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REVIEW ARTICLE

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A systematic review on treatment-related mucocutaneous reactions in COVID-19 patients

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Abstract

Most of drugs could have certain mucocutaneous reactions and COVID-19 drugs are not an exception that we focused. We systematically reviewed databases until August 15, 2020 and among initial 851 articles, 30 articles entered this study (20 case reports, 4 cohorts, and 6 controlled clinical trials). The types of reactions included AGEP, morbiliform drug eruptions, vasculitis, DRESS syndrome, urticarial vasculitis, and so on. The treatments have been used before side effects occur, included: antimalarial, anti-viral, antibiotics, tocilizumab, enoxaparin and and so on. In pandemic, we found 0.004% to 4.15% of definite drug-induced mucocutaneous reactions. The interval between drug usage and the eruption varied about few hours to 1 month; tightly dependent to the type of drug and hydroxychloroqine seems to be the drug with highest mean interval. Antivirals, antimalarials, azithromycin, and tocilizumab are most responsive drugs for adverse drug reactions, but antivirals especially in combination with antimalarial drugs are in the first step. Types of skin reactions are usually morbilliform/exanthematous maculopapular rashes or urticarial eruptions, which mostly may manage by steroids during few days. In the setting of HCQ, specific reactions like AGEP should be considered. Lopinavir/ritonavir is the most prevalent used drug among antivirals with the highest skin adverse reaction; ribarivin and remdisivir also could induce cutaneous drug reactions but favipiravir has no or less adverse effects. Logically the rate of dermatologic adverse effects among anivirals may relate to their frequency of usage. Rarely, potentially life-threatening reactions may occur. Better management strategies could achieve by knowing more about drug-induced mucocutaneous presentations of COVID-19.

KEYWORDS

adverse drug reaction, antibiotic, antimalarial, antiviral, azithromycin, biologic, corona virus, COVID-19, covid-19 therapies, covid-19 treatments, cutaneous, dermatology, drug eruption, drug induced, drug reaction, enoxaparin, hydroxychloroquine, JAK inhibitor, Janus kinase

Abbreviations: AGEP, acute generalized exanthematous pustulosis; CEBD, Centre of Evidence Based Dermatology; COVID-19, 'CO' stands for corona, 'VI' for virus, 'D' for disease, and '19' for 2019; CXR, chest x ray; DRESS, drug reaction with eosinophilia and systemic symptoms syndrome; EM, Erythema Multiform; HCQ, hydroxychloroquine; HCQ, hydroxychloroqine; IVIG, Intravenous immunoglobulin; JAK, Janus Kinase; PG, Pyogenic Granuloma; PR, Pityriasis Rosea; SJS, Stevens-Johnson-Syndrome; TEN, toxic epidermal necrolysis.

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inhibitor, mucocutaneous, mucosal, novel human coronavirus (SARS-CoV-2), skin, systematic review, targeted therapy, TNF-α inhibitor, tocilizumab, treatment-induced, treatment-reaction, treatment-related

1 | INTRODUCTION

1.1 | Rationale

Although COVID-19 does not have any targeted specific therapies for virus itself, but there are many proposed drug categories for using in this pandemic, each one affects on one or more well-known pathomechanisms of viral infection or infection-induce consequences. The most important drug categories for new coronavirus are: Antimalarials (Chloroquine, hydroxychloroquine), Azithromycin, Antivirals (Remdesivir, Oseltamivir/Favipiravir/Umifenovir, Ribavirin, Lopinavir/Ritonavir, sofosbuvir, nitazoxanide), biologic or chemical targeted therapies (janus kinase inhibitors, TNF-a inhibitors, Tocilizumab, Anakinra, Checkpoints inhibitors, Camostat mesylate), Classic Immunomodulators (Colchicine, Interferons, Corticosteroids, IVIG) and the Vaccines. Among these drugs, some affect virus itself, some affect virus-associated cytokine storm, immune dysregulation and organ failures and some (eg, Azithromycin) other than their anti-inflammatory characteristics, may positively affect on concomitant complications like possible bacterial infection.[1]

Naturally, every drug or drug category has its own adverse effects including mucocutaneous drug reactions that some of them are more prevalent, popular or serious. Dermatologist should aware of these drug-related mucocutaneous reactions for better approach to the COVID-19 affected patients during pandemic especially in the case of counseling cases.

1.2 | Objective

There are few reports about treatment-related mucocutaneous drug reactions of COVID-19, but since this infection is a pandemic concern with an increasing infection rate at many areas of the world, it is expected to encounter growing reports of drug-related adverse mucocutaneous reactions, such as, HCQ-induced AGEP or flare and aggravation of psoriasis course.[2,3] In overall, different types of drug categories, which may use for treatment of new corona virus with their own well-known dermatologic reactions also patients who are in a certain condition results from the virus and host interaction-induced immune-dysregulation and cytokine storm may provide higher tendency to emergence of well-known, new, severe and more complex mucocutaneous drug reactions or even aggravation and flare of a pre-existing dermatoses. So, in this systematic review, we focused on the treatment-related mucocutaneous drug reactions of COVID-19, to discuss on the clinical presentation types, differential diagnoses, severity, course, definite diagnosis and the managements or probable challenges.

2 | MATERIALS AND METHODS

2.1 | Protocol and registration

This study is implemented according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. The PRISMA flow chart has been shown in Figure S1 in the supplement file.

2.2 | Eligibility criteria

Inclusion criteria comprised all studies that report mucocutaneous drug reaction or skin and dermatologic manifestation in response to treatment of COVID-19 patients. PICO: population was COVID-19 patients, intervention was COVID-19 treatment, comparison was COVID-19 patients without taking any special treatment and outcome was mucocutaneous manifestations. The exclusion criteria consisted of animal studies, in vitro studies, review studies and all publications not meeting the above.

2.3 | Information sources

Databases PubMed (http:// pubmed.ncbi.nlm.nih.gov), Scopus (http://www.scopus.com), Embase (https://www.embase.com) and Google Scholar (https://scholar.google.com) and CEBD Covid-19 Resource for Dermatology (https://skin.cochrane.org/news/cebd-covid-19-resource-dermatology) have been searched for the evidence.

