Hydroxychloroquine-associated pigmentation after extravasation injury

Keunyoung Hur, MD,[a] Yoonjin Kwak, MD, PhD,[b] and Si-Hyung Lee, MD, PhD[a,c]
Seoul, South Korea

Key words: extravasation; hemosiderin; hydroxychloroquine; pigmentation; siderophage.

INTRODUCTION

The antimalarial drug hydroxychloroquine (HCQ) is also used for other medical conditions, including connective tissue diseases, and is known to cause pigmentation. Although the underlying mechanism is unclear, it has been suggested that it occurs secondary to ecchymosis or bruising.[1] Here, we report a case of hydroxychloroquine-associated pigmentation on the left antecubital fossa after extravasation injury.

CASE REPORT

A 14-year-old girl with history of Hashimoto's thyroiditis and systemic lupus erythematosus (SLE) presented with hyperpigmentation on the inner aspect of the left forearm. The pigmented skin lesion persisted for 1 year after minor extravasation injury during an intravenous cannulation procedure on the left forearm. Initial ecchymosis due to the extravasation injury changed to bluish-gray pigmentation in a few weeks. She denied previous history of any other trauma. She had previously been treated with oral steroids and cyclosporine for the management of SLE, but this changed to HCQ and mycophenolate mofetil 21 and 16 months prior, respectively. She had no prior history of hyperpigmentation at sites of trauma or hematoma prior to taking HCQ.

Physical examination demonstrated a palm-sized, bluish-gray patch on the inner aspect of the left forearm (Fig 1, *A*). At the time of extravasation injury, routine laboratory tests, including platelet count and coagulation panel, were all within the respective normal limits. Histological analysis revealed increased basal pigmentation in the epidermis and yellow-brown granular pigment deposition within macrophages in the mid-to-deep dermis (Fig 1, *B* and *C*). Additional staining to clarify the pigment in the dermis revealed positive staining for hemosiderin and negative staining for melanin, suggesting perivascular siderophage infiltration (Fig 1, *D* and *E*). The clinical and pathological findings strongly suggested a diagnosis of hydroxychloroquine-associated pigmentation.

Abbreviations used:

HCQ: hydroxychloroquine
SLE: systemic lupus erythematosus

DISCUSSION

Although reported in 7% of patients with SLE,[1,2] the pathogenesis of HCQ-associated pigmentation remains elusive. In addition, it is difficult to predict and prevent HCQ-associated pigmentation as there is no clear association with cumulative dose or duration of use.[1] Regarding the clinical features of HCQ-associated pigmentation, Jallouli et al[1] reported the largest study, comparing 24 SLE patients with HCQ-associated pigmentation to 517 SLE controls treated with HCQ. According to the study, hyperpigmentation was localized on the trauma-prone anterior side of the leg in all patients and in 21% of patients with arm involvement. Also, the majority of patients (96%) had at least 1 condition leading to a predisposition for easy bruising, such as treatment with oral anticoagulants and/or antiplatelet agents. Based on the aforementioned results, Jallouli et al[1] suggested that HCQ-

From the Department of Dermatology[a] and Department of Pathology, Seoul National University Hospital,[b] and the Department of Dermatology, Seoul National University College of Medicine.[c]

Funding sources: None.
IRB approval status: Not applicable.

Correspondence to: Si-Hyung Lee, MD, PhD, Department of Dermatology, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea. E-mail: always5515@gmail.com.

