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REVIEW

COVID-19 infection leading to acute pustular dermatoses

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Abstract
Viral infections, including SARS-CoV-2, the virus that causes COVID-19 infection, have been implicated in the development of pustular dermatoses, including generalized pustular psoriasis (GPP) and acute generalized exanthematous pustulosis (AGEP). We performed a literature review of existing cases of GPP and AGEP associated with COVID-19 infection and/or treatment reported over a period of 12 months. We summarize the clinical characteristics of these cases and report an additional six new cases of GPP and AGEP. Seven patients with COVID-19 infection were diagnosed with new-onset or exacerbated GPP, and 33 patients were diagnosed with AGEP. In 55% of the cases, no concomitant potential culprit drug trigger was identified. We present this review of cases of COVID-associated acute pustular dermatoses to further contribute to the spectrum of cutaneous eruption associated with SARS-CoV-2 infection.

Keywords COVID-19 · Pustular dermatoses · AGEP · Generalized pustular psoriasis

Introduction

SARS-CoV-2, the virus that causes COVID-19 infection, provokes a robust host inflammatory response involving cytokines such as IL-1, interferon gamma, and TNF-alpha [1]. A similar inflammatory cascade is implicated in the development of a number of pustular dermatoses, including acute generalized exanthematous pustulosis (AGEP) and generalized pustular psoriasis (GPP) [2–6]. Acute flares of generalized pustular psoriasis may arise in the background of viral infection, as nucleic acids from viruses can activate the innate immune system and increase the inflammatory cytokines involved in psoriasis [4]. Similarly, viruses may induce acute generalized exanthematous pustulosis, a primarily T-cell mediated response, by causing upregulation of cytotoxic T-cells thought to help regulate infection [5]. During the initial stages of AGEP, higher levels of interferon gamma and granulocyte/macrophage colony-stimulating factor stimulate T-cells and keratinocytes to release CXCL8, which recruits neutrophils to form sterile pustules [5]. The proinflammatory response elicited in patients with COVID-19 may precipitate an acute flare or onset of pustular disease in at-risk patients. In this review article, we summarize existing literature on patients diagnosed with acute pustular dermatoses in conjunction with a diagnosis of or treatment for COVID-19 infection, and we discuss four additional cases of acute generalized exanthematous pustulosis (AGEP) and two cases of generalized pustular psoriasis (GPP) in patients concomitantly diagnosed with COVID-19.

Methods

We performed a review of existing literature to identify case reports of patients with pustular dermatoses that have been reported thus far in conjunction with a recent diagnosis of or treatment for COVID-19 infection. Pubmed search terms included "pustular," "acute generalized exanthematous pustulosis (AGEP),"and "pustular psoriasis," along with the term "COVID" or "SARS-CoV-2 between April 30, 2020 to May 1, 2021. We additionally report six additional cases of new or acutely exacerbated pustular dermatoses that presented to the Northwestern University Department of Dermatology. These cases were identified via review of the inpatient dermatology consult record, including results from skin biopsy.

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Results

Study characteristics

The initial literature search yielded a total of 35 unique reports. However, 20 articles were eliminated as they lacked discrete patient information (age, symptoms, clinical course) or were not written in English. In the 15 articles published between May 2020 and April 2021, there were a total of 34 patients with COVID-19 infection diagnosed with either new-onset or acutely exacerbated GPP or AGEP. We present 2 additional cases of GPP and 4 additional cases of AGEP for a total of 40 cases (Table 1).

Generalized pustular psoriasis

A total of seven patients with COVID-19 infection were diagnosed with new-onset or exacerbated generalized pustular psoriasis. The median age at presentation was 50 years (range 28–64 years). 57 percent of patients were female (4 of 7). Average time to eruption onset from either diagnosis of COVID-19 infection, symptom onset, treatment initiation, or symptom resolution was 19 days (range 7–28 days). Cutaneous morphologies primarily included non-folliculocentric pustules on erythematous or psoriasiform plaques. Four patients had no associated systemic symptoms. Of the remaining three patients, one developed arthritis and two developed infectious symptoms such as fevers, myalgias, and cough. Three patients had a prior history of psoriasis, with one patient specifically having a history of pustular psoriasis. Five patients (71%) had concomitant administration of potential culprit drugs; most notably, three patients received hydroxychloroquine and two patients received methotrexate. Treatment strategies included topical corticosteroids in four patients, oral corticosteroids in three patients, loratadine in two patients, and oral acitretin and cyclosporine in one patient each, respectively.

