Acute generalized exanthematous pustulosis following treatment with remdesivir in a patient with SARS-CoV-2 infection, a case report

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Abstract

We hereby, present the first case of Acute generalized exanthematous pustulosis (AGEP) following treatment with remdesivir in a patient with COVID-19 without hydroxychloroquine use which serves as a reminder for considering remdesivir as a possible causative agent when dealing with AGEP presentation in COVID patients.

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Key Clinical Message:

We presented the first case of AGEP following treatment with remdesivir in a patient with COVID-19 without hydroxychloroquine use which could be an important issue when dealing with cutaneous rashes, considering the widespread use of Remdesivir in COVID era.

Abstract:

Acute generalized exanthematous pustulosis (AGEP) is an exanthematous condition, predominantly occurs as a result of drug reaction.

We hereby, present the first case of AGEP following treatment with remdesivir in a patient with COVID-19 without hydroxychloroquine use which serves as a reminder for considering remdesivir as a possible causative agent when dealing with AGEP presentation in COVID patients.

Key Words:

COVID-19; AGEP; drug reaction; Remdesivir

Introduction:

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been well-known for its multi-systemic involvement; besides respiratory manifestations, mucocutaneous symptoms have been among the most common presentations of SARS-CoV-2 infection(1). Cutaneous manifestations of SARS-CoV-2 infection can range from erythematous or maculopapular eruptions and urticaria to blisters, petechiae, and livedo reticularis(2). Skin involvement can occur as the sole manifestation of COVID-19 infection, intervene during the course of the infection, or appear after the infection has subsided(3, 4). On the other hand, cutaneous reactions can be a manifestation of a new-onset dermatosis, or exacerbation of a preexisting condition(5). The underlying cause for this phenomenon can be the virus direct invasion to the skin and mucosal surfaces, the immunologic inflammatory response elicited by the virus, or the side effect of therapeutics used in the settings of SARS-CoV-2 infection(6, 7).

Acute generalized exanthematous pustulosis (AGEP) is an exanthematous condition with abrupt onset, which predominantly occurs as a result of drug reaction. In fact, other factors such as infections, vaccination, chemicals contact and insect bite can also be triggering factors for AGEP(5). Since the beginning of the COVID-19 pandemic, increased rate of AGEP has been reported, which could be attributed to the high prevalence of the SARS-CoV-2 virus as the causative pathogen, or the result of medications used in this settings. Here, we report a case of COVID-19 associated AGEP with significant diagnostic challenges and complications, and present a brief literature review.

Case presentation

A 62-year-old woman presented to the dermatology clinic with generalized pruritic skin rash. She mentioned a history of SAR-CoV-2 infection one month earlier, for which she had undergone remdesivir treatment. Two days after the completion of treatment, she developed cutaneous reactions beginning in the trunk and extending to the extremities. She also mentioned a history of Addison's disease, for which she was taking prednisolone and fludrocortisone. On physical examination, widespread pustular eruptions with erythematous base were covering all over her body surface except for head and neck area (Figure 1). Hair and nails were intact. No mucosal involvement was detected. She was started on high dose oral prednisolone and cyclosporine in conjunction with acitretin and topical emollient. A few days later, she returned to the clinic with fever and toxicity. Laboratory evaluation revealed a thrombocytopenia and transaminitis. Therefore, we admitted her

for further workup. We initially stopped all the drugs she was taking, including cyclosporine and acitretin, and took a skin biopsy.

The histopathology report was indicative of linear neutrophilic parakeratosis with mild acanthosis and focal spongiosis, along with scattered necrotic keratinocyte, ectatic capillaries, and perivascular interstitial lymphocytic and eosinophilic infiltration in the dermis, all compatible with the diagnosis of AGEP (Figure 2). Then, we started her on methylprednisolone pulse and IVIG due to the possibility of idiopathic thrombocytopenia (ITP) in this patient. She was tested negative for COVID-19 and HIV Ab. Chest CT scan, as was expected, showed diffuse ground-glass opacities in both lungs compatible with convalescent pulmonary phase of SARS-CoV-2 infection (Figure 3). Three days after the initiation of intensive therapy, platelets count increased and liver enzymes decreased. The eruptions rapidly resolved within a few days, therefore, we switched the therapy to intravenous hydrocortisone and then to prednisolone with gradual tapering. At the time of discharge, post-pustular desquamation was demonstrated. At follow-up visits, the patient did not describe any relapses.

