# Metastatic Melanoma and Melanogenuria

Ohara Aivaz, MD; Erich M. Gaertner, MD; Scott A. Norton, MD, MPH, MSc

*We report a case of a 70-year-old Hawaiian man with an exophytic black nodule on the left suprascapular region of several years' duration. Histopathologic examination of the excised lesion showed a nodular melanoma with 17-mm Breslow thickness. The patient had firm fixed lymph nodes circumferentially around his neck. He underwent palliative cervical lymph node dissection to remove the compressive nodes but declined further therapy. One year later, the patient's skin was noted to have a generalized uniformly gray-brown color. Physical examination showed ulcerated masses on his trunk, right arm, and both axillae. A urine specimen initially was dark yellow but turned black after exposure to air at room temperature and ambient light for several minutes.*

*Black urine, termed* melanuria*, is a rare finding in patients with disseminated melanoma. In melanogenuria, the urine is yellow and darkens as the colorless melanin precursors oxidize in the presence of air. Detection of these urinary melanin precursors may someday help determine the prognosis of melanoma and monitor response to treatment.*

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## Case Report

A 70-year-old Hawaiian man presented with a slowly growing, lobulated, exophytic black nodule on the left suprascapular region of several years' duration (Figure 1). A biopsy performed at the time of initial presentation revealed an ulcerated epidermis with a confluent proliferation of markedly atypical melanocytes at the dermoepidermal junction with extension of single atypical melanocytes into the epidermis (pagetoid spread). Similar atypical melanocytes extended deep into the dermis with confluent growth and numerous mitoses. These findings were consistent with melanoma. The Breslow thickness was measured at 17 mm from the ulcerated surface. Results of a lymph node biopsy confirmed the diagnosis of widely metastatic melanoma. The patient had large, firm, fixed lymph nodes circumferentially around his neck. To reduce the risk for tracheoesophageal compression, he underwent a palliative

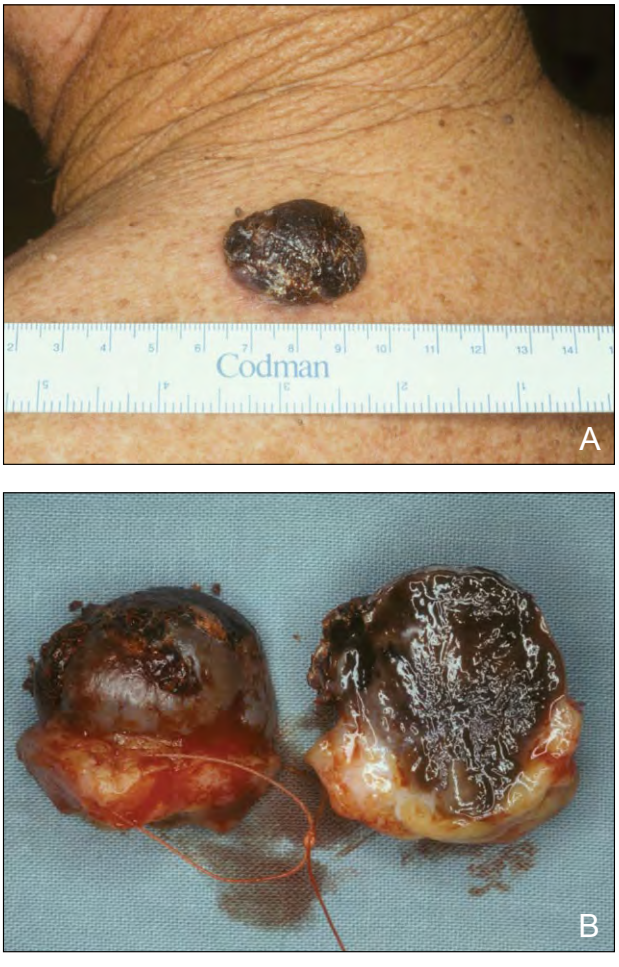


**Figure 1.** Suprascapular nodule (A). Gross examination of the nodule (bisected) with a Breslow thickness of 17 mm (B).

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cervical lymph node dissection. The patient declined further therapy.

