PATIENT-CENTERED FOCUSED REVIEW

Melanuria in a patient with BRAF-mutant metastatic melanoma of unknown primary: Insights on the pathophysiology, differential diagnosis, prognosis, and treatment

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ABSTRACT

Melanuria is the dark brown discoloration of the urine and an uncommon manifestation in patients with melanoma. It is an ominous sign, usually indicating widespread disease. In this article, through an illustrative case, we discuss the pathophysiological, clinical, and prognostic characteristics of melanuria in melanoma. Moreover, we aim to provide the available data for the prompt diagnosis and treatment of patients presenting with melanuria. We present the case of a 47-year-old man presenting with melanuria and diffure melanosis cutis, who was eventually diagnosed with a BRAF-mutated metastatic melanoma of unknown primary. The patient was started on a BRAF and MEK inhibitor, but he had a rapid disease progression and succumbed to the disease. There is only a limited number of case reports of melanoma patients with melanuria receiving targeted therapies or immune checkpoint inhibitors. In these reports, variable treatment responses have been described. In view of the increasing significance of targeted therapies and immunotherapy for melanoma, more cases are needed to improve our understanding on the prognostic significance of melanuria in the era of novel therapies for melanoma.

Keywords: Melanuria; Melanoma of unknown primary; Metastatic melanoma; BRAF mutation. **[Am J Med Sci 2022;■(■):1–5.]**

INTRODUCTION

The incidence of melanoma is increasing worldwide, especially in countries with moderate climates and a high percentage of sunny days during the year, alongside an increase of melanoma-related mortality.[1] Unlike most solid tumors, melanoma affects mostly young and middle-aged people, with a linearly increasing incidence between the ages of 25 and 50 years.[2]

Melanuria refers to the dark brown discoloration of the urine due to increased urine excretion of melanin precursors. Melanuria is not commonly observed in patients with metastatic melanoma, although it is consistently reported to occur in up to 15% of the cases, especially in patients with metastatic visceral disease.[3–5] This rate might be higher than expected in clinical practice and may include cases in which brown discoloration of urine is not macroscopically apparent, but increased levels of melanin precursors can be detected with laboratory methods. Interestingly, in cases of advanced melanoma, melanuria is often associated with a diffuse skin hyperpigmentation, termed as diffuse melanosis cutis (DMC).[5–7] In this article, we describe the case of a middle-aged melanoma patient presenting with melanuria and DMC who was treated with BRAF- and MEK-inhibitors.

CASE PRESENTATION

A 47-year-old Caucasian male was admitted due to non-productive cough, shortness of breath, malaise, and loss of body weight that began about one month before admission. In addition, the patient noticed dark discoloration of his urine a few days before presentation. His past medical history was unremarkable. The clinical examination revealed diffuse skin hyperpigmentation, crackles in lung auscultation, ascites, and pitting edema of both legs. Moreover, macroscopically dark urine was noticed (Fig. 1).

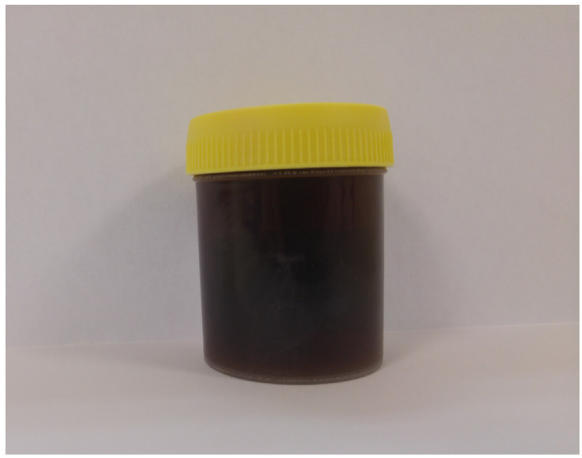

FIG. 1. Patient's dark urine.

A computed tomography (CT) revealed multiple metastatic lesions in the left lung, left pleura, liver, and peritoneum and one metastatic lesion in the cerebellum. The urinalysis revealed melanuria (positive sodium nitroprusside test) and the cytology of the urine showed numerous pigment-containing macrophages and clusters of atypical cells, with large nuclei and irregular nuclear membrane that were strongly positive for HMB-45 and S100 protein (Fig. 2a and b). Eventually, melanoma infiltration was confirmed histologically with a pleural biopsy.

