Longitudinal melanonychia and skin hyperpigmentation associated with hydroxychloroquine therapy

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INTRODUCTION

Antimalarials, including hydroxychloroquine (HCQ), may cause hyperpigmentation of the skin, mucous membrane, joints, and cartilage.[1-3] Longitudinal melanonychia, a linear brown-black nail plate band, is rarely reported with HCQ treatment, and histologic confirmation has not been previously published. HCQ is widely used for the treatment of various rheumatic and dermatologic diseases, including systemic lupus erythematosus, cutaneous lupus, and rheumatoid arthritis. It inhibits the replication of SARS-CoV-2 in vitro[4] and has been used to treat COVID-19. Herein, we present a case of skin hyperpigmentation and longitudinal melanonychia with a histology associated with HCQ therapy.

Abbreviation used:

HCQ: hydroxychloroquine

CASE REPORT

A 66-year-old woman, Fitzpatrick skin type II, with mixed connective tissue disease presented with a 7-year history of a pigmented band on her left thumbnail. She was treated with HCQ for 18 years, which was discontinued 4 years before the consultation because of progressive skin hyperpigmentation of the lower portion of the legs. At the time of the skin hyperpigmentation (3 years after HCQ initiation) and melanonychia (15 years after HCQ initiation) presentations, the cumulative dosages of HCQ were 438 g and 2190 g, respectively. Prior biopsy of the skin from the lower portion of the legs with histopathology showed dermal intracellular and extracellular yellow-to-brown granules positive for Fontana-Masson and Perl's stains. The medications at the time of the consultation included clopidogrel due to transient ischemic attacks, prednisone, bupropion, diltiazem, gabapentin, and levothyroxine. Physical examination was significant for hyperpigmented macules and patches involving the lower portion of the legs and a longitudinal gray-brown band of the left thumbnail (Fig 1, *A*). Nail dermoscopic evaluation revealed a gray-brown background with regular gray-brown lines (Fig 1, *B*). A tangential shave biopsy of the nail matrix and histopathology with hematoxylin-eosin staining showed brown nonrefractile and coarsely granular pigment deposition in the superficial dermis of the nail matrix (Fig 2, *A*). The pigment was extracellular and within macrophages and fibroblasts. The Fontana-Masson staining highlighted these granules, confirming the presence of melanin (Fig 2, *B*). The Perl's iron staining result was negative for hemosiderin. The histologic differential diagnosis included melanin incontinence secondary to postinflammatory pigmentary alteration and HCQ-induced hyperpigmentation. Due to these nail histologic findings and prior pathology confirming HCQ-induced skin hyperpigmentation, along with a high cumulative HCQ dose, a diagnosis of HCQ-induced hyperpigmentation was favored. Other causes of drug-induced melanonychia were excluded.

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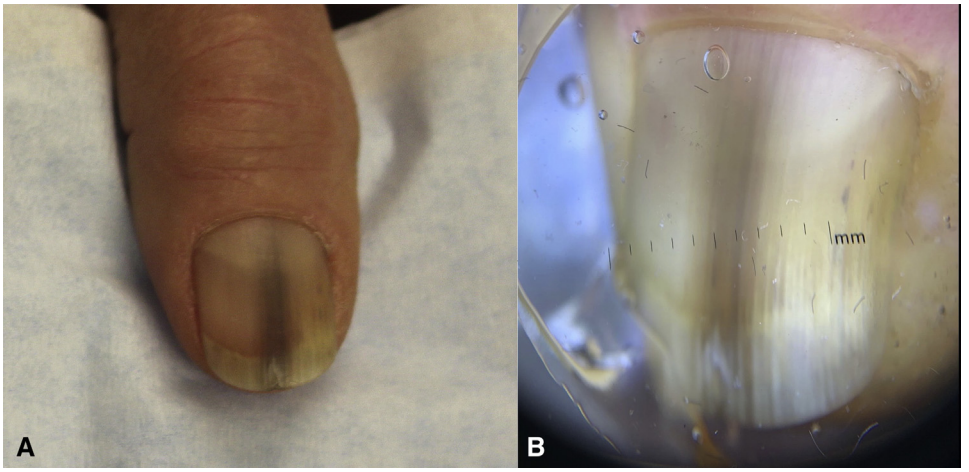

Fig 1. **A**, Left thumbnail with a central longitudinal gray-to-brown band originating in the distal matrix, 1 mm proximally and 2 mm distally, with a distal superficial split over the pigmented area. There was no pigment involving the nail folds or hyponychium. **B**, Dermoscopic appearance showing a gray-to-brown background with gray-to-brown lines of regular color, spacing, and thickness, without loss of parallelism.