2.4 | Search strategy

The search was performed by keywords COVID-19, corona viruses, COVID-19 symptoms, novel corona virus, corona virus pneumonia, corona virus disease, severe acute respiratory syndrome corona virus 2 and skin manifestations, drug reaction, adverse drug eruption, adverse drug reaction. Search was not limited to the entries to any condition. The search started and completed on August 15, 2020. The period of search was any articles published until August 15, 2020. The search strategy has been shown in Table S1.

2.5 | Study selection

Endnote X9 (Clarivate Analytics, Philadelphia) was used for study screening and data extraction. 851 articles assigned to the inclusion

and exclusion groups. In first step, the titles and abstracts of articles were read. And, if accepted has evaluated to second step; 186 articles went to the full-text screening; the authors read the full-text and executed the final inclusion articles. Disagreement situations regarding the inclusion process resolved through dialogue and no necessity for a third-party involvement occurred.

3 | RESULT

3.1 | Study selection

Finally, there were 30 articles that met inclusion criteria and the information of these articles are prepared in Tables 1-4.

3.2 | Study characteristics

We have evaluated 20 case reports including 25 cases of COVID-19 who were treated with multiple drugs in Table 1.[4-23] In Tables 2, 4 cohort studies are shown. In cohort studies based on the drugs have been used the overall rate of mucocutaneous dermatologic eruptions ranged from 0.004% to 4.15%. Antivirals, antimalarials, azithromycin, and tocilizumab were most responsive drugs for adverse reactions. It seems that antivirals especially in combination with antimalarial drugs may have the highest rate of skin reactions. Types of skin reactions are usually morbilliform/exanthematous maculopapular rashes or urticarial eruptions. Pruritus, bullous rashes and skin dyspigmentations were other observed dermatologic adverse effects of drugs used for management of COVID-19.[24-28]

Table 5 shows cohort studies reported dermatologic rashes in the setting of COVID-19 but with uncertainty about exact origin; means that exactly say about they were virus-related or drug-related.[28] The reported mucocutaneous reaction rate in these series of studies was about 5.7% to 45.5%, and the drugs were suspected as the cause of these drug reactions were mainly antimalarials, antivirals, azithromycin, systemic steroids, and tocilizumab with different prevalence distributions in various studies. Antimalarials, antivirals, azithromycin were the most prevalent drugs used for therapy and morbilliform/exanthematous maculopapular, purpuric, EM-like and PR-like eruptions were the most observed mucocutaneous reactions of these drugs.[28]

In Tables 3 and 4 controlled clinical trial studies have been shown which were 5 articles with 2 arms [29-33]and 1 article with 3 arms.[34] It seems that favipiravir has no or less skin adverse reactions in comparison with lopinavir/ritonavir. Remdisivir could induce mucocutaneous rash but the most probable cause of skin reactions between antivirals is related to lopinavir/ritonavir (21%). Ruxolitinib is another drug may cause mucocutaneous reactions (10%). Interferon-alfa my decrease rate of dermatologic reactions of antivirals such as ribavirin or lopinavir/ritonavir based on what we observed in combination therapy regimens. Logically it should be notified that the rate of dermatologic adverse effects among anivirals may relate to their frequency of usage and since lopinavir/ritonavir at the time of data gathering of this systematic review was the most prevalent used antiviral; so it is not unexpected to see the most dermatologic reactions among antivirals by this drug.

3.3 | Result of individual studies

In the antimalarials group; Acute generalized exanthematous pustulosis (AGEP), flares and exacerbations of psoriasis, urticaria, exanthematous rash, pruritus, dry skin, exfoliations, Stevens-Johnson-like syndrome, alopecia and hair whitening and mucocutaneous dyspigmentation, In the Antivirals group; Maculopapular or eczematous rash, exfoliative erythroderma, urticaria, angioedema, allergic or idiosyncratic cutaneous drug reactions, annular erythema and photosensitivity, skin dryness, pruritus and redness, SJS, 10 injection site reactions, localized scleroderma, lichenoid drug eruption, bite hypersensitivity, lipodystrophy, nail, oral, mucosa and skin hyperpigmentation, Hair loss and alopecia, paronychia and acneiform eruptions were the known reported dermatologic side effects. In biologic or chemical targeted therapies group; morbilliform or eczematous rash, urticaria, angioedema, photosensitivity, skin hypersensitivity reactions, exfoliations, psoriasis and psoriasiform-like lesions, palmoplantar pustulosis-like eruption, lupus-like syndromes, cutaneous vasculitis, lichenoid eruptions, pruritus, xerosis, injection or infusion-site reactions, alopecia, stomatitis, hyperhidrosis, vitiligo, hair color changes, impaired wound healing, periungual pyogenic granuloma-like lesions, various granulomatous reactions (sarcoidosis-like reactions, granulomatous panniculitis, granuloma annulare and granulomatous dermatitis…), skin infections (eg, infection of wounds, cellulitis, herpes zoster and herpes simplex activations…), melanoma and nonmelanoma skin cancers and cutaneous lymphoma, have been reported. In Classic Immunomodulators group; Anaphylactic reaction, diffuse, blanchable, violaceous, morbilliform rash, urticaria, maculopapular rash, eczematous drug reactions, psoriasis, lichenoid drug reactions, erythema multiforme, toxic epidermal necrolysis-like reaction, erythema-bullous and erythema-nodosum-like lesions, sarcoidosis, lupus, cutaneous vasculitis lesions, petechiae, injection site reactions, alopecia and hirsutism, transient and mild to moderate pruritus, dryness, burning, stinging, erythema, oedema, fissures, folliculitis, acneiform eruptions, papular and pustular lesions, skin atrophy, striae, telangiectasia and disease exacerbation, could be seen. Azithromycin may cause cutaneous severe skin reaction associated fever, angioedema, anaphylaxis, DRESS syndrome, generalized red or purple skin rash, blistering, skin peeling, fixed drug eruptions, toxic pustuloderma, eye burning, skin pain and cutaneous leukocytoclastic vasculitis.[1,35-39]

