Portuguese Journal of Dermatology and Venereology

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CASE REPORT

Hydroxychloroquine-induced hyperpigmentation in a patient with anti-synthetase syndrome

Hiperpigmentação induzida pela hidroxicloroquina numa doente com síndrome anti-sintetase

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Abstract

Hydroxychloroquine is a widely prescribed antimalarial drug to treat immune-mediated diseases, with a good safety profile. We present the case of a 37-year-old woman, Fitzpatrick's phototype IV, who presented to our outpatient Dermatology Department with a 1-year history of symmetrical blue-gray discoloration on the anterior aspect of the legs. The patient had a diagnosis of anti-synthetase syndrome, treated with prednisolone, hydroxychloroquine, rituximab, cyclosporine, and acetylsalicylic acid. The blood work was unremarkable. The skin biopsy revealed hemosiderin and melanin (Perl's and Fontana-Masson staining) deposits inside dermal histocytes. The diagnosis of antimalarial-induced hyperpigmentation was established. Cutaneous blue-gray discoloration is a common antimalarial skin toxicity, mainly in women with darker skin. Its pathophysiology is unclear, but local trauma, ultraviolet radiation, and the concomitant use of corticosteroids, anticoagulants, and antiplatelet drugs seem to contribute as triggers. This case illustrates that a high level of suspicion and adequate clinicopathologic correlation is necessary to establish a correct diagnosis.

Keywords: Antimalarials. Drug-induced abnormalities. Hydroxychloroquine. Hyperpigmentation. Idiopathic inflammatory myopathies.

Resumo

A hidroxicloroquina é um fármaco antimalárico frequentemente utilizado no tratamento de doenças imunomediadas, com bom perfil de segurança. Apresentamos o caso de uma mulher de 37 anos, fototipo IV de Fitzpatrick, encaminhada à consulta de Dermatologia por manchas cinzento-azuladas simétricas na face anterior das pernas com 1 ano de evolução. A doente tinha diagnóstico de síndrome anti-sintetase, medicada com prednisolona, hidroxicloroquina, rituximab, ciclosporina e ácido acetilsalicílico. A avaliação analítica não revelou alterações. A biópsia cutânea demonstrou depósitos de hemossiderina e melanina (colorações Fontana-Masson e Perls) em histiócitos na derme, compatível com hiperpigmentação induzida por antimaláricos. As discromias cinzento-azuladas são um efeito adverso cutâneo comum dos antimaláricos, sobretudo em mulheres de fototipo alto. A fisiopatologia não está completamente esclarecida, mas o trauma local, a radiação ultravioleta e a toma concomitante de

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Received: 05-06-2024
Accepted: 02-07-2024
DOI: 10.24875/PJDV.24000054

Available online: 15-07-2024
Port J Dermatol and Venereol. 2024;82(4):253-257
www.portuguesejournalofdermatology.com

corticosteroides, anticoagulantes e antiagregantes parecem contribuir como desencadeantes. Este caso ilustra que o diagnóstico da hiperpigmentação induzida pela hidroxicloroquina implica um elevado nível de suspeição e correlação clínico-patológica.

Palavras-chave: Antimaláricos. Alterações induzidas por fármacos. Hidroxicloroquina. Hiperpigmentação. Miopatias idiopáticas inflamatórias.

Introduction

Hydroxychloroquine is an antimalarial drug that is widely prescribed in dermatology and rheumatology, due to its immunomodulatory and photoprotective properties, namely in systemic and cutaneous lupus erythematosus and idiopathic inflammatory myopathies[1,2]. Although antimalarial drugs have a good overall safety profile, skin adverse events are not rare and are frequently overlooked[2,3]. Skin, nail, and mucous membrane blue-gray discoloration is one of the most common skin toxicities of antimalarial drugs and may occur in 10-25% of patients[2-4]. Herein, we report a case of hydroxychloroquine-induced hyperpigmentation in a patient with anti-synthetase syndrome that illustrates that a high level of suspicion and adequate clinicopathologic correlation is necessary to establish a correct diagnosis and to determine optimal patient management.

