Hydroxychloroquine-induced erythroderma

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Abstract:
Erythroderma is characterized by diffuse erythema and scaling of the skin involving more than 90% of the total body skin surface area. Drug-induced erythroderma has rarely been reported with hydroxychloroquine. We report a case of a 50-year-old female patient, with systemic lupus erythematosus, who developed itchy lesions all over the body 1 month after starting treatment with hydroxychloroquine. Drug-induced erythroderma was suspected. Hydroxychloroquine was withdrawn and the patient was treated with emollients, mid-potency corticosteroids, and oral antihistamines. A biopsy was done which confirmed the diagnosis of erythroderma. She recovered with treatment and was discharged. A careful history and clinical examination to search for potential causative factors will help prevent disabling sequelae in erythroderma.

Key words:
Erythroderma, hydroxychloroquine, systemic lupus erythematosus

Hydroxychloroquine, a 4-aminoquinolone derivative, is one of the drugs primarily used to treat systemic lupus erythematosus (SLE) due to its safety profile. The common adverse effects include gastrointestinal upset, headache, and lightheadedness. Cutaneous adverse drug reaction (ADR) like pruritic maculopapular lesion although common, rarely present as erythroderma.[1] Erythroderma is characterized by diffuse erythema and scaling of the skin involving more than 90% of the total body skin surface area.[2] Here, we review a case of erythroderma that occurred in a patient with SLE following treatment with hydroxychloroquine.

Case Report
A 50-year-old, female patient presented to the Dermatology Outpatient Department with complaints of itchy lesions all over the body for 1 month. The lesions were erythematous, scaly plaques which developed over the thigh followed by new lesions which appeared over the chest, back, upper limb, and face. History of joint pain and photosensitivity were present. She gave a history of being diagnosed with SLE, 10 years ago, and was on treatment with prednisolone 10 mg once a day. Hydroxychloroquine 400 mg once a day and methotrexate 7.5 mg twice a day pulse therapy every week were started 2 months back. General examination was normal. Cutaneous examination showed diffuse erythema of skin over the face, upper limb, trunk, and lower limb with exfoliation of the skin [Figures 1 and 2]. Annular scaly plaques were present over the trunks and limbs. The oral mucosal examination was normal. Nail examination showed beau’s lines over the finger and toenail [Figure 3]. Complete hemogram showed hemoglobin-11.8 g/dl, white blood cell count - 12,400 cells/cumm, and erythrocyte sedimentation rate - 45 mm/1st h. Blood sugar, liver function test, renal function test, and urine examination were normal [Table 1].

Based on the history and clinical examination, a provisional diagnosis of drug-induced erythroderma was made. Skin biopsy for histopathological examination and direct immunofluorescence were done. The biopsy done from erythematous scaly plaque showed hyperplastic stratified squamous epithelium with spongiosis and mild acanthosis. Underlying dermis showed numerous blood vessels surrounded by lymphocytic infiltrate in the fibrocollagenous stroma. Focal areas of neutrophilic inflammatory infiltrate admixed with parakeratosis were also present which confirmed erythroderma [Figure 4]. Direct immunofluorescence showed granular staining...
of basement membrane zone with IgG and C3 consistent with SLE. Hydroxychloroquine was withdrawn. The patient was treated with calamine lotion twice a day topical application, topical liquid paraffin once a day, topical fluticasone twice a day for new lesions, and tablet hydroxyzine 25 mg once a day. Prednisolone dose was increased to 20 mg once a day. The patient was in the recovery phase after a week of treatment and was discharged. Causality assessment with both WHO-UMC causality assessment scale and Naranjo ADR probability scale showed that the ADR is probable.\(^{[3,4]}\)

### Discussion

Erythroderma, also sometimes called exfoliative dermatitis, is defined as diffuse erythema and scaling involving more than 90% of the total body skin surface area.\(^{[2]}\) Most patients complain of pain and itching. Exfoliation begins within few days, but hair and nail changes occur after weeks to months. Complications include hemodynamic, metabolic disturbances and infections. A variety of cutaneous and systemic conditions can cause erythroderma. The most common cause is an exacerbation of preexisting dermatoses such as psoriasis.

**Table 1: Laboratory investigations in a patient with hydroxychloroquine-induced erythroderma**

| Investigations                | Result | Reference range |
|------------------------------|--------|-----------------|
| Fasting glucose (mg/dl)      | 73     | 70-100          |
| Postprandial glucose (mg/dl) | 130    | 100-140         |
| Total bilirubin (mg/dl)      | 0.5    | 0.3-1.2         |
| Direct bilirubin (mg/dl)     | 0.2    | Up to 0.2       |
| Total protein (g/dl)         | 6.6    | 6.0-8.3         |
| Albumin (g/dl)               | 3.7    | 3.2-5.5         |
| Globulin (g/dl)              | 2.9    | 1.8-3.4         |
| AST (U/L)                    | 22     | 5.0-40.0        |
| ALT (U/L)                    | 27     | 5.0-40.0        |
| Alkaline phosphatase (U/L)   | 74     | 40-129          |
| Urea (mg/dl)                 | 19     | 10-45           |
| Creatinine (mg/dl)           | 0.8    | 0.4-1.4         |

