Acute generalized exanthematous pustulosis following COVID19 infection: an additional case report from Tunisia

Mariem Mohamed[1], mouna korbi[1], sana bouzid[1], Rym Hadhri[1], and Jameleddine Zili[1]

[1]Fattouma Bourguiba University Hospital of Monastir

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Abstract

Coronavirus disease-19 (COVID-19) is an emerging global pandemic. Since its emergence, the COVID-19-associated cutaneous manifestations have been increasingly reported, and they are extremely polymorphic.We report a case of acute generalized exanthematous pustulosis (AGEP) developed in a Tunisian adult, a few days after recovery from severe COVID-19 infection

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Mariem Mohamed, Mouna Korbi, Sana Bouzid, Rym Hadhri*, Jameleddine Zili.

Dermatology Department, Fattouma Bourguiba University Hospital, Faculty of Medicine Monastir, Monastir University, Monastir 5000,Tunisia

Corresponding author : Mariem Mohamed, M.D.

Dermatology Department, * Pathology Department, Fattouma Bourguiba University Hospital, Faculty of Medicine Monastir, Monastir University, Monastir 5000,Tunisia

Phone: +21673106000

Email: mariemmohamed79@gmail.com

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Abbreviations: Coronavirus Disease 2019 (COVID-19); Severe Acute Respiratory Syndrome Related Coronavirus 2 (SARS-CoV-2); Reverse Transcription Polymerase Chain Reaction (RT-PCR); Acute Generalized Exanthematous Pustulosis (AGEP);

Abstract:

Coronavirus disease-19 (COVID-19) is an emerging global pandemic caused by "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2). Since its emergence, COVID-19-associated cutaneous manifestations have been increasingly reported, and are extremely polymorphic. Acute generalized exanthematous pustulosis (AGEP) is a rare exanthem characterized by the abrupt onset of numerous small non-follicular, sterile pustules arising on an erythematous base. Here, we report a case of acute generalized exanthematous pustulosis (AGEP) in a Tunisian adult a, few days after recovery from severe COVID-19. The direct and indirect role, of SARS-CoV-2 in the pathogenesis of this eruption is still debated and has not yet been established.

Introduction :

The novel coronavirus (SARS-CoV-2), the cause of the 2019 coronavirus disease (COVID-19), is rapidly spreading worldwide [1]. COVID-19 emerged in Tunisia in March 2020. Several cutaneous manifestations have been reported in association with COVID-19, such as urticaria, erythematous papular and/or vesicular rash, chilblains, livedo or purpura, and pustular eruptions such as acute generalized exanthematous pustulosis (AGEP) [2].

AGEP is a rare skin disease characterized by sudden skin eruption of numerous pinpoint, non-follicular, sterile pustules arising on an erythematous base. AGEP is mainly caused by drugs, especially antibiotics, such as amino-penicillins (beta-lactams) or macrolides [3]. Other etiologic agents have been reported to trigger AGEP such as spider bite, mercury and viral agents including coxsackie virus, cytomegalovirus (CMV), enterovirus, Epstein-Barr virus (EBV), hepatitis B virus, and parvovirus B19 (Parvo 19) [3].

To the best of our knowledge, only a few cases of AGEP related to COVID-19 have been reported [4-14].

Case report :

A 58 year-old male patient, with a medical history of chronic obstructive pulmonary disease (COPD), diabetes type 2 and hypertension presented to the emergency department with shortness of breath and fever, on December 19, 2020. A SARS-CoV-2 RNA nasopharyngeal swab, followed by real-time reverse transcription polymerase chain reaction (RT-PCR) and a chest computerized tomography scan, confirmed a severe case of COVID19. The patient was admitted to a specialized department for 2 weeks and treated with different antibiotics, including cefotaxime, imipenem/cilastatin, and teicoplanin.

The patient also received dexamethasone phosphate sodium, enoxaparin sodium, famotidine, vitamin C, and supplemental oxygen. According to the latest treatment guidelines, hydroxychloroquine was not used of (it was massively used off-label for COVID19 treatment during the first wave of the pandemic).

Seven days after total recovery and withdrawal of all antibiotics, systemic steroids, and famotidine, and only 2 days after withdrawal of enoxaparin and vitamin C, the patient developed a pustular eruption on an erythematous base that began in intertriginous areas (retroauricular folds) and rapidly affected more than 50% of the body surface area (Fig 1). The patient was febrile and there was no mucous membrane involvement. Laboratory test revealed leukocytosis with marked neutrophilia. The renal and liver functions were normal. Repeated blood and pustule bacterial culture yielded negative results. Viral serology (EBV, CMV, and parvoB19) was negative, and a new SARS-CoV-2 RNA nasopharyngeal swab, followed by RT-PCR, was negative. Skin biopsy revealed acanthosis and multiple spongiform subcorneal pustules. Edema and perivascular lymphocytic infiltration were observed in the dermis (Fig 2).

Based on the EUROSCAR criteria, our patient had a score of 12, indicating a definite diagnosis of AGEP (typical pustule (+2), typical erythema (+2), typical distribution of AGEP (+2), postpustular desquamation (+1), no mucosal involvement (0), acute onset $<$ 10 days (0), resolution $<$ 15 days (0), no fever (+1), no polymorphonuclear neutrophils $>$ 7000 (+1), and spongiform subcorneal pustule with papillary edema (+3)). The patient was treated with high-level topical corticosteroids, which resulted in progressive resolution of exanthema within a few days. The patient also received enoxaparin sodium without aggravation of the rash. The patient continued his chronic medication without any relapse of AGEP, one year later.

Our case raises a dilemma regarding whether such cutaneous lesions are related to COVID-19 or its treatment.

The relationship between AGEP and SARS-CoV-2 infection or its treatment remains poorly understood [4-14]. AGEP generally occurs within 48 hours of treatment initiation [3]. Almost all reported cases of AGEP following COVID-19 were associated with hydroxychloroquine and were characterized by a long incubation period of up to two-three weeks [4,9]. Only a few reported cases of AGEP following COVID-19 were related to other drugs such as cefepime, cefditoren, and cefrtiaxone, which occurred approximately seven7 days after starting the antibiotic [10, 11, 13]. Moreover, some authors have suggested a possible association between COVID-19 and late-onset AGEP (up to three months after COVID-19 recovery), based on a few reports of AGEP due to viral infections [12-14]. In fact, it has been reported some degree of similarity between inflammatory cytokine profile alterations during COVID-19 and AGEP [15]. Therefore, due to COVID-19 impact on the immune system, this infection may induce AGEP-like eruptions [13, 14]. In our patient, the eruption appeared seven days after withdrawal of all antibiotics, systemic steroids, and famotidine and two days after enoxaparin withdrawal. Additionall , enoxaparin was reintroduced without clinical aggravation. Therefore, we hypothesized that patient's vigorous immune response to COVID-19 may have triggered an unusual delay-onset reaction to one of the prescribed drugs or a late-onset skin manifestation mimicking AGEP in association with COVID-19.

Conclusion:

This case describes an unusual presentation of AGEP following COVID-19, which stresses the complexity of the association between AGEP and COVID-19, implicating not only drug intake but also the impact of SARSCoV2 on the immune system and the cytokine storm induced by this infection.

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Legends of Figures:

Fig. 1: skin eruption of numerous pinpoint, non-follicular, sterile pustules arising on an erythematous base on the trunk and intertriginous areas (A, B and C). Post inflammatory desquamation (D).

Fig. 2: subcorneal pustules with spongiosis(A: Hematoxylin Eosin X100; B: Hematoxylin Eosin X 400)