni I, Ciccarese G, Mandalà M, Spadola G, Pizzichetta MA, Ponti G, Tibiletti MG, *et al*: Insights into genetic susceptibility to melanoma by gene panel testing: Potential pathogenic variants in ACD, ATM, BAP1, and POT1. *Cancers (Basel)* 12: 1007, 2020.

6. Zocchi L, Lontano A, Merli M, Dika E, Nagore E, Quaglini P, Puig S and Ribero S: Familial melanoma and susceptibility genes: A review of the most common clinical and dermoscopic phenotypic aspect, associated malignancies and practical tips for management. *J Clin Med* 10: 3760, 2021.
7. Amaral T, Ottaviano M, Arance A, Gili R, Chiarion-Sileni V, Donia M, Dummer R, Garbe C, Gershenwald JE, Gogas H, *et al*: Cutaneous melanoma: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 36: 10-30, 2025.
8. Boutros A, Croce E, Ferrari M, Gili R, Massaro G, Marconcini R, Arecco L, Tanda ET and Spagnolo F: The treatment of advanced melanoma: Current approaches and new challenges. *Crit Rev Oncol Hematol* 196: 104276, 2024.
9. Vieira E, Brito D, Pereira J, Pereira-Lourenço M, Ricardo G and Rabaça C: Bladder tumour as a first manifestation of metastatic choroid melanoma. *Urol Case Rep* 42: 101996, 2022.
10. Ueno T, Kiwaki T, Betsunoh H, Ito K, Murashima T, Fujii M, Nagai T, Mukai S, Sawada A and Kamoto T: Metastasis of malignant melanoma to urinary tract: A case report. *J Med Case Rep* 18: 396, 2024.
11. Bates AW and Baithun SI: Secondary neoplasms of the bladder are histological mimics of nontransitional cell primary tumours: Clinicopathological and histological features of 282 cases. *Histopathology* 36: 32-40, 2000.
12. Velcheti V and Govindan R: Metastatic cancer involving bladder: A review. *Can J Urol* 14: 3443-3448, 2007.
13. Goldstein AG: Metastatic carcinoma to the bladder. *J Urol* 98: 209-215, 1967.
14. Walsh EJ, Ockuly EA, Ockuly EF and Ockuly JJ: Treatment of metastatic melanoma of the bladder. *J Urol* 96: 472-478, 1966.
15. deKernion JB, Golub SH, Gupta RK, Silverstein M and Morton DL: Successful transurethral intralesional BCG therapy of a bladder melanoma. *Cancer* 36: 1662-1667, 1975.
16. Arapantoni-Dadioti P, Panayiotides J, Kalkandi P, Christodoulou C and Delides GS: Metastasis of malignant melanoma to a transitional cell carcinoma of the urinary bladder. *Eur J Surg Oncol* 21: 92-93, 1995.
17. Ergen A, Balbay MD, Alexis R, Nardi PM and Grunberger I: Renal vein thrombosis and metastasis to the bladder: An unusual presentation of malignant melanoma. *Int Urol Nephrol* 27: 547-549, 1995.
18. Demirkenes O, Yaycioglu O, Uygur N, Demir G and Yalcin V: A case of metastatic malignant melanoma presenting with hematuria. *Urol Int* 64: 118-120, 2000.
19. Efesoğlu O and Cayan S: Bladder metastasis of malignant melanoma: A case report and review of literature. *Med Oncol* 28 (Suppl 1): S667-S669, 2011.
20. Wisenbaugh ES, Stanton ML, Grimsby GM, Tyson MD and Castle EP: Metastatic malignant melanoma to the bladder: A case series. *Curr Urol* 6: 53-56, 2012.
21. Rishi A, Anderson TA, Kirschenbaum AM and Unger PD: Metastatic malignant melanoma to urinary bladder: A potential pitfall for high-grade urothelial carcinoma. *Int J Surg Pathol* 22: 347-351, 2014.
22. Moez R, Khairredine MD, Sahnoun W, Zehani A, Bibi M, Ouannes Y, Sellami A, Rhouma SB and Nouria Y: Symptomatic bladder metastasis of malignant melanoma: A case report. *J Surg Case Rep* 2020: rjaa509, 2020.
23. Kumar RA, Batra N, Frankel J and Kumar U: Melanoma metastasis to the bladder: A case report. *Urol Case Rep* 40: 101941, 2021.
24. Machuca-Aguado J, Rodríguez-Zarco E, Carrero-García B and Vázquez-Ramírez FJ: Metastasis of Uveal melanoma in bladder: Presentation of two cases and review of the literature. *Arch Esp Urol* 75: 873-877, 2022.
25. Fernandes MC, Shoushtari A, Leitao MM Jr, Chui MH, Al-Ahmadie H and Petkovska I: Metastatic melanoma concurrent to the urinary bladder and endometrium: Case report. *J Med Imaging Radiat Oncol* 66: 643-646, 2022.
26. Boughaleb A, Kubiak M, Bourimi C, Tariqi R, Leroux PA and El Kentaoui H: Melanoma metastasis to the bladder: A case report of an underdiagnosed entity. *Int J Surg Case Rep* 122: 110048, 2024.
27. Do TA, Mai NT, Le UT, Nguyen DN, Vu PT and Van Nguyen C: Metastatic melanoma to the urinary bladder with synchronous or metachronous metastasis to other organs: Clinicopathological characteristics and outcome. *Int J Surg Case Rep* 120: 109789, 2024.
