

UC Davis

Dermatology Online Journal

Title

Acute generalized exanthematous pustulosis triggered by COVID-19

Permalink

<https://escholarship.org/uc/item/352987hd>

Journal

Dermatology Online Journal, 30(3)

Authors

Amoedo, Patricia

Cerejeira, Andre

Coelho, Ana Rita

et al.

Publication Date

2024

DOI

10.5070/D330363870

Copyright Information

Copyright 2024 by the author(s). This work is made available under the terms of a Creative Commons Attribution-NonCommercial-NoDerivatives License, available at

<https://creativecommons.org/licenses/by-nc-nd/4.0/>

Peer reviewed

Acute generalized exanthematous pustulosis triggered by COVID-19

Patrícia Amoedo¹ MD, André Cerejeira¹ MD, Ana Rita Coelho² MD, Ana Cristina Nogueira¹ MD, Filomena Azevedo¹ MD

Affiliations: ¹Department of Dermatology and Venereology, Porto, Portugal, ²Department of Pathology, Centro Hospitalar Universitário de São João, Porto, Portugal

Corresponding Author: Patrícia Amoedo, Centro Hospitalar Universitário de São João, Alameda Prof Hernâni Monteiro, 4200-319 Porto, Portugal, Tel: 351-917864971, Email: amoedo.p.patricia@gmail.com

Abstract

Acute generalized exanthematous pustulosis is a severe adverse skin reaction, usually caused by drugs, but in rare cases it can be associated with infections. Several cases related to COVID-19 have been reported, however, almost all were drug-related. Here we report a case of acute generalized exanthematous pustulosis associated with COVID-19 in a previously healthy 64-year-old woman, with no culprit drugs.

Keywords: acute, COVID-19, exanthematous, generalized, pustulosis, SARS-CoV-2

Introduction

Acute generalized exanthematous pustulosis (AGEP) is a severe skin reaction characterized by the rapid development of widespread, small, non-follicular, sterile pustules over an erythematous base [1,2]. Most cases are drug-induced; however, in rare cases, it can be associated with infections such as parvovirus B19, cytomegalovirus, Epstein-Barr, chlamydia, and others [3,4]. Organ involvement is rare and systemic manifestations are typically limited to fever and neutrophilic leukocytosis [1,5]. The pathogenesis is not entirely understood, but studies suggest a T cell-mediated neutrophilic inflammatory response, involving drug specific T cells (CD4+ and CD8+), Th17 cells, inflammatory cytokines, and chemokines [1,4,6,7]. The diagnosis is based on

clinical and histological criteria that form the AGEP validation score, developed by the Euroscar group [8].

Case Synopsis

Herein, we report a 64-year-old woman, with no relevant medical history, that presented to the emergency department with a generalized rash, whose onset coincided with the diagnosis of COVID-19, 10 days earlier. She described the sudden appearance of erythematous areas on the lower limbs, forearms, and trunk followed by desquamation after two days of fever; she denied other symptoms. She also denied a personal or family history of psoriasis or recent use of new drugs, except for paracetamol, which she had taken several times in the past without adverse effects. Physical examination revealed a generalized eruption of small non-follicular, confluent pustules over an erythematous base and intense desquamation, especially on the palmoplantar regions and lower limbs where it formed large collarettes (**Figure 1**). Mucosae were spared and the Nikolsky sign was negative. Laboratory tests, which included a complete blood count, a biochemical profile including total serum calcium, erythrocyte sedimentation rate, an immunological panel (antinuclear antibodies, C3, C4, extractable nuclear antibodies, and antineutrophil cytoplasmic antibody panels, rheumatoid factor, and anti-thyroid antibodies), serum protein immunoelectrophoresis,



Figure 1. A) Erythematous base formed by circular plaques that converge forming larger plaques, of polycyclic configuration, covered by small non-follicular confluent pustules forming small lakes. There are also scaly collarettes of varying sizes that correspond to pustules and clusters of ruptured pustules. **B)** Detail showing the non-follicular pustules, distributed around the periphery of the plaques, outlining their limits. Small lakes of pus resulting from their confluence are also present. **C)** Detail of the lamellar desquamation on the hands.