Acute generalized exanthematous pustulosis

A total of 33 patients with COVID-19 infection were diagnosed with acute generalized exanthematous pustulosis. The median age at presentation was 67 years (range 29–88 years). 56 percent of patients were male (18 of 32 reported). Average time to eruption onset from either diagnosis of COVID-19 infection, symptom onset, treatment initiation, or symptom resolution was 24 days (range 0–90 days). Cutaneous morphologies primarily included pustules scattered on erythematous plaques. Four of 33 patients developed fevers; the remainder had no associated systemic symptoms. One patient had a prior history of psoriasis, but no patients had a prior history of pustular dermatoses. Seventeen patients (52%) had concomitant administration of potential culprit medications. Most common potential drug triggers included cephalosporin antibiotics (24%, 8 of 33), hydroxychloroquine (18%, 6 of 33), and azithromycin (15%, 5 of 33). Notably, 16 patients (48%) who developed AGEP had no known administration of any culprit medications. Treatment strategies primarily included no treatment (30%, 10 of 33), topical corticosteroids (12%, 4 of 33), and oral corticosteroids (18%, 6 of 33).

Discussion

Several cutaneous eruptions associated with SARS-CoV-2 infection have been reported in the literature thus far, including erythema multiforme, papular-pustular lesions, livedo reticularis, chilblains, exanthematous and morbilliform reactions, petechiae, vesicular, and telogen effluvium [7]. We present this review of cases of acute pustular dermatoses to help further characterize the spectrum of cutaneous disease seen with COVID-19 infection.

Generalized pustular psoriasis, or GPP, is a psoriasis variant that typically presents with pustules on background erythematous skin. The pathogenesis of generalized pustular psoriasis is not fully understood. Mutations in the genes *IL36RN*, *CARD14*, and *AP1S3* have been associated with the proinflammatory pathophysiology of pustular psoriasis, as these mutations cause dysregulation of inflammatory cytokines [2–4]. Over fifty percent of cases of generalized pustular psoriasis in patients without a background of plaque psoriasis are thought to be a result of recessive mutations in the IL36RN gene, which encodes the interleukin-36-receptor antagonist responsible for antagonizing IL-1F6, IL-1F8, and IL-1F9, cytokines involved in pro-inflammatory signaling pathways. Mutation in the IL36RN gene results in unopposed disinhibition of these cytokines and activation of inflammatory pathways. In patients with a history of plaque psoriasis, mutations in the CARD14 gene are thought to be a predisposing factor. The CARD-14 gene is implicated in activation of the nuclear factor-kB signaling pathway, which is involved in the expression of pro-inflammatory molecules and cytokines such as TNF-alpha, IL-1, IL-6, and IL-8 [2]. Patients typically present with pustules overlying erythematous skin and often have associated systemic symptoms such as fever and malaise as well as elevated inflammatory markers (leukocytosis, elevated CRP levels, and eosinophilia). Many drug triggers have been described, including amoxicillin, hydroxychloroquine, and TNF-alpha inhibitors. A number of viral triggers have also been described, including varicella zoster virus, Epstein-Barr virus, and cytomegalovirus [2].

