REVIEW

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Cutaneous Findings of COVID-19: A Review of the Literature

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ABSTRACT

Many different cutaneous findings have been reported in coronavirus disease 2019 (COVID-19) patients. It is still uncertain whether these findings are associated with disease. On the other hand, lesions had different features, time of onset and prognostic relations. We reviewed published data in PubMed database with keywords of "COVID-19" and "cutaneous". We found out 34 articles consisted with 563 patients. Urticarial rash was the most common followed by chilblain-like and vesicular lesions. However, total number non-specified maculopapular rashes were higher than other lesions according to one article which included both confirmed and suspected patients. Livedo-like lesions and acro-ischemia tent to appear in severe COVID-19 patients. Chilblain-like lesions were reported more frequently in young patients at late periods of disease and also, in young normal population without history of COVID-19. Petechial and purpuric lesions were developed either true vasculitis or thrombogenic vasculopathy. Vesicular eruptions resembled to herpes simplex virus and varicella-zoster virus infections and these infections should strongly be considered. More studies and reports are needed to determine non-specific maculopapular and rare lesions such as mottling. Although many reports and classifications exist about cutaneous findings of COVID-19, their exact relationships remain to be elucidated especially for maculopapular and urticarial lesions which can also be seen in other viral exanthems and drug eruptions. Furthermore, clinical data and histopathologic features weren't reported in several articles. In conclusion, varied types of cutaneous lesions can be seen in COVID-19 and beneficial for suspicion of disease and prognosis.

Keywords: COVID-19, Cutaneous, Skin, Dermatology, Livedo-like lesions, Chilblain-like lesions, Maculopapular, Urticaria, Vesicular rash

Introduction

Since it was first reported in China on December 2019, coronavirus disease 2019 (COVID-19) has spread throughout the world rapidly [1]. Consequences were terrible and dreadful as it causes more than 250,000 deceased people in more than 180 countries worldwide [1]. World Health Organization (WHO) declared this out-brake as pandemic and governments took precautions which resulted huge impacts on socio-economic status of communities [1,2]. Suspected virus was described by WHO as Severe Acute Respiratory syndrome Coronavirus-2 (SARS-COV-2) that belongs to family of *Coronaviridae*, the same family of SARS and MERS out-brakes' agents [1,3]. It is single stranded RNA virus with envelope and transmits by inhaling of expelled droplets from patients by coughing and sneezing. Contact and carry of droplets to respiratory mucosa and conjunctiva is another important transmission path. Virus uses angiotensin-converting enzyme 2 (ACE-2) to hold on and invade respiratory epithelium [1]. Median incubation period is 5.2 (4-14) days. In most cases disease begins with fever, cough, fatigue in whom dyspnea, hypoxemia may accompany. Mortality is usually resulted by respiratory failure after 6-41 days from beginning of symptoms [4]. Diagnosis is confirmed by reverse-transcriptase polymerase chain reaction (PCR) test [1]. Although respiratory system is mostly involved, other organs can also be affected especially gastrointestinal tract [1,4]. It is not surprising because ACE-2 is expressed in many organs, particularly in small intestines [1]. The

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first report about skin findings is from China in which prevalence was reported as 0.2% [5]. Since then many cases with varied types of skin lesions were published however, it is not certain whether these findings were associated with disease [5,6]. Some of these are relatively specific to COVID-19 such as varicella like lesions on the other hand, maculopapular rash and urticarial rash are not and can be seen in other viral infections [6]. Lesions may appear before other symptoms and recognition is essential in such cases for early diagnosis and precautions [7,8]. It was also speculated that several of these lesions may predict complications and poor outcome [9]. Furthermore, not all articles presented photographs of patients and described pathological features [5]. In this paper we aimed to review reported skin lesions of COVID-19 confirmed patients in whom these lesions related to disease. We also intent to categorize these and search for existence of photographs and histopathologic investigation.

We searched for articles about skin findings of COVID-19 infection in PubMed database on May 27th, 2019. We use keyword combination of "COVID-19" and "cutaneous". All accessible articles that were written in English were evaluated. We reviewed articles that reported patients with confirmed COVID-19 infection and associated skin lesions. Articles that were reviews, not relevant with skin findings of COVID-19, written in other than English, with non-confirmed COVID-19 patients, reported skin findings not related with COVID-19 were excluded. Skin lesions that was evaluated by tele-dermatology were excluded too. We extracted demographic, clinical, histopathological data of patients and categorized them according to type of skin findings that were described by Wollina et al. [5]. Onset time of skin lesions was measured from beginning of respiratory signs of COVID-19 infection. If onset time of lesions was pointed according to hospital admission or COVID-19 diagnosis, it was also pointed in review. We also pointed existence of photographs.

Review of Cutaneous Findings of COVID-19

Searching of database reveled 85 articles. After evaluation 34 articles fulfilled the criteria and were included to the review. Six of them were studies and large case series, others were small case series and reports. Frequencies, which were reported in studies and large case series, were showed in Table 1. Characteristics of reported patients were shown in Table 2. Erythematous rash evaluated as different group due to several reports in which non-specific erythematous lesions were reported under this nomenclature.