The dermatological, ear, nose, and throat examination and the ophthalmological evaluation did not reveal any suspicious lesions for primary melanoma. Thus, the patient was diagnosed as having melanoma of unknown primary.

A large volume abdominal paracentesis was performed; the ascitic fluid was dark brown and its examination showed >250 polymorphonuclear leukocytes/mm,[8] a serum-ascites albumin gradient >1.1, while the cytology revealed melanoma cells in the fluid (Fig. 3a and b).

Molecular testing on the pleura specimen revealed a BRAF V600E mutation and the patient was started on vemurafenib (BRAF inhibitor) at 960 mg PO q12hr and cobimetinib (MEK inhibitor) at 60 mg PO daily. Under treatment, melanuria subsided temporarily for two weeks, while no response of skin discoloration was observed. In the next two months, the patient's condition deteriorated due to development of severe neurological symptoms owing to brain metastasis; at this point treatment was discontinued and further treatment with immunotherapy was declined by the patient and his relatives. He died two months later.

DISCUSSION

Pathophysiology

In metastatic melanoma, central ischemia of melanoma lesions, immunological responses, and antineoplastic therapies cause cytolysis. This results in the release of melanin precursors and melanosomes in the bloodstream. Urinary melanogens are indolic and phenolic compounds, which are excreted in an elevated amount in the urine of patients with melanoma.[5] They constitute colorless melanin precursors or derivatives formed during the synthesis or catabolism of melanin and have been investigated in the past as potential tumor markers for melanoma.[5,9] The dark brown color of the urine in melanuria is assumed to arise from autooxidation of pheomelanin (Fig. 4[10]) in the air after filtration by the glomerulus and extraction in the urine.[5,11] The levels of urinary melanogens have been correlated with the extent of melanoma, but since more than 40 melanogens have been detected and because their presence in the urine is also a normal phenomenon, especially in the summer as a result of stimulation of the pigmentary system by ultraviolet radiation, none of them was specific enough as a melanoma marker.[12,13] Vanilmandelic acid, homovalinic acid, 5,6-dihydroxyindole-2-carboxylic acid, tryptophan, 5-hydroxyindole-3-acetic acid and indole sulphate are

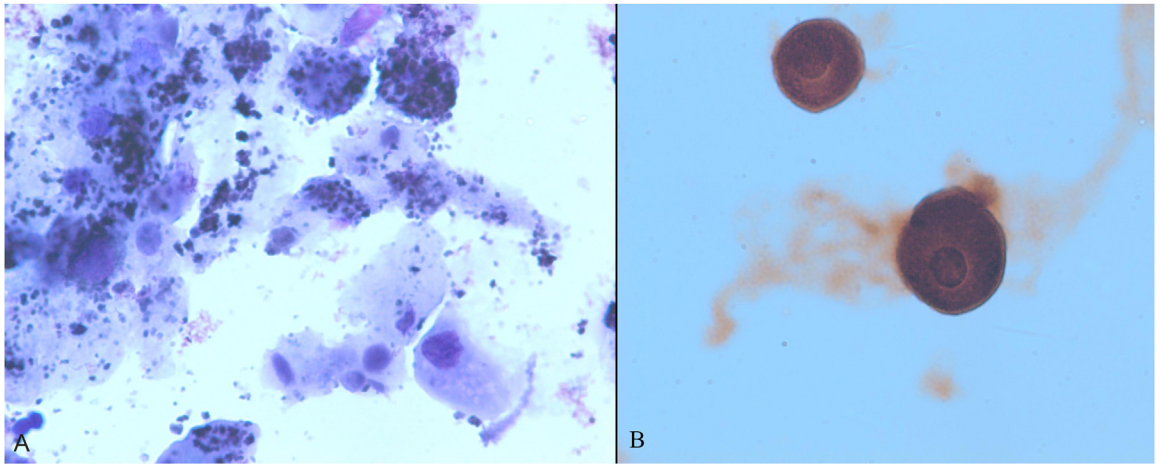

FIG. 2. A: Urine, May-Grunwald Giemsa stain, x1000. Numerous. pigment containing, macrophages and occasional atypical cells with large, hyperchromatic nuclei and irregular nuclear membrane. B: Urine, Positive immunostaining for Human melanoma black 45, x1000.

