Received: 17 June 2020 | Revised: 14 July 2020 | Accepted: 27 July 2020

DOI: 10.1111/dth.14145

LETTER

DERMATOLOGIC THERAPY WILEY

Hydroxychloroquine-induced erythroderma: A rare adverse effect of a commonly used drug

Dear Editor,

Hydroxychloroquine is considered a relatively safe drug when used for prolonged durations. We report a patient with rheumatoid arthritis (RA) who developed erythroderma with its use over a short span of time and review relevant literature on this association.

A 23-year-old female presented with generalized skin redness and scaling for a month. She had no history of any preceding cutaneous disease. The patient had been diagnosed with RA 4 months prior, and was started on hydroxychloroquine, sulfasalazine and nonsteroidal anti-inflammatory drugs (NSAIDS; si opus sit [SOS]) by a rheumatologist. However, she reportedly developed a generalized cutaneous rash with intense redness and scaling all over the skin surface a month later. The patient consulted a general physician, who diagnosed the condition as exfoliative dermatitis and stopped all her drugs. The physician also started oral steroids on which the rash resolved within 3 weeks. However, considering sulfasalazine as the culprit, her rheumatologist later restarted hydroxychloroquine following which her rash reoccurred within 1 month. At presentation, the patient had generalized erythema and scaling diffusely involving the face, both upper limbs, trunk, both lower limbs and scalp (Figure 1A,C), with fissuring over both ankles, wrist, inguinal folds, palms and soles. She also had