Maculopapular Rash

In our review we reached seven articles about maculopapular rash which consisted of 14 patients. Eight females and six males were reported. Female patients' mean age was 63.2 (range: 32-84) and males was 51.6 (6-88). Onset time of rash varied between 2 and 33 days from COVID-19 symptoms. Pictures of almost all lesions existed in papers [10,11,12,13,14,15,16]. Herrero-Moyano et al. [16] performed histopathological examination in 8 patients and observed varied findings. These were spongiosis, non-follicular sub-corneal pustules, neutrophilic interstitial infiltrates and exocytosis, rare eosinophils. They reported signs of vascular injury, microthrombi in capillaries, erythrocytes extravasation in several patients. They excluded existence of infectious agents [16]. Duration of lesions were varied between 4-16 days [10,11,12,13,14,15]. Avellana Moreno et al. [14] reported patient treated with intravenous corticosteroid and antihistamines whom lesions resolved in five days on the other hand, Morey-Olive et al. [13] reported lesions that healed in five days without treatment.

Erythematous Rash

Erythematous rash were reported by seven articles in our screen. Fifty-eight patients were reported in these papers. Age and gender data were missing in some patients [17,18,19,20,21,22,23]. De Giorgi et al. [22] reported frequency in their series as 70 percent (37 patients over 53). Most of these patients had mild itch. In one report 39-year-old female developed non-pruritic, annular fixed, erythematous and edematous plaques that located on upper extremities, chest, abdomen, neck and palms. Rash resolved in seven days and no therapy was reported in that patient [18].

Pityriasis Rosea Like Eruption

We found only two reports about Pityriasis Rosea like eruption. Galvan Casas et al. [24] reported 47 patients over 375 but, no clinical features were reported. Ehsani et al. [25] reported 27-year-old man developed erythematous and scaly annular plaques. These located on forearm, trunk and upper extremities and scattered like pine-tree branches. Rash had appeared three days after from low grade fever and non-specific symptoms and continued to appear five

Table 1. Reported frequencies of cutaneous findings in COVID-19 patients from studies and case series

Author	Frequency of skin findings in COVID-19 (reported from studies and case series) Number of patients and percentages
Fernandez-Nieto et al. [40]	24/53 (NR)
Hedou et al. [20]	5/103 (NR)
Recalcati [21]	18/88 (20.4%)
De Giorgi et al. [22]	53/678 (7.8%)
Guarneri et al. [23]	13/125 (10.4%)
Herrero-Moyano et al. [16]	8/1177 (0.7%)

NR: Non-reported, COVID-19: Coronavirus disease 2019

Table 2. Demographics and clinical characteristics of COVID-19 patients with cutaneous findings

Author	Patient number	Age and gender	Skin lesion type	Mucosal involvement	Skin rash before COVID-19	Time of onset (from symptomes)	Duration	Skin biopsy	Treatment for skin disease	Existance of photo	Relationship with severity and mortality
Cepeda-Valdes et al. [28]	2	50 F 20 F	Urticaria (2)	No	No	Soon after fever	2 days	No	Antihistamines and moisturizers	Yes	NR
Llamas-Velasco et al. [35]	1	61 M	Purple ischemic lesions and livedoid Purplish retiform patches on both feet and hands (livedo-like lesions with acro-ischemia)	No	No	Simultaneously	17 days	Yes	NR	Yes	Followed in ICU
Janah et al. [26]	2	17 M 29 M	- Erythematous maculopapular atypical targetoid eruption on palms (1) - Urticarial targetoid lesions on his palms (1) (atypical erythema multiforme)	No	Yes	+15 days +12 days	NR	No	NR	NR	NR
Gunawan et al. [29]	1	51 M	- Urticaria	No	No	+5 days	1 day	NR	Loratadine	NR	No
Jimenez-Cauhe et al. [27]	4	66.75 (58-77) Females	- Coalescing erythematous papules on upper trunk which progressively turned to erythemato-violaceous patches with a dusky center and a pseudo-vesicle in the middle and spread to back, face and limbs (4) - Accompanied typical target lesions (2) (EM-like lesions)	Palatal macules and petechia (3)	No	+19.5 (16-24)	2-3 weeks	Yes	Systemic corticosteroids	NR	NR
Fernandez-Nieto et al. [40]	24	40.5 (19-62). F/M:18/6	- The diffuse pattern is polymorphic with papules, pustules, vesicles and has a tendency to a widespread distribution on trunk, palms and soles (18) - The localized pattern is monomorphic with vesicles and only involves the trunk (6) (vesicular pattern)	No	2/24 -15 (10-20)	+14 days* (4-30) 3 patients with symptomes	10 days (4-22)	2/24	NR	Yes	NR

