

## CASE REPORT

# Hydroxychloroquine-induced hyperpigmentation in a 14-year-old female with systemic lupus erythematosus

Alexander KC Leung MBBS, FRCP (UK & Irel), FRCPC, FAAP<sup>1</sup>, Tara McMillan MD, FRCPC<sup>2</sup>,  
Andrea Human MD, FRCPC<sup>2</sup>, Joseph M Lam MD, FRCPC<sup>3</sup>

<sup>1</sup>The University of Calgary, The Alberta Children's Hospital, Calgary, Alberta, Canada;

<sup>2</sup>British Columbia Children's Hospital, University of British Columbia, Vancouver, British Columbia, Canada;

<sup>3</sup>Department of Dermatology and Skin Sciences, University of British Columbia, Vancouver, British Columbia, Canada

### Abstract

Hydroxychloroquine (HCQ)-induced hyperpigmentation is uncommon but is increasingly recognized. To our knowledge, HCQ-induced hyperpigmentation has not been reported in the pediatric age group. Herein, we present the case of a 14-year-old girl with systemic lupus erythematosus, who developed hyperpigmentation on her shins and dorsum of the left foot, approximately 3 years after initiating treatment with HCQ. Physicians who treat children with HCQ for reasons such as rheumatologic disorders, dermatologic disorders and, more

recently, coronavirus disease-19 should be aware of this less-known side effect of HCQ.

**Keywords:** chloroquine, COVID-19, dermatologic disorders, melanin, rheumatologic disorders.

### Citation

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## Introduction

Chloroquine-induced hyperpigmentation is well known.<sup>1</sup> On the other hand, hydroxychloroquine (HCQ)-induced hyperpigmentation is an uncommon but increasingly recognized side effect of HCQ therapy.<sup>1</sup> The hyperpigmentation may develop from a few months to a few years following the initiation of HCQ therapy.<sup>2,3</sup> To our knowledge, HCQ-induced hyperpigmentation has not been reported in the pediatric age group. Herein, we report on the case of a 14-year-old girl with systemic lupus erythematosus (SLE), who developed hyperpigmentation on her shins and dorsum of the left foot after treatment with HCQ for 3 years. No review board approval was necessary and was therefore not obtained. Signed consent was obtained.

## Case report

A 14-year-old Indigenous Canadian female with SLE presented with a 2-year history of asymptomatic hyperpigmentation on the bilateral shins and the dorsum of the left foot. The hyperpigmented patches first appeared over the bilateral shins and the dorsum of the left foot in areas of previous bruising. There was no history of trauma.

The patient's symptoms began at the age of 9 years, when she presented with polyarthritis, low serum C3 and C4 levels, positive antinuclear antibodies, anti-double-stranded DNA antibodies, and anti-Smith antibodies. She was seen by a pediatric rheumatologist who diagnosed her with SLE based on the clinical and laboratory findings. The patient was treated with oral methotrexate, 20 mg, weekly and oral HCQ at a dose of 1800 mg per week (200 mg daily on weekdays and 400 mg daily on weekends, averaging 4.8 mg/kg/day). During the course of her illness, she was also treated with cyclophosphamide, corticosteroids, rituximab, and mycophenolate mofetil at various points in time. She did not have a known coagulopathy and was not on anticoagulation therapy. Physical examination revealed Fitzpatrick type IV skin with symmetrical, bluish-grey patches bilaterally on the pretibial areas and dorsum of the left foot (Figure 1). There was no pigmentation at other body sites including the oral mucosa and the nails. A clinical diagnosis of HCQ-induced hyperpigmentation was made based on the typical appearance of symmetrical, bluish-grey patches bilaterally on both shins. The HCQ was discontinued. However, the patient expired from complications of lupus prior to the observance of any effect.

**Figure 1. Bilateral bluish-grey patches on the shins and dorsum of the left foot.**



## Discussion

HCQ was first developed as an antimalarial agent, and is now also used in the treatment of SLE, juvenile idiopathic arthritis, rheumatoid arthritis, Sjogren syndrome, dermatomyositis, actinic lichen planus, oral lichen planus, and sarcoidosis owing to its anti-inflammatory and immune-modulating properties.<sup>1,4-7</sup> Recently, HCQ has also been used in the treatment of coronavirus disease-19 (COVID-19).<sup>8-10</sup> HCQ has also been suggested as a candidate prophylactic agent for COVID-19 in populations at high risk for COVID-19, such as high-risk groups in New York and Italy.<sup>11</sup> HCQ is preferred to chloroquine because it is less toxic. For the treatment of COVID-19, HCQ works by blocking severe acute respiratory syndrome-related coronavirus (the causative virus for COVID-19) viral entry into host cells through inhibition of angiotensin-converting enzyme 2 receptor glycosylation, reducing viral replication, and blocking the export of newly constructed virions.<sup>8-10</sup>