Table 1 Summary of reported cases of new-onset or acutely exacerbated GPP or AGEP after COVID-19 infection

References	Patient age and sex	Days from either diagnosis of COVID, symptom onset, treatment initiation, or symptom resolution to development of exanthem	Morphology and distribution of eruption	Associated systemic symptoms	Previous diagnosis of AGEP or psoriasis?	Co-administration of potential drug culprits (timing of administration relative to eruption)	Timing of potential drug culprit relative to COVID diagnosis	Severity of illness/need for intubation or ICU	Treatment strategy
Generalized pustular psoriasis									
[6]	62, F	14	Erythematous, hyperkeratotic, papulopustular psoriasiform plaques over the palms, extremities, trunk, and scalp	None	None	None	None	Stable, no intubation or ICU admission	Topical corticosteroids
[13]	47, F	21	Pustular lesions over trunk and extremities	Fever, myalgia	Yes, specifically pustularpsoriasis	Methotrexate (taken 7.5 mg weekly for the past 9 months prior to eruption)	Methotrexate started 10 months before diagnosis	Stable, no intubation or ICUadmission	Hydroxychloroquine
[14]	60, M	26	Widespread erythematous patches and pustules	Vomiting, diarrhea, myalgia, and cough	Yes	Hydroxychloroquine (started 24 days before eruption), naproxen (started 24 days before eruption) linezolid (started 10 days before eruption), meropenem (started 10 days before eruption)	Hydroxychloroquine and naproxen started at time of diagnosis Linezolid, meropenem started 15 days after diagnosis	Stable, no intubation or ICU admission	Acitretin, oral corticosteroids
[15]	64, M	14–21	Non-follicular pustules on background of purpuric erythema over the trunk,extremities, scalp	None	None	Hydroxychloroquine, lopinavir/ritonavir, teicoplanin (started 2–3 weeks prior to eruption)	All medications started at time of diagnosis	Stable, no intubation or ICU admission	Topical corticosteroids, loratadine, oral corticosteroids

Table 1 (continued)

References	Patient age and sex	Days from either diagnosis of COVID, symptom onset, treatment initiation, or symptom resolution to development of exanthem	Morphology and distribution of eruption	Associated systemic symptoms	Previous diagnosis of AGEP or psoriasis?	Co-administration of potential drug culprits (timing of administration relative to eruption)	Timing of potential drug culprit relative to COVID diagnosis	Severity of illness/need for intubation or ICU	Treatment strategy
[15]	60, F	14–21	Non-follicular pustules on background of purpuric erythema with targetoid lesions noted over the trunk, extremities, scalp	None	None	Etanercept (taken weekly prior to eruption) Hydroxychloroquine, lopinavir/ritonavir, teicoplanin, azithromycin (all drugs started 2–3 weeks prior to eruption)	Etanercept started prior to diagnosis Hydroxychloroquine, lopinavir/ritonavir, teicoplanin, azithromycin started at time of diagnosis	Stable, no intubation or ICU admission	Topical corticosteroids, loratadine, oral corticosteroids
This case series	28, M	28	Confluent erythematous plaques with lakes of pus over the lower extremities, particularly over dorsal feet	None	Yes	Infliximab (taken every 8 weeks; last dose 1 week before eruption), methotrexate (taken every week; last dose 1 week before eruption), cephalexin (taken 4 days prior to eruption), emtricitabine-tenofovir (taken daily prior to eruption), cyclosporine (taken same time as eruption)	Methotrexate, emtricitabine-tenofovir, cyclosporine started before diagnosis Infliximab, cephalexin taken 22 days after diagnosis	Stable, no intubation or ICU admission	Topical corticosteroids, loratadine, oral corticosteroids, cyclosporine
This case series	31, F	7	Tender vesicles over the bilateral hands, left elbow, upper abdomen	Arthritis	None	None	None	Stable, no intubation or ICU admission	Topical corticosteroids

Table 1 (continued)

