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Short communication

Acute generalized exanthematous pustulosis with a focus on hydroxychloroquine: A 10-year experience in a skin hospital

Ali Nili[a,1], Ehsan Zarei[b,1], Azin Ghamari[a,c], Ali Salehi Farid[a], Soheil Tavakolpour[a,d], Maryam Daneshpazhooh[a], Hamidreza Mahmoudi[a,*]

[a] Autoimmune Bullous Diseases Research Center, Tehran University of Medical Sciences, Tehran 63911-11996, Iran
[b] Tehran University of Medical Sciences, School of Medicine, Tehran 14176-13151, Iran
[c] Growth and Development Research Center, Children's Medical Center, Tehran University of Medical Sciences, Tehran 14197-33151, Iran
[d] Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA 02215, USA

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ABSTRACT

Objective: Acute generalized exanthematous pustulosis (AGEP) is a severe skin pustular drug reaction that can lead to life-threatening consequences. In this study, we have investigated the characteristics and outcomes of patients with AGEP in a tertiary skin hospital.

Methods: From March 2007 to December 2019, medical records of all patients diagnosed with AGEP, were assessed. Demographic data, culprit drug, past medical history, laboratory tests, recurrence, and systemic organ involvement were all documented as well.

Results: Seventy-four patients, including 54 women (73%) and 20 men (27%), with a mean age of 44.3 ± 16.5 years were evaluated. The most common comorbidities among the patients were rheumatoid arthritis and diabetes. In addition, hydroxychloroquine, cephalosporin, and amoxicillin were found as the three most common medications associated with AGEP induction. Among the study group, seventeen (23%) patients had systemic organ involvement (nine (12.2%), six (8.1%), and five (6.8%) had hepatic, renal and pulmonary involvement, respectively). All patients responded to oral prednisolone within a median of five days (IQR = 4; ranged 2–14). The median duration of treatment was significantly longer in hydroxychloroquine group compared to other drugs (8 versus 5 days; HR 0.57,95%CI 0·35–0.91). Likewise, the median duration of treatment was significantly longer in febrile patients compared to the afebrile ones (7 versus 4 days; HR 0.46, 95%CI 0.25–0.85). Recurrence occurred in six patients after resuming treatment with the same medication. The mean Naranjo score was 7.6 ± 0.9 denoting a probable causal relationship.

Conclusion: In this study, we found that using hydroxychloroquine and presence of fever are the risk factors potentially leading to a prolonged treatment duration of AGEP.

1. Introduction

Acute generalized exanthematous pustulosis (AGEP) is a rare and severe skin reaction characterized by abrupt, widespread, sterile, and non-follicular pustules on an erythematous and edematous background. In spite of being mostly self-limited, it can be accompanied by systemic symptoms, such as fever and leukocytosis. The annual incidence of AGEP is estimated to be 1–5 per million in general population [1]. Although more than 90% of cases develop AGEP as a result of exposure to certain medications, acute viral infections and exposure to mercury could be also causative factors. The diagnosis of AGEP is based on characteristic clinical features and histopathologic findings [1].

Neutrophils have a prominent role in the pathogenesis of AGEP, and in-vitro experiments have shown T-cells to be the main orchestrator of this type of drug reaction [2]. The fundamental steps toward treating AGEP are as follows: discontinuation of the culprit drug(s) and then initiation of systemic corticosteroids [1]. It is worth noting that due to its potential association with serious complications, identifying the culprit drug is crucial for a successful management of this type of drug reaction.

The current observational study aims to investigate the epidemiology of AGEP, culprit medications, clinical features, management, and the response to treatment.

* Corresponding author at: Razi Hospital Vahdate-Eslami Square, 11996 Tehran, Iran.
E-mail address: hr_mahmoody@yahoo.com (H. Mahmoudi).
[1] These authors had an equal contribution.