JAAD Case Reports 2021;12:46-8.
2352-5126

https://doi.org/10.1016/j.jdcr.2021.04.007

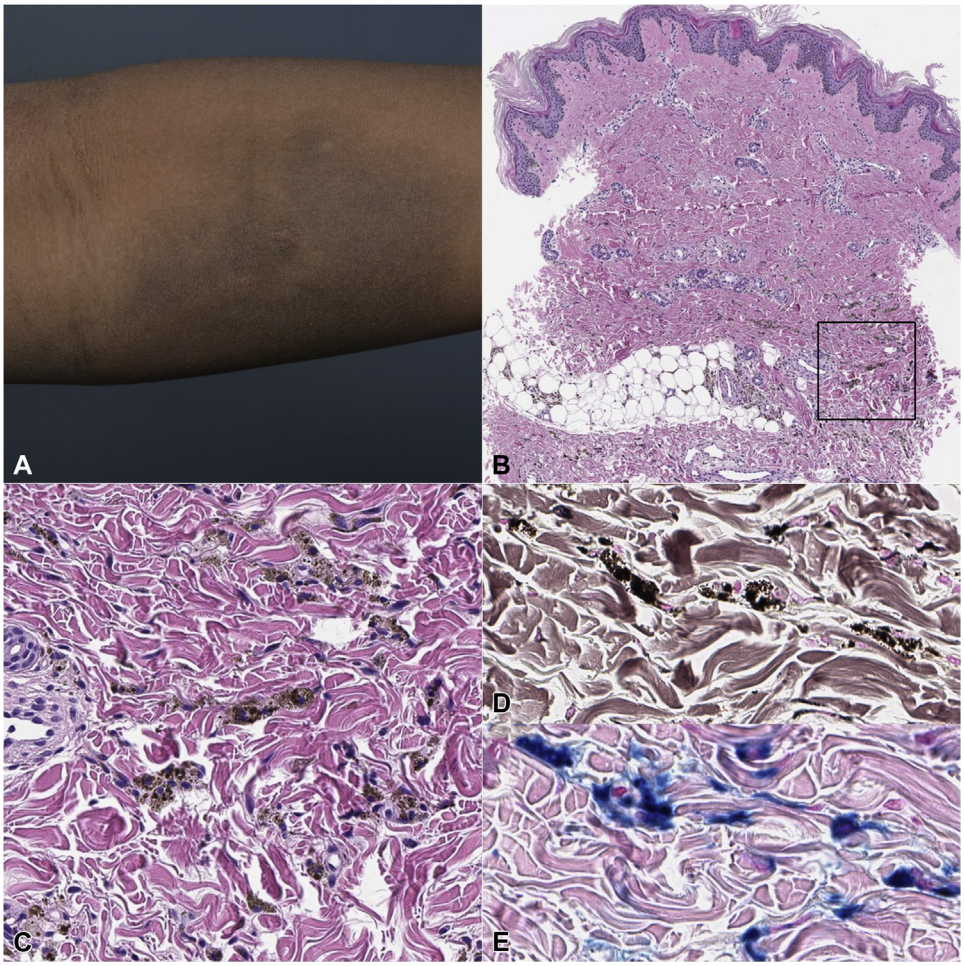

Fig 1. **A**, Clinical photograph of the bluish-gray patch on the inner aspect of the left forearm. **B** and **C**, Histologic images showing increased basal pigmentation in the epidermis and yellow-brown granular pigment deposition within macrophages in the mid-to-deep dermis. **C**, Showing high magnification of square division indicated in Fig 1, *B*. **D** and **E**, Special stains suggest perivascular siderophage infiltration in the mid-to-deep dermis. (**B** and **C**, Hematoxylin-eosin stain, **D**, Fontana-Masson stain, **E**, Perl's iron stain; original magnifications: **B**, ×40; **C**, ×400; **D**, ×400; **E**, ×400.)

associated pigmentation may occur secondary to ecchymosis or bruising. Our case supports this hypothesis and clearly shows that inappropriate intravenous cannulation, or trauma in a broad sense, can trigger pigmentation in patients taking HCQ. Previous histologic findings of HCQ-induced pigmentation suggest the importance of both melanin and iron deposition.[1,3-5] In the case of melanin deposition, basal layer hyperpigmentation in the epidermis and the presence of melanophages in the superficial dermis have been commonly observed.[3-5] In contrast, the predominant roles of iron and the presence of siderophages in the dermis have also been documented in some cases in which the median concentrations of iron were 10 times higher in the pigmented lesions than in normal skin along with statistical significance.[1,3,5] The presence of hemosiderin, not melanin, in our case further strengthens the pivotal role of trauma and subsequent extravasation in HCQ-induced pigmentation. To our knowledge, this is the first report indicating iatrogenic injury as a direct cause of HCQ-associated hyperpigmentation. It is also notable that the patient had no predisposing conditions to easy bruising at the time of extravasation injury. Therefore, special care should be taken in patients taking HCQ to prevent trauma, especially iatrogenic injury, including extravasation injury. However, it is unclear how siderophages can persist in the dermis and whether HCQ affects their clearance. It has been shown that HCQ can affect the function of macrophage lysosomes through pH alteration[6]; however, further studies are required to

elucidate the mechanism underlying HCQ-induced pigmentation.

Conflicts of interest

None disclosed.

REFERENCES

1. Jallouli M, Frances C, Piette JC, et al. Hydroxychloroquine-induced pigmentation in patients with systemic lupus erythematosus: a case-control study. *JAMA Dermatol*. 2013;149(8):935-940.
2. Skare T, Ribeiro CF, Souza FH, Haendchen L, Jordao JM. Antimalarial cutaneous side effects: a study in 209 users. *Cutan Ocul Toxicol*. 2011;30(1):45-49.
3. Coulombe J, Boccara O. Hydroxychloroquine-related skin discoloration. *CMAJ*. 2017;189(5):E212.
4. Puri PK, Lountzis NI, Tyler W, Ferringer T. Hydroxychloroquine-induced hyperpigmentation: the staining pattern. *J Cutan Pathol*. 2008;35(12):1134-1137.
5. Tracy CL, Blakey B, Parker G, Roebuck J. Hydroxychloroquine-induced hyperpigmentation. *J Clin Rheumatol*. 2013;19(5):292.
6. Fox RI. Mechanism of action of hydroxychloroquine as an antirheumatic drug. *Semin Arthritis Rheum*. 1993;23(2 Suppl 1):82-91.