References	Patient age and sex	Days from either diagnosis of COVID, symptom onset, treatment initiation, or symptom resolution to development of exanthem	Morphology and distribution of eruption	Associated systemic symptoms	Previous diagnosis of AGEP or psoriasis?	Co-administration of potential drug culprits (timing of administration relative to eruption)	Timing of potential drug culprit relative to COVID diagnosis	Severity of illness/need for intubation or ICU	Treatment strategy
Acute generalized exanthematous pustulosis									
[11]	12 pts (8 M, 4F), 54–84 (mean 75)	Variable	Variable, but includes diffuse superficial bullae on erythematous base, Erythema with small papules with erosion, Erythema with many nonfollicular micropustules and focal desquamation, Erythematous confluent macules, atypical target lesions	Variable, but includes fever and facial edema	None	None	None	All patients had symptoms of respiratory distress, at least one patient was admitted to ICU, now deceased	Oral corticosteroids, variety of other drugs including hydroxychloroquine, azithromycin, ritonavir, darunavir
[12]	33, M	90	Pustules on erythematous base over face, trunk, extremities	None	None	Azithromycin (started 90 days prior to eruption)	Azithromycin started at time of diagnosis	Stable, no intubation or ICU admission	None
[16]	34, M	4	Pustules on erythematous base over face, trunk, and extremities	None	None	Azithromycin, ceftazidime, ceftriaxone, clindamycin, hydroxychloroquine, interferon beta, lopinavir, oseltamivir, prednisolone, ribavirin (started 3 weeks prior to eruption)	All medications started at time of diagnosis	Stable, no intubation or ICU admission	Topical corticosteroids, promethazine, paracetamol, calcipotriol

Table 1 (continued)

References	Patient age and sex	Days from either diagnosis of COVID, symptom onset, treatment initiation, or symptom resolution to development of exanthem	Morphology and distribution of eruption	Associated systemic symptoms	Previous diagnosis of AGEP or psoriasis?	Co-administration of potential drug culprits (timing of administration relative to eruption)	Timing of potential drug culprit relative to COVID diagnosis	Severity of illness/need for intubation or ICU	Treatment strategy
[17]	78, M	0	Pustules on erythematous base over trunk, upper extremities	Fever, hypotensio n	None	Cefepime (started 7 days prior to eruption)	Cefepime started at time of diagnosis	Admitted to ICU, no intubation	Topical emollients, discontinuation of cefepime
[18]	39, F	18	Erythematous pustular plaques spreading cephalocaudally	Fever	None	Hydroxychloroquine (started 18 days prior to eruption), enoxaparin (started 18 days prior to eruption)	Hydroxychloroquine started at time of diagnosis	Received supplemental oxygen, patient deceased from pulmonary embolism	Discontinuation of hydroxychloroquine
[19]	70, F	21	Pustular, scaly eruption on erythematous, edematous base with some targetoid lesions over face, trunk, and extremities	Fever	None	Hydroxychloroquine (started 3 weeks prior eruption), lopinavir/ritonavir (started 3 weeks prior) to eruption, prednisone (started 7 days prior to eruption)	Hydroxychloroquine, lopinavir/ritonavir started at time of diagnosis	Stable, no intubation or ICU admission	Oral corticosteroids
[20]	76, M	14	Generalized pustules on erythematous base	Fever	None	Azithromycin (started 10 days prior to eruption), ceftriaxone (started 10 days prior to eruption), hydroxychloroquine (started 10 days prior to eruption)	All medications started 7–10 days after diagnosis	Required intubation and ICU admission, deceased from pulmonary embolism	Drug discontinuation

Table 1 (continued)

References	Patient age and sex	Days from either diagnosis of COVID, symptom onset, treatment initiation, or symptom resolution to development of exanthem	Morphology and distribution of eruption	Associated systemic symptoms	Previous diagnosis of AGEP or psoriasis?	Co-administration of potential drug culprits (timing of administration relative to eruption)	Timing of potential drug culprit relative to COVID diagnosis	Severity of illness/need for intubation or ICU	Treatment strategy
[21]	58, M	29	Generalized coalescing erythematous violaceous macules and papules	None	None	None	None	Severity of illness not given	None
[21]	84, F	12	Coalescing erythematous macules and papules over trunk and flexural surfaces	None	None	Ceftriaxone, hydroxychloroquine, lopinavir, ritonavir (started at least 2 weeks prior to eruption)	Time of administration relative to diagnosis not given	Severity of illness not given	None
[21]	82, F	29	Ill-defined erythematous patches over the trunk and flexural surfaces	None	None	Fosfomycin (started at least 2 weeks prior to eruption)	Time of administration relative to diagnosis not given	Severity of illness not given	None
[21]	68, F	28	Ill-defined erythematous patches over the trunk and flexural surfaces	None	None	Amiodarone, linezolid, metamizole, piperacillin-tazobactam (all drugs started at least 2 weeks prior to eruption)	Time of administration relative to diagnosis not given	Severity of illness not given	None
[21]	51, M	28	Coalescing erythematous macules over trunk and proximal extremities	None	None	None	None	Severity of illness not given	None