Table 2. Continued

Author	Patient number	Age and gender	Skin lesion type	Mucosal involvement	Skin rash before COVID-19	Time of onset (from symptomes)	Duration	Skin biopsy	Treatment for skin disease	Existance of photo	Relationship with severity and mortality
Sachdeva et al. [10]	3	71 F 77 F 72 F	- Maculopapular itchy rash appeared on the trunk resembling a grover disease - Maculopapular exanthem (morbilliform) on the trunk - Papulo-vesicular, pruritic eruption appeared on sub-mammary folds, trunk and hips (maculopapular rash)	No	NR	10 days NR 4 days	NR NR 10 days	NR	NR	Yes	NR
de Masson et al. [36]	25+	NR	- Acral lesions (7) - Chilblain-like lesions (NR)	NR	NR	NR	NR	NR	NR	NR	NR
Castelnovo et al. [30]	2	NR	- Widespread urticarial rash on thigh and perimalleolar area (1) - Vasculitic purpura on legs with erythematous rash (1)	NR	NR	NR	2 days	NR	Steroid	Yes (vasculitic purpura)	NR
Ehsani et al. [25]	1	27 F	- Erythematous and scaly annular plaque on left form arm which progressed to widespread papules and plaques. (pityriasis rosea like eruptions)	NR	No	+3 days*	NR	NR	Topical corticosteroid and antihistamine (cetirizine)	Yes	NR
Paolino et al. [11]	1	37 F	Craniocaudal spreading erythematous maculopapular rash on the trunk, neck, and face, nummular erythematous lesions with a peripheral slight white halo, assuming an urticaria-like feature on the lower limbs.	NR	No	+3 days	8 days	NR	NR	Yes	NR
Zengarini et al. [17]	1	67 F	Itchy erythematous confluent rash.	No	No	+1 mo*	7 days	Yes	NR	Yes	NR
Ahouach et al. [12]	1	57 F	Diffuse fixed erythematous maculopapular rash, which was asymptomatic over the limbs and trunk, but, burning on the palms.	No	No	+2 days	9 days	Yes	NR	NR	NR

Table 2. Continued

Author	Patient number	Age and gender	Skin lesion type	Mucosal involvement	Skin rash before COVID-19	Time of onset (from symptomes)	Duration	Skin biopsy	Treatment for skin disease	Existance of photo	Relationship with severity and mortality
Galvan Casas et al. [24]	375⊥	NR	- Itchy or painful acral areas of erythema with vesicles or pustules (pseudo-chilblain) (19%) - Itchy vesicular eruptions on trunk and limbs (9%) - Itchy urticarial lesions on trunk (19%) - Other maculopapular eruptions: Perifollicular, pityriasis rosea like; Erythema elevatum diutinum like, Erythema multiforme like eruptions on extremities (47%) - Livedo or necrosis on trunk or acral sites (6%).	NR	Yes 22/275	NR	12.7 days 10.4 days 6.8 days 8.6 days NR	NR	NR	Yes	Less severe: Pseudo-chillbalin; More severe: Urticarial, maculopapular, livedo or necrosis
Morey-Olive et al. [13]	2	6 M, 2 mo F	- Erythematous, confluent, nonpruritic maculopapular rash began on trunk and neck, spread to cheek, extremities, palms and soles (1) - Itchy urticaria (1)	No	Without COVID-19 symptom	Without COVID-19 symptom	5 days	NR	No spesific treatment	Yes	NR
Tammaro et al. [41]	3	NR	- Pruritic isolated herpetiform lesions on their trunk (2) - Vesicular isolated lesions on her back (1) (vesicular eruption due to HSV)	NR	NR	NR +8 days*	NR	NR	NR	NR	NR
Avellana Moreno et al. [14]	1	32 F	- Pruritic, sudden-onset, generalized morbilliform rash that progressed cephalocaudally.	Yes	No	+6 days	4 days	NR	i.v. corticosteroid and antihistamines	Yes	NR
Amatore et al. [18]	1	39 M	Febrile, erythematous and edematous non-pruritic annular fixed plaques on upper limbs, chest, neck, abdomen and palms (febrile erythematous rash).	No	No	At same time with fever	7 days	Yes	NR	Yes	NR

Table 2. Continued

Author	Patient number	Age and gender	Skin lesion type	Mucosal involvement	Skin rash before COVID-19	Time of onset (from symptomes)	Duration	Skin biopsy	Treatment for skin disease	Existance of photo	Relationship with severity and mortality
Van Damme et al. [31]	1	71 F	- Extensive acute urticaria	NR	Yes Few days	- Few days	Started to improve but die	No	Bilastine	No	NR
Gianotti et al. [19]	3	59 F 89 F 57 M	- Widespread erythematous macules on arms, trunk and lower limbs (1) - Exanthem on trunk and arms (1) - Widespread, pruritic erythematous macules and papules (1) (erythematous rash).	NR	No	3 days* Admission 2 days	5-10 days	Yes	NR	Yes	NR
Hedou et al. [20]	5	F/M: 71/32; 47 (20-88)	- Itchy erythematous rash on face and upper body (2) - Urticaria on face and upper body (2) - HSV activation (1)	NR	Yes. Urticarial rash (1)	During illness (4) Prod-rome (1)	Median: 2 days (1-6)	NR	NR	NR	NR
Magro et al. [34]	3	32 M 66 F 40 F	- Retiform purpura with extensive surrounding inflammation on buttocks (1) - Dusky purpuric patches on palms and soles (1) - Purpuric reticulated eruption with livedo racemosa on chest legs and arms (1) (purpuric eruption, livedo-like eruption).	NR	No	11 days 19 days 14 days	11-19 days	Yes	NR	Yes	NR
Henry et al. [32]	1	27 F	Pruritic disseminated erythematous plaques particularly located on face and acral sites (urticarial rash).	NR	Yes, 2 days	-2 days	NR	No	Antihistamines	Yes	NR
Estebanez et al. [48]	1	28 F	Pruritic red yellow confluent papules on heels which hardened and progressed to plaques (non-specified).	NR	No	13 days*	NR	NR	Topical steroid	Yes	NR