AGEP was reported in three patients with hydroxychloroquine treatment on average 10 days after taking the drug, in one patient with Lopinavir/Ritonavir treatment and one patient with cefditoren treatment. we should consideration that Pustular Psoriasis (PP) and acute generalized exanthematous pustulosis (AGEP) are clinically resemble each other. So, in patients specially with psoriasis history

TABLE 1 Case reports studies

First author	title	Case characteristic	COVID-19 sign and symptoms	Patients comorbidity	Type of drug	Time of onset the reactions	Type of reactions	Skin biopsy	Managements of reactions	Time of the reaction resolution (week after management initiated)
A.Sernicola	"Toxic erythema" and eosinophilia associated to tocilizumab therapy in a COVID-19 patient	70-year-old man	dry cough, rising fever (38,4°C), asthenia and dyspnea	Not reported	lopinavir/ritonavir, hydroxychloroquine (200 mg twice daily), intravenous tocilizumab 600 mg	Few hours after the administration of tocilizumab	itching generalized cutaneous "toxic erythema-like" rash with eosinophilia, DRESS*	Not reported	Methylprednisolone 20 mg twice daily	2
E. Robustelli Test	Acute Generalized Exanthematous Pustulosis with Erythema Multiform-Like lesions in a COVID-19 woman.	70-year-old woman	pneumonia	Not reported	Lopinavir/Ritonavir (200/50 mg 2 tablets), HCQ (200 mg bid for 10 days)	Three days after the withdrawal of the treatment	Diffuse, pruritic pustular eruption, erythematous-edematous base, with scattered pinhead-sized pustules and scales, involving the face, trunk and upper limbs. Targetoid lesions studded with small pustules were present in a symmetric pattern over buttocks, thighs and legs. Mucous membranes, palms and soles were spared	sub corneal pustule with mild focal acanthosis and spongiosis, neutrophilic exocytosis, sparse keratinocyte necrosis, and a perivascular lymphocytic infiltrate with rare neutrophils and eosinophils consistent with AGEP	Oral prednisone 0.3 mg/Kg daily. Gradually taper prednisone within 30 days	Not reported
N. LITAIEM	Acute generalized exanthematous pustulosis after COVID-19 treatment with hydroxychloroquine	39-year-old woman	dry cough , dyspnea, and fever	Not reported	HCQ (600 mg daily), enoxaparin	Eighteen days after HCQ initiation	pruritic cephalocaudal spread of erythematous and pustular plaques	AGEP	Withdrawal of HCQ	Patient expired due to massive pulmonary emboli
N. Skroza	A late onset widespread skin rash in a previous Covid-19 infected patient: viral or multidrug effect?	47-year-old man	Syncope and pulmonary ground-glass opacifications in CT	Hypertension, impair glucose tolerance	Ceftriaxone, Lopinavir/ Ritonavir, Hydroxychloroquine, Enoxaparin	Four days after administration	multiple, raised erythematous wheals, alone or in cluster, some of them with central purple hyperpigmentation, predominantly localized on head, trunk and upper arms	Orthokeratotic hyperkeratosis, spongiosis, focal vacuolar degeneration of basal keratinocytes and focal lymphocytic exocytosis. Slight inflammatory lymphomorphonuclear infiltrate of superficial dermis with minimal perivascular neutrophilic component was observed, with	tapering Prednisone, Bilastine and Pantoprazole	1

TABLE 1 (Continued)

First author	title	Case characteristic	COVID-19 sign and symptoms	Patients comorbidity	Type of drug	Time of onset the reactions	Type of reactions	Skin biopsy	Managements of reactions	Time of the reaction resolution (week after management initiated)
								occasional aspects of vessel wall damage, compatible with drug reaction/ Urticarial Vasculitis		
Vanegas Ramirez, A.	Drug-induced vasculitis in a patient with COVID-19	57-year-old woman	nonproductive cough and intermittent fever	Not reported	intravenous bolus of prednisolone as well as antihistamines and topical glucocorticoids, amoxicillin, ibuprofen and metamizole	2-day history of symmetrically distributed pruritic pink -red maculopapular exanthema on the trunk and extremities	vasculitis	vasculitis	120 mg of prednisolone per day	2
JérémieDelaleu	Acute generalized exanthematous pustulosis induced by hydroxychloroquine prescribed for COVID-19	76-year-old man	First week: Cough and diarrhea, bilateral, patchy, ground glass involvement CT, Second week: Asthenia, dyspnea, fever, Positive COVI-19 PCR	diabetes mellitus	Hydroxychloroquine (200 mg orally 3 times daily)	9 days after hydroxychloroquine initiation	pustular rash with background of edematous erythema / intertriginous areas (intergluteal, axillary, and inguinal),AGEP	spongiform subcorneal and intracorneal neutrophilic pustules, rare keratinocyte necrosis, acanthosis, dermal inflammatory infiltrate of neutrophils with perivascular accentuation	Withdrawal of the HCQ	2
Valeria Gaspari	Side effects of ruxolitinib in patients with SARS-CoV-2 infection: Two case reports	74-year-old man	cough and fever acute confusional state and severe dyspnea, Positive COVID PCR	not reported	Tocilizumab (162 mg subcutaneous injections two times weekly, then 5 mg twice a day for 2 days and then 5 mg four times a day for 3 days then tapered)	5 days after tapering tocilizumab	purpuric lesions on dorsal and upper limbs,	Not reported	Ruxolitinib was stopped steroids and antibiotics was adminestered	Not reported
Valeria Gaspari	Side effects of ruxolitinib in patients with SARS-CoV-2 infection: Two case reports	63-year-old woman	fever and mild dyspnea, positive COVID 19 PCR.	hypothyroidism	Ruxolitinib (Day 1–3:5 mg orally twice daily, then double)	7 days after administration	erythrodermic rash on whole body surface	Not reported	Ruxolitinib was stopped, steroid therapy was administered for 5 days.	Not reported
Tobias Janowitz	Famotidine use and quantitative symptom tracking for COVID-19 in non-hospitalized patients: a case series	20-year-old woman	Dyspnea headache, fatigue, and anosmia, general unwellness,body ache, Sinusitis, congested nose.	obesity	Famotidine (80 mg three times daily for 12 days)	One week after treatment	dry skin	Not reported	nothing	Not reported
I. Abadías-Granado	Generalized Pustular Figurate Erythema. First Report in Two	64-year-old-man	positive COVID 19 PCR.	diffuse large B-cell lymphoma	Hydroxychloroquine (Day 1:400 mg twice a day, Day 2-10:200 mg	Two to three weeks after starting medications	pruritic purpuric erythematous rash with non-follicular	intracorneal, subcornea and intraepidermal pustules, acanthosis	0.05% betamethasone cream (twice a day) loratadine (10 mg	4