Table 1 (continued)

References	Patient age and sex	Days from either diagnosis of COVID, symptom onset, treatment initiation, or symptom resolution to development of exanthem	Morphology and distribution of eruption	Associated systemic symptoms	Previous diagnosis of AGEP or psoriasis?	Co-administration of potential drug culprits (timing of administration relative to eruption)	Timing of potential drug culprit relative to COVID diagnosis	Severity of illness/need for intubation or ICU	Treatment strategy
[21]	88, M	31	Coalescing erythematous macules and papules over the face, trunk, and proximal extremities	None	None	Furosemide (started at least 2 weeks prior to eruption)	Time of administration relative to diagnosis not given	Severity of illness not given	None
[21]	69, F	33	Coalescing erythematous macules, papules, and pustules over the face, trunk, and flexural surfaces over the trunk	None	None	None	None	Severity of illness not given	None
[21]	78, M	30	Ill-defined erythematous patches	None	None	Piperacillin-tazobactam, Meropenem (started at least 2 weeks prior to eruption)	Time of administration relative to diagnosis not given	Severity of illness not given	None
[22]	29, F	17	Erythematous macules, edematous papules coalescing into plaques over the face, trunk and extremities with facial edema	None	None	Azithromycin (started 12 days prior to eruption), doxycycline (started 12 days prior to eruption), prednisone (started 12 days prior to eruption), hydroxychloroquine (started 4 days prior to eruption)	Azithromycin, doxycycline, prednisone started at time of symptom onset Hydroxychloroquine started 8 days after symptom onset	Stable, no intubation or ICU admission	Oral corticosteroids, topical corticosteroids

Table 1 (continued)

References	Patient age and sex	Days from either diagnosis of COVID, symptom onset, treatment initiation, or symptom resolution to development of exanthem	Morphology and distribution of eruption	Associated systemic symptoms	Previous diagnosis of AGEP or psoriasis?	Co-administration of potential drug culprits (timing of administration relative to eruption)	Timing of potential drug culprit relative to COVID diagnosis	Severity of illness/need for intubation or ICU	Treatment strategy
[23]	49, F	32	Pustules on erythematous base over the face, trunk, and axillary surfaces	None	None	Azithromycin, cefditoren, ceftriaxone, hydroxychloroquine, interferon beta, lopinavir, methylprednisolone, ritonavir, tocilizumab (all drugs started at least 24 h before eruption)	All medications started at time of diagnosis	Intubated and admitted to ICU	Oral corticosteroids, discontinuation of cefditoren
[24]	Not provided	7	Pustules on erythematous base over the trunk and extremities	None	None	Cefpodoxime (started 6 days prior to eruption)	All medications started at time of diagnosis	Admitted to ICU	None

Table 1 (continued)

