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Generalized Pustular Figurate Erythema in Patients with COVID-19 Treated with Hydroxychloroquine: A Systematic Review

Fatimah Al Muqarrab[1], Robert A. Schwartz[2], Amer A. Almohssen[3]

[1]King Saud University, King Khalid University Hospital, Dermatology Department, Riyadh, Saudi Arabia; [2]New Jersey Medical School, Rutgers University, Englewood, United States; [3]Alfardan Medical and Northwestern Medicine, Doha, Qatar

Corresponding author:
Fatimah Al Muqarrab, Consultant Dermatologist
Saudi Board of Dermatology,
Arab Board of Dermatology and V enereology
Al Ashaa, Saudi Arabia
fatimah.muq12@gmail.com

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ABSTRACT A severe distinctive cutaneous drug reaction, generalized pustular figurate erythema, closely linked with hydroxychloroquine (HCQ), has been documented. It is distinguishable from AGEP by its longer incubation, more varied morphology (initially urticarial and later targetoid, arcuate plaques), recalcitrance to therapy and longer disease course.
Aim of the article is to review the recognized entity associated with ingestion of hydroxychloroquine in patients infected with COVID-19.
A systematic review using electronic search was performed. Inclusion criteria: n patients with COVID-19 demonstrated by PCR, with typical clinical features of AGEP/GPFE or atypical features associated with typical histopathology. We used the (JBI) Critical Appraisal Checklist for Case Reports for the qualitive assessment.
We included 13 publications. Their overall quality was good to moderate. Only 27.3% of the patients had a severe COVID-19 course. The mean lag time between trigger exposure and rash development was 24 days. Only 15.38% of the reported AGEP were clinically typical, while the remaining 69.23 % were suggestive of GPFE. Unfortunately, 2 patients died secondary to massive pulmonary embolism.
In COVID-19 infection, we suggest reconsidering treating established COVID-19 empirically with HCQ, as both triggers can augment the subsequent cytokine storm, inducing a severe drug reaction and possibly increasing the risk of thrombo-embolic events.

KEY WORDS: drug eruption, generalized pustular figurate erythema, Schwartz-Janniger syndrome, acute generalized exanthematous pustulosis, hydroxychloroquine, Steven-Johnson syndrome, toxic epidermal necrolysis, COVID-19, hydroxychloroquine

INTRODUCTION

The novel SARS-CoV-1 coronavirus causing the COVID-19 disease was first discovered in December 2019 in the Chinese city of Wuhan and declared a global pandemic (1,2). Both the cutaneous manifestations of COVID-19 infection and the cutaneous adverse reactions to the medications used for the treatment of COVID-19 (3,4) have been described since the beginning of the pandemic and remain of clinical concern. Generalized pustular figurate erythema (GPFE) is a severe cutaneous drug reaction that has been continuously reported over the last year by several authors. Since the onset of the pandemic, treatment measures have been undertaken to decrease the morbidity and mortality of this novel virus. A potential antiviral effect of hydroxychloroquine against SARS-CoV-1 was reported (5). Some recent

publications have also supported the efficacy of hydroxychloroquine (HCQ) against COVID-19, improving the clinical outcomes of disease mortality. However, the published articles were of a retrospective observational design that included confounding effects (6,7). The large randomized "Solidarity Trial", on the other hand, showed little to no mortality rate reduction in hospitalized patients who received HCQ compared with patients who did not (8).

Severe cutaneous adverse reactions associated with COVID therapy are not common. Generalized pustular figurate erythema (GPFE), acute generalized exanthematous pustulosis (AGEP), and Stevens-Johnson syndrome are rare severe adverse cutaneous reactions triggered overwhelmingly by medications (9). The time of the onset of the eruption is important: 1-8 weeks for Stevens-Johnson syndrome, 1-3 weeks for GPFE, and only 24-48 hours for AGEP (Table 1). Infections have been linked to only a subset of these patients; however, the EuroSCAR study found no significant risk of infections (8,10).

