Clinical Letter

Dimethyl fumarate-associated ashy dermatosis

DOI: 10.1111/ddg.14889

Dear Editors,

dimethyl fumarate (DMF) is an orally administered drug indicated for the treatment of moderate to severe plaque psoriasis in adults in need of systemic therapy. Considered a drug with a favorable safety profile [1], the most frequently reported adverse events stemming from the use of DMF are diarrhea, abdominal pain, flushing and lymphopenia [2].

Cutaneous adverse events, mostly mild, have also been reported: erythema, burning, pruritus and allergic contact dermatitis. However, to our knowledge, DMF is not associated to pigmentary changes [3].

We hereby present a case of histologically confirmed ashy dermatosis (AD) associated with DMF therapy in a patient with psoriasis.

The patient, a 47-year-old Hispanic male with Fitzpatrick IV skin type, has been suffering from plaque type psoriasis for three years.

Despite the initial effectiveness of UVB phototherapy, new psoriatic plaques soon appeared on the trunk and legs. Consequently, the patient started treatment with DMF.

At first, the drug was quite effective, but, around six months after the beginning of treatment, itchy gray hyperpigmented patches appeared on the legs. The lesions were first interpreted as post-inflammatory hyperpigmentation, which occurs frequently in darker phenotypes. After nine months of therapy, the psoriasis had completely cleared and DMF treatment was interrupted, though the pigmented lesions were still present (Figure 1a–b). Consequently, ashy dermatosis or lichen planus pigmentosus were suspected. Three months later, the pigmented patches had not regressed, and a skin biopsy was performed. Histopathology revealed vacuolar interface dermatitis, mild epidermal hyperplasia, perivascular inflammatory infiltrates in the dermis and many melanophages in the upper dermis (Figure 2a–c). These findings were compatible with the diagnosis of AD [4].

Since no known triggers of AD were present, and no other medication was initiated during this period, DMF was identified as the culprit drug. The lesions were treated with topical steroids, with slight and gradual improvement. However, six months after the suspension of DMF, psoriasis reappeared, so the patient started treatment with tildrakizumab.

Ashy dermatosis is an acquired macular hyperpigmentation characterized by symmetrically distributed, gray plaques of unknown pathophysiology, typical of subjects of Central and South American origin. Ashy dermatosis is typically asymptomatic, although atypical lesions can be accompanied by a peripheral erythematous border, pruritus or scaling. While the etiology of ashy dermatosis is currently unknown, numerous predisposing factors have been described, including parasitic and viral infections, ingestion of ammonium nitrate, orally administered X-ray contrast media, drugs such as ethambutol, fluoxetine, chlorothalonil and omeprazole [5].

Our patient had no family history of pigmentary disorders, no personal history of toxic exposure, and he did not present any sign or symptom of infection or allergy. Routine blood tests were also within normal ranges. The patient did not take any drug besides DMF, which we consequently identified as the most likely trigger of the condition.

To our knowledge, no cases of ashy dermatosis or lichen planus pigmentosus occurring during treatment with DMF have been reported. Furthermore, we believe this is the first report of pigmentary changes associated with DMF.

Our case had a score of 6 on the *Naranjo Adverse Drug Reaction Probability Scale*, which indicates a probable relationship between the dermatologic adverse effects and DMF [6].

However, the pathogenetic mechanism of hyperpigmentation due to DMF is not easy to hypothesize. The anti-inflammatory properties of DMF are due to the inhibition of NF-kB