AST=Aspartate aminotransferase, ALT=Alanine aminotransferase
and atopic dermatitis. Uncommon causes include cutaneous T-cell lymphoma and other internal malignancies. In the case of drug-induced erythroderma, onset may be abrupt with morbilliform or urticarial eruptions which coalesce later into red erythematous patches with islands of sparing, which resolves faster than other causes. Histopathology shows hyperkeratosis, acanthosis, spongiosis, and perivascular inflammatory infiltrates.\textsuperscript{[5‑8]}

Hydroxychloroquine and chloroquine are 4-aminoquinolone derivatives which have shown to be effective in SLE since quinine was first used more than 100 years ago. They are structurally similar, only differing in the replacement of ethyl group in chloroquine by hydroxyethyl group in hydroxychloroquine. They have a variety of action; the most important among them is the lysosomotropic action. Hydroxychloroquine is a weak base which accumulates and raises the acidic pH of lysosomes and interferes with biologic functions which are dependent on it. This may lead to its immunomodulatory, anti-inflammatory, anti proliferative, and photoprotective effects. Hydroxychloroquine is preferred to chloroquine because of its safety profile and is the first-line drug in patients with SLE.\textsuperscript{[10]}

Hydroxychloroquine has rarely been reported as a cause of erythroderma.\textsuperscript{[9]} Cutaneous ADRs are also less common in patients with SLE compared with those with dermatomyositis. Roughly 25% of all dermatomyositis patients experience hypersensitivity reactions, drug eruptions during antimalarial treatment, and may represent a disease-specific idiosyncratic reaction in such patients.\textsuperscript{[10]} Drugs implicated include carbamazepine (57.1%), phenytoin (14.3%), phenobarbital (9.5%), lithium (4.8%), penicillin (4.8%), vancomycin (4.8%), and co-trimoxazole (4.8%).\textsuperscript{[9]} The exact pathogenesis of erythroderma is unknown but is thought to be due to complex interaction of cytokines, chemokines, and intercellular adhesion molecules which lead to recruitment of inflammatory cells and increased epidermal turnover. The increased mitotic rate and decreased transit time of epidermal cells lead to exfoliation and loss of proteins and nucleic acid through the skin. The initial management remains similar irrespective of the cause including monitoring of hemodynamic status and temperature; correction of fluid and electrolyte imbalance; and nutritional support. Symptomatic treatment of skin inflammation and pruritus includes the use of emollients, low to mid-potency corticosteroid, and oral antihistamines.\textsuperscript{[5‑8]}

**Conclusion**

Cutaneous ADRs are usually not severe, but can sometimes be life-threatening or result in disabling sequelae. Drug-induced erythroderma is one such ADR where early diagnosis can avoid serious outcomes. Early recognition of the condition can also be achieved with adequate patient education when drugs with the potential to cause erythroderma are prescribed. Management is mainly symptomatic and supportive. The patient should also be educated that reexposure to the offending agent can lead to more serious ADR in the future.

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**Conflicts of Interest**

There are no conflicts of interest.

**References**

1. Rynes RI. Antimalarial drugs in the treatment of rheumatological diseases. Br J Rheumatol 1997;36:799‑805.
2. Grant-Kels JM, Fedeles F, Rothe MJ. Exfoliative dermatitis. In: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K, editors. Fitzpatrick’s Dermatology in General Medicine. 8th ed. New York: McGraw Hill; 2008. p. 266‑79.
3. World Health Organization. The Use of the WHO‑UMC System for Standardised Case Causality Assessment. Available from: http://www.who‑umc.org/Graphics/24734.pdf. [Last cited on 2015 Oct 02].
4. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239‑45.
5. Marzano AV, Borghi A, Cugno M. Adverse drug reactions and organ damage: The skin. Eur J Intern Med 2016;28:17‑24.
6. Akhyani M, Ghodsi ZS, Toosi S, Dabbaghian H. Erythroderma: A clinical study of 97 cases. BMC Dermatol 2005;5:5.
7. César A, Cruz M, Mota A, Azvedo F. Erythroderma: A clinical and etiological study of 103 patients. J Dermatol Case Rep 2016;10:1‑9.
8. Hulmani M, Nandakishore B, Bhat MR, Sukumar D, Martin J, Kamath G, et al. Clinico-etiological study of 30 erythroderma cases from tertiary center in South India. Indian Dermatol Online J 2014;5:25‑9.
9. Slagel GA, James WD. Plaquenil-induced erythroderma. J Am Acad Dermatol 1985;12 (5 Pt 1):857‑62.
10. Pelle MT, Callen JP. Adverse cutaneous reactions to hydroxychloroquine are more common in patients with dermatomyositis than in patients with cutaneous lupus erythematosus. Arch Dermatol 2002;138:1231‑3.