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Severe Acute Generalized Exanthematous Pustulosis Induced by Hydroxychloroquine Mimicking Toxic Epidermal Necrolysis

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Abstract

Anti-malarial drugs may induce numerous cutaneous adverse drug reactions as well as exacerbation of psoriasis. Acute generalized exanthematous pustulosis (AGEP) is a clinical reaction pattern that is principally drug induced and is characterized by acute, extensive formation of non-follicular sterile pustules on an erythematous and oedematous substrate. Hydroxychloroquine (HCQ), an anti-malarial drug widely used to treat rheumatic and dermatologic diseases, has been described as an uncommon cause of AGEP.

We report a 45-year-old woman who developed severe bullous AGEP mimicking toxic epidermal necrolysis after the intake of HCQ.

Introduction

Acute generalized exanthematous pustulosis (AGEP) is a clinical reaction pattern that is principally drug induced and is characterized by acute, extensive formation of non-follicular sterile pustules on an erythematous and

oedematous substrate. Hydroxychloroquine (HCQ), an anti-malarial drug widely used to treat rheumatic and dermatologic diseases, has been described as an uncommon cause of AGEP.

Case Report

A 45-year-old woman, without personal or familiar history of psoriasis, was referred to Dermatology for an acute pruriginous pustular eruption. She had started prednisone 10 mg daily 6 months before and hydroxychloroquine 400 mg daily 10 days before for sero-negative polyarthritis under investigation.

The erythematopustular eruption was initially predominantly on the trunk and proximal limbs, accompanied by intense pruritus, fever 39°C. The face and mucous membranes were not involved. Within 5 days, the pustular eruption has rapidly spread to all teguments realizing an erythroderma with significant oedema **(fig. 1)**. Hydroxychloroquine was immediately discontinued.

Laboratory studies have showed an elevated erythrocyte sedimentation rate (46mm/h), marked leukocytosis 16890 with an elevated neutrophil count (80%). Electrolyte levels and results of urinalysis, renal and liver function tests were normal. Skin biopsy revealed subcorneal spongiform pustules, oedema of the papillary dermis and a mixed inflammatory infiltrate with exocytosis of neutrophils **(fig. 2)**.