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2. Materials and methods

2.1. Data collection

This is a retrospective study from March 2007 to December 2019 in the dermatology wards of Razi Hospital, Tehran, Iran, based on the medical records of admitted patients diagnosed with AGEP. The criteria for AGEP diagnosis were based on the study conducted by Sidoroff et al. in 2001 [1]. Demographic data, etiology of AGEP, past medical history, laboratory tests, treatments, and recurrence(s) were extracted from the medical records. Systemic involvement was considered to be positive, in case of any of the following criteria being detected:

1. The serum creatinine level rising above > 1.5 times higher than the baseline, or a BUN/Cr level of above 20 within 48 h after the initiation of the treatment and hydration;

2. Elevated liver function tests being more than two times higher than reference limit, and lasting at least two days (with either hepatocellular, cholestatic or mixed pattern);

3. Presence of dyspnea, a respiratory rate of more than 20 breaths per minute, or the oxygen saturation level being below 90%.

In order to evaluate the causal relationship between the culprit drug and AGEP, the Naranjo adverse drug reaction probability scale was used [3]. Scores more than eight were interpreted as definite, 5–8 as probable, 1–4 as possible, and below one as doubtful drug reaction [3].

2.2. Statistical analysis

The data were analyzed using GraphPad Prism version 8.0.1 (GraphPad Software, La Jolla, CA, USA). The continuous parametric and non-parametric variables were presented by mean ± standard deviation (SD) and median [interquartile range (IQR)], respectively. In addition, for parametric variables, independent samples *t*-test, and for non-parametric variables, the Mann-Whitney test were applied. Chi-Square test was used for evaluating the difference between the binary variables. To compare time required for discontinuation of the treatment of different culprit drugs, the Kaplan-Meier and log-rank test were employed following elimination of the patients who relapsed and whose hazard ratio (HR) was estimated with 95% confidence interval (95% CI). P-values less than 0.05 were considered significant.

3. Results

3.1. Patients characteristics

In total, 74 patients with a mean age of 44.3 ± 16.5 years, including 54 (73%) women and 20 (27%) men were identified. Forty-four (59.5%) patients suffered from at least one underlying condition, the most common of them being rheumatic arthritis (28.4%) and diabetes (13.4%).

3.2. Clinical characteristics and underlying causes

Seventeen (23%) patients had systemic organ involvement, which were all drug-induced; 9 (12.2%) patients had hepatic involvement, whereas the renal and pulmonary involvements were documented in 6 (8.1%) and 5 (6.8%) of the cases, respectively. Fever (> 38 ^{0}C) was detected in 76.5% of the patients with systemic organ involvement, while 64.9% of patients without systemic involvement were febrile (P-value: 0.6). No significant correlation was noticed between systemic organ involvement and either sex, age, culprit drugs, or comorbidities.

AGEP was attributed to drug and infection in 72 (97.3%) and 2 (2.7%) cases, respectively. The most common culprit drugs were hydroxychloroquine, cephalosporin, and amoxicillin (Table 1). Regarding laboratory findings, neutrophilia, eosinophilia, and leukocytosis were detected in 58 (78.4%), 56 (75.7%), and 55 (74.3%) patients, respectively. Elevation in liver function tests was another common finding; 18 (24.3%), 7 (9.5%), and 10 (13.5%) patients showed elevated ALT, AST, and ALP, respectively.

Seventeen (23%) patients had systemic organ failure; among which hepatic, renal, and respiratory involvements were the most common. No patient required admission to intensive care unit (ICU), and there was no case of mortality.

Table 1
Characteristics, laboratory data, and outcomes of AGEP patients (n = 74).