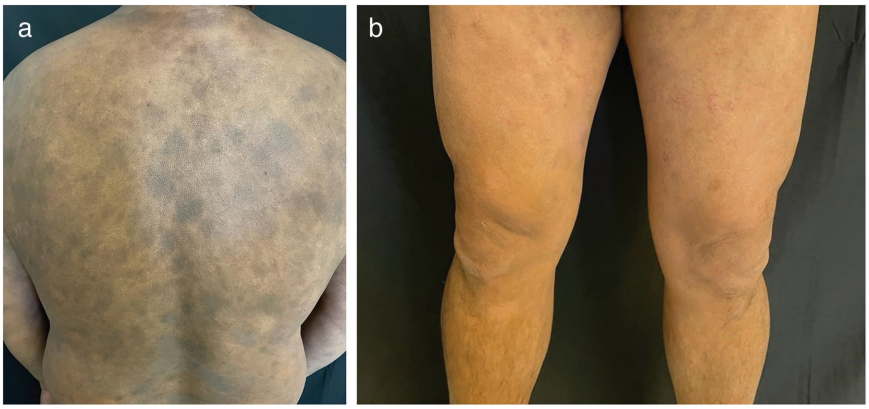

Figure 1 Clinical appearance of the lesions: gray hyperpigmented patches on the trunk (a) and legs (b).