VDRL (venereal disease research laboratory), serologies for HIV, hepatitis A, B and C, *Chlamydia pneumoniae*, Epstein-Barr, cytomegalovirus and parvovirus-19, showed only mild leukocytosis ($12 \times 10^9/l$) and elevation of C-reactive protein (80mg/dl; normal <3mg/dl). The skin biopsy revealed diffuse spongiosis and subcorneal micropustules with neutrophilic content (**Figure 2**), and periodic acid-Schiff, and Gram stains were negative. Based on these findings, a diagnosis of AGEP likely to be related to COVID-19 was made and oral prednisolone (40mg per day) was started. Symptom resolution occurred rapidly and no recurrence was noted after a one-year follow-up. A patch test for paracetamol (concentrations of 5%, 10% and 20%, in petrolatum base, with reads at 72 and 96 hours) performed 6 months later was negative.

Case Discussion

In the literature, we found 30 cases of AGEP associated with COVID-19. Nevertheless, 26 of those were drug-related, with hydroxychloroquine implicated in 21 cases (**Table 1**), [2,3,6,7,9-15]. The association between hydroxychloroquine and AGEP is well documented. However, most of those patients were polymedicated, making it difficult to determine the causative drug [16]. Other culprit drugs were ceftriaxone, cefepime, cefditoren, azithromycin, remdesivir, and favipiravir/enoxaparin [2,7,11,15,17-19]. In one case, a positive patch test to ceftriaxone confirmed the causality [7]. Acute generalized exanthematous pustulosis is a delayed type IV

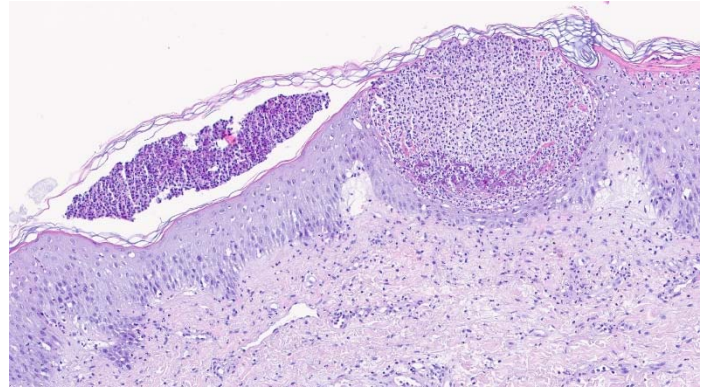


Figure 2. H&E histopathology. Subcorneal and intraepidermal micropustules with neutrophilic content, neutrophilic dermal infiltrate, and diffuse spongiosis, 10x.

hypersensitivity reaction and several authors have suggested a role for these tests in identifying the responsible drug. However, its sensitivity is still unknown [5,8]. In one study, 58% of AGEP cases had positive skin tests, suggesting some diagnostic use to patch tests [3].

According to our research, only three drug-unrelated cases were reported, one of which developed three months after the COVID-19 infection, making this association unlikely [10]. Interestingly, the other two cases presented with multisystemic involvement and shock [4,5]. Although uncommon, AGEP can be associated with systemic involvement [20] but, in this context, it can be questioned whether this is related to AGEP or to the COVID-19 immune response, which can trigger type IV hypersensitivity reactions, namely hemophagocytic lymphohistiocytosis (sHLH), macrophage activation syndrome (MAS), and multisystem inflammatory syndrome in children mediated by $IFN\gamma$ -related immune response [5,21]. Even when there are liable drugs, a possible role of COVID-19 infection or an interaction between both factors cannot be excluded. In fact, due to the similarities between the inflammatory cytokine profiles of AGEP and COVID-19, some authors have suggested that SARS-CoV-2 infection may predispose to AGEP-like eruptions [10,19].

Conclusion

In our patient, the appearance of AGEP concurrently with the diagnosis of COVID-19 made the association

Table 1. Reported cases of acute generalized exanthematous pustulosis in patients with COVID-19.