Case report

A 37-year-old woman, Fitzpatrick's phototype IV, presented to our outpatient dermatology department with a 1-year history of asymptomatic, bilateral dark patches on her lower limbs. Her past medical history was relevant for anti-synthetase syndrome, which was diagnosed when she was 32 years old due to proximal muscle weakness, polyarthritis, and fingers' hyperkeratosis and fissuring (mechanic's hands). The patient's autoimmune serology was positive for anti-Jo-1 antibodies and anti-Ro/SSA and negative for the remaining antibodies. She was under treatment with prednisolone 10 mg/day, hydroxychloroquine 400 mg/day, and rituximab pulses every 6 months, which were initiated 4 years before the cutaneous discoloration began. One year before, the patient was also prescribed cyclosporine 200 mg/day and acetylsalicylic acid 150 mg/day, given her wish for childbearing. The patient denied taking any other drugs than the ones mentioned before or applying any specific topical products. She also denied pain or pruritis, previous local trauma, preceding skin eruption, chronic venous insufficiency complaints, and any other local or systemic symptoms.

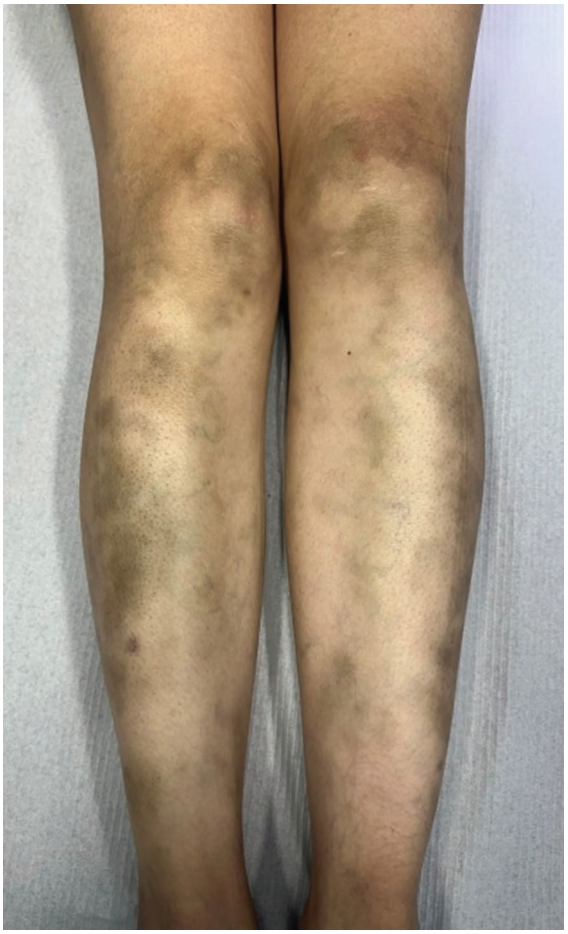

Figure 1. Clinical image. Symmetrical, ill-defined, mottled blue-grey patches on the anterior aspect of both legs and knees.

On physical examination (Fig. 1), there were non-tender, symmetrical, ill-defined, mottled blue-grey patches on the anterior aspect of both legs and knees. There was no pigmentation at other body sites including the oral mucosa and the nails. The diagnostic hypothesis of antimalarial drug-induced skin discoloration was considered. Laboratory examination revealed a normal complete blood count, normal coagulation studies and platelet function tests, normal iron and ferritin levels, and was otherwise unremarkable. Histopathologic examination of a punch skin biopsy (Fig. 2) showed hemosiderin (Perls staining) and melanin (Fontana-Masson staining)