Mean Age ± SD, years	44.3 ± 16.2
Mean BMI ± SD, kg/m2	26.2 ± 3.3
Sex-n. (%)	
Female	54 (73)
Underlying disease-no. (%)	
Rheumatoid arthritis	21 (28.4)
Hypertension	7 (9.5)
Diabetes	4 (5.5)
Systemic Lupus Erythematosus	3 (4.1)
Psoriasis, Pemphigus, Epilepsy, Multiple sclerosis each	2 (2.7)
Bechet's disease, Coronary artery disease each	1 (1.4)
Culprit drugs-no. (%)	
Hydroxychloroquine	26 (36.1)
Cephalosporin	10 (13.9)
Amoxicillin	5 (6.9)
Rituximab	4 (5.6)
Macrolide	3 (4.2)
Metronidazole, Herbal, Diltiazem, Penicillin	2 (2.8)
Carbamazepine, Topical diltiazem, Valproate sodium, Allopurinol, Griseofulvin, Bromhexine, Radiopaque contrast agents, Acyclovir, Acarbose, Imipenem each	1 (1.4)
Polydrug use	
Cephalosporin + Herbal	1 (1.4)
Penicillin + Cephalosporin	1 (1.4)
Captopril + Hydrochlorothiazide	1 (1.4)
Amoxicillin + Metronidazole	1 (1.4)
Cephalosporin + Metronidazole	1 (1.4)
Amoxicillin + Macrolide + Carbamazepine	1 (1.4)
Fever-no. *(%)*	50 (67.6)
Laboratory findings	
Mean hemoglobin ± *SD*, g/L	12.6 ± 1.6
Mean white blood cell count ± *SD*, × 10^9 /L	17.3 ± 6.5
Leukocytosis- no. (%)	55 (74.3)
Mean lymphocyte count ± *SD*, × 10^9 /L	2.9 ± 1.3
Mean neutrophil count ± *SD*, × 10^9 /L	13.6 ± 6.4
Neutrophilia-no. (%)	58 (78.4)
Mean eosinophil count, × 10^9 /L	0.19[0.22]
Eosinophilia-no. (%)	56 (75.7)
Median AST, U/L [IQR]	18.0[12]
Elevated AST*–no. (%)	7 (9.5)
Median ALT, U/L [IQR]	22.0[24]
Elevated ALT*–no. (%)	18 (24.3)
Median ALP$, U/L [IQR]	185[136]
Elevated ALP-no. (%)	10 (13.5)
Mean NARANJO score ± *SD*	7.57 ± 0.93
Systemic involvement-no. (%)	17 (23.0)
Hepatic involvement	9 (12.2)
Renal involvement	6 (8.1)
Pulmonary involvement	5 (6.8)
Treatment	
Mean prednisolone dosage ± *SD*, mg	31.8 ± 14.0
Median time to discharge, days [IQR]	5[4]

BMI, body mass index; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Leukocytosis, value > 11000 × 10^9 /L; Neutrophilia, value > 7000 × 10^9 /L; Eosinophilia, value > 0.7 × 10^9 /L.
*Normal value is less than 40 U/L.
$Normal value is less than 290 U/L.

3.3. Management and outcomes

All patients completely responded to the treatment (0.5–1 mg/kg oral prednisolone) within a mean period of 6.2 ± 2.9 days (range: 2–14). The median duration of the treatment (time of discontinuation of oral prednisolone) was significantly higher in the hydroxychloroquine

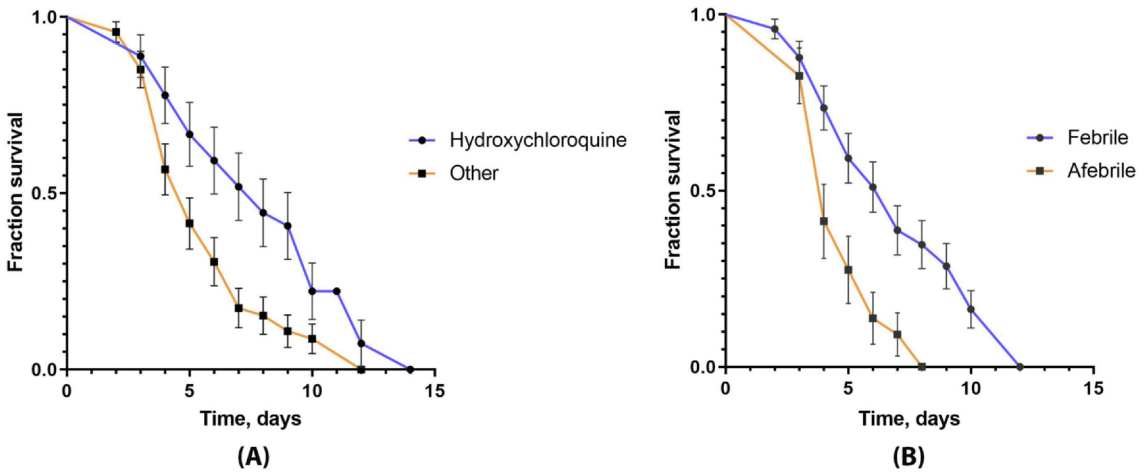

Fig. 1. "Meier curves and standards error bars of treatment duration for A) Hydroxychloroquine versus other drug-induced acute generalized exanthematous pustulosis B) Febrile versus afebrile subjects."

group compared to other drugs (8 [IQR = 6] days versus 5 [IQR = 3] days; HR 0.57, 95% CI: 0·35–0.91). Likewise, the median duration of treatment was significantly longer in febrile patients (4 [IQR = 2] days versus 7 [IQR = 6] days in afebrile and febrile patients, respectively; HR 0.46, 95% CI: 0.25–0.85).