References	Patient age and sex	Days from either diagnosis of COVID, symptom onset, treatment initiation, or symptom resolution to development of exanthem	Morphology and distribution of eruption	Associated systemic symptoms	Previous diagnosis of AGEP or psoriasis?	Co-administration of potential drug culprits (timing of administration relative to eruption)	Timing of potential drug culprit relative to COVID diagnosis	Severity of illness/need for intubation or ICU	Treatment strategy
This case series	78, F	40	Pustules on erythematous base over the axillae, upper chest, and abdomen	Fever	None	Cefepime (started 4 days prior to eruption), hydralazine (started 5 days prior to eruption), linezolid (started 4 days prior to eruption), meropenem (started same day as eruption), fentanyl (started 4 days prior to eruption) Piperacillin/Tazobactam (started 30 days prior to eruption)	Piperacillin/Tazobactam started Cefepime, hydralazine, linezolid, meropenem, fentanyl, started 36 ~ days after diagnosis	Intubated and admitted to ICU	Oral corticosteroids, topical corticosteroids
This case series	63, M	28	Macules and papules over the chest and groin	Fever	None	Cefepime (started 10 days prior to eruption), ceftriaxone (started 19 days prior to eruption),	Ceftriaxone started 7 days after diagnosis, all other medications	Intubated and admitted to	Discontinuation of ciprofloxacin
This case series	67, M	0	Exanthematous eruption with small pustules over the trunk and lower extremities	None	None	None	None	Intubated and admitted to ICU, now deceased	Topical corticosteroids

Table 1 (continued)

References	Patient age and sex	Days from either diagnosis of COVID, symptom onset, treatment initiation, or symptom resolution to development of exanthem	Morphology and distribution of eruption	Associated systemic symptoms	Previous diagnosis of AGEP or psoriasis?	Co-administration of potential drug culprits (timing of administration relative to eruption)	Timing of potential drug culprit relative to COVID diagnosis	Severity of illness/need for intubation or ICU	Treatment strategy
This case series	58, F	21	Thin red plaques with scattered pustules on plantar surfaces	None	Yes	Metformin (started taking 3 months prior to eruption), montelukast (started taking 9 months prior to eruption)	All medications taken 2 months before diagnosis	Stable, no intubation or ICU admission	Topical corticosteroids, apremilast

Acute generalized exanthematous pustulosis is most commonly classified as an adverse drug eruption associated with administration of a variety of medications, including aminopenicillin, sulfonamide, and quinolone antibiotics; hydroxychloroquine; diltiazem; and certain anti-fungal medications. Rarely, however, viral triggers including parvovirus B19 and cytomegalovirus have also been described. The eruption is thought to develop after exposure to a causative agent causes CD4 and CD8 T cell activation, ultimately leading to apoptosis of epidermal keratinocytes causing vesicle and pustule formation and destruction of tissue. These activated T cells predominantly display a Th1 type cytokine profile, producing mediators such as CXCL8, a neutrophilic cytokine, as well as interferon gamma and granulocyte/macrophage colony-stimulating factor. Some patients also display high levels of T cells with Th2 as well as Th17 cytokine patterns, leading to increased production of IL-4/IL-5 and IL-17/IL-22, respectively. Additionally, although IL36RN gene mutation is not directly linked to development of AGEP, mutation of this gene was found to be significantly higher in patients who developed AGEP compared to controls [3]. In addition, patients with HLA B51, DR11, and DQ3 may also have a genetic predisposition in developing AGEP [8].

In this case series, patients diagnosed with COVID-19 infection with concomitant GPP or AGEP were primarily noted to have non-folliculocentric pustules with 3 of 7 GPP patients (42%) and 7 of 33 AGEP patients (21%) presenting also with head and neck involvement. Among the subset of 33 patients diagnosed concomitantly with SARS-CoV-2 and AGEP, 16 patients (48%) were not documented to have concomitant administration of a potential culprit medication and thus are favored to have AGEP triggered primarily by COVID-19 infection, although we acknowledge co-administration of potential culprit medications among the remaining 17 patients as a major limitation of this review. Among this subset of patients without co-administration of a potential culprit medication, time to eruption onset is only available for four patients, with a mean time to onset of 22.5 days, range 0–33 days. None of these patients were specifically noted to have fever, although two were noted to have respiratory distress severe enough to require intubation and ultimately passed away. The EuroSCAR diagnostic scoring criteria for the diagnosis of AGEP includes fever of greater than or equal to 38 degrees Celsius, and in one review of 58 patients with AGEP, approximately 17% were noted to have internal organ involvement, including hepatic, pulmonary, and renal dysfunction. Patients with classic drug-triggered AGEP typically develop reaction onset within 72 h of drug exposure, with antibiotic-associated AGEP developing within 24 h [9]. Compared to drug-associated AGEP, patients with AGEP triggered by the SARS-CoV-2

virus were thus noted to have longer time to eruption onset and less likely to be febrile.

