Diffuse melanosis associated with melanoma is a rare condition characterized by rapidly acquired skin pigmentation that usually occurs in the setting of advanced metastatic melanoma in association with melanuria (dark urine). Diffuse melanosis remains an enigma; although the skin is darkening in the setting of metastatic melanoma, individual single-cell melanoma metastasis within the pigmented skin is reported in only 20% of cases. Imiquimod cream has been used with efficacy in small studies on malignant melanoma in situ. Perhaps increased dosing and duration could be applied to treating other conditions with imiquimod.

This rare condition is not completely understood, as only approximately 20% of cases have shown individual melanoma metastases within the pigmented skin. In our patient, as in the majority of cases, we were unable to detect individual metastases within the pigmented skin. This case is unique because diffuse melanosis was confined to an extremity. The clearing of the pigmented skin was impressive. Imiquimod may have activity against melanoma, melanoma in situ, and diffuse melanosis associated with melanoma, as demonstrated in our case.

Diffuse melanosis is a rare condition with 54 cases reported in the English-language literature, according to a recent review. The original description is ascribed to either Wagner in 1864 or Legg in 1884. We report a case of localized diffuse melanosis associated with melanoma on the lower left leg that successfully responded to treatment with imiquimod cream 5%. We reviewed 31 of the best documented cases (ie, cases with a full description of the original melanoma, the color and distribution of the melanosis, and other associated findings) to facilitate a general understanding of this disease and
determine where our case falls within the melanosis spectrum. Of the 31 patients, 16 were male and 15 were female. In the cases we reviewed, the primary melanomas were not amelanotic or site specific. In 3 of them a primary melanoma was never found.

**Case Report**

A 70-year-old woman presented with diffuse blue-black discoloration extending from the knee to the proximal dorsal aspect of the left foot of 6 months' duration. The patient reported no history of minocycline or amiodarone use. Her medical history was remarkable for a melanoma (Clark level IV [depth, 0.62 mm]) on the posterior aspect of the left calf that was widely excised 15 years prior. There was no evidence of systemic or lymph node involvement. Eleven years later, the patient developed a lesion on the left shin that was diagnosed as a new primary melanoma (Breslow thickness, 0.9 mm). The lesion was treated with wide excision and was repaired with a full-thickness skin graft harvested from the anterior aspect of the left thigh.

At the current presentation 4 years later, a blue-black discoloration of the left shin and medial aspect of the left lower leg was noted within the borders of the prior skin graft as well as on the surrounding skin (Figure 1). No involvement was noted at any other anatomic sites. Initial evaluation of the blue-black discoloration included a punch biopsy, which revealed pigmented cells in the mid to deep dermis (Figure 2). The pigmentation was granular, brown, and predominantly cytoplasmic. The pigment turned black on Fontana-Masson silver staining and bleaching completely removed the pigment (Figure 3). A tissue iron stain was performed and the pigment was not hemosiderin. These characteristics confirmed the presence of melanin. Additional immunoperoxidase stains were performed and counterstained with a red chromogen. Immunoreactivity of CD68 in the pigmented cells indicated a histiocytic origin. The cells were not immunoreactive for melan-A or S-100 proteins, indicating that no melanocytes or melanoma cells were present in the dermis. The overall histologic evaluation revealed that the pigmented cells were melanophages, and a pathologic diagnosis of deep dermal melanosis was made. An additional 4-mm punch biopsy was obtained from the medial aspect of the left lower leg. Similar histologic findings were noted, with pigment present in cells in the mid to deep dermis and in a prominent perivascular distribution.

During the initial investigation, the patient also was seen by a vascular surgeon who obtained a non-invasive duplex ultrasonography of the right and left lower extremities that showed no chronic or acute deep vein thrombosis and/or superficial or deep vein reflux. It was suggested that the patient visit a tertiary melanoma center or a local oncologist for a full metastatic workup; however, the patient refused and never underwent the investigation.

After reading several reports in the literature suggesting improvement of both metastatic melanoma and melanoma in situ with imiquimod, the patient was prescribed imiquimod 5% cream and was instructed to apply the cream twice a day for 6 weeks. After the 6 weeks, the discoloration was markedly reduced (Figure 4). The patient was lost to follow-up and the discoloration eventually cleared completely.

**Figure 1.** Diffuse melanosis localized to the left leg.

**Figure 2.** A punch biopsy showed granular, brown, predominantly cytoplasmic pigmented cells in the mid to deep dermis (H&E, original magnification ×100).