Table 2. Continued

Author	Patient number	Age and gender	Skin lesion type	Mucosal involvement	Skin rash before COVID-19	Time of onset (from symptomes)	Duration	Skin biopsy	Treatment for skin disease	Existance of photo	Relationship with severity and mortality
Fernandez-Nieto et al. [33]	1	32 F	Urticarial rash	NR	No	6 days	5 days	Yes	Oral antihistamines	Yes	NR
Kamali Aghdam et al. [42]	1	15 M	Mottling	NR	No	Exist at admission	2 days	NR	NR	NR	NR
Recalcati [21]	18	NR	- Erythematous rash (14) - Urticaria (3) - Chickenpox-like vesicle on trunk (1) - Itching was observed but, not in all patients.	NR	NR	8 at onset 10 after hospitalization	Few days	NR	NR	NR	NR
Dominguez-Santas et al. [38]	1	71 F	Pruritic purpuric macules and papules on thighs, legs and ankles (purpuric eruption).	No	No	7 days	3 weeks	Yes	Topical betamethasone propionate	Yes	NR
De Giorgi et al. [22]	53	M/F: 60/40; 55.9 (28-69)	- Itchy erythematous rash (70%) - Diffuse urticaria (2%) - Vesicular eruption (4%) - Petechiae, purpura and acro-ischemia (13) Lesions located on trunk and upper limbs.	NR	Yes (44%) Exist at diagnosis	+2-23 days* (56%)	Mean: 3 days (2-5)	NR	NR	NR	NR
Mayor-Ibarguren et al. [39]	1	83 F	- Palpable purpura and serohaematic blisters on lower legs, feet, toes (petechia and purpura).	NR	No	+1 mo	10 days	Yes	30 mg/day prednisone	Yes	NR
Guarneri et al. [23]	13	NR	- Widespread urticarial rash (2) - Panniculitis (3) - Erythematous rash (2) - Chilblains-like lesions (1) - Acro-cyanosis in (2); one resulted with amputation - Itchy urticaria with angioedema (1) Lesions located on trunk, upper and lower limbs.	NR	NR	Exist at admission in 2 patients	3-18 days (erythematous rash)	NR	NR	NR	NR

Table 2. Continued

Author	Patient number	Age and gender	Skin lesion type	Mucosal involvement	Skin rash before COVID-19	Time of onset (from symptomes)	Duration	Skin biopsy	Treatment for skin disease	Existance of photo	Relationship with severity and mortality
Papa et al. [37]	1	11 F	Erythematous chilblain-like lesions and several ulcers on feet. Dyschromia of the nails.	NR	NR	NR	15 days	NR	Parasetamol and mupirocin ointment	Yes	NR
Putra et al. [15]	1	29 M	Multiple, discrete, 3 mm sized, lenticular redness papules on extremities with sensation of pins and needles on tips. Tips thickened and exfoliated (maculopapular rash).	Aphthous stomatitis	No	3 days	10 days	NR	NR	Yes	NR
Herrero-Moyano et al. [16]	8	F/M: 4/4 72.2	Ill-defined erythematous and coalescent maculopapular rash on trunk, back and folds. Pustules and desquamation appeared after.	NR	No	27.6 days	Mean: 11.6 days	Yes	NR	Yes	NR

NR: Non-reported, COVID-19: Coronavirus disease 2019, M: Male, F: Female, ICU: Intensive care unit, HSV: Herpes simplex virus, mo: Month, i.v.: Intravenous
*: Onset time was reported according to admission or diagnosis, not beginning of symptoms
⊥: Both confirmed and suspected cases were included
+: Confirmed patients with cutaneous findings but, only few patients' lesions were explained

days, became pruritic and disseminated. Patient were treated with topical steroids and cetirizine.

Erythema-multiforme Like Lesions

Three articles reported erythema-multiforme like lesions. Janah et al. [26] reported two patients with ages of 17 and 29. Both developed atypical targetoid lesions on palmar regions. No mucosal lesions and history of recurrent herpes virus infection was reported. Rash appeared after 12 and 15 days from COVID-19 symptoms. Photographs existed in papers but histopathological features didn't. Jimenez-Cauhe et al. [27] reported four patients with varied ages between 58-77. They developed rash after 16-24 days from COVID-19. However, in three of them lesions appeared after discharging from clinic. All patients had lesions on face, trunk, extremities but not on palmoplantar regions. Mucosal lesions as macules and petechia, especially on palatal sites, were reported in three patients. Histopathological features were similar in all patients. These were basket-weave stratum corneum, mild-moderate spongiosis, dilated vessels filled with neutrophils, extravasation of red blood cells, perivascular and interstitial lymphocytes. Basal vacuolar changes and lymphocytic exocytosis were observed in each different patient. All patients' lesions subsequently resolved in 2-3 weeks with systemic corticosteroids. Galvan Casas et al. [24] also reported erythema-multiforme like lesions in their series consisted of 375 patients but, however, clinical data were lack.