Clinically, GPFE first becomes observable in 1-3 weeks, in the form of erythematous facial papules and plaques with facial edema and widespread urticarial or erythema multiforme-like plaques over the entire body, with non-follicular pustules atop evolving and sometimes atypical targetoid plaques converging into annular and arcuate patterns, particularly prominent on the trunk and extremities (11,34). Pustular erythema may be evident along active borders. Enough cutaneous sloughing and excoriations with blisters or erosions may be visible to suggest consideration of Stevens-Johnson syndrome. However, with GPFE there is little or no mucosal involvement. With AGEP, typical lesions appear after 24-48 hours of drug initiation (12), on the form of pinhead-sized non-follicular pustules over an erythematous edematous base commencing in the flexures and then spreading out to the trunk and extremities. The patient is almost always febrile, and the rash is sometimes pruritic. Twenty percent of cases have minimal mucosal lesions. The rash typically resolves within 15 days after drug discontinuation with desquamation.

The course of GPFE is different from that of AGEP, the former having delayed onset and more prolonged course, often being more difficult to treat. The clinical presentation and course nature of HCQ-induced GPFE was described by Schwartz and Janniger (11) as a distinct entity. It has been called the Schwartz-Janniger syndrome (9). In addition to the long lag period of GPFE compared with AGEP, it is clinically distinguished by atypical targetoid lesions studded with pustules, prominent facial edema, and erythema. It usually fades with desquamation, blisters, and erosions including the palms and soles (11).

Pustular psoriasis is also considered in the differential diagnosis, as it may have overlapping features with GPFE and AGEP (11,13). A recent systematic review investigating the role of hydroxychloroquine in the development or exacerbation of pustular psoriasis failed to attribute the risk to HCQ alone (14). Although it may be difficult to differentiate between the three entities based on the clinical pictures alone, the more predominant clinical involvement of the flexures, shorter duration of the febrile pustular eruption, and recent drug initiation 24-48 hours earlier favor AGEP, whereas a more urticarial and annular pattern favors GPFE. However, positive past history of psoriasis, the presence of arthritis, and hypocalcemia may favor pustular psoriasis (13); history of antimalarial ingestion 1-3 weeks earlier suggests GPFE.

Histologically, it is sometimes difficult to distinguish GPFE and AGEP from pustular psoriasis (11,13). Pustules may be present within the subcorneal, intraepidermal and/or intracorneal neutrophilic pustules. Epidermis acanthosis and mild spongiosis at the margins of the pustules may be observed, as well as mild papillary dermal edema and extravasation of erythrocytes plus a modest perivascular lymphocytic infiltrated with occasional neutrophils (12,34). Dilated papillary dermal blood vessels in a closely touching the epidermis and epidermal psoriasiform acanthosis favor pustular psoriasis (15-17).

We conducted a systematic review of the GPFE cases, often reported prior to GPFE being classified as AGEP, atypical AGEP, or Steven-Johnson overlap, secondary, atypical AGEP, recalcitrant AGEP, pustular DRESS syndrome, AGEP/SJS overlap, AGEP/TEN overlap, and Sweet's syndrome following hydroxychloroquine usage for COVID-19 treatment, in order to summarize the existing evidence (18-28). Such systematic reviews can identify unrecognized or rare associations, most common features of the disease, co-existing factors, treatment approaches, and end sequalae of such serious reactions. Hypotheses can be generated subsequently for further studies investigating the pathogenesis and possibly identifying the most appropriate treatment lines in order to decrease the hypothesized morbidity and mortality. Raising the awareness among clinicians about GPFE as a serious side-effect of HCQ in the era of the current COVID-19 pandemic and building an evidence-based health care system is a secondary outcome of our review.

METHODS

Data searches

We followed the PRISMA guidelines (29) in our data selection strategy summarized in the study flow