**Figure 3.** The pigment turned black on Fontana-Masson staining (original magnification ×80).
Diffuse Melanosis of Melanoma

Diffuse melanosis typically presents as a slate gray to blue-black discoloration of the skin, usually arising in the setting of advanced metastatic malignant melanoma. Patients presenting with diffuse melanosis associated with melanoma typically die within weeks to months. In the cases we reviewed, the average duration of survival was 4.8 months (range, 10 days to 1 year [excluding patients who were alive when this article was written]). Almost all of the patients had associated melanuria or black urine; exceptions included this case report as well as 3 others from the literature,20,26,28 including 1 patient who was anuric due to renal failure.20 Generally, urine samples must be exposed to light and air after prolonged standing to turn black. One case reported a patient with acute renal injury that was thought to be from too much melanin.30 Melanin (or its precursors) usually are found in the urine in patients with diffuse melanosis associated with melanoma, though there have been reports of melanoma cells detected in the glomeruli.16 Melanuria can occur without melanosis in association with metastatic melanoma.30

Although advanced metastatic disease, melanuria, and brief survival are virtual hallmarks of melanosis, the distribution and color of the dyspigmentation is variable. Most commonly, the discoloration is photodistributed (eg, face, v of the neck) and dispersed evenly on the affected areas; the skin then begins to darken and the affected areas become generalized, which was documented in 16 of 31 cases reviewed.5-10,13-16,18,20,22,23,25,31 Along with our patient, we found 2 reports of localized cases,24,26 which are exceptions to the typical presentation of this disease. Although most of the remaining cases lacked description of the distribution,1,12,17,19,27,28 some cases clearly did not show photoaccentuation and/or the appearance of the melanosis was mottled rather than evenly dispersed.4,7,21 Progressive darkening was reported in virtually all of the 16 photodistributed patients, with the color ranging from light silver-blue, tan, slate gray, brown, and blue-black. Another common finding was darkening of the hair.9,21,25,27 There also was mucous membrane involvement in more than one-third of cases we reviewed.4,7,10,13-15,18,20,22,25,31

Although we could not observe inflammation with the plastic wrap, she continued to apply the imiquimod under plastic wrap occlusion. The patient did not develop systemic symptoms or lymph node involvement. She remains in perfect health and has not lost weight or appetite. After 1.5 years, imiquimod was stopped. Three months after stopping the patient remains clear.

Comment

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Figure 4. Following 2 weeks of application of imiquimod cream 5%, the skin on the left shin was severely eroded, but the more deeply pigmented skin on the medial aspect of the lower leg had lightened.

Figure 5. Clearance of diffuse melanosis of the left leg was achieved after the patient was instructed to apply imiquimod cream 5% to the affected area and cover with plastic wrap overnight for 1 year.
Diffuse Melanosis of Melanoma

Melanosis of the internal organs, sometimes including bone marrow, was observed with or without melanoma metastases.\textsuperscript{4,5,7,9,11,14,16,18,21,30}

Diffuse melanosis associated with melanoma remains an enigma despite the frequently associated advanced metastatic disease. In our review, melanoma cells within the pigmented skin were found in only 6 cases.\textsuperscript{4,10,13,21,23,26} It was initially theorized that an unlimited spread of melanoma cells throughout the dermis was responsible for the melanin deposition\textsuperscript{10}; however, subsequent authors failed to find tumor cells in the dermis and theorized that melanin was diffusely released and spread vascularly for deposition into numerous perivascular melanophages.\textsuperscript{16} Additional studies theorized that the dermal pigmentation was related to activation of melanocyte peptide growth factors, with subsequent melanophage distribution in a perivascular and diffuse dermal pattern.\textsuperscript{25} Increased epidermal pigmentation without melanoma cells was seen in 5 cases,\textsuperscript{8,9,20,23,25} implying stimulation of normal epidermal melanocytes as another mechanism of the pigmentation in the minority of cases.

Our case represented diffuse melanosis associated with melanoma that was localized to an extremity; we found 1 similar case in a patient who did not have distant metastasis but had melanoma cells in the pigmented skin of the arm where the melanoma originally occurred.\textsuperscript{26} All other cases of diffuse melanosis we reviewed had an identified focus of melanoma metastasis within the pigmented skin. In our patient, the blue-black discoloration presented on the lower left leg, which was the site of 2 previously treated melanomas. The histology of dermal accumulation of melanin in histiocytes was typical for diffuse melanosis. No enlargement of the inguinal lymph nodes was noted, and the patient was otherwise in good health. It is likely that the melanin source was an undetected melanoma or melanoma in situ, though anecdotal cases have been published.\textsuperscript{14,41,43} Imiquimod could be administered in cases of melanoma that are more likely to reoccur locally or when there are small scattered cutaneous metastases near the original excision site. Similar to isolated limb perfusion chemotherapy, imiquimod could be applied locally to treat or even prevent metastasis.

Although new dosing schedules for imiquimod are constantly added, occlusion or increased frequency of daily dosages also may be beneficial. A transdermal delivery system could possibly be developed for imiquimod. In our patient, application of imiquimod to a larger surface area over a longer period of time was effective and well tolerated. Although our patient's discoloration cleared, treatment with imiquimod was continued, as she did not experience ongoing side effects and virtually all diffuse melanosis patients die. Perhaps the cure rate for melanoma in situ might be higher if imiquimod treatment was continued past clinical clearance or even indefinitely.

**Conclusion**

This case report and review of the literature serves to illustrate the diverse spectrum of this rare condition characterized by dermal deposition of melanin and darkening of skin color in a patient with melanoma. Dramatic clearance after prolonged and extensive application of imiquimod should generate further interest in applying this immunomodulator to the treatment of different aspects of melanoma.

**REFERENCES**


39. Wolf IH, Kôdama K, Cerroni L, et al. Nature of inflammatory infiltrate in superficial cutaneous malignancies...