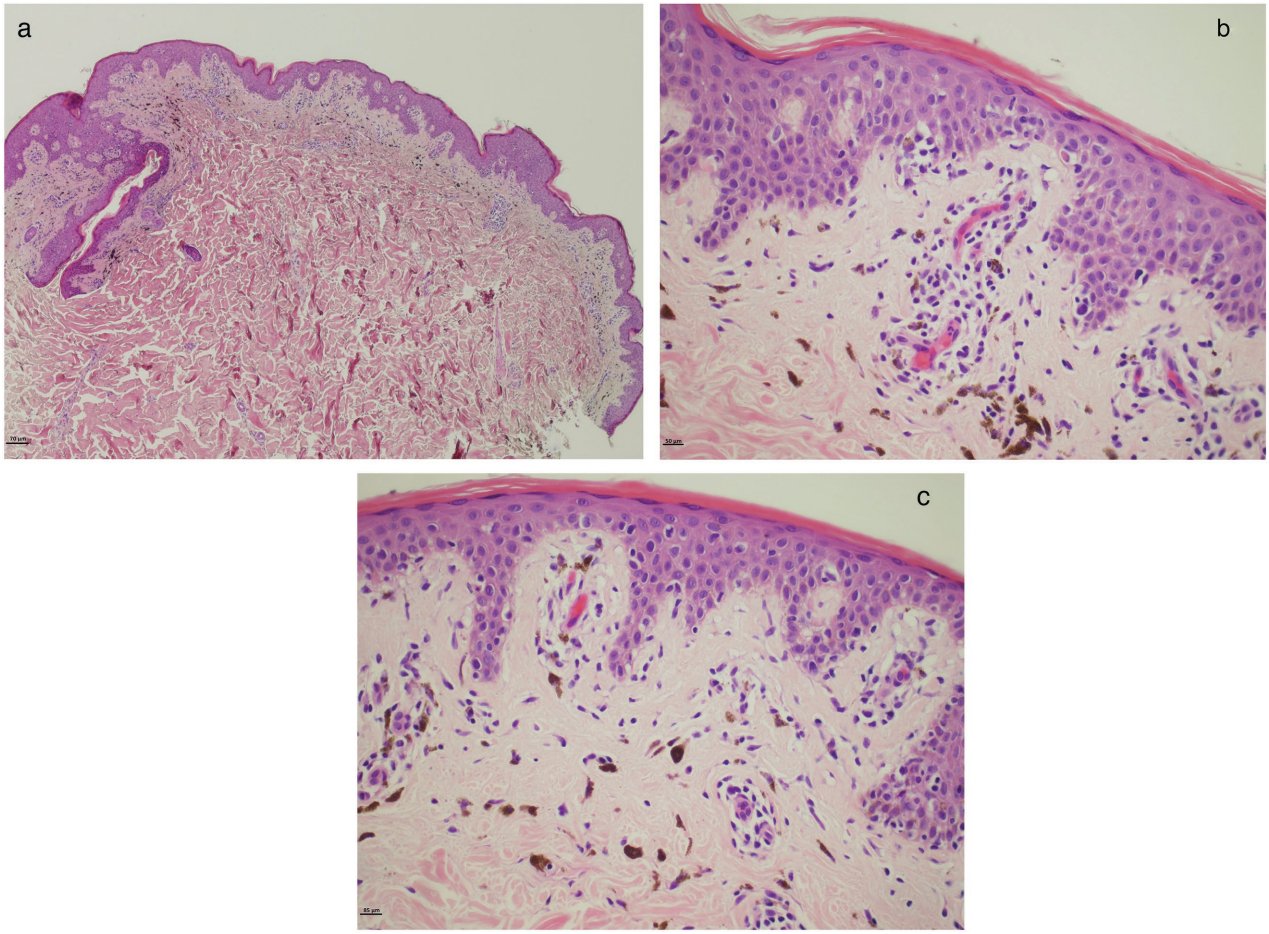

Figure 2 Hematoxylin and eosin stain (HE): the histological examination shows an epidermis with hyperkeratosis, mild irregular acanthosis and basal cell vacuolar changes (a). Rare dyskeratotic cells are observed in the epidermis (HE) (b). Within the papillary dermis, a mild inflammatory infiltrate composed of lymphocytes, rare plasma cells and numerous melanophages is present with lymphocytic exocytosis. Focally, fibrosis is observed (c).

[7], a transcription factor known to induce p53, leading to transcription of POMC, the precursor of melanocyte stimulating hormones [8]. The promotion of melanogenesis by DMF therefore appears to be a paradoxical effect. However, as the effects of DMF on immune function are complex, another molecular pathway besides NF-kB signaling may be involved.

Ashy dermatosis is notoriously difficult to treat, and no gold standard of treatment exists. In this case, we chose at first to prescribe a high-potency topical steroid (desoximetasone 0.25 %) and emollients. This treatment proved moderately effective. Other possible topical options are calcineurin inhibitors, hydroquinone and tretinoin, while suggested systemic treatments are dapsone, minocycline, tranexamic acid, clofazimine, pentoxifylline and macrolids. UVB phototherapy and light therapy in combination with topical treatments have also been reported as effective. Since our patient's psoriasis relapsed soon after the diagnosis of ashy dermatosis, we prioritized the treatment of active lesions and prescribed tildrakizumab in association with topical calcipotriol-betamethasone.

We describe a case of ashy dermatosis (AD) associated with DMF therapy in a patient with psoriasis. We highlight both the role of clinical suspicion and histological examination in solving a difficult medical case. However, we are unable to hypothesize a pathogenetic mechanism underlying the promotion of hyperpigmentation by DMF.

Acknowledgement

Open Access Funding provided by Universita degli Studi di Genova within the CRUI-CARE Agreement.

Conflict of interest

None.

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References

1 Reich K, Thaci D, Mrowietz U et al. Efficacy and safety of fumaric acid esters in the long-term treatment of psoriasis – a retrospective study (FUTURE). J Dtsch Dermatol Ges 2009; 7(7): 603–11.
2 Blair HA. Dimethyl fumarate: a review in moderate to severe plaque psoriasis. Drugs 2018; 78(1): 123–30.
3 Almirall SA. Skilarence (dimethyl fumarate) [package insert]. EMA website. 2017. Available from: https://www.ema.europa.eu/en/documents/product-information/skilarence-epar-product-information_it.pdf 2017 [Last accessed February 24, 2022].
4 Rutnin S, Udompanich S, Pratumchart N et al. Ashy dermatosis and lichen planus pigmentosus: the histopathological differences. Biomed Res Int 2019; 2019: 5829185.
5 Nguyen K, Khachemoune A. Ashy dermatosis: a review. Dermatol Online J 2019; 25(5): 13030/qt44f462s8.
6 Naranjo CA, Busto U, Sellers EM et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30(2): 239–45.
7 Kirby B, Fletcher JM. Mechanism of action of dimethyl fumarate: a small molecule with big effects. Br J Dermatol 2021; 185(3): 483–4.
8 Schallreuter KU, Kothari S, Chavan B, Spencer JD. Regulation of melanogenesis – controversies and new concepts. Exp Dermatol 2008; 17(5): 395–404.