Year	Author	Sample size	Gender/age	Possible culprit drugs	Latency period (after COVID-19 diagnosis ^a)
2020	Litaiem et al. [6]	1	F/39y	<u>HCQ</u>	18 days
2020	Robustelli et al. [3]	1	F/70y	<u>HCQ</u> , lopinavir/ritonavir	21 days (13 days after HCQ)
2020	Torres-Navarro [11]	1	F/49y	HCQ, <u>cefditoren</u> , IFN β , HCQ, DEX, ceftriaxone, lopinavir/ ritonavir; MP and tocilizumab	31 days (7 days after cefditoren ^b)
2020	Delaleu et al. [14]	1	M/76y	<u>HCQ</u> , AZM and ceftriaxone	10 days (9 days after HCQ)
2020	Ayatollahi et al. [10]	1	M/33y	AZM	3 months ^{c1}
2020	Haraszti et al. [2]	1	M/78y	<u>Cefepime</u>	0 days ^e (7 days after cefepime)
2020	Alzahrani et al. [13]	1	F/34y	HCQ, AZM, oseltamivir, ribavirin, lopinavir, ceftriaxone, clindamycin, IFN β , ceftazidime and prednisolone	22 days
2020	Punyaratabandhu et al. [15]	1	M/48y	Chloroquine, lopinavir/ritonavir	9 days
2021	Tosun M. et al. [15]	1	M/47y	HCQ	3 days
2021	Sánchez-velásquez et al. [12]	1	F/31y	HCQ	9 days
2021	Stingeni et al. [7]	1	F/73y	<u>Ceftriaxone</u> ⁱ , HCQ, AZM, darunavir/cobicistat and DEX	25 days
2021	Pezzarossa et al. [9]	12	8M, 4F/54-84y	HCQ, darunavir, ritonavir, heparin, ceftriaxone and AZM	MD ^f
2021	Ordonez NA et al. [5]	1	F/44y	DEX (1 dose) and long-term medication ^d	0 days ^e (1 day after DEX)
2021	M. F. Atak et al. [18]	1	M/20y	Favipiravir	16 days
2021	Daye M et al. [19]	1	M/54y	<u>Favipiravir</u> , enoxaparin	1 month
2021	Demircioglu D et al. [16]	1	F/28y	HCQ	8 days
2022	Etaee et al. [15]	1	F/49y	HCQ; AZM	11 days
2022	Polat M et al. [4]	1	F/10 days	none	5 days
2022	Mohaghegh F et al. [17]	1	F/62y	<u>Remdesivir</u> AZM, DEX, naproxen	4 weeks

Drugs that were considered by the authors to be the causative agents of AGEP are underlined.

AZM, Azithromycin; DEX, Dexamethasone; F, Female; HCQ, Hydroxychloroquine; M, Male; MP, methylprednisolone; y, years.

^aThe precise onset of COVID-19 was difficult to establish based on the information in the reports, so we use the day of diagnosis as a reference. In most cases, this day coincides with the treatment onset.

^bCefditoren was considered the culprit drug, however the patient was treated with HCQ days before.

^cPatch test was positive to Ceftriaxone.

^dLosartan, atorvastatin and AAS.

^eIn this two reports, COVID-19 diagnosis coincide with AGEP presentation.

^fA polymerase chain reaction for RNA SARS-CoV-2 performed on frozen skin was negative in 5 of 6 patients.

with other causes unlikely. In addition, the absence of a history of psoriasis, the histological findings, and the complete resolution with no recurrence, make other forms of pustulosis unlikely. To the best of our knowledge, this is the first case of AGEP associated

with COVID-19, without associated drugs or multisystemic involvement.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

- Goyal PK, Mohammed TO, Mahmoud A, Zaidi AJ, Nguyen CV. COVID-19 infection leading to acute pustular dermatoses. *Arch Dermatol Res.* 2023;315:685-697. [PMID: 36319703].
- Haraszti S, Sendil S, Jensen N. Delayed Presentation of Acute Generalized Exanthematous Pustulosis Following Treatment with Cefepime in a Patient with COVID-19 without the Use of

