

LETTER

Acute generalized exanthematous pustulosis due to hydroxychloroquine

Dear Editor,

Hydroxychloroquine (HCQ) is a commonly used medication for various diseases such as malaria, rheumatoid arthritis, and systemic lupus erythematosus. Since 2019, due to the pandemic, its use has dramatically increased in patients with SARS-CoV-2 infection.¹ HCQ use is associated with a wide range of adverse reactions; among them, cutaneous reactions are commonly described.

We report the case of a 74-year-old woman presenting with papules and macules on the neck rapidly spreading to the trunk and face with also erythema multiforme-like lesions and fever.

The mucosae were not initially involved; Nikolsky sign was negative. Blood exams revealed neutrophilic leucocytosis ($18.61 \times 10^2 \mu\text{l}$, normal values $2.00\text{--}7.50 \times 10^2 \mu\text{l}$) and increase of transaminases (ALT 46 U/L, normal values $<35 \text{ U/L}$). Repeated Covid-19 swabs were negative.

A treatment with HCQ was started 20 days prior for osteoarthritis. Chronic drug history included omeprazole, atorvastatine, and ramipril+hydrochlorotiazide.

Suspecting an adverse drug reaction to HCQ, the drug was immediately discontinued. Due to the pandemic the patient refused hospitalization, therefore a therapy with intramuscular methylprednisolone 60 mg/die was started.

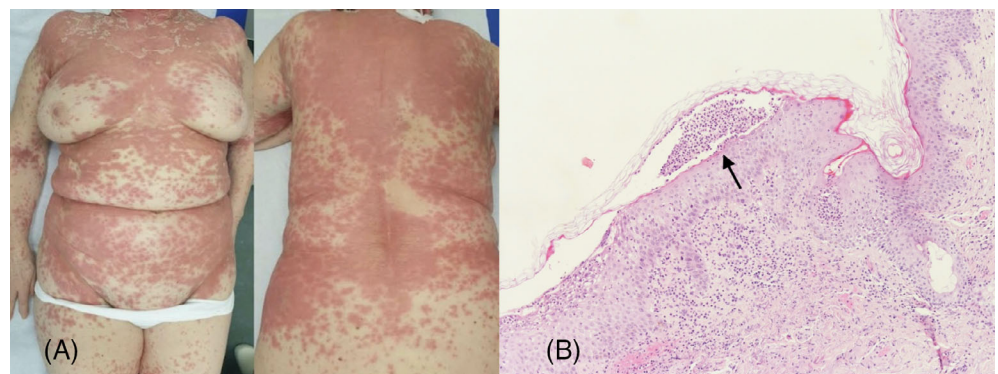
The rash kept spreading, involving new areas, including oral and vulvar mucosae, with a centrifugal extension; we also noticed pustules and erosions affecting symmetrically the neck and the trunk, developing upon confluent erythematous plaques (Figure 1A). A skin biopsy was performed from the abdomen. The histological examination revealed spongiosis, numerous neutrophils scattered over epidermal and superficial derma, subcorneal, and intracorneal separations with neutrophils infiltration (Figure 1B).

Based on the clinical and the histopathological findings, a diagnosis of acute generalized exanthematous pustulosis (AGEP) was made.

A progressive improvement in terms of clinical signs, symptoms and lab tests was observed. AGEP completely resolved in 40 days during which the steroid therapy was tapered.

HCQ is an anti-malarian drug widely used in rheumatic and dermatologic diseases for its anti-inflammatory and immunosuppressive properties. Since 2019, due to the pandemic, its use has already involved millions of patients, who often receive no screening prior to starting the drug. HCQ is a generally well-tolerated medication, but short-term side effect can be observed (days to weeks, up to 2 months of treatment), the most common is gastrointestinal toxicity (nausea, abdominal pain, anorexia, and diarrhea). Rashes, followed by cutaneous hyperpigmentation, pruritus, Stevens–Johnson syndrome, and toxic epidermal necrolysis are described as common skin adverse effects. AGEP, urticaria, psoriasis, and drug reaction with eosinophilia and systemic symptoms are more rarely reported, and related to lower mean cumulative doses (e.g., less than 100 g).^{2,3} AGEP is a severe cutaneous adverse reaction characterized by the sudden onset of numerous small, not follicular, sterile pustules on a base of edematous erythema. It is usually associated with high fever, peripheral neutrophilia, and an acute evolution.⁴ The exact pathophysiology of AGEP is still not completely understood, but it is known that T cells have a fundamental role in the initiation of this process. Activated T cells release CXCL8 and interleukin (IL)-5, which recruit neutrophils and eosinophils respectively. T-helper (Th)1, Th2 and Th17 also play a central role in the initiation and perpetuation of the cutaneous reaction. Antibiotics, mainly B-lactams, are the most frequent causative agents of AGEP,⁵ with a latency of 48 hours between the beginning of the therapy and the skin reaction. HCQ was described

FIGURE 1 (A) Clinical presentation of the patient's papulo-pustular rash; (B) histological presentation of AGEP: subcorneal neutrophilic pustule (red arrow), spongiosis of the stratum spinosum, perivascular infiltrate consisting of neutrophils and lymphocytes.



as a rare cause of AGEF, but in recent times, descriptions of HCQ-induced AGEF have increased.³

In case of HCQ-induced AGEF, the latency period appears to be longer (ranging from 4 to 30 days⁶) than in antibiotics-related cases, and the eruption tends to be more serious and resistant to treatments.^{7,8} A differential diagnosis could have been HCQ-induced generalized pustular figurate erythema (GPFE), which has been recently described in two patients with COVID-19;⁹ however, our patient was febrile and the cutaneous presentation was more consistent with AGEF than GPFE.

In our opinion, clinician should be aware of cutaneous skin adverse events, such as AGEF, associated with HCQ, which is still frequently used for various diseases.¹⁰

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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