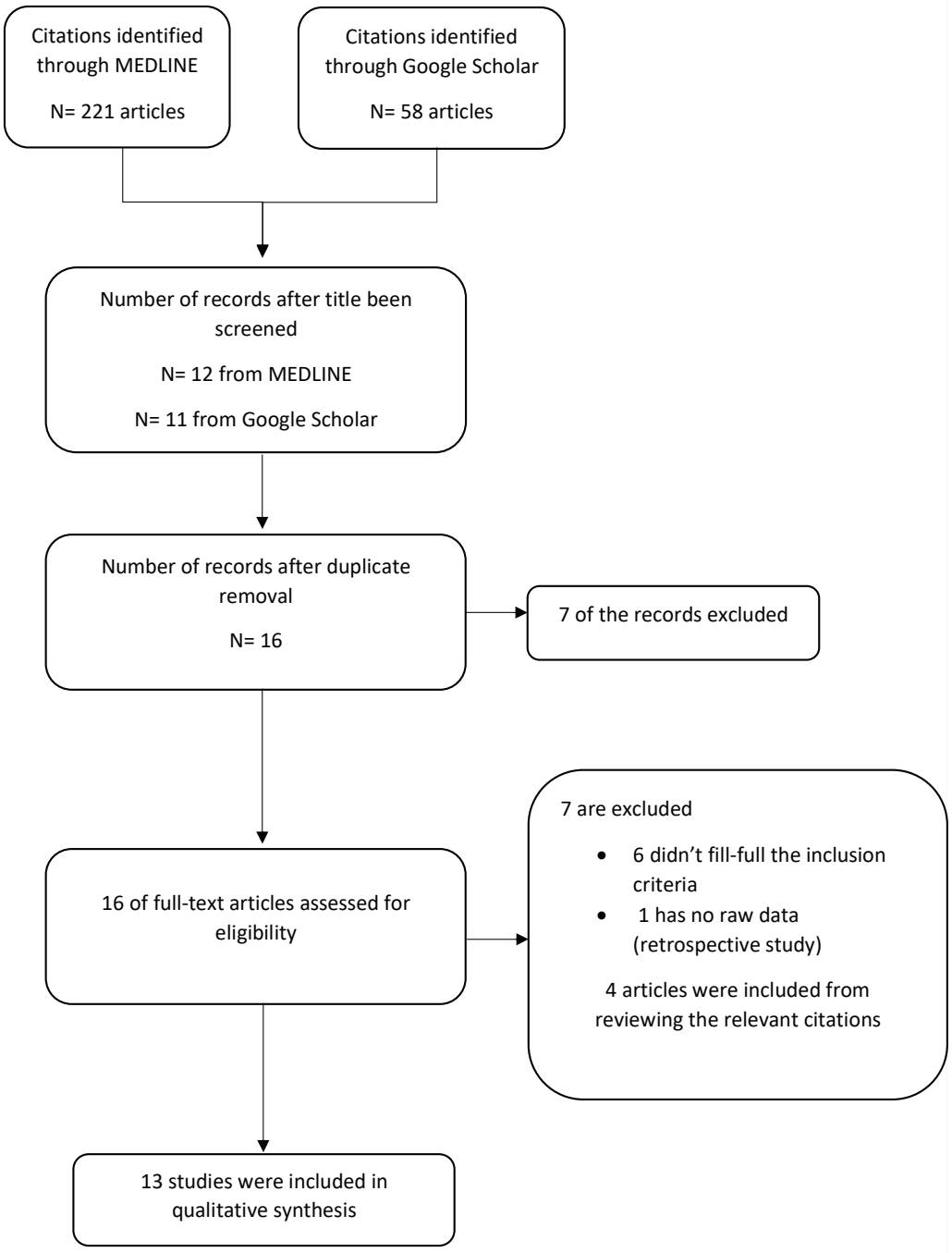

chart. Our eligibility criteria were created based on the PICO (Population/problem, Intervention, Comparison and Outcome) search worksheet. An electronic literature search of the Cochrane database of systematic reviews and PROSPERO (international prospective register of systematic reviews) database (International prospective register of systematic reviews) failed to identify any ongoing or published similar review. This review is registered in PROSPERO with ID number CRD42021232499. A parallel search was conducted using MEDLINE and Google Scholar databases from January 2020 to January 2021. We used the search terms (acute), (generalized), (exanthematous), (pustulosis), (pustular), (erythema), (COVID-19), (coronavirus), (hydroxychloroquine), (HCQ). The search strategy yielded 279 potential articles. References of the included articles along with the relevant citations were searched manually, retrieving an additional 4 articles.

Table 1.