There is some evidence in the literature that viral nucleic acids act as strong agonists of the innate immune system and can trigger the release of inflammatory cytokines such as IL-36 that are implicated in psoriasis pathogenesis [4]. One such study that provides support is a small cohort study of 25 patients with psoriasis (21 with psoriasis vulgaris, 4 with generalized pustular psoriasis), who presented with 31 total psoriasis flares after respiratory tract infections. These patients received PCR testing of 16 viral pathogens and 4 bacterial pathogens by nasopharyngeal swab at time of psoriasis flare. 21 of these 25 patients (84%) were found to have at least one positive PCR test, with a rhinovirus and a coronavirus being the most frequently detected pathogens. 24 out of 31 flares (77%) were not noted to have any other associated trigger, and median delay between first symptoms and flare onset was 2 days [10]. Of note, median time to eruption onset among our patients with COVID-19 infection and GPP is longer than described in this small case series (19 days, range 7–28 days). Data on infectious triggers and their potential pathophysiology in acute generalized exanthematous pustulosis is more scant, although parvovirus B19 reactivation in the setting of amoxicillin administration, *Chlamydia pneumoniae* infection, and cytomegalovirus infection have all been reported in conjunction with AGEP [11].

SARS-CoV-2, the virus that causes COVID-19 infection, is thought to cause viral-mediated cell death in airway epithelial cells causing release of damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs), leading to recognition by Toll-like receptors and nucleotide-binding domain leucine-rich repeat proteins. This ultimately triggers production of proinflammatory cytokine transcription factors such as NF-kappa-beta, activation of interferon regulatory factors, and activation of inflammasomes and conversion of proIL-1-beta to active IL-1-beta. Taken together, this leads to increased secretion of proinflammatory cytokines such as IL-6 and interferon-gamma as well as pulmonary recruitment of immune cells such as dendritic cells and macrophages. In a majority of patients, this immune response leads to SARS-CoV-2 clearance from the pulmonary system. In patients who ultimately develop severe COVID-19 infection, however, a dysregulated combined Th1 and Th2-type immune response occurs to initial viral infection, leading to increased levels of inflammatory mediators (IL-6, IL-2, IL-10, IL-7, G-CSF, and IFN-gamma) and greater disease severity and mortality [1]. It is possible a genetic predisposition may play increase the risk for these reactions. As described above, a similar inflammatory cascade is implicated in the development of generalized pustular psoriasis and acute generalized exanthematous pustulosis. We thus postulate that this inflammatory response triggered by SARS-CoV-2 infection may precipitate an acute flare or onset of disease in patients genetically at risk for or already living with a pustular dermatosis.

Author contributions PKG and TOM wrote the main manuscript text. All authors reviewed the manuscript.