- Hydroxychloroquine. *Am J Case Rep.* 2020;21:e926901 [PMID: 33097683].
3. Robustelli Test E, Vezzoli P, Carugno A, et al. Acute generalized exanthematous pustulosis with erythema multiforme-like lesions induced by Hydroxychloroquine in a woman with coronavirus disease 2019 (COVID-19). *J Eur Acad Dermatol Venereol.* 2020;34:e457-e459. [PMID: 32386448].
 4. Polat M, Parlakay AÖ. Acute Generalized Exanthematous Pustulosis Associated With a COVID-19 Infection. *Pediatr Infect Dis J.* 2022;41:e406. [PMID: 35703310].
 5. Ordoñez NA, Sepulveda VG, Vargas LP, Moreno JM. COVID-19 presenting as acute generalized exanthematous pustulosis associated with multiorgan dysfunction in a 44-year-old female patient. *Rev Inst Med Trop Sao Paulo.* 2021;63:e42. [PMID: 34037158].
 6. Litaïem N, Hajlaoui K, Karray M, Slouma M, Zeglaoui F. Acute generalized exanthematous pustulosis after COVID-19 treatment with hydroxychloroquine. *Dermatol Ther.* 2020;33:e13565. [PMID: 32401410].
 7. Stingeni L, Francisci D, Bianchi L, et al. Severe adverse drug reaction in SARS-CoV-2 infection: AGEP induced by ceftriaxone and confirmed by patch test. *Contact Dermatitis.* 2021;85:366-368. [PMID: 33834491].
 8. de Groot AC. Results of patch testing in acute generalized exanthematous pustulosis (AGEP): A literature review. *Contact Dermatitis.* 2022;87:119-141. [PMID: 35187690].
 9. Pezzarossa E, Ungari M, Caresana G, et al. Acute Generalized Exanthematous Pustulosis (AGEP) in 12 Patients Treated for SARS-CoV-2 Positive Pneumonia. *Am J Dermatopathol.* 2021;43:342-348. [PMID: 33405402].
 10. Ayatollahi A, Robati RM, Kamyab K, Firooz A. Late-onset AGEP-like skin pustular eruption following COVID-19: A possible association. *Dermatol Ther.* 2020;33:e14275. [PMID: 32885892].
 11. Torres-Navarro I, Abril-Pérez C, Roca-Ginés J, Sánchez-Arráez J, Botella-Estrada R. A case of cefditoren-induced acute generalized exanthematous pustulosis during COVID-19 pandemics. Severe cutaneous adverse reactions are an issue. *J Eur Acad Dermatol Venereol.* 2020;34:e537-e539. [PMID: 32455478].
 12. Sánchez-Velázquez A, Arroyo-Andrés J, Falkenhain-López D, et al. Hydroxychloroquine-induced acute generalized exanthematous pustulosis: an adverse reaction to keep in mind during COVID-19 pandemic. *J Dtsch Dermatol Ges.* 2021;19:896-898. [PMID: 33617141].
 13. Alzahrani MJ, Moussa MM, Alfaraj D. Acute Generalized Exanthematous Pustulosis After COVID-19 Infection: A Case Report From Saudi Arabia. *Cureus.* 2020;12:e11609. [PMID: 33240733].
 14. Delaleu J, Deniau B, Battistella M, et al. Acute generalized exanthematous pustulosis induced by hydroxychloroquine prescribed for COVID-19. *J Allergy Clin Immunol Pract.* 2020;8:2777-2779.e1. [PMID: 32525093].
 15. Etaee F, Ghanei N, Naguib T, Daveluy S. Acute generalized exanthematous pustulosis: a complication of COVID-19 infection or therapy?. *J Cosmet Dermatol.* 2022;21:1784-1787. [PMID: 35319163].
 16. Demircioğlu D, Karabıyık N, Durmaz EÖ, Demirkesen C, Şahin S. AGEP sine pustulosis induced by hydroxychloroquine used for COVID-19 infection. *Dermatol Ther.* 2022;35:e15263. [PMID: 34907646].
 17. Mohaghegh F, Hatami P, Aryanian Z, Fatemi F, Mohseni Afshar Z. Acute Generalized Exanthematous Pustulosis following SARS-CoV-2 Virus: Remdesivir as a Suspected Culprit. *Case Rep Med.* 2022;2022:9880827. [PMID: 35991338].
 18. Atak MF, Farabi B, Akbayrak A, Kalelioğlu MB, Rao BK. Acute generalized exanthematous pustulosis following treatment with favipiravir in a patient with COVID-19 without hydroxychloroquine use: Report of the first case. *J Cosmet Dermatol.* 2021;20:2387-2389. [PMID: 34139069].
 19. Daye M, Oltulu P. An AGEP case due to COVID-19 or favipiravir or enoxaparin. *J Cosmet Dermatol.* 2022;21:13-15. [PMID: 34826196].
 20. Lesterhuis WJ, Tjioe M, Stumpfenhausen GA, van Crevel R. Acute generalised exanthematous pustulosis mimicking septic shock. *Am J Med.* 2004;116:574-575. [PMID: 15063828].
 21. Costa PA, Costa BMLA, Milikowski C, St Onge JE. Acute generalised exanthematous pustulosis associated with shock. *BMJ Case Rep.* 2020;13:e235846. [PMID: 33127730].