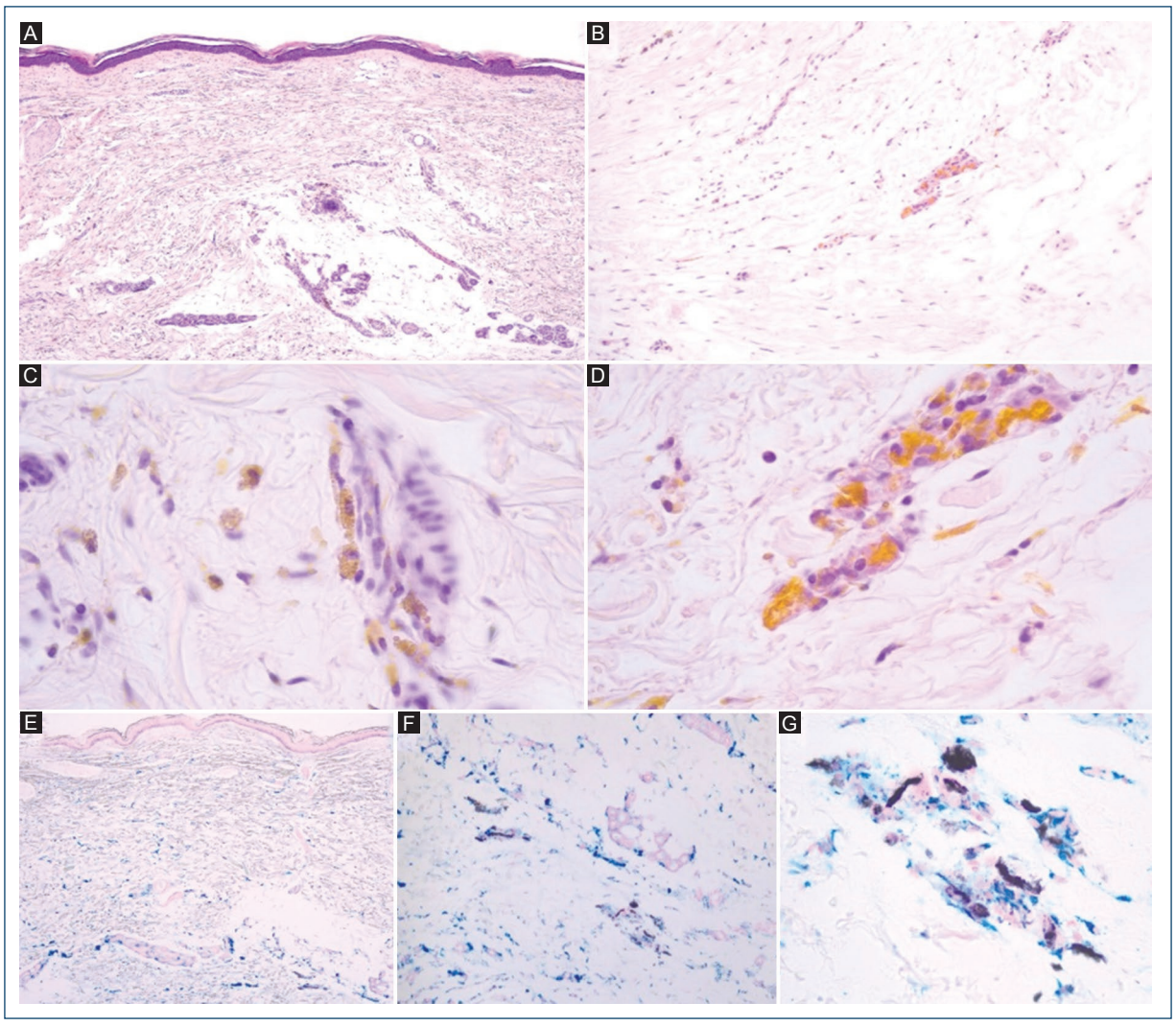

Figure 2. Histopathological examination. **A:** hematoxylin-eosin, original magnification ×40) yellowish-to-brown interstitial and perivascular pigmented granules throughout the dermis, of different qualities. **B:** hematoxylin-eosin, original magnification ×100): darker (superior left corner of the image) and lighter (center of the image) pigment deposits. In higher magnification, there are fine dark-brown intrahistiocytic pigment granules. **C:** hematoxylin-eosin, original magnification ×400), and thick yellow-brown intrahistiocytic and interstitial pigment granules. **D:** hematoxylin-eosin, original magnification ×400). Simultaneous Perls/Fontana-Masson staining demonstrated that these pigment granules corresponded to intrahistiocytic melanin, and intrahistiocytic, and interstitial hemosiderin. **E-G:** Perls/Fontana-Masson staining, original magnification ×40, ×100, and ×400, respectively).

deposits inside dermal histocytes. The diagnosis of hydroxychloroquine-induced cutaneous hyperpigmentation was established. The patient had an ophthalmology appointment that excluded retinopathy and other ocular toxicities.

A multidisciplinary discussion of the different management approaches for this case was conducted, including Dermatology, Rheumatology, Obstetrics, and Ophthalmology. The treatment options were also discussed with the patient. We took into consideration that the patient had an anti-synthetase syndrome with present signs of disease activity, that she had a previous late fetal loss, and had positive anti-Ro/SSA antibodies with increased pregnancy and neonatal risk (namely for neonatal lupus), and also that interrupting the treatment did not guarantee clinical resolution of the discoloration. Therefore, we decided to maintain treatment with hydroxychloroquine. The patient was treated with azelaic acid cream 200 mg/g twice a day and photoprotective measures, with moderate improvement.

Discussion

Cutaneous blue-gray discoloration is a common antimalarial drug skin and mucous membrane toxicity, affecting up to 10-25% of patients, and it seems to be more frequent with chloroquine than hydroxychloroquine[2-4]. It mainly affects women with darker skin types[1,3,4], such as our patients.