	SJS/TEN (14,15)	GPFE	AGEP
Onset	1-8 weeks	1-3 weeks	24-48 hours
Skin findings	Atypical targetoid dusky macular lesions coalescing in the trunk, then spreading out with large areas of denudation and ulceration	Atypical targetoid lesions studded with pustules Prominent facial edema and erythema Usually fades with desquamation, blisters, and erosions including the palms and soles	Pinhead-sized non-follicular pustules over an erythematous edematous base commencing on the face and flexures and then spreading out to the trunk and extremities
Systemic findings	Fever, malaise, pharyngitis, headache, cough, rhinorrhea Ocular, genitourinary, gastrointestinal and pulmonary involvement	One third of the patients are febrile Rarely, hypercoagulability possibly linked with pulmonary emboli	The patient is almost always febrile Lymphadenopathy Leukocytosis with an elevated neutrophil count Rarely; internal organ involvement (liver, kidney, lung)
Mucosal involvement	Flaccid bullae, skin erosions, and painful inflammation and ulceration in the oral cavity, ocular mucosa and/or genital mucosa.	Little to no involvement	20% has minimal mucosal involvement
Clinical course	High morbidity and mortality rate (25-30%) and may increase up to 90% if delayed in the diagnosis or left untreated, needs special considerations for early recognition and discontinuation of the causative agent, prevention of the systemic sequalae, transfer the patient to a specialized burn unit and sepsis prevention measures.	Prolonged recalcitrant clinical course, often needs systemic interventions for the rash resolution	Resolves within 15 days after drug discontinuation with supportive or topical treatments 5% mortality rate if systemic organs are involved and the diagnosis is delayed

Study selection

The screening of the relevant articles was carried out by an independent investigator. Firstly, the titles and the abstracts were screened, after which the full text of the potentially relevant articles was reviewed. Owing to the current COVID-19 restrictions, consensus was conducted virtually to resolve any discrepancies. Articles were only included if they reported cases of GPFE, AGEP, or atypical AGEP following HCQ with or without other treatments for COVID-19 infection. We considered the nasopharyngeal swab for PCR analysis to be the gold standard method of identifying COVID-19 infection. To meet the definition of AGEP or GPFE, typical clinical features of the disease or atypical clinical features with typical histopathologic features were required. GPFE and AGEP both present with pustules within the subcorneal, intraepidermal, and/or intracorneal neutrophilic pustules. Epidermis acanthosis and mild spongiosis at the margins of the pustule may be visible, with mild papillary dermal edema and extravasation of erythrocytes plus a mild perivascular lymphocytic infiltrated with occasional neutrophils (12,34).

A time frame between the drug initiation and AGEP development was not chosen, as there was a frequently reported possibility of prolonged lag time in cases of HCQ-induced AGEP, most or all of which are probably best classified as GPFE (11). Nevertheless, studies were excluded if the COVID-19 infection was suggested only by clinical symptoms, the histopathologic features were non-conclusive, or if the reaction developed secondary to HCQ usage for non-COVID-19 clinical purposes.

Data extraction and quality assessment

Data were extracted by one reviewer and cross-checked by another. We extracted data on the possible co-triggers of AGEP, socio-demographic data of the patients, past drug and medical history, COVID-19 clinical course and treatments used, time lag of AGEP following HCQ use, and end sequela of the patients' conditions.

We used the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports (last amended in 2017) (30) for the quality assessment. The assess-

Table 2.