Urticarial Rash

Urticarial lesions were reported in 104 patients by 11 articles that consisted of five case series and six case reports. One patient developed urticarial rash accompanied with angioedema. These patients were included 79 confirmed and 24 suspected cases [13,21, 22,23,24,28,29,30,31,32,33]. Age and gender data were available in several articles. In these articles urticarial rash tent to be more frequent in females and ages were varied between two months and 71 years [13,31]. Development time of lesions were highly varied in reports. In series of Galvan Casas et al. [24] 73 patients with COVID-19 and urticarial rash were reported. In this series three patients developed lesions before and 43 at the same time with COVID-19 symptoms, 25 did after that. Henry et al. [32] reported lesions appeared before

two days, on the other hand, in case report of Fernandez-Nieto et al. [33] after six days from COVID-19 symptoms. Furthermore, Morey-Olive et al. [13] reported two-month-old infant with only fever and urticarial lesions in absence of other COVID-19 symptoms. Mean time of duration of symptoms was reported 6.8 days [standard deviation (SD): 7.8] by Galvan Casas et al. [24], seven of them were treated with systemic corticosteroid. Gunawan et al. [29] reported duration time as one day. Histopathologic investigation revealed upper dermal edema, perivascular lymphocytic infiltrates and some eosinophils [33]. There was lack of data about relation between prognosis and rash.

Vascular Lesions

Many lesions that concerning vascular involvement have been reported in COVID-19 patients. These are livedo-like lesions, chilblain-like lesions, ischemic ulcers, petechia, purpura and necrotic lesions [5]. Histopathological investigations of several COVID-19 patients revealed vascular injury with or without vasculitis, microthrombi and also complement system activation and deposition in both lesions and normal skin [34].

Few varied reports exist about livedo-like, ischemic and necrotic lesions on acral sites. Livedo-like lesions consist of livedo racemosa, purple round or reticular patches located on trunk, thigh, legs, arms feet and hands [24,34,35]. Accompanied acral ischemia and retiform purpura were also reported [34,35]. Skin symptoms varied in reports from asymptomatic to painful, burning and itchy

Table 3. Types and patient numbers of cutaneous findings

Type of cutaneous finding	Number
Total patient number	563
Urticarial rash	104
Maculopapular rash	14
Erythematous rash	59
Vesicular lesions	64
Petechiae, purpura, acroischemia, livedo, necrosis	43
Chilblains-like lesions	73
Perifollicular; pityriasis rosea like; erythema elevatum diutinum like, erythema multiforme like eruptions	183
Acral lesions	7
HSV activation	3
Panniculitis	3
Grover disease-like lesions	1
Pruritic red yellow confluent papules on heels (non-specified)	1
Chickenpox-like vesicle on trunk	1
Mottling	1

HSV: Herpes simplex virus

[24,34,35]. In a study of Galvan Casas et al. [24], which included both confirmed and suspected COVID-19 patients, together these and acro-ischemic lesions were reported in 29 patients (6% percent). This group patients showed higher mortality on the other hand, patients that showed transient lesions experienced mild disease. In that study mean age of these patients were 63.1 with SD of 17.3 and 10 of them were females (48%). Also confirmed cases were much more compared to suspected ones (81% vs. 19%). Eighteen of them (86%) developed lesions at the same time with other symptoms, 1 before, 2 after and in 8 data wasn't reported. Mean time of duration of lesions 9.4 days with SD of 5.4. Llamas-Velasco et al. [35] reported 61-year-old male patient with livedo-like lesions on hands and accompanied acro-ischemia which appeared at the same time with COVID-19 symptoms. Followed in intensive care unit (ICU), lesions showed some improvement after 19 days. Magro et al. [34] reported three patients with skin lesions concerning vascular involvement. One of them, 40-year-old female developed retiform purpura and livedo racemosa on chest, legs and arms. Lesions noted at admission and she had had symptoms for 14 days. Exact time of appearance and duration of lesions and progress of disease weren't reported but, d-dimer and INR levels were elevated. Histopathological features were reported in only two reported cases. Magro et al. [34] reported in their patient perivascular lymphocytic infiltrate and microthrombi without vasculitis in venules of the deep dermis. They also investigated patients for complement activation and observed vascular C5b-9 and C4 deposition in both lesion and normal skin biopsy that obtained from deltoid area. Llamas-Velasco et al. [35] also observed deep-dermis seated thrombi but, in larger arterial vessels that were surrounded with limited neutrophils and showed focal fibrinoid necrosis. Additionally, dilated vessels that were filled with thrombi and surrounded by mild neutrophilic components were seen in papillary dermis. Upper dermis and eccrine sweat gland necrosis, particularly in secretory parts, were also accompanied.