One year later, the dermatologist visited the patient at his home and observed that the patient's skin had a generalized uniformly gray-brown color. Physical examination at this time showed large tumors with an ulcerated surface on his trunk, right arm, and both axillae (Figure 2). Palpable lymph nodes were present in the axillae. During the visit, the patient mentioned that incontinent urine stained his undergarments brown. The patient's urine had a dark yellow color upon voiding but darkened to black after exposure to air at room temperature and ambient light for several minutes (Figure 3A). Microscopic analysis of the urine sediment showed scattered macrophages containing brown pigment consistent with melanin (Figure 3B). The patient declined additional therapy, announced that he was ready for *ka pahu* (the box/coffin), and died 1 week later.

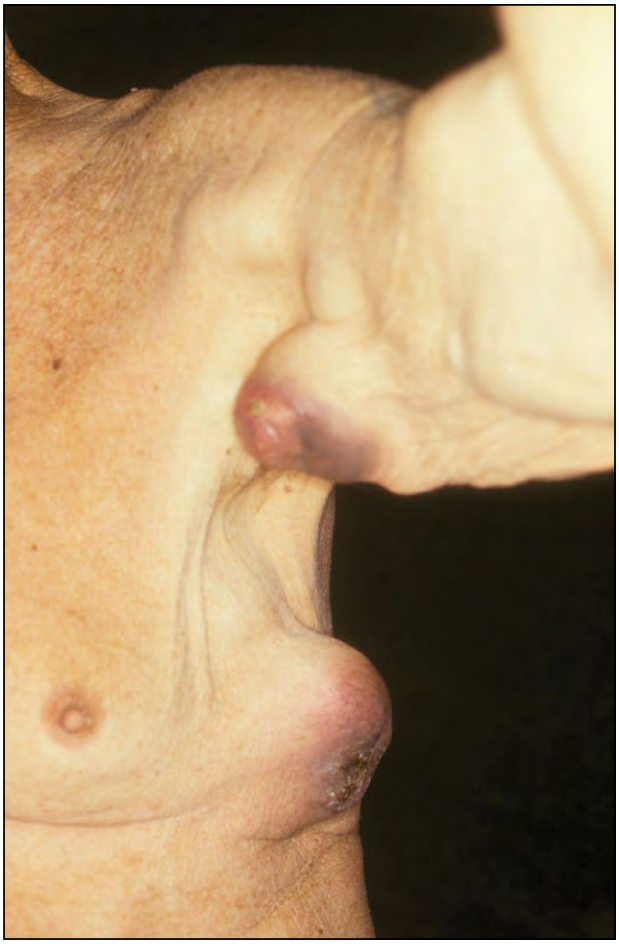
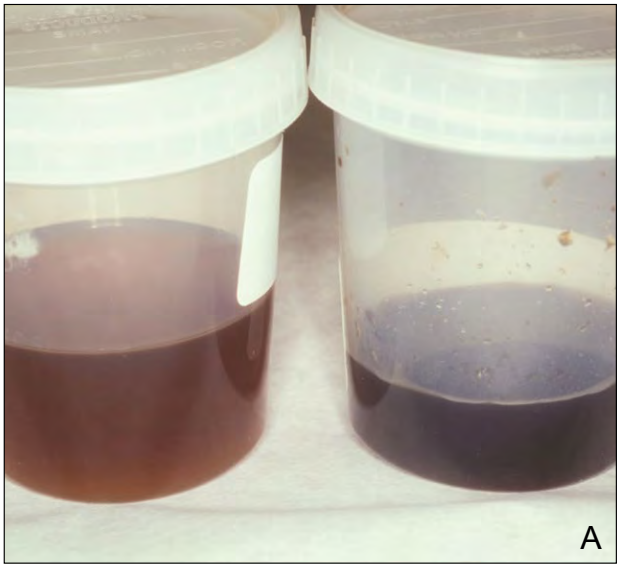


**Figure 2.** Gross tumors.

## Comment

Black urine, termed *melanuria*, is present in 10% to 20% of cases of disseminated melanoma.[1] Less commonly, these patients develop generalized cutaneous melanosis. Broadly speaking, melanuria can be divided into 2 types based on clinical and laboratory features: true melanuria sensu stricto and