28. Anandratni M, Maini V, Asarian A and Xiao P: Metastasis of malignant melanoma to the urinary bladder & descending colon: A case report and literature review. *Urol Case Rep* 57: 102883, 2024.
29. Patil RV, Woldu SL, Lucas E, Quinn AM, Francis F and Margulis V: Metastatic melanoma to the bladder: Case report and review of the literature. *Urol Case Rep* 11: 33-36, 2017.
30. Calomarde-Rees L, García-Calatayud R, Requena Caballero C, Manrique-Silva E, Traves V, García-Casado Z, Soriano V, Kumar R and Nagore E: Risk factors for lymphatic and hematogenous dissemination in patients with stages I to II cutaneous melanoma. *JAMA Dermatol* 155: 679-687, 2019.
31. Feldman A, Borak S, Rais-Bahrami S and Gordetsky J: Secondary malignancies of the bladder: Avoiding the diagnostic pitfall. *Int J Surg Pathol* 26: 120-125, 2018.
32. Peinado H, Zhang H, Matei IR, Costa-Silva B, Hoshino A, Rodrigues G, Psaila B, Kaplan RN, Bromberg JF, Kang Y, *et al*: Pre-metastatic niches: Organ-specific homes for metastases. *Nat Rev Cancer* 17: 302-317, 2017.
33. Abdou CA, Wolff EH, Tracey AT and Klausner AP: Metastatic melanoma to the bladder presenting as autonomic dysreflexia in a patient with paraplegia. *Urol Case Rep* 39: 101820, 2021.
34. Patnana M, Bronstein Y, Szklaruk J, Bedi DG, Hwu WJ, Gershenwald JE, Prieto VG and Ng CS: Multimethod imaging, staging, and spectrum of manifestations of metastatic melanoma. *Clin Radiol* 66: 224-236, 2011.
35. Wong VK, Lubner MG, Menias CO, Mellnick VM, Kennedy TA, Bhalla S and Pickhardt PJ: Clinical and imaging features of noncutaneous melanoma. *AJR Am J Roentgenol* 208: 942-959, 2017.
36. Ogunremi O, Sirjuesingh D and Deshpande A: Metastatic melanoma to the urinary bladder: A rare cause of visible haematuria. *Case Rep Urol* 2024: 5516547, 2024.
37. Venyo AK: Melanoma of the urinary bladder: A review of the literature. *Surg Res Pract* 2014: 605802, 2014.
38. Paterson A, Sut M, Kaul A, Altieri V, Mutch F, Patel J and Sharma H: Metastatic malignant melanoma of the urinary bladder: Case report and literature review. *Cent Eur J Urol* 65: 232-234, 2012.
39. Wells A, Clark A, Bradshaw A, Ma B and Edington H: The great escape: How metastases of melanoma, and other carcinomas, avoid elimination. *Exp Biol Med* (Maywood) 243: 1245-1255, 2018.
40. Guida M, Bartolomeo N, De Risi I, Fucci L, Armenio A, Filannino R, Ruggieri E, Macina F, Traversa M, Nardone A, *et al*: The management of Oligoprogression in the landscape of new therapies for metastatic melanoma. *Cancers* (Basel) 11: 1559, 2019.
41. Li W, Gu J, Fan H, Zhang L, Guo J and Si L: Evolving cancer resistance to anti-PD-1/PD-L1 antibodies in melanoma: Comprehensive insights with future prospects. *Crit Rev Oncol Hematol* 201: 104426, 2024.
42. Zheng S, Wang W, Shen L, Yao Y, Xia W and Ni C: Tumor battlefield within inflamed, excluded or desert immune phenotypes: The mechanisms and strategies. *Exp Hematol Oncol* 13: 80, 2024.
43. Puza CJ, Bressler ES, Terando AM, Howard JH, Brown MC, Hanks B, Salama AKS and Beasley GM: The emerging role of surgery for patients with advanced melanoma treated with immunotherapy. *J Surg Res* 236: 209-215, 2019.
44. Deutsch GB, Flaherty DC, Kirchoff DD, Bailey M, Vitug S, Foshag LJ, Faries MB and Bilchik AJ: Association of surgical treatment, systemic therapy, and survival in patients with abdominal visceral melanoma metastases, 1965-2014: Relevance of surgical cure in the Era of modern systemic therapy. *JAMA Surg* 152: 672-678, 2017.
45. Sandru A, Voinea S, Panaitescu E and Blidaru A: Survival rates of patients with metastatic malignant melanoma. *J Med Life* 7: 572-576, 2014.
46. Rasmussen M, Durhuus JA, Nilbert M, Andersen O and Therkildsen C: Response to immune checkpoint inhibitors is affected by deregulations in the antigen presentation machinery: A systematic review and meta-analysis. *J Clin Med* 12: 329, 2023.
47. Phadke MS, Li J, Chen Z, Rodriguez PC, Mandula JK, Karapetyan L, Forsyth PA, Chen YA and Smalley KSM: Differential requirements for CD4+ T cells in the efficacy of the anti-PD-1+LAG-3 and anti-PD-1+CTLA-4 combinations in melanoma flank and brain metastasis models. *J Immunother Cancer* 11: e007239, 2023.