Acro-ischemic changes without livedo-like lesions were also reported. These lesions consisted of finger and toe cyanosis [23]. Aforementioned study from Spain included acro-ischemic lesions without livedo into livedo/necrosis group and as mentioned before, reported frequency was six percent [24]. Guarneri et al. [23] reported two patients with leg thrombosis. One of them experienced amputation due to thrombosis. De Giorgi et al. [22] reported 13 patients with petechia, purpura, acro-ischemia. These group consisted of more severe patients several of whom were cared in ICU and had clotting disorders.

Chilblain-like lesions consisted of erythematous and edematous lesions which located on acral sites. Accompanied vesicles or pustules were also reported. Skin symptoms of itch, pain or burning can be seen. Galvan Casas et al. [24] reported 71 patients

(19%) in their series. Mean age of these patients was 32.5 (SD: 21.8) and 48 of them were females (68%). Most of them developed the lesions after COVID-19 symptoms (42 patients, 59%). Twenty-four patients (34%) developed lesions at the same time of disease symptoms and 5 patients (7%) before. Mean duration of lesions were 12.7 days and more frequently seen in mild patients. Forty-two of these patients (59%) weren't confirmed by virologic tests. Guarneri et al. [23] reported 1 confirmed patient with chilblain-like lesion but, clinical features weren't pointed. On the other hand, they did research with tele-dermatology for chilblain-like lesions. They found 22 patients who were scanned for COVID-19 with rhino-pharyngeal swab samples. Mean age was 14.3 with a range of 6-30 and 19 were children. COVID-19 diagnosis was confirmed in 6 of them of whom 5 were children. de Masson et al. [36] reported several cases in their series. Papa et al. [37] reported 11-year-old girl with chilblain-like lesions with erythema and several ulcers. They also observed dyschromia on nails. There was no sign of any disease in her medical history. SARS-COV-2 wasn't detected in nasopharyngeal swab but, IgG antibodies against virus was. Lesions completely resolved with topical antibiotics and analgesic in 15 days.

Petechia and Purpuric Rash

Reported petechial and purpuric rashes could be induced by either vasculitis or vascular occlusion without inflammation [34,38]. It consisted of palpable purpura, dusky purpuric patches or retiform purpura surrounded by inflammation located on lower extremities and palms and soles [30,34,38,39]. Pruritus was reported in several patients and Koebner phenomenon in one [30,38]. De Giorgi et al. [22] reported 13 patients with petechia, purpura and acro-ischemia over 53 COVID-19 patients which was pointed above. These patients were more severe and association with coagulation disorders was observed. Magro et al. [34] reported two patients; 32-year-old male with retiform purpura with surrounding inflammation located on thighs and 66-year-old female with dusky purpuric patches located on palms and soles. Lesions appeared after 11 and 19 days from COVID-19 symptoms, respectively. Castelnovo et al. [30] reported one patient with itching purpura on legs which suggested vasculitis. Erythematous rash accompanied to lesions. This patient developed severe respiratory failure. Lesions resolved in few days with steroid treatment. Dominguez-Santas et al. [38] reported 71-year-old man with pruritic purpuric macules and papules on both legs which extended from ankle to thighs. Koebner phenomenon was positive. Lesions appeared seventh day of COVID-19 symptoms and resolved in three weeks with topical steroid. Mayor-Ibarguren et al. [39] reported 83-year-old woman with palpable purpura and serohaematic blisters on lower legs, feet and toes with a history of five days. This patient didn't have COVID-19 symptoms at admission but, she had experienced pharyngeal complaints one-month before from admission. Serologic evaluation revealed IgG and IgM antibodies against SARS-COV-2. Lesions healed in 10 days with systemic steroid treatment. Histopathologic features were depending on lesion type. Palpable purpura was characterized by basal layer necrosis, small vessel injury with fibrinoid necrosis, neutrophilic infiltration vessel walls, leukocytoclasia and erythrocyte extravasation [38,39]. Purpuric patches and retiform purpura showed vascular ectasia, thrombi in deep-seated vessels and thrombogenic vasculopathy with perivascular and interstitial neutrophilic infiltration with leukocytoclasia. Extensive necrosis of epidermis, adnexal structures and eccrine coil was also accompanied [34]. Complement deposition were observed in both types of lesions [34,38].

Vesicular Eruption

Two specific clinical patterns have been reported about vesicular eruptions. Fernandez-Nieto et al. [40] performed a study about vesicular rashes that developed in COVID-19 patients and they observed two main specific eruptions in 24 individuals: diffuse pattern and localized pattern. Diffuse pattern was seen in 18 patients and characterized with widespread polymorphic lesions consisted with 7-8 mm sized papules, vesicles, pustules mainly located on trunk, palms and soles. Localized pattern consisted with monomorphic, 3-4 mm sized vesicles involved more than one region but, primarily trunk. No difference in demographics, clinical features and COVID-19 severity was found between two groups. In total mean age was 45 (range: 19-65) and 18 of them were females. Two patients developed rash before COVID-19 symptoms and three with at the same time of symptoms began. Nineteen patients' lesions appeared after COVID-19 symptoms with a mean latency period of 14 days (4-30). Mean duration of lesions were 10 days (4-22). COVID-19 RNA was searched in four patients' vesicles but, it wasn't presented. Ten patients developed pneumonia and one of them required ICU. Others showed mild disease. Galvan Casas et al. [24] reported 34 patients over 375 suspected and confirmed COVID-19 patients (9%). Lesions consisted with itching monomorphic vesicles located on trunk and limbs which progressed bigger and diffuse lesions with serohemorrhagic content in several patients. Patients were middle-aged (mean: 45.6; SD: 20) and 19 of them were female (56%). Five of them developed lesions before and 10 patients after COVID-19 symptoms (15%). Nineteen at the same time with COVID-19 symptoms. These patients tent to show COVID-19 in moderate severity. Duration of lesions were 10.4 (SD: 9.3) days. Recalcati [21] reported one patient with chickenpox-like vesicles over 84 COVID-19 patients. De Giorgi et al. [22] reported two patients with varicelliform, scattered, vesicles in whom herpes simplex virus (HSV) and varicella-zoster virus (VZV) infections were excluded by PCR analysis. Vesicular lesions due to HSV infection