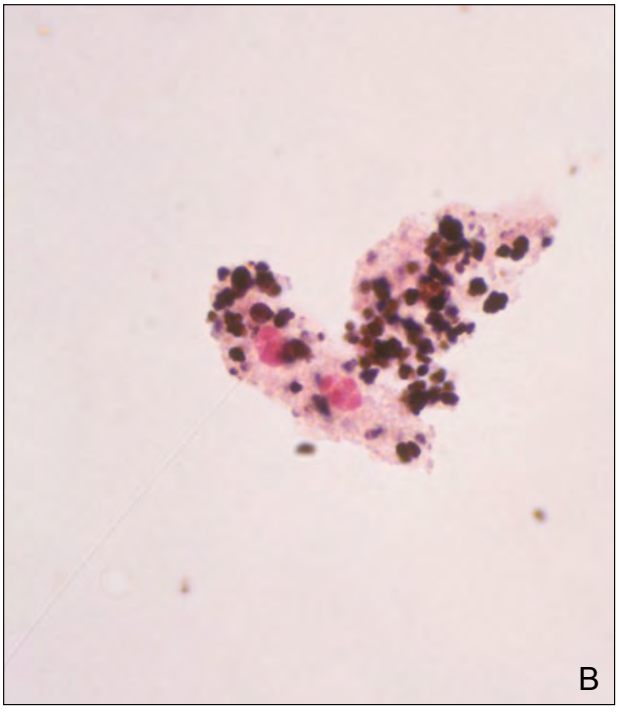




**Figure 3.** Gross urine at 5 minutes (left) and 15 minutes (right)(A). Microscopic analysis of the urine showed scattered macrophages containing brown pigment consistent with melanin (B).

melanogenuria. In true melanuria, the urine is brown when excreted because it contains melanin pigment, either free or within macrophages and endothelial cells. The physiologic origin of true melanuria is unclear because melanin pigment is too large to filter easily through renal glomeruli. One possible etiology includes embolization of melanoma cells to the glomerulus, which damages the glomerulus and allows for deposition of melanin and other cell debris in the renal tubules.[2] The differential diagnosis for dark urine includes gross hematuria; biliary obstruction; alkaptonuria; rhabdomyolysis; several types of porphyria; and use of various medications such as levodopa, antimalarials, and metronidazole.[2,3]

In melanogenuria, the urine contains melanin precursors, called melanogens, when excreted. The initially normal-colored urine will darken as the colorless melanogens oxidize in the presence of air (Figure 3A). Melanin precursors include indoles and phenols that oxidize spontaneously (without the need for tyrosinase) to eumelanins and pheomelanins, respectively, thus giving melanogenic urine its characteristic color (Figure 4).[4,5]

Laboratory analysis of the dark urine can confirm the diagnosis. The 2 basic laboratory tests for melanogenuria are the Thormählen test, which differentiates between eumelanin and pheomelanin precursors, and the modified von Jaksch (ferric chloride) test. These colorimetric assays that date from the late 19th century are cumbersome to perform and can give conflicting results that are open to variable interpretation.[4] Fontana-Masson silver staining is a simpler way to detect melanin in cells in the urine. A Fontana-Masson silver reaction is positive when melanin-containing cells in the urinary sediment stain black.[2]

Our patient's urine sediment contained macrophages laden with melanin pigment. Macrophages are uncommon in urine sediment and generally indicate renal injury. The exact origin of the pigment within the macrophages is unclear, but it is likely related to phagocytosis of either extracellular melanogens or melanin produced by the tumor. In autopsy studies,