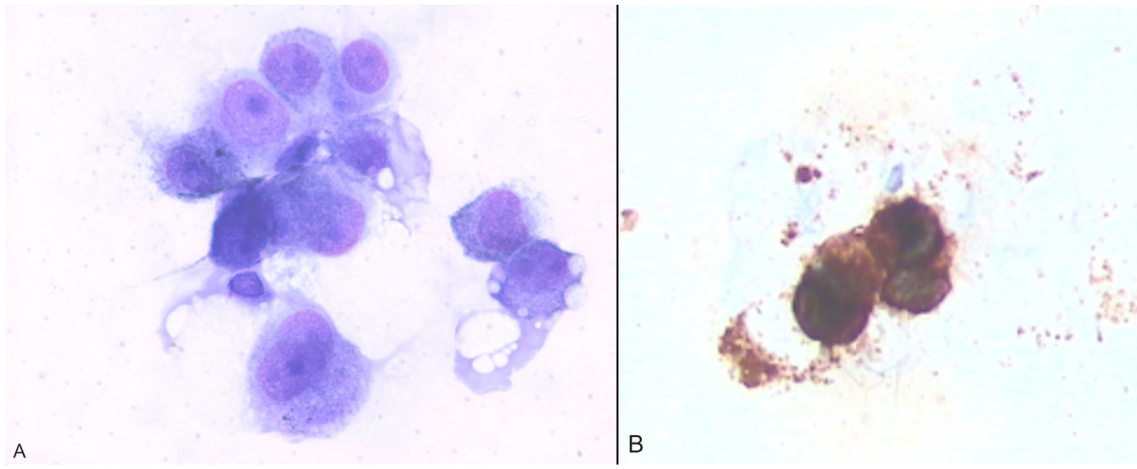

FIG. 3. A: Melanoma cells in the ascitic fluid of the patient. May-Grünwald-Giemsa stain, x 1000. B: Ascitic fluid, Positive immunostaining for Human melanoma black 45, x1000.

some examples of melanogens that have been identified in the urine of melanoma patients.[14]

DMC refers to the dark grey discoloration of the skin and mucosa, sometimes accompanied by darkening of hair, sputum, and peritoneal fluid.[15] In histopathological specimens of patients with DMC, melanin deposition can be found in histiocytes and fibroblasts, as well as in extracellular dermal connective tissue.[6] Interestingly, histiocytes harboring melanosomes show a characteristic perivascular distribution.[7] The exact pathophysiological mechanism of DMC remains unknown. According to one of the most widely accepted theories, DMC arises through absorption and processing of auto-oxidized freely circulating pheomelanin precursors into melanin by dermal histiocytes.[7,16]

Differential diagnosis

Dark urine appears in a limited number of possible diagnoses. The differential diagnosis includes melanuria, hemoglobinuria, myoglobinuria, ochronosis (alkaptonuria), and copper or phenol poisoning.[17]

In patients with known metastatic melanoma, dark urine may be due to other metabolic causes, such as hemoglobinuria and myoglobinuria, due to drug toxicities, or even severe bilirubinuria in cases of obstructive jaundice due to metastases. Although in patients with known metastatic melanoma melanuria is an easy diagnosis, in patients without such a history, a presentation with dark urine may be challenging.

The diagnosis of melanuria is based on the macroscopic and microscopic examination of the urine, the ferric chloride tube test, and/or the sodium nitroprusside test. In the ferric chloride tube test, melanin will react with ferric chloride leading to a gray or black precipitate that can be easily differentiated from the reactions produced by other amino acid products. In the sodium nitroprusside (or Thormählen) test, melanin will react with sodium nitroprusside producing a red color of the specimen.[18] The distinctive characteristic of urine with melanin precursors is that it becomes dark after its exposure to oxygen, in contrast to homogentisic acid urine which turns dark after becoming alkaline.[19] As mentioned previously, melanuria is usually caused by urine secretion of melanogens, which are colorless precursors of the melanin pigment. Autooxidation in the air provides the dark brown color of the urine. In these cases, the urine usually is not dark colored when freshly voided.[5]

The microscopic examination of the urine may reveal the presence of atypical cells, dark brown casts with positive melanin stain, and pigment containing macrophages.[20] After confirming the presence of melanuria, cytology may reveal the presence of melanoma cells in the urine in a significant percentage of cases. Thus, investigation of patients with dark urine in the absence of a known diagnosis of melanoma should include microscopic examination of the urine, sodium nitroprusside test and urine cytology.