(Continues)

TABLE 1 (Continued)

First author	title	Case characteristic	COVID-19 sign and symptoms	Patients comorbidity	Type of drug	Time of onset the reactions	Type of reactions	Skin biopsy	Managements of reactions	Time of the reaction resolution (week after management initiated)
	COVID-19 Patients on Hydroxychloroquine				*twice a day), lopinavir/ ritonavir (200 mg/50 mg twice a day) and teicoplanin*		*pustules/ trunk and limbs and armpits and scalp, with negative Nikolsky's sign*	*and parakeratosis epidermis, spongiosis at the periphery of the intraepidermal pustules. Erythrocyte extravasation and mild edema in upper dermis, lymphocytes and neutrophils and rare eosinophils perivascular infiltrated with dilated capillaries.*	*once daily) and methylprednisolone (40 mg once daily)*	
I. Abadías-Granado	*Generalized Pustular Figurate Erythema. First Report in Two COVID-19 Patients on Hydroxychloroquine*	*60-year-old woman*	*positive COVID 19 PCR.*	*Rheumatoid arthritis*	*Hydroxychloroquine (Day 1:400 mg twice a day, Day 2–10:200 mg twice a day), lopinavir/ ritonavir (200 mg/50 mg twice a day) and teicoplanin and azithromycin*	*Two to three weeks after starting medications*	*pruritic purpuric erythematous rash with non-follicular pustules/ neck and face and targetoid lesions on the back, with negative Nikolsky's sign*	*intracorneal,subcornea and intraepidermal pustules.acanthosis and parakeratosis epidermis, spongiosis at the periphery of the intraepidermal pustules. Erythrocyte extravasation and mild edema in upper dermis, lymphocytes and neutrophils and rare eosinophils perivascular infiltrated with dilated capillaries.*	*0.05% betamethasone cream (twice a day) loratadine (10 mg once daily) and methylprednisolone (40 mg once daily)*	*4*
Juan monte serrano	*Hydroxychloroquine-induced erythema multiforme in a patient with COVID-19*	*55-year-old woman*	*Respiratory symptoms, CT: bilateral interstitial pneumonia, positive COVID 19 PCR.*	*Not reported*	*hydroxychloroquine*	*12 days after HCQ initiation*	*pruritic skin rash with erythematous targetoid macules on trunk and upper limbs*	*eosinophil infiltration and interface dermatitis*	*withdrawal of the HCQ*	*Not reported*
Pablo chicharro	*SDRIFE-like rash associated with COVID-19, clinicopathological correlation.*	*73-year-old woman*	*severe hypoxemia, fever, cxr: bilateral pneumonia, positive COVID 19 PCR.*	*Not reported*	*Hydroxychloroquine, azithromycin*	*2 days after HCQ initiation*	*erythematous rash on both axillae and antecubital fossae and antecubital fossae, trunk and the inner thighs*	*infiltrates of lymphocytes and eosinophils and subcorneal pustules*	*withdrawal of the HCQ and azithromycin and systemic steroids, and broad-spectrum antibiotic*	*1*
Hayakawa J	*COVID-19-related cutaneous manifestations associated with multiple drug*	*44-year-old man*	*Fever, Fatigue, headache, CT: bilateral ground-glass opacification, positive COVID 19 PCR.*	*No comorbidity*	*loxoprofen sodium hydrate, acetaminophen, favipiravir*	*6 days after administration medications*	*erythematous macules and petechiae on both legs (knee, flexural thigh and popliteal fossae)*	*Not reported*	*withdrawal of the Loxoprofen*	*1*

TABLE 1 (Continued)