Recurrence was observed in six cases; three in patients treated with hydroxychloroquine, one with macrolide, griseofulvin, and cephalosporins. There was no correlation between AGEP recurrence and either gender, age, systemic involvement, or existence of comorbidities.

The mean Naranjo score was 7.6 ± 0.9, indicating a probable causal relationship. Laboratory findings, Naranjo score, and average treatment period based on different culprit drugs are brought in Table 1.

4. Discussion

In this retrospective study on 74 hospitalized patients with AGEP, it was found that patients using hydroxychloroquine endured a prolonged course of the disease and needed a longer treatment time. Meanwhile, systemic organ involvement was present in 17 (23%) of cases; with hepatic, renal, and respiratory involvements being the most common systemic findings [2].

AGEP can occur in almost all age groups. The EuroSCAR study described 97 known cases of AGEP with a mean age of 56 years, and female preponderance [4]. The mean age in the current study was 44.3 + 16.3 years, which is relatively lower. A female dominance was also witnessed in this study.

Systemic organ involvement is an important finding in AGEP patients, which may possibly result in intensive care admission and poor outcome. It has been shown that an increased absolute neutrophil count and C-reactive protein may imply systemic organ involvement [5]. Meanwhile, mortality is reported in about 5% of cases occurring due to multiorgan failure [2]. The risk factors of mortality include the presence of comorbidities and also diffuse or mucous membrane involvements [2,6]. Previous studies reported systemic involvement in 14.5–75% of the patients manifesting most commonly as pulmonary, renal, and hepatic dysfunction [2,7]. In the present study, 17 (23%) patients had systemic organ failure. Also, none of the studied patients needed ICU admission, and no case of mortality was found. Similar to the findings of the present study, no mortality was reported among reported AGEP patients in the USA, Taiwan, Thailand, and France [7–10].

Histologic features of AGEP include subcorneal and/or intraepithelial neutrophilic microabscesses concomitant with papillary dermal edema, a mixed dermal infiltration consisting of neutrophils and eosinophils as well as vasculitis [2]. The exact pathophysiology of AGEP is not entirely understood. Reproducing AGEP with a patch test showed that T cells have a fundamental role in the initiation of this reaction. Drug-specific T cells have been found in the vicinity of keratinocytes in the early stages of AGEP. These activated T cells release CXCL8 and interleukin (IL)-5, which are potent chemotactic factors for neutrophils and eosinophils, respectively. T-helper (Th)1, Th2, and Th17 cells are also known to have a prominent role in the initiation and potentiation of this severe cutaneous reaction. Furthermore, a mutation in the IL-36 signaling pathway has been shown to predispose patients to AGEP. In the case of viral-induced AGEP, it has been supposed that T-helper immune response, initiated by a viral infection and subsequent release of inflammatory cytokines, including IL-8 and granulocyte macrophage-colony stimulating factor (GM-CSF) facilitates the neutrophilic reactions [2].

Several drugs have been reported to be associated with AGEP and in the EuroSCAR study, pristinamycin, ampicillin/amoxicillin, quinolones, hydroxychloroquine, sulfonamides, terbinafine, diltiazem, ketoconazole, and fluconazole were found to be the most prevalent drugs [4,11]. Macrolides, oxicam nonsteroidal anti-inflammatory drugs, and antiepileptic drugs were reported less frequently [4,11]. In line with the previous study, the most culprit drugs in the present study were hydroxychloroquine, cephalosporin, and amoxicillin. AGEP was observed in one patient after using topical diltiazem for the treatment of anal fissure. Although this patient had widespread skin involvement, no other evidence related to systemic involvement was found and the patient was successfully managed using a high-dose of systemic corticosteroids.