Declarations

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Bohn MK, Hall A, Sepiashvili L, Jung B, Steele S, Adeli K (2020) Pathophysiology of COVID-19: mechanisms underlying disease severity and progression. Physiology 35(5):288–301
2. Hoegler KM, John AM, Handler MZ, Schwartz RA (2018) Generalized pustular psoriasis: a review and update on treatment. J Eur Acad Dermatol Venereol 32(10):1645–1651
3. Bachelez H (2018) Pustular psoriasis and related pustular skin diseases. Br J Dermatol 178(3):614–618
4. Bachelez H (2020) Pustular psoriasis: the dawn of a new era. Acta Derm Venereol. 100(3):adv00034
5. Szatkowski J, Schwartz RA (2015) Acute generalized exanthematous pustulosis (AGEP): a review and update. J Am Acad Dermatol 73(5):843–848
6. Mathieu RJ, Cobb CBC, Telang GH, Firoz EF (2020) New-onset pustular psoriasis in the setting of severe acute respiratory syndrome coronavirus 2 infection causing coronavirus disease 2019. JAAD Case Rep 6(12):1360–1362
7. Almeida G, Arruda S, Marques E, Michalany N, Sadick N (2021) Presentation and management of cutaneous manifestations of COVID-19. J Drugs Dermatol 20(1):76–83
8. Bernard P, Lizeaux-Parneix V, Miossec V et al (1995) HLA et prédisposition génétique dans les pustuloses exanthématiques (PEAG) et les exanthémes maculo-papuleux (EMP). Ann Dermatol Venerol 122:S38
9. Hotz C, Valeyrie-Allanore L, Haddad C et al (2013) Systemic involvement of acute generalized exanthematous pustulosis: a retrospective study on 58 patients. Br J Dermatol 169(6):1223–1232. https://doi.org/10.1111/bjd.12502
10. Sbidian E, Madrange M, Viguier M et al (2019) Respiratory virus infection triggers acute psoriasis flares across different clinical subtypes and genetic backgrounds. Br J Dermatol 181(6):1304–1306. https://doi.org/10.1111/bjd.18203
11. Pezzarossa E, Ungari M, Caresana G et al (2021) Acute Generalized Exanthematous Pustulosis (AGEP) in 12 patients treated for SARS-CoV-2 positive pneumonia. Am J Dermatopathol. https://doi.org/10.1097/DAD.0000000000001819 (**Publish Ahead of Print**)
12. Ayatollahi A, Robati RM, Kamyab K, Firooz A (2020) Late-onset AGEP-like skin pustular eruption following COVID-19: a possible association. Dermatol Ther 33(6):e14275
13. Shakoei S, Ghanadan A, Hamzelou S (2020) Pustular psoriasis exacerbated by COVID-19 in a patient with the history of psoriasis. Dermatol Ther 33(6):e14462
14. Shahidi Dadras M, Diab R, Ahadi M, Abdollahimajd F (2020) Generalized pustular psoriasis following COVID-19. Dermatol Ther 27:e14595
15. Abadías-Granado I, Palma-Ruiz AM, Cerro PA et al (2021) Generalized pustular figurate erythema first report in two COVID-19

patients on hydroxychloroquine. J Eur Acad Dermatol Venereol 35(1):e5–e7
16. Alzahrani MJ, Moussa MM, Alfaraj D (2020) Acute Generalized Exanthematous Pustulosis after COVID-19 infection: a case report from Saudi Arabia. Cureus 12(11):e11609
17. Haraszti S, Sendil S, Jensen N (2020) 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 21:e926901
18. Litaiem N, Hajlaoui K, Karray M, Slouma M, Zeglaoui F (2020) Acute generalized exanthematous pustulosis after COVID-19 treatment with hydroxychloroquine. Dermatol Ther 33(4):e13565
19. Robustelli Test E, Vezzoli P, Carugno A et al (2020) 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 34(9):e457–e459
20. Delaleu J, Deniau B, Battistella M et al (2020) Acute generalized exanthematous pustulosis induced by hydroxychloroquine prescribed for COVID-19. J Allergy Clin Immunol Pract 8(8):2777-2779.e1
21. Herrero-Moyano M, Capusan TM, Andreu-Barasoain M et al (2020) A clinicopathological study of eight patients with COVID-19 pneumonia and a late-onset exanthema. J Eur Acad Dermatol Venereol 34(9):e460–e464
22. Enos T, Jeong HS, Vandergriff T, Jacobe HT, Chong BF (2020) Acute generalized exanthematous pustulosis induced by empiric hydroxychloroquine for presumed COVID-19. Dermatol Ther 33(6):e13834
23. Torres-Navarro I, Abril-Pérez C, Roca-Ginés J, Sánchez-Arráez J, Botella-Estrada R (2020) 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 34(10):e537–e539
24. Sanchez A, Sohier P, Benghanem S et al (2020) Digitate Papulosquamous Eruption Associated with severe acute respiratory syndrome coronavirus 2 infection. JAMA Dermatol 156(7):819–820