Dermatology Practical & Conceptual

Diffuse Melanosis Cutis in the Era of Targeted Therapy

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Introduction

Metastatic melanoma can rarely present as a diffuse bluish-gray discoloration of the skin, known as diffuse melanosis cutis (DMC) [1,2]. As it can negatively influence quality of life, therapeutic options for hyperpigmentation are crucial.

Case Presentation

A 47-year-old woman was referred to the dermatology department to investigate a diffuse hyperpigmentation of the skin. She reported starting with progressive skin darkening 5 months prior and having very dark urine 9 months prior to her appointment. She had a diagnosis of cutaneous melanoma 6 years earlier and had discovered hepatic metastasis 3 years after the melanoma diagnosis. Upon physical examination, the patient presented with a diffuse blue-gray hyperpigmentation, which was more accentuated on the face (Figure 1). Histopathology and Fontana–Masson stain of the skin showed melanophages in a superficial perivascular localization, compatible with dermic melanosis (Figure 2). The diagnosis of diffuse melanosis cutis (DMC) was established.

Since the melanoma was positive for BRAF/V600E mutation with indeterminate PDL-1 expression, treatment with dabrafenib and trametinib had been instituted. She reported that the urine alterations resolved rapidly after initiating this treatment, but had little improvement in skin hyperpigmentation.

As an attempt to attenuate the hyperpigmentation, we prescribed 5% imiquimod for eight weeks, without any improvement. We also attempted two sessions of Q-Switched laser with no response after two sessions.

Conclusions

The exact physiopathology of DMC is still unclear [3]. It is postulated that metastatic melanoma releases melanin precursors in the circulation (after cytolysis as a result of rapid turnover of neoplastic deposits, central ischemia, immunological responses or oncologic therapies), which are converted into melanin in the dermis and may be phagocytosed by native histiocytes, causing hyperpigmentation [2]. Melanin precursors can also be excreted in urine causing melanuria [2]. Other theories include the possibility that

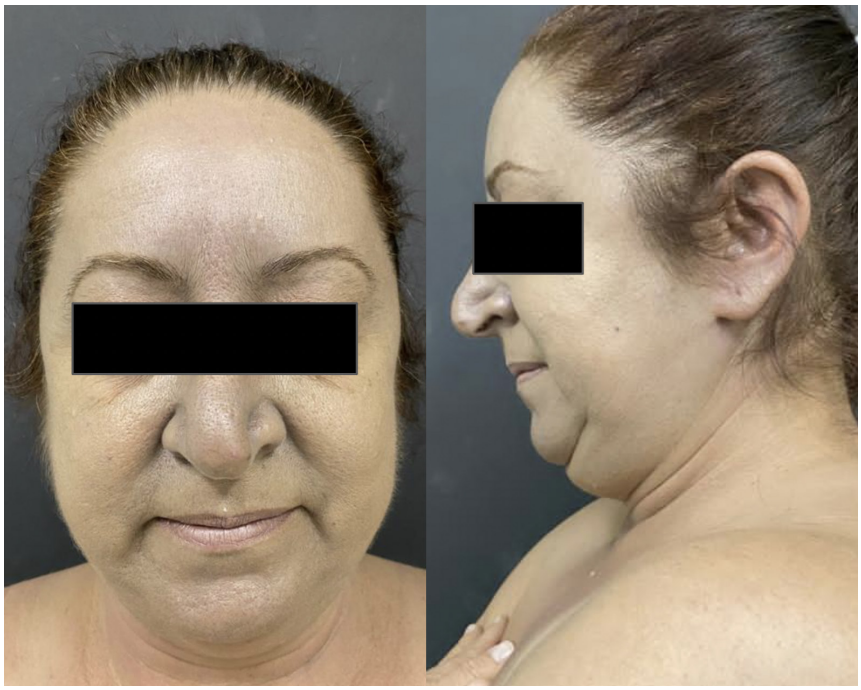

Figure 1. Diffuse blue-gray hyperpigmentation, more accentuated on the face.