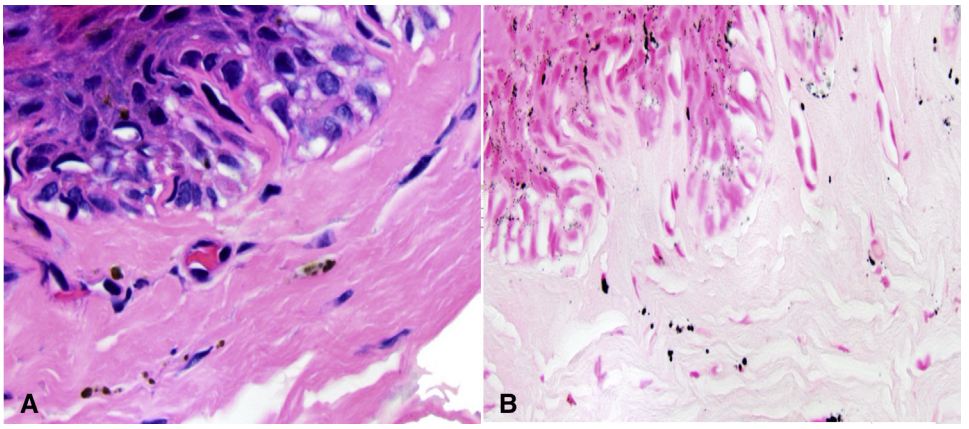

Fig 2. Histologic characteristics. Intracellular and extracellular brown pigment granules in the superficial dermis (**A**, hematoxylin-eosin stain; original magnification: ×600.) A Fontana-Mason stain highlighting melanin granules within the dermis and epidermis (**B**, Fontana-Mason stain; original magnification: ×600.)

DISCUSSION

After drug rash/eruption (52%), gray/blue skin hyperpigmentation (17%) is the most common dermatologic manifestation of HCQ treatment.[3] Since there is an increased iron concentration in hyperpigmented skin,[1] it has been hypothesized that trauma and bruising with increased levels of hemosiderin activate melanocytes.[5] In a retrospective case-control study including 24 and 517 HCQ-treated systemic lupus erythematosus patients with and without HCQ-induced skin hyperpigmentation, respectively, 96% (23/24) of the patients with hyperpigmentation had a predisposition to bruising, including the use of platelet antiaggregants and/or oral anticoagulants.[5] Although there is no significant dose-dependent relationship,[5] HCQ-induced melanonychia and skin hyperpigmentation have been reported with cumulative dosages of $\geq$230 g and $\geq$452 g, respectively.[3] The histopathologic findings of HCQ-induced hyperpigmentation are yellow-to-brown granules within macrophages and fibroblasts and extracellularly in the dermis.[2,5] The granules stain positive for either melanin[2] or both melanin and hemosiderin,[5] typically demonstrating hemosiderin around capillaries and melanin in the deeper layers of the dermis.[2]

In the present case, the histologic evaluation revealed the presence of melanin and absence of

hemosiderin. Although drug-induced melanonychia typically involves several nails,[6] HCQ was likely causative of skin/nail hyperpigmentation for a number of reasons. Skin hyperpigmentation and melanonychia occurred 3 (cumulative dosage = 438 g) and 15 years (cumulative dosage = 2190 g) after the HCQ initiation, respectively, with skin pigmentation worsening during the treatment. The patient reported that her leg hyperpigmentation followed bruising, with the histologic evaluation confirming the presence of melanin and hemosiderin. She also took clopidogrel and systemic corticosteroids, both of which can facilitate bruising. Finally, the grayish color of her skin and nail was consistent with HCQ hyperpigmentation.[3] The most important differential diagnosis of longitudinal melanonychia is nail-unit melanoma, a life-threatening but potentially treatable form of cancer if diagnosed and managed at early stages. A nail biopsy is often necessary to differentiate between drug-induced melanonychia and subungual melanoma with the involvement of a single nail unit. HCQ-induced skin/nail hyperpigmentation may fade after drug discontinuation but may not disappear completely.[2,5] To the best of our knowledge, this is the first histopathologically confirmed case of melanonychia and skin hyperpigmentation associated with HCQ therapy.

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