Discussion

Acute generalized exanthematous pustulosis (AGEP) is an acute pustular dermatosis with abrupt onset of a great number of pustules with edematous and erythematous base(8).

Several conditions, including infections, vaccination and medications have been mentioned as precipitating factors of AGEP(9). The COVID-19 pandemic has unveiled a wide range of dermatologic disorders, new-onset or flare, in SARS-CoV-2 infected patients. Therefore, this virus should also be listed in the infectious causes of AGEP(10).

Medications most commonly associated with AGEP include pristinamycin, aminopenicillins, fluoroquinolones, antimalarials, sulphonamides, terbinafine, azoles, protease inhibitors, dapsone, pantoprazole, diltiazem, corticosteroids, azithromycin, NSAIDs, and antiepileptic agents(8). Among the common therapeutics used during a SARS-CoV-2 infection with the probability of inducing AGEP, we can name hydroxychloroquine, which is the most notorious medication for inducing AGEP, favipiravir, azithromycin, NSAIDs, protease inhibitors such as lopinavir-ritonavir, anticoagulants, and glucocorticoids(11-19). Our patient had received azithromycin, dexamethasone, naproxen, and remdesivir for SARS-CoV-2 infection. Therefore, the onset of AGEP could be attributed to any of the mentioned agents, although there has been no definite report of remdesivir-associated AGEP.

In AGEP, the duration of drug exposure before onset of the symptoms is varying from a few hours to a few weeks depending on the causative drug (17). Our case has presented with AGEP 4 weeks after receiving COVID treatment which was a longer latency period compared to AGEP reported in COVID-19 infected patients in the recent literature which make it difficult to attribute the AGEP to these medications. However, one can infer that combination of each of these medications including remdesivir and genetic disposition with COVID-19 induced cytokine storm led to delayed development of AGEP in this case. Hence, AGEP might be considered as an unreported side effect of remdesivir which has been widely used during COVID era. Further reports will shed more light on this issue.

Eliminating the causative trigger, such as ceasing the drug or treating the infection, is the cornerstone of AGEP management. Other potentially useful options include moist dressings and topical antiseptics, systemic antibiotics if superinfection intervenes, and topical or systemic corticosteroids(20-21). However, in severe or recalcitrant cases, cyclosporine and intravenous immunoglobulin may be beneficial(22).

Conclusion:

we reported a case of AGEP which might has been triggered with COVID-19 infection itself or be considered as an unreported possible side effect of remedesivir to emphasize the necessity of paying more attention to history taking and clinical suspicion as key factors to reaching the correct diagnosis [23-28]. Furthermore, one can infer from our report that when dealing with skin findings, remdesivir should be kept in mind as a causative agent.

Written Consent from the patient:

written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Ethics statement:

Ethical approval from the Medical Ethics Committee of Isfahan University of Medical Sciences was provided.

Author contribution:

F.M visited the patient. F.M and P.H. gathered the data. All authors discussed the results. F.F supervised the project. Z.M and Z.A. provided the initial draft. P.H and Z.A wrote the final version.

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Conflict of interests:

The authors declare that they have no competing interests.