First author	title	Case characteristic	COVID-19 sign and symptoms	Patients comorbidity	Type of drug	Time of onset the reactions	Type of reactions	Skin biopsy	Managements of reactions	Time of the reaction resolution (week after management initiated)
	sensitization as shown by lymphocyte transformation test.									
Mazan P,	*Maculopapular rash in COVID-19 patient treated with lopinavir/ritonavir*	*35-year-old man*	*optic neuritis, positive COVID 19 PCR*	*No comorbidity*	*lopinavir/ritonavir (400/100 mg orally twice a day), methylprednisolone (16 mg)*	*10 days after lopinavir/ritonavir administration*	*itchy, non-tender erythematous maculopapular rash/ bilateral and symmetrical on neck, trunk and upper extremities*	*Not reported*	*increase the dose of systemic corticosteroids topical corticosteroid and oral antihistamines*	*2*
Herman A	*Drug reaction with eosinophilia and systemic symptoms syndrome in a patient with COVID-19.*	*50-year-old man*	*acute respiratory distress syndrome and fever, positive COVID-19 positive IgM and IgG antibodies against SARS-CoV-2*	*Not reported*	*Azithromycin, hydroxychloroquine*	*18 days after azithromycin and 17 days after hydroxychloroquine administration*	*generalized maculopapular rash and edema on more than 70% of body surface area and hands and face edema*	*dermis edema and lymph histiocytic cells and eosinophils perivascular infiltration*	*withdrawal of the medications and methylprednisolone intravenous 1 mg/kg daily*	*3*
Jimenez AC	*First case of DRESS syndrome caused by hydroxychloroquine with a positive patch test.*	*37-year-old woman*	*Fever, bilateral pneumonia suspected COVID-19*	*Not reported*	*Hydroxychloroquine (Day 1-5:200 mg twice daily)*	*2–3 weeks after hydroxychloroquine administration*	*Maculopapular, purpuric and itchy rash on trunk and limbs (not palms and soles), facial edema, periorbital angioedema, oral mucosa Exanthema and Bilateral cervical lymphadenopathy*	*Not reported*	*Not reported*	*Not reported*
Davoodi L	*Hydroxychloroquine-induced Stevens-Johnson syndrome in COVID-19: a rare case report*	*42-year-old woman*	*Fever, dry cough, CT: patchy ground-glass involvement, positive COVID 19 PCR*	*No comorbidity*	*Hydroxychloroquine (200 mg twice daily)*	*2 days after hydroxychloroquine administration*	*pruritic erythematous maculopapular rash and flat atypical targets and oral blisters, entire body, orolabial blisters, mucosal involvement, with positive Nikolsky's sign*	*Not reported*	*Hydroxychloroquine was changed to lopinavir/ritonavir (400 mg twice daily), Loratadine (10 mg twice daily), Diphenhydramine (50 mg three times daily)*	*1*
Demirbaş A	*A case of erythema multiforme major in a patient with COVID 19: The role of corticosteroid treatment.*	*37-year-old-woman*	*confirmed COVID-19 pneumonia*	*No comorbidity*	*Hydroxychloroquine (Day 1:400 mg orally twice a day, Day 2-4:200 mg orally twice a day), azithromycin (Day 1:500 mg orally once a day, Day*	*5 days after COVID-19 treatment*	*erythematous targetoid lesions / both side of the hands and elbows lip, tongue, and palate ulceration*	*was not performed*	*withdrawal of the medications, methylprednisolone 40 mg orally once a day and then tapered), Topical anesthetic and antiseptic for mouth washing*	*1*

(Continues)

TABLE 1 (Continued)

First author	title	Case characteristic	COVID-19 sign and symptoms	Patients comorbidity	Type of drug	Time of onset the reactions	Type of reactions	Skin biopsy	Managements of reactions	Time of the reaction resolution (week after management initiated)
					2-4:250 mg orally once a day), oseltamivir (Day 1-5:75 mg orally once a day)					
Sardana K,	Cutaneous side effects of hydroxychloroquine in health care workers in a COVID referral hospital - implications for clinical practice.	26-years-old woman	nothing	Not reported	Hydroxychloroquine (Day 1:400 mg orally twice a day, Week 1-7:400 mg orally weekly)	2 days after hydroxychloroquine initiation	Urticaria and maculopapular rash, Palmoplantar Itching	Not reported	Cetirizine (Day 1-14:10 mg orally once daily) and doxepin (Day1-14:20 mg orally once every night), Methylprednisolone (Day1-7: orally 16 mg)	2
Sardana K,	Cutaneous side effects of hydroxychloroquine in health care workers in a COVID referral hospital - implications for clinical practice.	37-year-old woman	nothing	Not reported	Hydroxychloroquine (Day 1:400 mg orally twice a day, Week 1-7:400 mg orally weekly)	7 days after hydroxychloroquine initiation	Urticaria	Not reported	Cetirizine (Day 1-7:10 mg orally once daily) and doxepin (Day1-7:20 mg orally once every night)	1
Sardana K,	Cutaneous side effects of hydroxychloroquine in health care workers in a COVID referral hospital - implications for clinical practice.	22-year-old woman	nothing	Not reported	Hydroxychloroquine (Day 1:400 mg orally twice a day, Week 1–7:400 mg orally weekly)	7 days after hydroxychloroquine initiation	Palmplantar Itching	Not reported	Cetirizine (Day 1–14:10 mg orally once daily), doxepin (Day1-14:20 mg orally once every night)	2
Sardana K,	Cutaneous side effects of hydroxychloroquine in health care workers in a COVID referral hospital - implications for clinical practice.	26-year-old woman	nothing	Not reported	Hydroxychloroquine (Day 1:400 mg orally twice a day, Week 1–7:400 mg orally weekly)	1 month after hydroxychloroquine initiation	Urticaria	Not reported	Cetirizine (Day 1–7:10 mg orally once daily) and doxepin (Day1-14:20 mg orally once every night)	1
Enos T	Acute generalized exanthematous pustulosis induced by empiric hydroxychloroquine for presumed COVID-19.	29-year-old woman	fever, cough, and sore throat	Protein S deficiency and Stevens-Johnson syndrome with cefaclor	hydroxychloroquine (200 mg twice daily)	4 days after hydroxychloroquine initiation	Red-pink and Pruritic rash, erythematous macules and edematous papules and plaques on neck, trunk, face and extremities, facial swelling, non-follicular pustules on the abdomen and lateral neck, hyperemic oral mucosa,AGEP	subcorneal pustule with neutrophils and eosinophils	withdrawal of the hydroxychloroquine, methylprednisolone (500 mg intravenous single dose), topical triamcinolone 0.1%	5

TABLE 1 (Continued)

First author	title	Case characteristic	COVID-19 sign and symptoms	Patients comorbidity	Type of drug	Time of onset the reactions	Type of reactions	Skin biopsy	Managements of reactions	Time of the reaction resolution (week after management initiated)
Torres-Navarro I	*A case of cefditoren-induced Acute Generalized Exanthematous Pustulosis during COVID-19 pandemics. Severe Cutaneous Adverse Reactions (SCARs) are an issue.*	*49 -year -old -woman*	*Fever and severe respiratory failure, cxr: bilateral upper and middle lung opacities, positive COVID 19 PCR*	*morbid obesity*	*cefditoren (400 mg twice a day)*	*1 day after cefditoren initiation*	*red macular rash and small pustules on trunk, neck and neck folds, face, arms, and axillary,AGEP*	*superficial dermis and perivascular infiltrate of neutrophils and few eosinophils, papillary edema, subcorneal pustules*	*withdrawal of the cefditoren and methylprednisolone*	*Not reported*

that take hydroxychloroquine for covid-19 treatment, generalized pustular presentations like hydroxychloroquine-induced pustular reaction who do not completely fall within PP or AGEP categories.[40]