Studies	Gender	Age	Comorbidities	Past drug history	COVID-19 clinical course	Medications used to treat COVID-19	Past history of psoriasis	Time lag of the AGEP (days)	Sequalae of AGEP
Abadas *et al.* ([34])	Male	64	large B cell lymphoma	Chemotherapy	unclear	hydroxychloroquine, lopinavir/ritonavir and teicoplanin	unclear	21	resolved with systemic treatment
Abadas *et al.* (34)	Female	60	Rheumatoid arthritis	etanercept and low dose prednisone	unclear	hydroxychloroquine, lopinavir/ritonavir, teicoplanin and azithromycin	unclear	21	resolved with systemic treatment
Alzahrani *et al* (35)	male	34	none	None	moderate course required admission in the ward	azithromycin, oseltamivir, ribavirin, lopinavir, hydroxychloroquine, prednisolone, ceftriaxone, clindamycin, interferon (IFN) beta and ceftazidime	no	21	unclear (author is contacted: resolved with systemic treatment)
Dadras *et al,* (36)	Male	60	HTN, osteopenia, subacute thyroiditis	unclear	moderate course required admission in the ward	naproxen, hydroxychloroquine, Meropenem, linezolid, vitamin D3, heparin, and intravenous pulse methylprednisolone	yes	14	resolved with systemic treatment
Delaleu *et al.* (37)	Male	76	diabetes mellitus	unclear	severe course required admission in the ICU	HCQ, azithromycin and ceftriaxone	unclear	10	death
Enos *et al.* (38)	female	29	protein S deficiency + past SJS 2 to cefaclor	unclear	mild course, managed at home	azithromycin, doxycycline, prednisone and HCQ	unclear	4	resolved with systemic treatment
Haraszti *et al.* (39)	Male	78	prostatic hyperplasia, coronary artery disease, and atrial fibrillation	unclear	mild course, managed at home	Cefepime for pseudomonas UTI	unclear	7	resolved with topical treatment
Litaiem *et al.* (40)	Female	39	unclear	unclear	moderate course required admission in the ward	HCQ	unclear	18	death
Punyaratabandhu *et al.* (41)	Male	48	unclear	unclear	mild course, managed at home	HCQ, lopinavir/ritonavir	unclear	9	resolved with systemic treatment
Robustelli *et al.* (42)	female	70	unclear	No	mild course, managed at home	HCQ, lopinavir	no	21	resolved with systemic treatment
Suarez-Valle *et al.* (43)	Female	75	unclear	unclear	moderate course required admission in the ward	HCQ	unclear	21	resolved with systemic treatment
Torres-Navarro *et al.* (44)	Female	49	morbid obesity	unclear	severe course required admission in the ICU	interferon beta, hydroxychloroquine; azithromycin, ceftriaxone, lopinavir-ritonavir, methylprednisolone and tocilizumab	unclear	30	resolved with systemic treatment
Herrero-Moyano et al. (45)	Female	69	unclear	unclear	severe course required admission in the ICU	HCQ, lopinavir, ceftriaxone	unclear	33	unclear
Ayatollahi et al. (46)	Male	33	none	None	mild course, managed at home	azithromycin	no	90	unclear

ment was carried out by one investigator and cross-checked by another. The items checked for quality assessment were:

1. The patient and their clinical condition were adequately described.
2. Convincing evidence of diagnosis or assessment methods.
3. The implemented interventions were clearly described.
4. Post-intervention outcomes were adequately discussed.

Items ratings were: yes, no, unclear, seek further information from the author. One case report did not adequately fulfill our inclusion items, but contacting the author provided additional information (35).

Data synthesis and analysis

Data were summarized in an excel sheet, and tables and graphs were generated. Descriptive statistics were summarized with percentages and frequencies for analyzing the dichotomous variables and with means and standard deviations for continuous variables.

RESULTS

Publication characteristics

A total of 279 citations were retrieved (study flow chart). We identified 20 relevant citations which were subsequently reviewed. We excluded 6 publications reporting cases not fulfilling the inclusion criteria and one publication from which raw data were not retrievable. We included 13 publications for final qualitative synthesis. Cases from Spain were most common (30.7%), followed by the USA (15.3%), and Iran (15.3%).

Quality appraisal

The overall quality of the reports was good to moderate. A majority of the articles reported an adequate description of the current and past patient medical history (92.8%). Accurate descriptions of convincing evidence of diagnosis was reported in 85.7% of the cases, while the descriptions of the interventions undertaken after final diagnosis and the sequalae of the disease were provided in 78.5% of the cases.

Patients characteristics

The mean age of the patients was 54 years (standard deviation: 16.6 years); 53.8% of them were women. Patients were categorized into 3 major groups based on the clinical course of COVID-19 disease. Group 1 included 36.36% of the patients with a mild clinical course who required treatment at home. Group 2 included 36.36% of the patients with a moderate clinical course requiring admission to the general ward. Finally, Group 3 included 27.3% of the patients with severe clinical course who required ICU admission and invasive respiratory support (Figure 1).