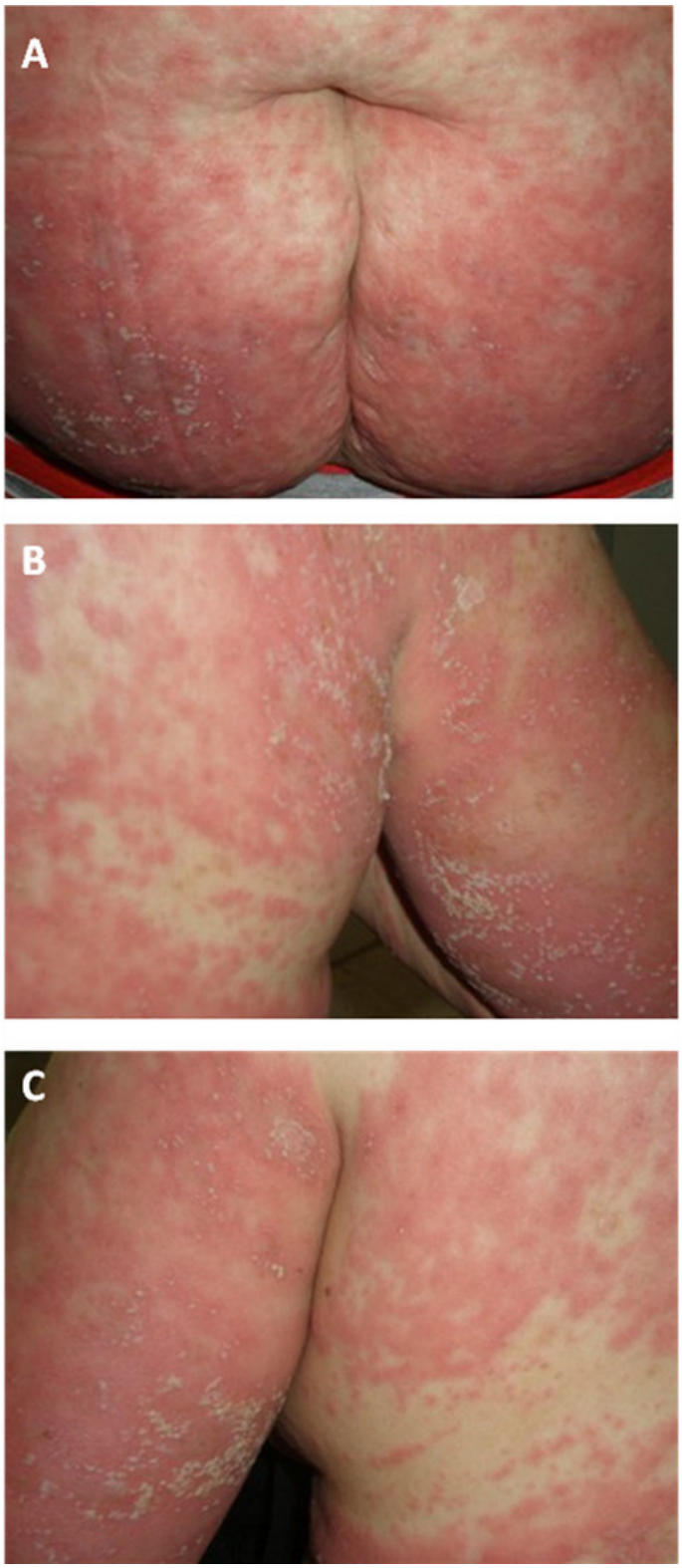

Fig 1: Erythemato-pustular eruption; **(A)** Trunk, **(B)** and **(C)** proximal limbs.

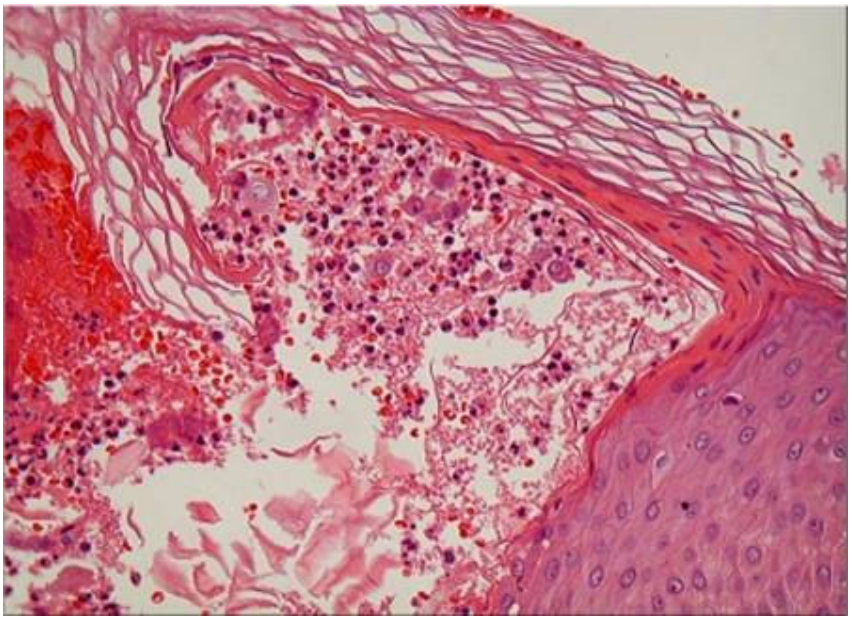

Fig 2: Histopathological examination showing sub-corneal spongiform pustules and oedema of the papillary dermis.

After one week of treatment withdrawal, the eruption continued to progress, involving the face, conjunctival erythema, cheilitis and alopecia. Large bullae appeared and broke down to form erosions involving 40% of the total body area mimicking the clinical picture of the toxic epidermal necrolysis (TEN). The patient was immediately transferred into the burn specialized service. Within 15 days, the eruption resolved with re-epithelialisation of erosions and appearance of widespread post-pustular desquamation.

The Pharmaco-vigilance enquiry has suspected HCQ (I2B3) because of the latent period between the intake of the culprit and the appearance of AGEP and the slow resolution of eruption, compatible with the drug's kinetic elimination.

Discussion

AGEP is an uncommon eruption most often induced by drugs in than 90% of the cases [1], by acute infections with enteroviruses, or by mercury [2,3]. It is a rare disease that has been classified as pustular psoriasis of von Zumbush type for years [4]. In 1968 Backer and Rayan were the first to assume that AGEP represents its own entity [5]. Subsequently, this disorder was better characterized by Beylot et al. [6] and Roujeau et al. [7], who clarified its relationship to pustular psoriasis and assessed the place of drugs in its aetiology.

HCQ possesses anti-malarial actions and also exerts a beneficial effect in lupus erythematosus (chronic discoid or systemic) and acute or chronic

rheumatoid arthritis. The precise mechanism of action is not known. Use of Hydroxychloroquine sulfate in patients with psoriasis may precipitate a severe attack of psoriasis [8].

Dermatologic reactions to Hydroxychloroquine sulfate may occur, include bleaching of hair, alopecia, pruritus, skin and mucosal pigmentation, photosensitivity, and skin eruptions (urticarial, morbilliform, lichenoid, maculopapular, purpuric, erythema annulare centrifugum, Stevens-Johnson syndrome, AGEP, and exfoliative dermatitis) [8].