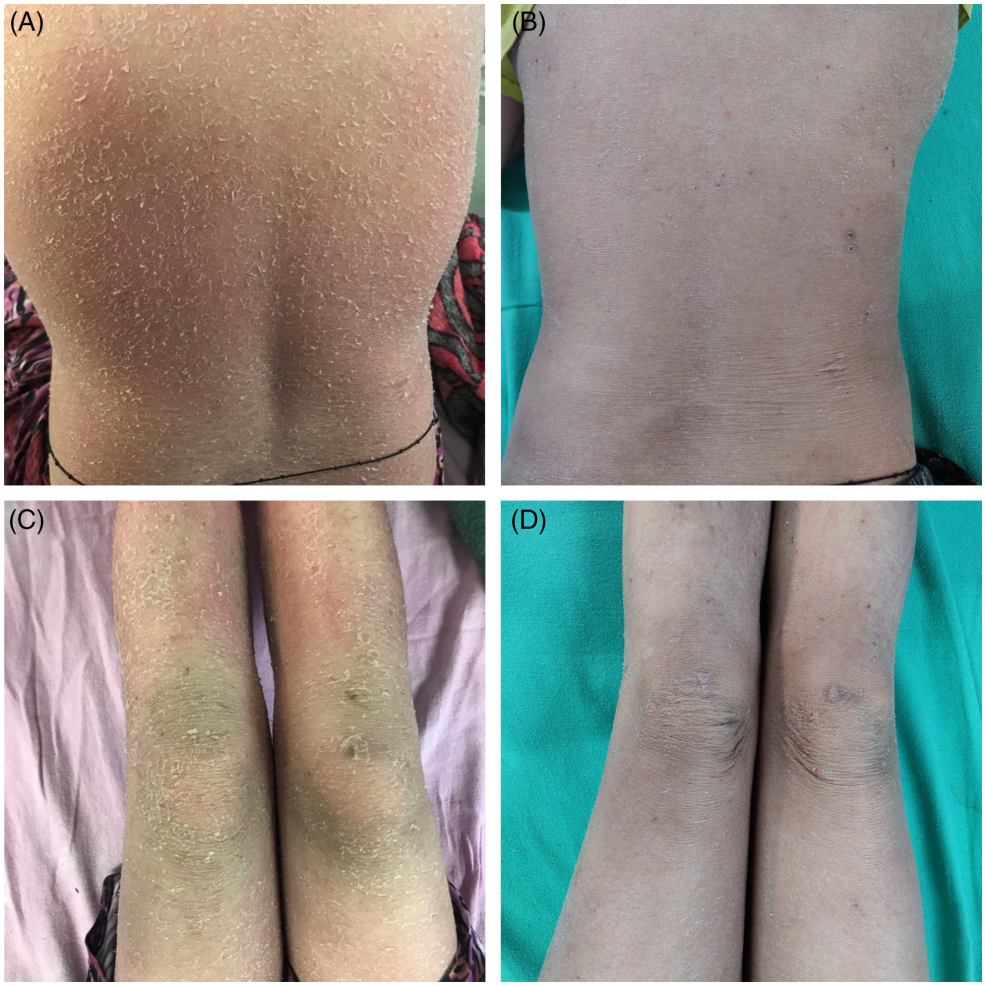

FIGURE 1 A,C, Erythema and scaling involving back and lower limbs. B,D Resolution of lesions after 3 weeks of therapy

generalized lymphadenopathy and facial and pedal edema. Nails and all mucosae were normal.

Her laboratory parameters were hemoglobin 11.3 g/dL, white blood cell count 12 000 cells/mm^3, erythrocyte sedimentation rate 29 mm/first h and C-reactive protein >10 mg/dL. RA factor was positive and absolute eosinophil count was 750/μL (normal range: 40-400 cells/μL). Other biochemical parameters were normal. Viral markers were nonreactive. Skin biopsy from the back showed parakeratosis, marked spongiosis and an eosinophil-predominant dermal infiltrate consistent with drug-induced erythroderma (Figures 2 and 3).

Naranjo adverse drug reaction (ADR) probability scale score was 9 (Table 1) suggesting a "definite" association with hydroxychloroquine, while the RegiSCAR score was 4, thus not fulfilling the criteria for a definite drug rash with eosinophilia and systemic symptoms (DRESS) syndrome. A final diagnosis of hydroxychloroquine-induced erythroderma was thus made. Hydroxychloroquine was stopped and a tapering course of oral steroids (starting with 1 mg/kg/d) was started. The patient was discharged 3 weeks later with complete resolution of skin lesions (Figure 1B,D) and off oral steroids.

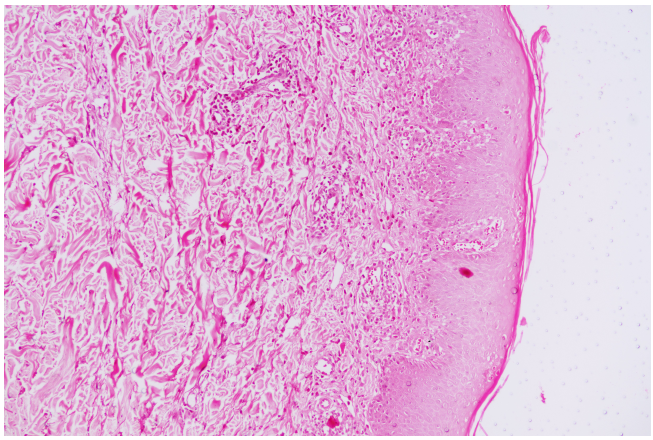

FIGURE 2 Low-power photomicrograph showing hyperkeratosis, focal parakeratosis, acanthosis and mild spongiosis. Dermis shows mild perivascular inflammatory infiltrate (hematoxylin and eosin, ×100)

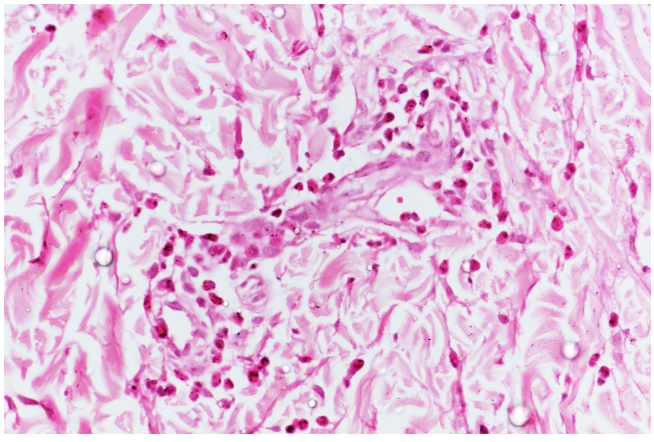

FIGURE 3 High power highlights perivascular mixed inflammatory infiltrate with many eosinophils (hematoxylin and eosin, ×400)