GPFE co-triggers

In terms of triggering the described events, triggers were classified into three categories (Figure 2). Category 1 included COVID-19 as a possible trigger of the reaction with HCQ plus other medications (including beta lactam antibiotics, lopinavir/ritonavir, and azithromycin) as co-triggers. Category 2 included COVID-19 as a possible trigger plus HCQ alone as a possible co-trigger. Category 3 included COVID-19 as a possible trigger plus azithromycin alone as a possible co-trigger. Category 1 represented the majority of the patients, wherein 69.23% of the patients with COVID-19 received more than one suspected medication. Category 2 was the second most common, with 23.08% of the patients with COVID-19 receiving HCQ as the only possible trigger. Only 7.69% of the cases received azithromycin as a sole co-trigger. One patient was treated empirically with HCQ for presumed COVID-19 infection following contact with a known case; however, PCR testing was negative (38). Watson *et al.* (31) reported that if the pre-test probability of COVID-19 is high, anyone with negative test result may have a 74% chance of having the infection, so we decided to include the case in the data synthesis. Another patient was treated with cefepime for pseudomonal urinary tract infection, after which developed AGEP along with a new asymptomatic pulmonary infiltrate (39). He was incidentally found to be COVID-19 positive. HCQ was not used in the treatment of his COVID-19 infection, so we excluded the case from the data analysis.

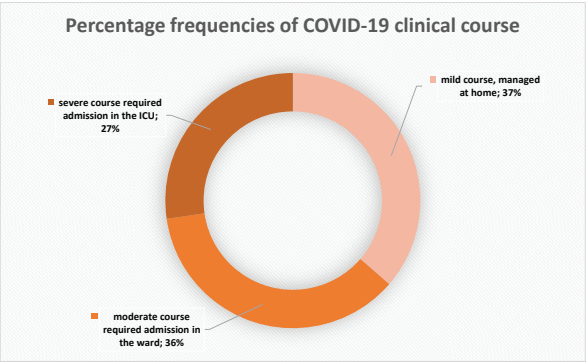

Figure 1. Percentage frequencies of COVID-19 clinical course.

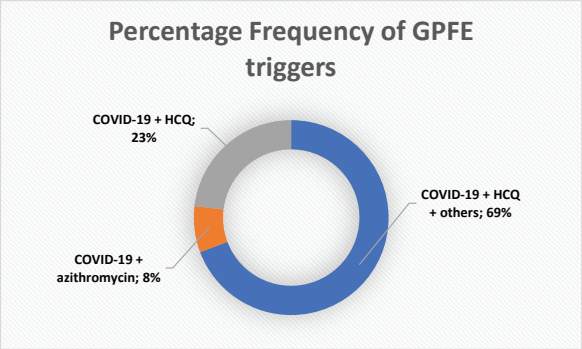

Figure 2. Percentage frequencies of GPFE triggers.

Clinical features

The mean lag time period between trigger exposure and rash development was 24 days (standard deviation, 21.36 days). Only 15.38% of the reported AGEP clinical courses were typical, and 69.23 % of the cases showed features more suggestive of GPFE. The classic pustular lesions over an erythematous edematous base were described in the reported cases; fever was reported by 38.46% of the cases; involvement of the head and neck with facial edema was described in 84.62% of the cases, and intense pruritus was reported in 53.85%. The atypical features of purpuric and targetoid lesions were only observed in 23.0% of the cases. 76.9% of the cases had well-described histopathologic findings.

The most commonly reported treatment was a systemic steroid, with 81.8% of the cases observed to have slow resolution following such therapy along with termination of the offending medication. Unfortunately, 2 patients (18.18% of the reported sequalae) died secondary to a massive pulmonary embolism. One of the reported deaths was an elderly man who exhibited a severe COVID-19 course before the eruption began, while the other was a young woman with a moderate COVID-19 clinical course (Figure 3).

DISCUSSION

GPFE is an HCQ-induced pustular reaction clearly delineated as a unique reaction, sometimes overlapping in features with pustular psoriasis (PP), AGEP, and SJS. Behrangi *et al.* (32) retrospectively studied 20 patients with this HCQ-induced pustular reaction. Approximately 75% of these patients were biopsied more than once because their clinical and histopathologic features were not completely compatible with AGEP or PP, and GPFE had not yet been established.