were also reported in COVID-19 patients. Hedou et al. [20] reported HSV type 1 activation in intubated patient cared in ICU. Tammaro et al. [41] reported three patients from two hospitals. Two of them had itchy herpetiform vesicles with erythematous halo on trunk. Other patient had numerous vesicles on back. They suggested lesions were caused by agents belonging to *Herpesviridae* family. Reported histopathologic features were acantholysis, intraepidermal vesicles and ballooned keratinocytes [40].

Mottling

Only one patient has been reported with mottling. Fifteen-day-old neonate in whom fever, tachycardia (heart rate: 170 beat per minute), tachypnea (respiratory rate: 66 per minute), mild subcostal retractions were accompanied to rash at admission. He was care in ICU because of respiratory distress. He was discharged after six days [42].

Discussion

In our review we found 34 relevant articles which consisted of 563 COVID-19 patients with cutaneous findings (Table 3). Details of articles and authors can be found in Table 2. The most frequent cutaneous findings were urticarial rashes followed by chilblain-like lesions. Other frequent skin findings were vesicular lesions, erythematous rash, livedo-like lesions and acro-ischemia, respectively. Interestingly, in case series of Galvan Casas et al. [24] the total number of other maculopapular lesions such as perifollicular lesions, pityriasis rosea like lesions, erythema elevatum diutinum like lesions, erythema-multiforme like lesions were higher than all other eruptions.

Urticarial and maculopapular rashes are common lesions and may be related to many different conditions. Most important differential diagnosis is drug eruptions and lots of COVID-19 patients had already taken drugs before rashes appeared. Galvan Casas [24] suggested that these lesions weren't enough for diagnosis but, on the other hand, rash usually onset with COVID-19 symptoms therefore, they might be beneficial for suspecting COVID-19. Although these authors reported that these lesions tent to be developed in more severe patients, De Giorgi et al. [22] didn't observe correlation between these lesions and prognosis [24].

Reports of livedo-like lesions and acro-ischemia are few and reported demographic and clinical features were varied. Although specific data of age were varied and missing in several articles, it seems that lesions were observed in patients around age of 60 [24,35]. On the other hand, these lesions might be related with severe disease, requirement of ICU, increased mortality [9,24,34,35]. Galvan Casas et al. [24] reported mortality of these patients as 10 percent [35]. But, however, reports were few. Due to reticulated pattern and cyanosis, vascular involvement was suspected [34,35]. Magro et al. [34] reported patient with altered coagulation markers and complement deposition which might lead to further activation of coagulation in tissues. Reported histopathological feature in two patients revealed thrombosis in deep dermal vessels without obvious vasculitis [34,35]. Also, two reported patients with acro-ischemia showed leg thrombosis [23]. It is not surprising because hypercoagulable state and tendency to clotting is well-known features of COVID-19 disease and can be responsible for this skin manifestations through released cytokines [9,24,34].

Chilblain-like lesions were one of the most argued cutaneous findings of COVID-19 for its nomenclature and association with disease. Due to its acral involvement these lesions were mostly confused with acro-ischemia. Of course, vascular involvement possibly existed but, necrosis was absent. Furthermore, features of these lesions were similar with chilblains. Finally, literature review and suggestion has been made by Piccolo and Bassi [43] who concluded that lesions were different from acro-ischemia and should be called "chilblain-like lesions". Other argued aspect is specifity for COVID-19. In a study of Galvan Casas et al. [24] both confirmed and suspected (couldn't had been confirmed by virologic tests) patients were reported. In their report only 41% of patients with chilblain-like lesions had got certain diagnosis of COVID-19. As aforementioned before, tele-dermatologic observation of individuals with chilblain-like lesions by Guarneri et al. [23] showed only 26.3% positivity in PCR analysis of nasopharyngeal swabs. Docampo-Simon et al. [44] prospectively followed 58 individuals with acral lesions during pandemic. Forty-two of them (72.4%) had chilblain-like lesions. Thirty-nine of them were tested with PCR and only one of them resulted positive whom lesions regarded as not to be related with COVID-19. de Masson et al. [36] reported 106 individuals with chilblain-like lesions. Only several of them gave positive result for SARS-COV-2. Recalcati et al. [45] reported 11 children and three adults with chilblain-like lesions. Only three of them gave history of cough and fever before three weeks from appearance of rash. Some of these individuals were negative for COVID-19 and others weren't tested. All lesions resolved in 2-4 weeks and no etiologic factors were found. Cordoro et al. [46] reported six adolescents with chilblain-like lesions. Each three of them were clustered in two families. They reported viral upper respiratory infection symptoms 1-2 weeks before onset of rash. All were negative for SARS-COV-2 PCR test. Due to few data and individuals with negative PCR tests, several authors suggested that chilblain-like lesions weren't related with COVID-19 [44]. However, some of these individuals were seen in relatively warmer weathers which was unexpected because nature of chilblains suggests triggering by cold [24,36,43]. Furthermore, clustered cases with chilblain-like lesions into same families were also reported [24,45,46]. On the other hand, it seems that this kind