Interestingly, four of the 74 patients (two patients with pemphigus; two with multiple sclerosis) developed AGEP after rituximab,.

Meanwhile, some studies have described infections as the etiology of AGEP. It is not fully clear whether the infection or the consumed antibiotic is responsible for the condition. In the current study, AGEP was attributed to infection in 2.7% of the patients.

The prolonged AGEP following the use of hydroxychloroquine was formerly reported in the literature as case reports [12–15]. However, to the best of our knowledge, no study has yet to compare the improvement time of hydroxychloroquine-induced AGEP with other drugs. In the current study, time of reaction and the necessary time of treatment in hydroxychloroquine-induced AGEP were found to be significantly higher compared to those of other drugs (Fig. 1). The precise mechanism of the prolonged AGEP after hydroxychloroquine is not understood well. Given the extensive tissue uptake of the this drug, specifically by the skin, and its slow release to the circulation, the half-life of the drug is estimated at 40–50 days [16]. Given that complete

elimination of the culprit drug and its metabolites is the fundamental step in management of all drug reactions, the long half-life and slow elimination of hydroxychloroquine can explain the slow onset, as well as recalcitrant and the prolonged nature of AGEP after this drug. The prolonged duration of AGEP becomes even more important during the Coronavirus disease 2019 (COVID-19) pandemic. Although the evidence for the efficacy of hydroxychloroquine in COVID-19 is getting weaker, it is still being used widely and physicians should be wary of the risk of hydroxychloroquine-induced AGEP more than before [17,18].

AGEP should be differentiated from pustular psoriasis, which can be sometimes challenging. The presence of papillary edema, dermal eosinophilic infiltration, and keratinocyte necrosis is in favor of AGEP. Other severe drug reactions, such as toxic epidermal necrolysis, Exanthematous Drug Eruptions, and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) should also be considered as differential diagnoses of AGEP.

The fundamental steps in the management of AGEP are discontinuation of the culprit drug and administration of systemic and topical corticosteroids. Antibiotics should be administered only when superinfection is present [2]. There are some reports of successful use of infliximab and Intravenous immunoglobulin (IVIg) in patients with AGEP and toxic epidermal necrolysis (TEN) overlap [2,15]. All patients in this study fully recovered after using oral prednisone 0.5 to 1 mg/kg per day.

Recurrence of AGEP after the administration of the causative drug has been rarely reported in the literature. For instance, previous studies have shown the recurrence of AGEP after using beta-lactam antibiotics, ceftriaxone, pemetrexed, and omeprazole [9,19,20]. In this study, AGEP recurred in 6 patients following the reintroduction of hydroxychloroquine, macrolide, griseofulvin, and cephalosporins.

The retrospective nature of the study leading to some clinical data missing, lack of long-term follow-up, the limited number of patients, inability to evaluate the effects of a single drug in cases using combination drugs, and lack of patch test were the main limitations of the present study. Furthermore, data extraction was restricted solely to inpatient AGEP cases admitted in the dermatology ward of a skin referral hospital. Therefore, information about patients treated in outpatient care, and those hospitalized in general hospitals were not available. Hence, a multicenter study with a larger sample size would be more informative.

In conclusion, AGEP is considered one of the most severe drug reactions and bears special attention. The presence of fever is a risk factor for prolonged treatment duration. Besides, hydroxychloroquine is one of the most important culprit drugs in this reaction, which follows a more recalcitrant and prolonged nature.

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CRediT authorship contribution statement

Ali Nili: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Ehsan Zarei:** Investigation, Project administration, Validation, Writing - original draft. **Azin Ghamari:** Project administration, Software, Validation, Visualization. **Ali Salehi Farid:** Resources, Validation, Visualization, Writing - original draft, Writing - review & editing. **Soheil Tavakolpour:** Validation, Visualization, Writing - original draft. **Maryam Daneshpazhooh:** Investigation, Project administration, Supervision, Writing - original draft, Writing - review & editing. **Hamidreza Mahmoudi:** Conceptualization, Data curation, Funding acquisition, Investigation, Project administration, Resources, Supervision, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2020.107093.

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