4 | DISCUSSION

There are some studies reporting aggravation course of a pre-existing dermatologic disorders which have induced by the treatment of COVID-19 that one of the well-known entities in this area is aggravation of psoriasis by HCQ.[6] But the focus of this study is on newly emerging COVID-19 treatment-related mucocutaneous drug reactions. Due to the fact that there is still no specific treatment protocol for patients with COVID-19, the use of multiple treatments is still common even inevitable for these patients. In addition, some of these drugs, such as, hydroxychloroquine, can have many potential side effects, such as, *acute generalized exanthematous pustulosis (AGEP)*.[35,36] Dermatologic lesions in patients with COVID-19 may be the mucocutaneous manifestation of virus disease and the related consequences itself or could be due to drug reactions.[12] In evaluation of the mentioned case reports, the incidence of drug reactions in these patients is not rare even speedily growing in the literatures. However, these side effects were controlled by withdrawal of responsible drug and usually with concomitant use of topical or systemic steroids and antihistamines. Based on Table 1 about case reports of dermatologic drug reactions in COVID-19 patients, we found that these patients had no sign or symptoms of any pre-existing dermatologic disease at the onset of their disease and detailed information of these cases are exist in Table *1* that here we describes some of them for example: in the case report by Sernicola et al. they have reported a drug reaction in the form of DRESS syndrome (itching generalized cutaneous "toxic erythema-like" rash with eosinophilia) in few hours after the administration of tocilizumab, which had improved with systemic steroid.[4] The patient recovered after 10 days. In the case report by Robustelli Test et al. they reported a drug reaction in the form of acute generalized exanthematous pustulosis (AGEP) 3 days after the withdrawal of the treatment with Lopinavir/Ritonavir and hydroxychloroquine.[5] The diagnosis confirmed with skin biopsy. In addition, the patient had Erythema Multiform-Like lesions, too. The patient was treated with systemic steroid. In another study by Litaim et al. A drug reaction in the form of acute generalized exanthematous pustulosis (AGEP) was reported 18 days after hydroxychloroquine initiation.[6] Unfortunately, the patient was expired due to massive pulmonary emboli. In the study by Skroza et al. they reported the drug reaction in the form of Urticarial Vasculitis with the skin manifestation of multiple, raised erythematous wheals, alone or in cluster, some of them with central purple hyperpigmentation.[7] The diagnosis was confirmed by skin biopsy and the histopathology of drug reaction/Urticarial Vasculitis. The drug eruption occurred 4 days after administration of Ceftriaxone, Lopinavir/Ritonavir, Enoxaparin and hydroxychloroquine. The reaction was treated with oral Prednisone, Bilastine and Pantoprazole and the complete remission achieved in about a week. In the last case report by Ramirez et al. they present the drug reaction in

TABLE 2 Cohort studies

First author	title	Main covid-19 therapy	Sample size	Age (mean) (years)	Sex ratio (percentage of males)	Percentage of patient skin drug reaction reported	Type of skin reactions	comorbidity conditions
Matthieu Million	*Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: A retrospective analysis of 1061 cases in Marseille, France*	*HCQ (200 mg three times daily for ten days) + AZ (500 mg on day 1 followed by 250 mg daily for the next four days)*	*1061*	*43.6*	*46.4%*	*0.004%*	*Urticaria & Erythematous bullous& rash*	*Chronic respiratory disease: 10.5% Cancer: 2.6% Diabetes: 7.4% Coronary artery disease: 4.3% Hypertension: 14% Obesity: 5.8%*
Ji Sun	*Incidence of Adverse Drug Reactions in COVID-19 patients in China: an active monitoring study by Hospital Pharmacovigilance System*	*Umifenovir& lopinavir/ritonavir & Chloroquine*	*217*	*45.7*	*48.8%*	*4.15%*	*Rash & Pruritus & Skin discoloration*	*underlying basic diseases: 28.6% History of drug allergies: 4.6%*
Valentina Morena	*Off-label use of tocilizumab for the treatment of SARS-CoV-2 pneumonia in Milan, Italy*	*Tocilizumab (400 mg intravenously and repeated after 12 hours or 8 mg/kg and repeated after 12 hours)*	*51*	*60*	*78.4%*	*2%*	*rash*	*Cardiovascular diseases: 49.0% Hypertension: 29.4% Diabetes: 11.8% Chronic lung diseases: 9.8% Cancer: 5.9%*
Ji-Won Kim	*Lopinavir-ritonavir vs hydroxychloroquine for viral clearance and clinical improvement in patients with mild to moderate coronavirus disease 2019*	*lopinavir-ritonavir (400/100 mg oral twice daily for 11 days)*	*31*	*64.3*	*35.5%*	*3.2%*	*rash*	*Diabetes: 22.6% Hypertension: 25.8% Cardiovascular disease: 22.6% Chronic lung disease: 22.6% Chronic kidney disease: 9.7%*

the form of vasculitis 2 days after administration of amoxicillin, ibuprofen, metamizole, intravenous prednisolone and antihistamine.[8] The skin biopsy confirmed drug-induced vasculitis. The patient was treated with high dose systemic steroid and complete remission was achieved 9 days after treatment. According to case reports studies drug dependent skin manifestations may occur a few hours to a month after taking the drug and usually last less than a week. *The* interval between drug usage and the eruption varies about few hours to 1 month and it is tightly dependent on the type of drug was used; hydroxychloroquine seems to be the drug with highest mean interval. Antibiotics and antivirals (especially lopinavir/ritonavir) usually have shorter lag times of mucocutaneous adverse eruptions in comparison with HCQ, so we may expect COVID-19 related delayed drug eruptions even after discharge of patients that needs more awareness to better management of patients. Based on cohort studies we may expect 0.004% to 4.15% of definite drug-induced mucocutaneous reactions but in the case with uncertainly about the origin of dermatologic reaction (as primary virus-induced or drug eruption), this rate reaches to 5.7% to 45.5%.[24-28] Antivirals, antimalarials, azithromycin and tocilizumab are most responsive drugs for adverse drug reactions, but antivirals especially in combination with antimalarial drugs are in the first step and in this setting of therapy the clinicians may expect the highest rate of mucocutaneous reactions. Types of skin reactions are usually morbilliform/exanthematous maculopapular rashes and urticarial eruptions which mostly may manage by steroids during few days. Pruritus, bullous rashes, skin dyspigmentations, purpuric, EM-like and PR-like eruptions are other probable observed dermatologic adverse effects of drugs in COVID pandemic. Based on the best we know, lopinavir/ritonavir is the most prevalent used drug with the highest skin adverse reaction among antivirals, ribarivin and remdisivir also could induce mucocutaneous drug reactions (about 10%). It seems that favipiravir has no or less skin adverse reactions in comparison with lopinavir/ritonavir. Ruxolitinib is another drug may cause mucocutaneous reactions (10%). Interferon-alfa my decrease rate of dermatologic reactions of antivirals such as ribavirin or lopinavir/ritonavir based on what we observed in combination therapy regimens.[29-34] It should be notified that logically the rate of dermatologic adverse effects among antivirals is related to their frequency of usage,

