An Usual Dermite Ocre of the Lower Limbs: A Quiz

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A 65-year-old Caucasian woman presented for the follow-up of a leg ulcer diagnosed as distal calciphylaxia treated by local injection of sodium thiosulfate. Her past medical history was notable for hypertension, non-toxic multi-nodular goitre, systemic lupus and osteoporosis. Her regular medication included currently and notably, antihypertensive treatments (candesartan and lercanidipin), prednisolone, azathioprine, oral calcium and vitamin D supplementation, bisphosphonate (ibandronate) and citalopram.

Upon presentation, leg ulcer had closed. Examination disclosed a striking asymptomatic dark-brown hyperpigmentation of the lower limbs that involved the whole legs (Fig. 1). The pigmentation has been present for several years according to the various medical records. It was sometimes considered as a "*dermite ocre*" in a context of venous insufficiency. However, doppler ultrasound imaging of the veins of the lower limbs failed to find any remarkable venous insufficiency. A vascular surgeon had ruled out any arterial or venous lower limbs insufficiency. The rest of skin, nails and mucosa were free of any pigmentation. However, an additional information (omitted here on purpose in the present text) in the anamnesis provided the diagnosis of this hyperpigmentation.

What would you have asked to the patient? What is your diagnosis?
See next page for answer.

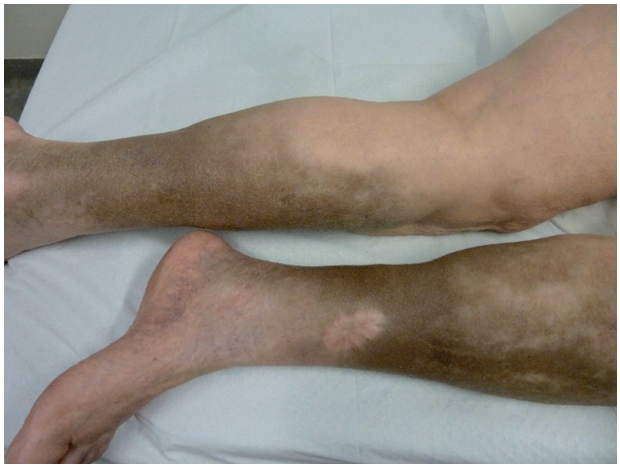

Fig. 1. Intense brown pigmentation of the lower limbs.

An Usual Dermite Ocre of the Lower Limbs: A Commentary

***Diagnosis*: Hydroxychloroquine-induced hyperpigmentation**

What would you have asked to the patient ?

Because of systemic lupus, our patient was asked whether she was treated by hydroxychloroquine (HCQ). She acknowledged taking HCQ regularly "for a long time". We could trace back in the computer medical file that she has been receiving HCQ at least since 2004, at the dosage of 300 mg/day. Upon interrogation, the patient recalled that the pigmentation had been evolving for years, without being able to give a precise time frame.

Pigmentary changes of the skin, the nails, the oral mucosa constitute the main cutaneous complication of all antimalarials (HCQ, chloroquine, mepacrine and structurally related quinidine). It affects approximately from 10 to 25% of the patients (1, 2). To date, approximately 40 cases related specifically to HCQ pigmentation have been reported in the literature (2, 3). Clinical presentation is variable according to patients. The pigmentation presents as a bluish-grey to dark pigmentation, for which the severity ranges from isolated localized macules to larger lesions that can sometimes be extensive (4), as illustrated also in our case. Pigmentation may be located on both sun-exposed and sun-covered areas such as the face, neck, trunk, abdomen, extremities, but also on scars, nails (longitudinal, transversal or diffuse hyperpigmentation) and the oral mucosa (hard palate and gums) (1–5). Additional pigmentation of the joint tissue, sclera and cartilage have been described (6). However, the anterior side of the legs are always involved (2). The appearance of pigmentation is very often preceded by ecchymosis (2). According to Jallouli et al. (2), patients often mention the onset as "bruises that did not disappear". Interestingly, the same authors found that antiplatelets or oral anticoagulation intake was associated significantly with the occurrence of HCQ-induced pigmentation. If performed, microscopic analysis will disclose intracellular (macrophages) and extracellular yellow to dark brown pigments granules in the superficial and deep dermis (1). Perls iron stain is not always positive according to studies (2, 6, 7) while Fontana-Masson stain confirms the presence of melanine (7). The pigmentation usually develops after variable delay ranging from several months to over 20 years after initiation of the therapy. A median delay of 6 years was reported recently (2). The pigmentation is said to be related to dosage, but this is not always easy to assess (6). In their retrospective control study, Jallouli et al. (2) did not find any association between pigmentation and HCQ duration or cumulative HCQ dosage. Besides, after treatment withdrawal, the pigmentation is expected to decrease progressively, but a complete resolution is far from being seen (4, 5). Therefore, treatment disruption should be decided with the patient according to the benefit – risk balance (3). Some authors suggest to perform systematically in case of such skin pigmentation an ophthalmologic examination and an ECG to rule any systemic anti-malarial toxicity.

The precise mechanism of pigmentation is not clear but it is speculated that, as for chloroquine, melanin would bind to HCQ (6). Localization on the shin, association with factors facilitating bruising, interviews with patients, and data from skin biopsies support however the hypothesis that HCQ-induced pigmentation is secondary to ecchymosis or bruising (2).

Our case illustrates that HCQ pigmentation may be extensive on the lower limbs, and easily misdiagnosed in the elderly as "*dermite ocre*".

The author declares no conflict of interest.

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