HCQ has a relatively favorable safety profile, is generally well tolerated, and is readily available at relatively low cost.<sup>4</sup> HCQ-induced hyperpigmentation of the skin is increasingly recognized as a side effect of HCQ therapy.<sup>12</sup> Although infrequently reported in the literature, a recent cross-sectional study found that 29% of patients on HCQ

developed HCQ-induced hyperpigmentation.<sup>2</sup> In this regard, hyperpigmentation associated with chloroquine therapy is more common than that of HCQ.<sup>1,13</sup> Typically, HCQ-induced hyperpigmentation presents as bluish, blue-grey macules/patches most commonly on the shins, but can also be seen on the arms, forearms, face, oral mucosa, trunk, nails, and axilla.<sup>2,4,6,14</sup> There is no apparent predilection for sun-exposed areas and oral mucocutaneous hyperpigmentation also occurs.<sup>14,15</sup> The involvement is typically bilateral,<sup>14</sup> although unilateral involvement has rarely been reported.<sup>16</sup> The differential diagnosis includes erythema nodosum, ecchymosis, minocycline dyspigmentation, and erysipelas.<sup>17</sup> The color, chronicity, and associated HCQ use help to distinguish HCQ-induced hyperpigmentation from these other disorders. There are no formal criteria for HCQ-induced hyperpigmentation as the diagnosis is usually clinically apparent. A skin biopsy is often not required but can help confirm the diagnosis.

Our patient presented with symmetrical, poorly defined, grey patches bilaterally on the shins and the dorsum of the left foot. Cutaneous pigmentation occurs in 10–25% of patients after a few months to a few years of treatment with HCQ.<sup>2,3,6,18</sup> In one study of 41 patients treated with HCQ, pigmentation appeared after a median duration of HCQ treatment of 32 months (range 6–108 months).<sup>2</sup> There is no clear association with duration of treatment or cumulative dose of HCQ.<sup>19</sup> In the present case, the child developed hyperpigmentation on the shins and dorsum of the right foot approximately 3 years after initiating HCQ therapy. To our knowledge, HCQ-induced hyperpigmentation of the skin has not been reported in children. As such, our patient represents the first case reported in the pediatric age group. HCQ-induced hyperpigmentation usually resolves within 6 months after HCQ has been discontinued<sup>6,13,20,21</sup> but, occasionally, the hyperpigmentation may persist.<sup>22</sup> If possible, HCQ should be substituted with another medication that has similar therapeutic effects. The use of a Q-switched 755-nm alexandrite laser may be considered for the treatment of persistent hyperpigmentation.

The exact pathogenesis for the development of HCQ-induced hyperpigmentation is not known. A strong association has been found with preceding ecchymosis or bruising, which suggests that the mechanism may be, at least in part, due to localized trauma.<sup>6</sup> Other predisposing factors include the use of oral anticoagulants or antiplatelet agents, long-term use of corticosteroids, and antiphospholipid syndrome.<sup>2,3,13,18,19</sup> HCQ-induced damage of dermal vessels with leakage of erythrocytes is another possibility.<sup>1</sup> Histopathological examination of the hyperpigmented lesion shows yellow-brown granules within macrophages in the dermis, melanin in reticular dermis, and perivascular iron/hemosiderin on special staining.<sup>6,23</sup> HCQ can accumulate within the skin and has a strong binding affinity to melanin.<sup>4,14,24</sup> It has been suggested that the hyperproduction of melanin by epidermal melanocytes can be under the direct influence of HCQ.<sup>1</sup> HCQ-induced hyperpigmentation is more

common in dark-skinned individuals likely due to greater melanin levels in dark skin.<sup>2</sup>

Other HCQ-induced cutaneous manifestations include xerosis, pruritis, nail hyperpigmentation, hair discoloration, alopecia, urticarial and lichenoid skin rash, toxic epidermal necrolysis, Stevens–Johnson syndrome, and exacerbation of pre-existing psoriasis.<sup>1,6,25</sup> Non-cutaneous adverse effects of HCQ include nausea, diarrhea, prolongation of QT-interval, corneal lens opacity, retinopathy, ciliary body dysfunction, posterior subcapsular lens opacity, myopathy, and ochronosis.<sup>5,11,26,27</sup> Some authors suggest that HCQ-induced hyperpigmentation is a marker of increased risk of retinopathy.<sup>16,20,27</sup>

## Conclusion

HCQ-induced hyperpigmentation of the skin is increasingly recognized as a side effect of HCQ therapy. Typically, HCQ-induced hyperpigmentation presents as bluish, blue–grey macules/patches most commonly on the shins. To our knowledge, the condition has not been described in the pediatric age group. HCQ has been used widely in the treatment of a variety of rheumatologic and dermatologic conditions and, recently, by some physicians in the prophylaxis and treatment of COVID-19. Physicians who use HCQ in children should be aware of this less-known side effect of HCQ so that an accurate diagnosis can be made, and unnecessary investigations and inappropriate treatment can be avoided.

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**Correspondence:** Alexander KC Leung, The University of Calgary, Alberta Children’s Hospital, #200, 233 – 16th Avenue NW, Calgary, Alberta, Canada T2M 0H5. [aleung@ucalgary.ca](mailto:aleung@ucalgary.ca)

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