TABLE 3 Control trials studies with 2 arms

First author	title	Main covid-19 therapy Group1	Sample size	Age (mean) (year)	Sex ratio (male percentage)	Patient comorbidities	Percentage of patient skin drug reaction reported	Type of skin reactions	Main covid-19 therapy Group2	Sample size	Age (mean) (year)	Sex ratio (male percentage)	Patient comorbidities	Percentage of patient skin drug reaction reported	Type of skin reactions
Qingxian Cai	*Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study*	*Favipiravir (Day 1:1600 mg orally twice daily, Days 2-14:600 mg twice daily) plus IFN-a (5 million U aerosol inhalation twice daily)*	*35*	*43*	*40.0%*	*Not reported*	*0%*	*–*	*Lopinavir ritonavir (Days 1-14:400 /100 mg orally twice daily) plus IFN-a (5 million U aerosol inhalation twice daily)*	*45*	*49*	*46.7%*	*Not reported*	*8.89%*	*rash*
Yeming Wang	*Remdesivir in adults with severe COVID-19: a randomized, double-blind, placebo-controlled, multicenter trial*	*Remdesivir(Day 1:200 mg infusion once a day, days 2-10:100 mg infusion once daily)*	*155*	*66·0*	*56%*	*Hypertension: 46%, Diabetes: 25%, Coronary heart disease: 9%*	*7%*	*rash*	*placebo (infusion for 10 days)*	*78*	*64.0*	*65%*	*Hypertension: 38%, Diabetes: 21%, Coronary heart disease: 3%*	*3%*	*rash*
Bin Cao	*A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19*	*Lopinavir-Ritonavir: (Day1-14:400/100 mg orally)*	*95*	*58*	*61.6%*	*Diabetes:10.1%, Cerebrovascular disease: 5.1%, Cancer: 5.1%*	*2.1%*	*Self-limited skin eruptions*	*Standars care*	*99*	*58*	*59.0%*	*Diabetes: 13.0%, Cerebrovascular disease: 8.0%, Cancer: 1.0%*	*0*	*–*
SpinelloAntinori	*Compassionate remdesivir treatment of severe Covid-19 pneumonia in intensive care unit (ICU) and Non-ICU patients: Clinical outcome and differences in post-treatment hospitalization status*	*Remdesivir:(Day1:200 mg Intravenous once daily, Days 2-10:100 mg Intravenous once daily)*	*18*	*60.5*	*77.8%*	*Diabetes: 16.7%, Hypertension: 27.8%, Cancer: 5.6%*	*0*	*–*	*Remdesivir: (Day1:200 mg Intravenous once daily, Days 2–10:100 mg Intravenous once daily)*	*17*	*64.0*	*70.6%*	*Hypertension: 41.2%*	*11.8%*	*Maculo-papular rash*
Yang Cao	*Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): A multicenter, single-blind, randomized controlled trial*	*Ruxolitinib:(5 mg orally twice a day)*	*20*	*63*	*60.0%*	*Hypertension:35%, Diabetes:25%, Coronary artery heart disease:10%*	*10%*	*rash*	*Placebo (100 mg vit c twice a day)*	*21*	*64*	*57.1%*	*Hypertension:42.9%, Diabetes:14.3%, Coronary artery heart disease:4.8%*	*4.8%*	*rash*

TABLE 4 Control trials studies with 3 arms

First author	title	Main covid-19 therapy Group1	Sample size	Age (mean) (year)	Sex ratio (male percentage)	Percentage of patient skin drug reaction reported	Type of skin reactions	Main covid-19 therapy Group2	Sample size	Age (mean) (year)	Sex ratio (male percentage)	Percentage of patient skin drug reaction reported	Type of skin reactions	Main covid-19 therapy Group3	Sample size	Age (mean) (year)	Sex ratio (male percentage)	Percentage of patient skin drug reaction reported	Type of skin reactions
Yin-Qiu Huang	*No Statistically Apparent Difference in Antiviral Effectiveness Observed Among Ribavirin Plus Interferon-Alpha, Lopinavir/Ritonavir Plus Interferon-Alpha, and Ribavirin Plus Lopinavir/Ritonavir Plus Interferon-Alpha in Patients with Mild to Moderate Coronavirus Disease 2019: Results of a Randomized, Open-Labeled Prospective Study*	*Ribavirin (Day 1:2 g intravenous once a day. Day2-14:400-600 mg orally 3 times a day) Interferon-Alpha:(Day1-14:5 million or 50 mg inhalation twice a day)*	*33*	*40.3*	*55%*	*9%*	*rash*	*Lopinavir/ Ritonavir (Day 1–14:400/100 mg orally twice a day) Interferon-Alpha: (Day1-14:5 million or 50 mg inhalation twice a day)*	*36*	*43.3*	*53%*	*0*	*–*	*Ribavirin (Day 1:2 g intravenous once a day, Day2-14:400–600 mg orally 3 times a day) Lopinavir/Ritonavir (Day 1-14:400/100 mg orally twice a day) Interferon-Alpha (Day1-14:5 million or 50 mg inhalation twice a day)*	*32*	*43.8*	*28%*	*6.3%*	*rash*