Clinically, hydroxychloroquine-induced hyperpigmentation presents as bluish or blue-grey macules and patches that most commonly occur bilaterally on the anterior aspects of the legs, but can also less frequently be seen on the arms, forearms, face, oral mucosa, trunk, nails, and axilla[1,2,4]. The latency of this skin adverse event is variable. In most series, the majority of cases occur within the first 5 years of treatment, with a median duration of 3 years[1,3,5].

The pathophysiology of this skin discoloration is not completely understood, and there is no significant association with the cumulative dose of hydroxychloroquine[1,3,4]. Some reports have demonstrated that local trauma, ultraviolet radiation, and the concomitant use of corticosteroids, anticoagulants, and antiplatelet drugs may contribute to triggers[1-3]. It is believed that local trauma and the use of antithrombotic drugs, alongside hydroxychloroquine-induced damage of dermal vessels, may lead to erythrocyte extravasation, with hemoglobin release into the extracellular space. The subsequent heme breakdown induces iron deposits in the form of interstitial and intra-histiocytic hemosiderin complexes in the dermis. The hemosiderin deposition then causes melanocyte activation, with increased production of melanin[1-3]. Cutaneous histopathologic studies of patients with hydroxychloroquine-induced hyperpigmentation demonstrate the presence of both hemosiderin and melanin dermal deposits (as in our patient) and also show significantly higher iron concentrations in biopsy specimens of pigmented lesions compared with normal skin, corroborating this theory[1-3,5]. However, several other mechanisms may be implied, such as direct melanocyte stimulation by hydroxychloroquine and accumulation of drug metabolites[3].

The association between skin discoloration and ocular adverse events (retinopathy, corneal, and lens opacities) in patients taking hydroxychloroquine is still controversial[1,2,5]. Although some authors believe that antimalarial drug-induced pigmentation may be a marker for patients at risk of ocular complications[2,6], these data mostly refer to patients taking chloroquine and this correlation has not yet been significantly established in the literature[1,5]. Further studies are still needed to better understand this potential association, and in view of this, patients receiving antimalarial therapy who develop pigment abnormalities should have frequent ophthalmological examinations[6,7].

Nevertheless, most reports in the literature to this date state that other than possible esthetic or psychosocial impact (which was not relevant in our patient), skin pigmentation has no other systemic consequences for patients. Furthermore, the hyperpigmentation may not resolve after drug discontinuation[3,5], and in patients who keep taking the drug, the pigmentation seems to remain stable[1]. Therefore, drug discontinuation is not always necessary[1], especially if ocular complications have been excluded and the benefits outweigh the potential risks, as in our patient.

Conclusion

This case of hydroxychloroquine-induced hyperpigmentation in a patient with anti-synthetase syndrome illustrates that skin discoloration is a common cutaneous adverse event of this drug, but that it is not necessarily associated with other serious side effects such as retinopathy, and therefore does not always imply drug discontinuation. This case also highlights that a high level of suspicion and adequate clinicopathologic correlation are necessary to establish a correct diagnosis and that a multidisciplinary approach is crucial in these complex cases to determine the optimal management for each specific patient.

Funding

None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor the creation of images, graphics, tables, or their corresponding captions.

References

1. Bahloul E, Jallouli M, Garbaa S, Marzouk S, Masmoudi A, Turki H, et al. Hydroxychloroquine-induced hyperpigmentation in systemic diseases: prevalence, clinical features and risk factors: a cross-sectional study of 41 cases. Lupus. 2017;26:1304-8.
2. Jallouli M, Francès C, Piette JC, Thi Huong DL, Moguelet P, Factor C, et al. Hydroxychloroquine-induced pigmentation in patients with systemic lupus erythematosus: a case-control study. JAMA Dermatol. 2013;149:935-40.
3. Leung AK, McMillan T, Human A, Lam JM. Hydroxychloroquine-induced hyperpigmentation in a 14-year-old female with systemic lupus erythematosus. Drugs Context. 2020;9:2020-5-8.
4. Bajoghli A, Hernandez G, Cardis MA. Hydroxychloroquine-induced hyperpigmentation. J Rheumatol. 2020;47:1721-2.
5. Coulombe J, Boccara O. Hydroxychloroquine-related skin discoloration. CMAJ. 2017;189:E212.
6. Tuffanelli D, Abraham RK, Dubois EI. Pigmentation from antimalarial therapy. Its possible relationship to the ocular lesions. Arch Dermatol. 1963;88:419-26.
7. Skare T, Ribeiro CF, Souza FH, Haendchen L, Jordão JM. Antimalarial cutaneous side effects: a study in 209 users. Cutan Ocul Toxicol. 2011;30:45-9.