Data availability Statement:

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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Figures:

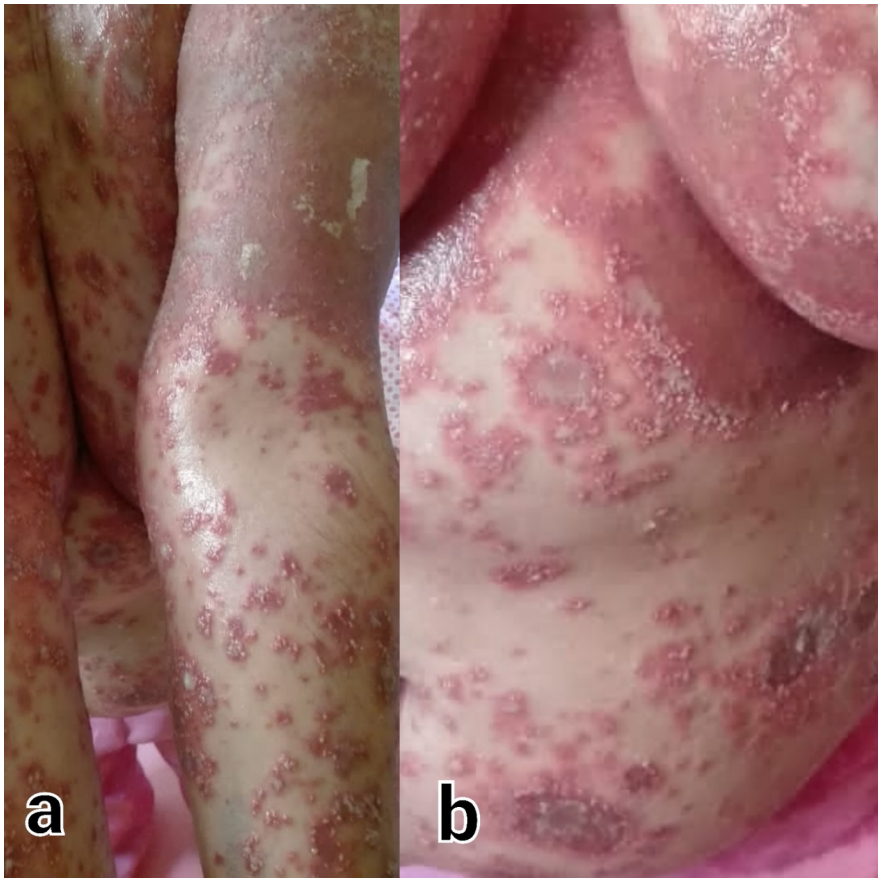

Figure 1. Generalized pustular eruptions with erythematous base on body (b) and extremities (a).