TABLE 5 Uncertain virus or drug related skin manifestation

First author	title	Main covid-19 therapy	Sample size	Age (mean) (Years)	Sex ratio (percentage of males)	Percentage of patient skin drug reaction reported	Type of skin reactions	Sign of skin lesions	Location of skin reactions	Duration of cutaneous disease (days)	Sign of skin lesions
Alba Català	*Maculopapular eruptions associated to COVID-19: a sub analysis of the COVID-19 Piel study*	*Chloroquine / hydroxychloroquine: 30.6%* *Lopinavir / ritonavir: 19.4%* *Azithromycin: 25.0%* *Systemic corticosteroids:5.6%* *Tocilizumab: 2.8%*	*80*	*61.1*	*48.8%*	*45.5%*	*Morbilliform eruptions*	*Itch: 93.1%*	*79% trunk*	*7.2*	*93.1% itching*
		Chloroquine / hydroxychloroquine: 56.3% *Lopinavir / ritonavir: 40.0%* *Azithromycin: 26.3%* *Systemic corticosteroids: 20.0%* *Tocilizumab: 10.0%*	*36*	*50.3*	*33.3%*	*20%*	*Other maculopapular eruptions*	*Itch: 82.6%*	*81% trunk and the limbs*	*11.8*	*82.6% itching*
		Chloroquine / hydroxychloroquine: 52.0% *Lopinavir / ritonavir: 28.0%* *Azithromycin: 16.0%* *Systemic corticosteroids: 4.0%* *Tocilizumab: 0.0*	*25*	*54.6*	*60%*	*14.2%*	*Purpuric eruptions*	*Itch:90.9%*	*32% trunk, 32% upper limbs*	*7.4*	*100% itching*
		Chloroquine / hydroxychloroquine: 47.1% *Lopinavir / ritonavir: 47.1%* *Azithromycin: 35.3%* *Systemic corticosteroids: 11.8%*	*17*	*61.5*	*11.8%*	*9.7%*	*Erythema multiforme-like*	*Itch:72.7%*	*70.6% Trunk*	*9.7*	*72.7% itching*
		Chloroquine / hydroxychloroquine 10.0% *Lopinavir / ritonavir: 10.0%* *Azithromycin: 0.0) %* *Systemic corticosteroids: 10.0%*	*10*	*36.0*	*60.0%*	*5.7%*	*Pytiriasisrosealike*	*Itch:100%*	*90% trunk*	*12.1*	*100% itching*

too. Since, adverse drug reactions of skin are frequently observed in pandemic area, dermatologist and specialists of other fields really need to be more informed about drugs with more mucocutaneous adverse reactions and the type of reactions and some of these reactions may be severe or even life-threatening also management of patients in such conditions could be really challenging regarding skin eruption and concomitant COVID infection.[4,19,20] The authors of this study have been focused on various aspects of COVID-19 especially in the field of dermatology and now it seems that focus on this topic is of great importance. Some clinical and therapeutic features of COVID-19 and its probable final sequels may become more clear and evident during time especially about its virus-related or drug-related mucocutaneous signs, which needs more focus in future studies also discuss about management of patients with a specific dermatologic disorder in the pandemic era, multi-potential drugs for Therapy, or approach to the elective treatments of primarily common cutaneous disorders or cutaneous presentations of systemic disorders especially in elderly people may could be logically postponed; like cosmetic procedures, non-emergent surgeries or some chronic insignificant medical skin disorders.[39,41-44]The field of COVID is of interest of the authors of this review and they have focused to somehow on the all mentioned topics.[45-47]

5 | CONCLUSION

Given that the drugs used to treat COVID-19 could potentially have several side effects, the incidence of mucocutaneous drug reactions in these patients is not unexpected. In this pandemic, during treatment with common therapeutic protocols for COVID-19, numerous dermatologic drug side effects should be considered and more investigate for better diagnoses and approaches especially regarding the point that large number of the patients may visit by physicians of multiple services, so logically knowing more about the mentioned presentations is really of great value for many subspecialists even other than the dermatologists.

Since the lack of enough evidence about treatment-related mucocutaneous drug reactions of COVID-19, we decided to systematically search the literature for these types of dermatologic reactions. In future perspective we expect encounter to growing reports of drug-related adverse mucocutaneous reactions of COVID-19, which could be well-known, new, severe or more complex due to the pandemic concerns, new-emerging proposed therapies, increasing infection rate of new corona virus at many areas of the world and also virus-host induced certain immune abnormalities that may affect the nature of the drug reactions. We found that drug reactions in patients with COVID-19 could be common and skin side effects is not an exception due to the multiplicity of drugs and the type of drugs are used so the risk of drug reactions with these drugs should be considered in any prescription treatment.

We found 0.004% to 4.15% of definite drug-induced mucocutaneous reactions in pandemic area. The interval between drug usage and the eruption varies about few hours to 1 month tightly dependent to the type of drug and usually last less than a week; hydroxychloroqine seems to be the drug with highest mean interval. Antivirals, antimalarials, azithromycin and tocilizumab are most responsive drugs for adverse drug reactions, but antivirals especially in combination with antimalarial drugs are in the first step. Types of skin reactions are usually morbilliform/exanthematous maculopapular rashes and urticarial eruptions which mostly may manage by steroids during few days. In the setting of HCQ, specific reactions like AGEP should be considered. lopinavir/ritonavir is the most prevalent used drug with the highest skin adverse reaction among antivirals; ribarivin and remdisivir also could induce cutaneous drug reactions but favipiravir has no or less adverse effects. It should be notified that logically the rate of dermatologic adverse effect among antivirals is related to their frequency of usage, too. Although very rare, we may encounter challenging sever or potentially life threatening mucocutaneous adverse drug reaction. Knowing more about the probable drug-induced mucocutaneous presentations of COVID-19, is really of great value for better management of encountered cases.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTION

The authors contribute equally to all stages of this study. The team has reviewed the manuscript and the data, and all contributors were in full agreement.

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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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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