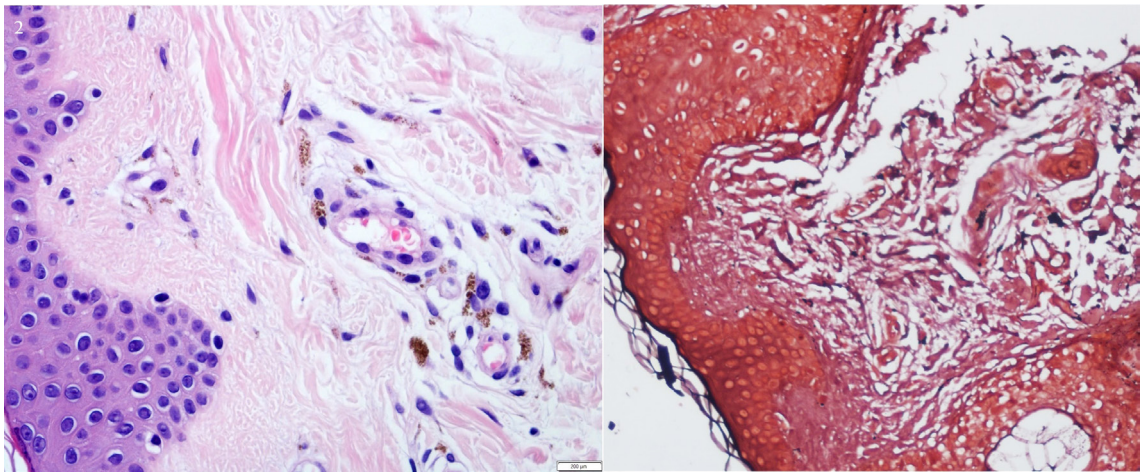

Figure 2. Histopathology (H&E and Fontana–Masson stains) showing melanin deposition in the superficial dermis with a perivascular distribution.

melanocyte proliferation might be stimulated by growth factors released by cancer cells or that DMC may be caused by dermal micrometastasis producing melanin [4]. Furthermore, more than one pathway may contribute to the etiopathogenesis of DMC. Pigmentation is most frequently seen in a photo-distributed pattern [5]. Histologic findings include increased melanin in dermal histiocytes, free pigment between collagen stroma and epidermal hyperpigmentation [2]. Melanophages extending to subcutis and skeletal muscle can also be seen [6].

There is no treatment for DMC. Successful treatment of localized melanosis cutis with imiquimod cream 5% has been described [5], although our patient did not present with the same outcome. DMC is a bad prognosis marker, with a mean life expectancy after developing hyperpigmentation of 4 to 5 months [2]. It is a presentation of metastatic melanoma, considered by some authors as a paraneoplastic condition, that can assist in the diagnosis of advanced melanoma [4].

BRAF-MEK inhibitors have significantly expanded life-expectancy in metastatic melanoma. Our patient died 24 months after first developing DMC. Interestingly, as previously reported, our patient melanuria completely resolved after initiating treatment with dabrafenib and trametinib, although no improvement in skin hyperpigmentation was seen [1].

Even though our attempts to treat DMC were not successful, we believe this is a field which ought to be studied further. The cosmetic impact of DMC on patients has not been explored as it was associated with a very poor prognosis. However, since the advent of targeted therapy and

immunotherapy, these patients are living longer, so treatments for melanosis might improve their quality of life.

References

1. Minocha R, Kefford R, Uribe P, et al. Diffuse melanosis cutis in the setting of BRAF ^{V600E} mutant melanoma and treatment with targeted therapies: DMC treated with targeted therapies. *Australas J Dermatol.* 2015;56(2):128–130. DOI: 10.1111/ajd.12187. PMID: 25159853.
2. Sebaratnam DF, Venugopal SS, Frew JW, et al. Diffuse melanosis cutis: A systematic review of the literature. *J Am Acad Dermatol.* 2013;68(3):482-488. DOI: 10.1016/j.jaad.2012.08.018. PMID: 23219556.
3. Piana S, Longo C. Diffuse Melanosis and Melanuria. *N Engl J Med.* 2019;380(12):1166. DOI: 10.1056/NEJMicm1810151. PMID: 30893538.
4. Chinai B, Piazza M, Patel R, Roy S. Diffuse melanosis cutis: a rare manifestation of metastatic melanoma. *BMJ Case Rep.* 2019;12(8):e230396. DOI: 10.1136/bcr-2019-230396. PMID: 31473636. PMCID: PMC6720706.
5. Fields K, Milikowski C, Jewell T, Fields J. Localized diffuse melanosis associated with melanoma successfully treated with imiquimod cream 5%: a case report and review of the literature. *Cutis.* 2014;93(3):145–150. PMID: 24738096.
6. Sebaratnam DF, Martin LK, Venugopal SS, et al. Diffuse melanosis cutis in the setting of BRAF(V600E) metastatic melanoma. *Int J Dermatol.* 2014;53(11):1409–1411. DOI: 10.1111/ijd.12614. PMID: 25257244.