In parallel to our findings, Behrangi *et al.* (32) reported a mean time interval between drug intake and reaction development of 3 weeks. 55% of their patients exhibited a prolonged course with frequent relapses during the treatment course and afterwards, possibly acting as one might anticipate with PP. GPFE has been similarly described as a pustular reaction with longer time interval between drug initiation and reaction development along with a more prolonged course of the disease. It may have clinical findings overlapping with serious cutaneous drug reactions including DRESS and SJS, with prominent facial erythema edema along with atypical targetoid, and with arcuate lesions.

Additionally, Pezzarossa *et al.* (33), in their retrospective review of the HCQ-induced eruptions in patients with COVID-19, reported prominent facial edema and atypical targetoid lesions. The reported cases in our review parallel those of Pezzarossa *et al.* (33), with distinctive clinical features, a 1-3 week interval between the drug intake, reaction development, and having a more prolonged course with a slow response to systemic treatments.

Bi-allelic mutation in the gene encoding IL36 was identified as the susceptibility locus for pustular psoriasis, while HLA-B51, DR11, and DQ3 alleles were identified as susceptibility loci for AGEP. Specifically, alleles HLA-B51, HLA-B15, HLA-DR1101,04, and HLA-DQ03,05 were identified in a case of HCQ-induced GPFE reported as AGEP (47).

The COVID-19 cytokine storm appears to be related to an IL17/23 proposed inflammatory axis, which may affect neutrophil function (9,48-51). IL-17A immunohistology staining was highly expressed in the inflammatory infiltrate of a HCQ-induced GPFE reported as AGEP, which was resistant to systemic steroid treatment, but successfully treated with the anti-IL-17 monoclonal antibody ixekizumab (51). In addition, similar to generalized pustular psoriasis, another case of HCQ-induced GPFE resistant to systemic steroid was successfully treated with etretinate (52), highlighting the possible IL17/23 axis role in this eruption. Thus, a possible augmenting effect of the COVID-19 cytokine storm and HCQ-induced GPFE may play crucial role in the increasingly reported

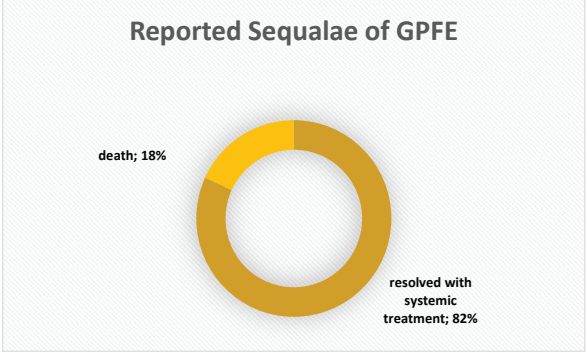

Figure 3. Reported sequalae of GPFE.

GPFE often reported as AGEP following the era of HCQ treatment for COVID-19 infection.

Mortality can be significant with serious drug eruptions, sometimes higher than the estimated COVID-19 mortality rate (1,2,8), and thrombo-embolic events remain the major cause of mortality in both diseases (8,53). In parallel with the previous findings, our review found 2 fatalities (37,40) secondary to massive pulmonary emboli, which cannot be conclusively attributed to either cause. Collectively, coagulopathy may be the result of an augmenting effect of COVID-19 infection with severe HCQ-induced GPFE.

CONCLUSION

In conclusion, GPFE is a severe cutaneous drug reaction linked to HCQ that may parallel the pathogenesis of the COVID-19 cytokine storm. Although GPFE is rarely linked to non-HCQ co-triggering factors, the consistent factor in our study, i.e., COVID-19, supports the claim of the augmenting effect of COVID-19 and HCQ cytokine storms on the development of GPFE. GPFE is a recognizable entity owing to its distinctive morphology, time to onset in weeks rather than hours, and tendency for a prolonged recalcitrant clinical course. In terms of COVID-19 infection, we suggest reconsidering treating established COVID-19 infection empirically with HCQ, as both of the triggers can augment the subsequent cytokine storm, inducing a severe drug reaction and possibly increasing the risk of a thrombo-embolic event. Patch testing, whenever is possible, is a useful tool for diagnoses when the clinical picture is non-conclusive, and early termination of the offending medication is a critical point of patient management in such cases (9).

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