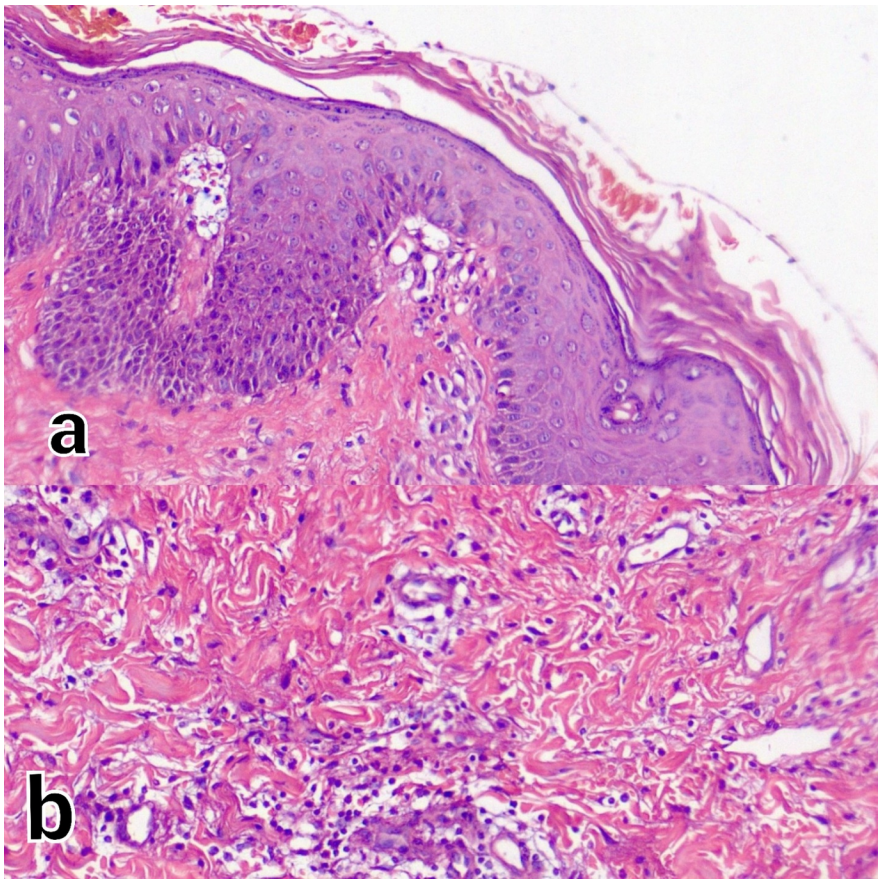

Figure 2. Neutrophilic parakeratosis with mild acanthosis and focal spongiosis, along with scattered necrotic keratinocyte, ectatic capillaries, and perivascular interstitial lymphocytic and eosinophilic infiltration. (H&E ×40)(a), (H&E ×100)(b).

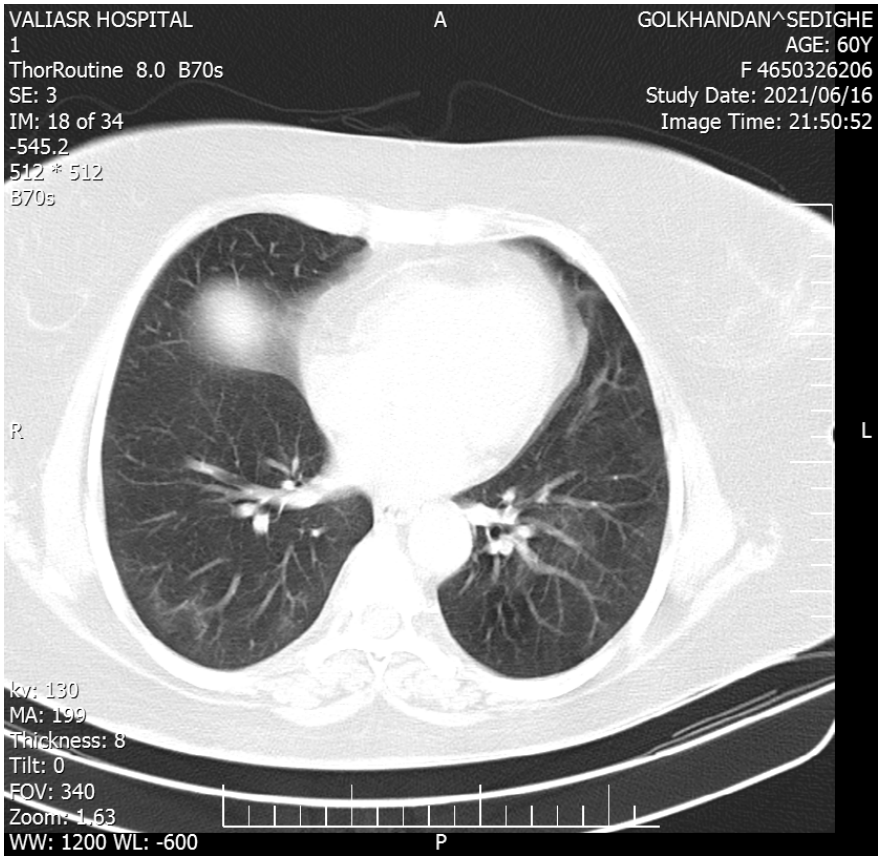

Figure 3. Diffuse ground-glass opacities in both lungs compatible with convalescent pulmonary phase of SARS-CoV-2 infection.