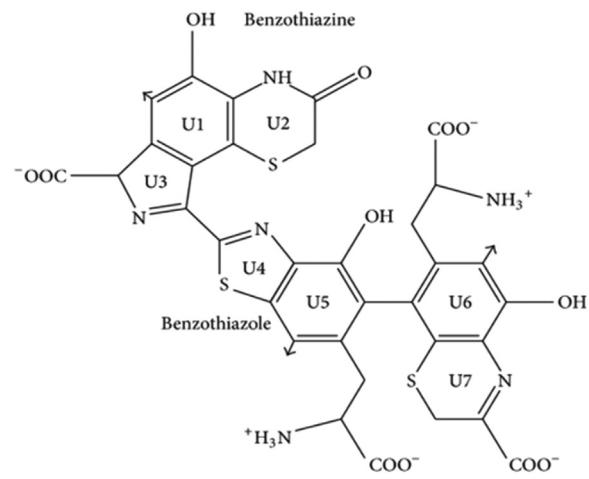

FIG. 4. The chemical structure of pheomelanin.[10]

Clinical implications and prognosis

Melanuria represents an uncommon complication of advanced or metastatic melanoma and is considered to be an ominous sign.[4,17] Interestingly, there is a significant association of melanuria with DMC, as in 77% of all published DMC cases until 2013 presence of melanuria was also reported.[7] The positive association of DMC and melanuria might be theoretically explained by the increased cytolysis rate in patients with disseminated melanoma, which leads to elevated serum concentrations and therefore increased skin deposition or urine excretion of melanin precursors.

It is currently unknown whether resolution of melanuria upon treatment initiation might represent a favorable prognostic indicator in patients with melanoma. Perez et al. described a patient with melanuria with bone and spleen metastases, whose urine color returned to normal after six cycles of palliative treatment with dacarbazine.[7] It is worth mentioning that in patients with advanced melanoma response rates to dacarbazine have been described to be between 5% and 15%.[21]

There are only a few reports regarding the use of BRAF-inhibitors or immune checkpoint inhibitors in patients with melanuria. A patient with a BRAFV600E mutant melanoma with DMC and melanuria who showed a good response to treatment with a BRAF inhibitor was reported in 2014.[22] In another case of BRAFV600E positive melanoma with diffuse hyperpigmentation and melanuria, the patient died two weeks after presentation despite treatment initiation with BRAF inhibitors.[23] In 2019, Yamaguchi and colleagues published a case of melanuria which was responsive to treatment with an immune checkpoint inhibitor as assessed by a macroscopical change of urine color from dark brown to yellow and reduction of urine melanin levels in the Thormählen test. The authors suggested that measurement of urine melanin might be useful in determining treatment response.[24] On the contrary, there is a report of two patients with BRAF wild-type melanoma developing melanuria while under treatment with pembrolizumab.[25]

In conclusion, melanuria is an unusual presentation of metastatic melanoma, usually combined with DMC. The prognosis of these patients is poor, and the median survival depends on the extent of melanoma and response to treatment. In the era of targeted therapies for melanoma, more data are needed to unravel the impact of melanuria on the prognosis of melanoma patients.

AUTHOR CONTRIBUTIONS

P.D., G.P. and E.C.: Writing - original draft, Formal analysis, Software P.D.: Conceptualization, Methodology, Investigation G.P., A.G. and O.B.: Data curation P. M. and G.K.: Data curation, Visualization H.G.: Project administration, Resources, Supervision P.D., E.C. and H. G.: Validation, Writing - review & editing

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ETHICS APPROVAL AND WRITTEN CONSENT

Every effort was made to preserve the anonymity of the patient. Moreover, written informed consent from the patient's next of kin was obtained.

DECLARATION OF COMPETING INTEREST

PD reports personal fees from Roche and Novartis, outside the submitted work. HG reports grants and personal fees from BMS, grants and personal fees from Roche, grants and personal fees from MSD, personal fees from Novartis, personal fees from Amgen, personal fees from Pierre Fabre, outside the submitted work. The remaining authors report no conflict of interests.

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