Hydroxychloroquine is commonly used in the treatment of autoimmune and rheumatological conditions. The main mechanism for its antirheumatic effect is an interference with "antigen processing" by increasing vacuolar pH within antigen-presenting cells. In the current times, hydroxychloroquine has also found worldwide use as a prophylactic and therapeutic agent against coronavirus disease 2019 (COVID-19).[1]

The drug has a good tolerability with gastrointestinal adverse effects being an occasional reason for drug discontinuation. The incidence of antimalarial-associated pruritus and cutaneous eruptions has been reported to be 10% to 20%.[2] The varied cutaneous ADRs (CADR) reported include mild reactions such as maculopapular rash, hyperpigmentation and bleaching of hair to severe reactions such as Steven Johnson syndrome/toxic epidermal necrolysis and acute exanthematous generalized pustulosis.

Drug-induced erythroderma is abrupt in onset and resolves faster than other causes once the drug is withdrawn.[3] Affected patients often have facial edema and peripheral eosinophilia.[3] The drugs commonly implicated are carbamazepine, allopurinol, dapsone, phenytoin, isoniazid, lithium and co-trimoxazole.[3] There has been only one previous report of hydroxychloroquine-induced erythroderma, described in a patient with systemic lupus erythematosus (SLE) who developed erythroderma a month into treatment,[3] while hydroxychloroquine-induced DRESS has been reported a few times before.[4] Another report mentions the development of psoriatic erythroderma in a patient with coexistent psoriasis and SLE.[5] Although antimalarial-induced exacerbation of psoriasis and induction of erythroderma in psoriatics is possibly related to inhibition of transglutaminase and resultant decreased epidermal differentiation,[6] the mechanism of induction of de novo erythroderma by the drug, as in our patient, remains to be elucidated in view of the rarity of the condition.

In a patient on multiple drugs like the presented one, the suspicion undoubtedly goes onto the drug with maximum reports in literature—like sulfasalazine here. However, in severe cases, often multiple drugs may be needed to be stopped as the culprit drug is not obvious and, although uncommon, a true multiple drug hypersensitivity may also develop.[7] Furthermore, a rechallenge is avoided in severe ADRs though it was inadvertently done in our patient, lending further weight to the association, as determined by Naranjo scoring.

With a wider use of hydroxychloroquine in the present times, beyond rheumatological conditions, and by medical specialists with less prior experience with the drug, it is pertinent to be aware of this rare but potentially severe drug complication. Finally, a severe CADR is also a known risk factor for the development of further severe

TABLE 1 Naranjo algorithm—ADR probability scale

Question	Yes	No	Do not know	Patient's score
1. Are there previous *conclusive* reports on this reaction?	+1	0	0	+1
2. Did the adverse event appear after the suspected drug was administered?	+2	−1	0	+2
3. Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0	+1
4. Did the adverse event reappear when the drug was readministered?	+2	−1	0	+2
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	−1	+2	0	+2
6. Did the reaction reappear when a placebo was given?	−1	+1	0	0
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0	+1
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	0
Total score				9

Abbreviation: ADR, adverse drug reaction.

CADRs.[7] This risk needs to be understood by the treating clinician and explained to the patient, especially those with chronic diseases requiring prolong multidrug treatment.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Dr Ananta Khurana and Dr Anusha Katare conceived the presented idea and wrote the manuscript with support from Dr Aastha Agarwal and Dr Priyadharshini Kathirvel. Dr Ananta Khurana supervised the findings of this work. Dr Arvind Ahuja provided the histopathological images. All authors discussed and contributed to the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in pubmed, scihub.tw, that issues datasets with DOIs.

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