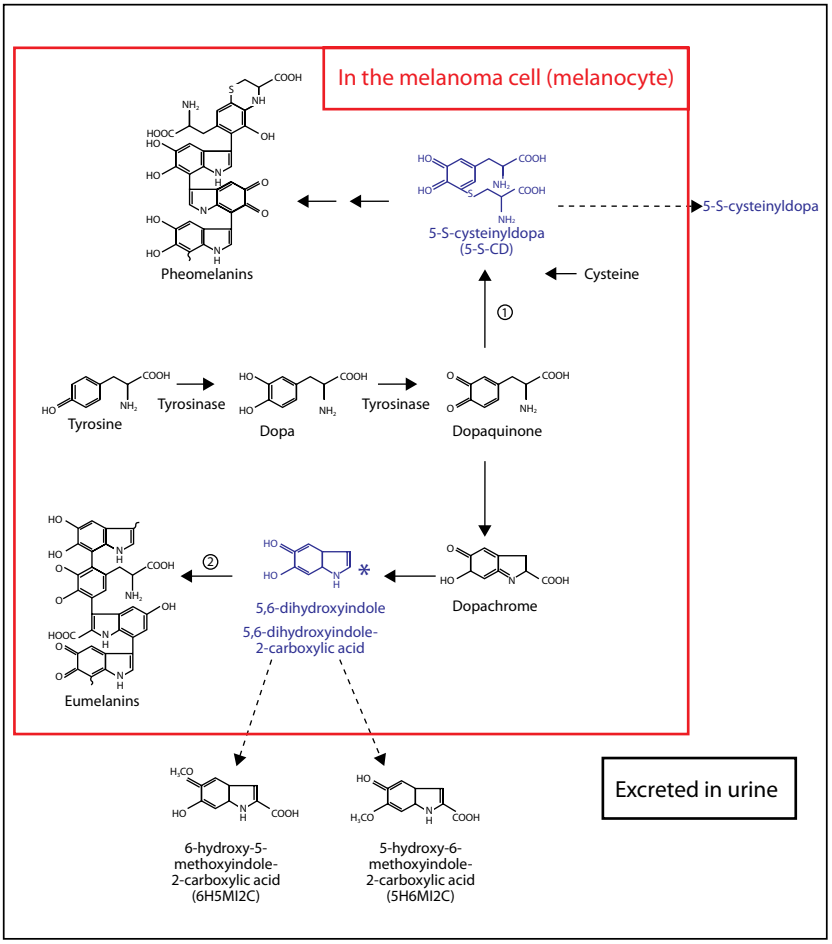



**Figure 4.** Urinary melanogens (shown in blue) are precursors along tyrosine's biosynthetic pathway leading to melanin. These chromogens are of 2 basic chemical groups: the indoles (including 5,6-dihydroxyindole and 5,6-dihydroxyindole-2-carboxylic acid) that lead to eumelanins, and the phenols (5-S-cysteinyldopa) that lead to pheomelanins. The enzyme tyrosinase initiates melanin biosynthesis by converting tyrosine to dopa, and also catalyzes later enzymatic steps toward melanin production.[4,6-8] Other known enzymes in the synthesis of melanogens include γ-glutamyl transpeptidase (1) and dopachrome oxidoreductase (2). A carboxyl group added to the location marked with an asterisk on 5,6-dihydroxyindole will form 5,6-dihydroxyindole-2-carboxylic acid.

individuals with positive urine cytology generally had widespread visceral metastases and associated diffuse melanin staining of the kidneys, ureters, and bladder.[1,9,10] The pigment-containing cells within the voided urine must be differentiated from true melanoma cells, which have been reported in isolated case reports only.[1,9,11]

Melanogenuria is a dramatic finding, but its clinical significance is unclear. A large portion of eumelanin and pheomelanin precursors leak from melanoma tumors into the bloodstream and ultimately are excreted in the urine (Figure 4).[12] These urinary precursors of eumelanins (6-hydroxy-5-methoxyindole-2-carboxylic acid [6H5MI2C]) and of pheomelanins (5-S-cysteinyldopa [5-S-CD]), therefore, have been studied as markers for melanoma metastasis. In a study of 571 melanoma patients, 60% of 161 patients with metastases had elevated urine levels of 5-S-CD, while approximately 98% of 410 patients without metastases had urinary 5-S-D excretion below the pathologic level (400 μg daily).[12,13] Another study found no statistically significant differences in the urine levels of melanogen precursors in healthy control patients and metastasis-free melanoma patients.[14] However, patients with metastatic melanoma had markedly elevated levels of 6H5MI2C and 5-S-CD, and a linear correlation between the urinary melanin precursors and melanoma metastasis load was demonstrated in 2 patients. Because urinary pheomelanin precursors can be elevated in normal healthy patients, especially after sunlight exposure, urinary levels of eumelanin precursors may be a more reliable marker of melanoma metastasis.[14]

Studies have shown a positive correlation between a patient's melanoma stage and urine melanogens[14]; nevertheless, melanogenuria occurs only in approximately 10% to 20% of cases of disseminated melanoma.[6] Therefore, elevated excretion of urinary melanogens lacks clinical utility in the diagnosis of early melanoma. Detection of elevated melanogen precursors, however, may someday help determine the prognosis of the disease and monitor response to treatment. At this time, national practice guidelines from the National Academy of Clinical Biochemistry state that further research is needed before serum or urinary melanin precursors can be used in clinical practice for the prognosis and management of melanoma.[7]

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