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Generalized melanosis and melanuria in a patient with metastatic melanoma

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We describe a case of generalized melanosis and melanuria in a patient with metastatic melanoma and review the pathogenesis and prognostic implications of this phenomenon.

A 62-year-old man with Fitzpatrick skin type II presented with a 3-month history of changes in a mole on his back.

Histological examination of a biopsy found an incompletely excised superficial spreading melanoma (Breslow thickness 9 mm, Clark level V, nonulcerated, perineural and perivascular invasion, mitotic rate 21/mm²) with microsatellite deposits at the deep margin. A whole-body positron emission and computed tomography (PET-CT) scan revealed no evidence of distant metastatic disease, and baseline liver profile, full blood count and lactate dehydrogenase (LDH) level were normal. A 20-mm wide local excision down to the fascia was performed and reported as an incompletely excised in-transit metastasis.

Fourteen months after the initial surgery, the patient presented with a 3-month history of right-sided chest pain, and diffuse slate-grey hyperpigmentation of the skin, which was more pronounced in sun-exposed areas; (b) melanuria, which resolved after chemotherapy.

Figure 1 (a) Diffuse slate-grey hyperpigmentation of the skin, which was more pronounced in sun-exposed areas; (b) melanuria, which resolved after chemotherapy.

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skin (Fig. 1a) that was more pronounced in sun-exposed areas, mucosal sites, and the nail bed. The patient’s urine became dark (Fig. 1b), with increased amounts of melanin precursors being found (dopamine creatinine ratio 1088 μmol/L; normal range 37–185). A repeat PET-CT scan revealed disseminated disease with spleen and bone metastases but no liver involvement (Fig. 2a–d). LDH was 1964 IU/L (normal range 240–480) and renal function was preserved. Histological examination of a skin biopsy taken from an area of diffuse melanosis in the left retroauricular area found a normal epidermis, scattered perivascular papillary dermal macrophages containing melanin that stained with Fontana–Masson, and no evidence of malignancy (Fig. 2e,f).

The patient was treated with palliative chemotherapy (dacarbazine 850 mg/m$^2$ three times weekly and zoledronic acid 4 mg every 4 weeks) with marked improvement in his performance status. A repeat PET-CT scan after six cycles indicated a partial response to treatment with reduction of fluorodeoxyglucose uptake within the splenic and bone marrow deposits. LDH level normalized and urine colour returned to normal, although the cutaneous melanosis became more accentuated.

Figure 2 (a) Coronal image of positron emission tomography/computed tomography scan performed after the initial diagnosis of superficial spreading melanoma showed no distant fluorodeoxyglucose uptake that would indicate avid disease. (b) Coronal image at the time of development of diffuse melanosis with multiple foci of uptake within the bones and the spleen. The spleen seemed to have increased in size, while the liver was unremarkable. (c) Identical pattern of disease after three cycles of chemotherapy but the spleen was somewhat less prominent than previously, suggesting a slight response to treatment. (d) Coronal image after completion of palliative chemotherapy (six cycles). A further reduction in the size and uptake of the individual lesions within the spleen could be seen, and the uptake within marrow seemed to be slightly less than previously. (e) Scattered perivascular papillary dermal macrophages containing melanin (haematoxylin and eosin, original magnification ×200), highlighted with (f) further staining (Fontana–Masson, original magnification ×200).
Generalized melanosis is a rare complication of metastatic melanoma with no more than 30 cases described in the English literature by 2001. It is considered an ominous sign, with a median survival of 6 months. It is characterized by slate-blue discoloration, often more accentuated in sun-exposed areas. Mucosal sites and nail beds are also affected. Most cases are associated with liver metastases.

Mucosal melanosis is far more common, occurring in approximately 15% of cases of metastatic melanoma and is due to excretion of melanin precursors that undergo auto-oxidation to melanin in air or extracellular melanin granules in the urine. It can lead to acute renal injury.

The pathogenesis of this phenomenon remains puzzling. Several hypotheses have been postulated: (i) oxidation of a melanin precursor generated by the tumour, which leaks into the dermis through the capillary membrane and is finally processed by macrophages; (ii) circulating melanophages that migrate to the dermis; (iii) deposition of melanosomes in the skin; (iv) alteration of dermal lymphatics that lead to obstruction of lymphatic channels and deposition of pigment; (v) dermal invasion of pigmentated single-cell metastases (almost never observed); and (vi) excessive melanogenesis followed by pigment incontinence due to increased melanocyte peptide growth factors (α-melanocyte stimulating hormone, hepatocyte growth factor and endothelin-1). Histologically, it is characterized by the presence of dermal pigment predominantly found in macrophages around superficial vessels. Single-cell metastases are almost never seen.

In conclusion, diffuse melanosis is a recognized rare and ominous, complication of advanced melanoma, the exact pathogenesis of which remains unknown. Response to chemotherapy is often poor. Dacarbazine is a standard treatment for advanced melanoma with response rates between 5 and 15%. Our patient has had a favourable response to treatment to date; it remains to be seen whether it will be durable.

**Note added in proof**

Our patient passed away 1 year after initial presentation with diffuse melanosis and melanuria. This is very much in keeping with mean survival time described in previous case reports.

**References**