It is important to remember this rare, but severe, side effect otherwise, in some cases, AGEP may progress into a TEN-like picture making the diagnosis more difficult [9].

In an important 16 year review of 207 cases of severe pustular eruptions notified to the French Pharmaco-vigilance Centre [10], hydroxychloroquine was the third medication associated to AGEP and death occurred in 4 cases (2%). Because it is essential to discontinue the causative drug as soon as possible if a pustular eruption occurs, the notification of side effects by physicians to pharmaco-vigilance centres is important to public health dissemination of warnings.

AGEP is characterized by acute, extensive formation of non-follicular sterile pustules on erythematous background, fever, and peripheral blood leukocytosis. The interval between the administration of the drug and the onset of the eruption is usually 2 or 3 days for antibiotics and longer (3-18 days) for drugs other than antibiotics. Our patient started HCQ 10 days before the eruption [11].

Histologically, AGEP is characterised by subcorneal or superficial intra-epidermal pustules and a mild spongiform change at the margins of the pustules. The papillary dermis is usually oedematous, and perivascular neutrophils or eosinophils infiltrate are shown in the upper dermis and the presence of necrotic keratinocytes in the epidermis is seen [12].

A standard oral provocation test is a sensitive diagnostic tool, and it may provide an early confirmatory diagnosis of drug induced skin eruption, include AGEP. In this case, initial drug dose for an oral provocation test may be started at 100 mg (half of the therapeutic dosage). If there are no eruptions after administration of initial drug dose, an additional dose of 100 mg may be given after an appropriate time interval [13].

The withdrawal of the responsible drug is the main treatment for AGEP, in combination with topical corticosteroids and antipyretics [1,6].

To our knowledge HCQ has been described as an uncommon cause of AGEP.

Conclusion

This article reports a case of AGEP related to administration of HCQ. HCQ-induced AGEP is a rare but severe, extensive, and acute reaction. No specific therapy is available, and correct diagnosis generally leads to spontaneous resolution once the causative drug has been withdrawn.

References

1. Sidoroff A, Halevy S, Bavinck JN, Vaillant L, Roujeau JC. Acute generalized exanthematous pustulosis (AGEP) - a clinical reaction pattern. J Cutan Pathol 2001; 28: 113-119

2. Feio AB, Apetato M, Costa MM, Sa J, Alcantara J. Acute generalized exanthematous pustulosis due to Coxsackie B4 virus. Acta Med Port 1997; 10: 487- 491

3. Roujeau JC, Bioulac-Sage P, Bourseau C, Guillaume JC, Bernard P, Lok C et al. Acute generalized exanthematous pustulosis: analysis of 63 cases. Arch Dermatol 1991; 127: 1333- 1338

4. Britschgi M, Steiner UC, Schmid S et al. T-cell involvementin drug-induced acute generalized exanthematous pustulosis. J Clin Invest 2001; 107: 1433-1441

5. Baker H and Rayan T. Generalized pustular psoriasis. A clinical and epidemiological study of 104 cases. Br J Dermatol 1968; 80: 771- 793

6. Beylot C, Bioulac P and Doutre MS. Pustuloses exanthématiques aigues généralisées. A propos de 4 cas. Ann. Dermatol. Venereol 1980; 107: 37- 48

7. Roujeau J, Bioulac-Sage P and Bourseau C. Acute generalized exanthematous pustulosis: analysis of 63 cases. Arch Dermatol 1991; 127: 1333-1338

8. Plaquenil (hydroxychloroquine sulphate) tablets. Adverse reactions [Internet]. Bridgewater (NJ): Sanofi; 2006 Oct 5. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/009768s041lbl.pdf.

9. Evans CC, Bergstresser PR. Acute Generalized Exanthematous Pustulosis precipitated by Hydroxychloroquine. J Am Acad Dermatol 2004; 50(4): 650-651

10. Saissi EH, Beau-Salinas F, Jonville-Béra AP, Lorette G, Autret-Leca E. Médicaments Associés à La Survenue d'Une Pustulose Exanthématique Aigue Généralisée. Ann Dermatol Venereol 2003; 130: 612- 618

11. Machet L, Martin L, Vaillant L. Pustulose exanthématique aigue

généralisée. Ann Dermatol Venereol 2001; 128: 73- 79

12. Burrows NP, Russel Jones RR. Pustular drug eruptions: a histopathological spectrum. Histopathology 1993; 22: 569- 573

13. Das J, Mandal AC. A study of drug eruptions by provocative tests. Indian J Dermatol Venereol Leprol 2001; 67: 238- 239