of lesions tent to be develop in younger patients and later period of COVID-19 which might explain negative PCR results [9,24,45]. Chilblain-like lesions seem to be suggestive for COVID-19, seen in younger patients, developed in later periods of disease, and may aid to find out asymptomatic and mild patients.

Petechial and purpuric lesions may be occurred due to vasculitis or thrombogenic vasculopathy [5]. Pathologic features of vasculitis consisted of leukocytoclastic vasculitis and may be caused by immune response against viral antigen accumulation [38,39]. Dominguez-Santas et al. [38] searched for SARS-COV-2 RNA in lesions but, they couldn't find out. They explained that finding with responsible immune complexes didn't contain compact viruses. Although absence of absence of viral RNA in lesions they suggested that reported patient related to COVID-19 and any cutaneous small vessel vasculitis observed during pandemic shouldn't be regarded as idiopathic unless COVID-19 ruled out. Thrombogenic vasculopathy related purpura might be caused by complement activation due to either systemic cytokine escape or direct induction of viral particles seated on lesions [9,30,34]. Magro et al. [34] showed co-localization of SARS-COV-2 spike and envelope proteins with Complement 4d and C5b-9 membrane attack complexes on vessels of lungs. They also suggested that focally activated complement system subsequently lead to microvascular injury coagulation and fibrin deposition. They also reported elevated d-dimer levels in serum of their patients. Although reported age and related COVID-19 prognosis were varied in articles, it seems that these kinds of lesions tend to occur in advanced aged patients with coagulation problems and poor prognosis [22,30,39].

Pathologic features of vesicular rash in COVID-19 patients resembled other viral infections and acantholysis seemed to be important mechanism in intra-epidermal blistering. Although Fernandez-Nieto et al. [40] couldn't detect SARS-COV-2 RNA in blister fluid, they pointed that drug usage before appearance of lesions existed in few patients and medical history of patients strongly suggested that vesicles were related with COVID-19. They explained undetected RNA in vesicle contents with false negativity of PCR and absence of standardized methods. However, several authors related their patients' lesions to herpes virus infections, and they suggested that these kinds of lesions weren't specific to COVID-19 [20,41]. Nevertheless, both chicken pox like vesicles and monomorphic scattered lesions were observed in many COVID-19 patients in most of whom drug eruption was unlikely and relationship with disease was strongly suggested [24,40,47]. Therefore, more studies and reports were required to reveal relationship between this kind of lesion type and COVID-19 [41].

In conclusion, reported cutaneous findings in COVID-19 were varied in their clinical appearance. Classification seems to be beneficial to identify these lesions however, different categorizations and nomenclatures exist in articles. Also, association of these lesions with COVID-19 is still speculative and more studies are needed to clarify. Maculopapular and urticarial rash can be seen in other viral exanthems and drug eruptions. But, nevertheless, these conditions were searched, and association was suggested in reports. Livedo-like lesions and acro-ischemia may be related hypercoagulable state in COVID-19 patients and also predict poor prognosis. Chilblain-like tend to appear young patients at late stages of mild diseases. Interestingly, these lesions were also reported in clustered normal patients during warm weathers unexpectedly. These patients might had exposed to subtle or asymptomatic disease before admitted to health-care centers. Thus, chilblain-like lesions may be beneficial to catch asymptomatic patients. Petechial lesions seem to be relatively specific to COVID-19 and can occurred due to either true vasculitis or thrombogenic vasculopathy. The latter condition may be associated with severe disease. HSV, VZV and other viral infections should be considered for vesicular lesions that appeared in COVID-19. More articles and studies are needed to determine features of other maculopapular lesions and less frequently reported cutaneous findings such as erythematous rash, mottling, erythema multiforme-like lesions and pityriasis rosea like lesions. We observed that different classifications, lack of patient and clinical data and photographs in some articles, scarcity of histopathological investigations. These needed to be updated and reorganized and caused limitations to our review. Other limitations were searching articles in only one database, couldn't access publications with languages other than English and databases for COVID-19. More specific studies, extended case series and reports with histopathological examination are necessary to clarify characteristics, pathogenesis and relations with COVID-19.

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: M.C.K., H.S., Design: M.C.K., H.S., Data Collection or Processing: M.C.K., H.S., Analysis or Interpretation: M.C.K., H.S., Literature Search: M.C.K., H.S., Writing: M.C.K., H.S.

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