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REVIEW ARTICLE

Cutaneous manifestations and dermatological sequelae of Covid-19 infection compared to those from other viruses

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ABSTRACT

In the last few months, there have been numerous reports describing a variety of cutaneous signs associated with COVID-19. Clinicians from Italy were the first to describe the cutaneous manifestations of COVID-19, which were later observed in other parts of the globe. In some cases, cutaneous signs were the only manifestation of COVID-19 rather than the typical syndrome of fever and upper respiratory tract symptoms. However, there is considerable heterogeneity amongst the cutaneous signs described so far, which has been published extensively. Our aim is to summarise the latest studies that have reported the early and late cutaneous signs of COVID-19 and compare them to the most common established viral exanthems.

Key words: Coronavirus 19, COVID-19, exanthem, skin.

INTRODUCTION

Viruses can cause distinctive exanthems which help the clinician hypothesise a diagnosis even before the results of diagnostic investigations become available. Contrary to the initial belief, severe acute respiratory syndrome caused by a new coronavirus (SARS-CoV2; also known as COVID-19) doesn't have a specific exanthem but can present with various cutaneous manifestations which are important to recognise. Erythema infectiosum, varicella, infectious mononucleosis and measles are some examples of specific viral exanthems which are well established and share some similarities with the cutaneous signs of COVID-19. Our aims are twofold, firstly to describe the various cutaneous manifestations of COVID-19 that have been observed so far based on their morphology and time of onset, and secondly, to compare their similarities and differences with other established viral exanthems.

METHODS

A comprehensive literature review was conducted via PubMed for the search terms 'COVID-19 and skin'; 'COVID-19 and dermatology'; 'coronavirus and skin' and 'coronavirus and dermatology'. Additional studies were sourced through a Google search and reference lists of a few recent review articles. A total of 576 articles were carefully screened, and 55 articles were further evaluated for cutaneous signs of COVID-19. Only patients with a confirmed diagnosis of COVID-19 using polymerase chain reaction diagnostic assay of nasopharyngeal (NP) swab samples and/or antibody testing were included in the study. Eight studies were further excluded as they used a clinical diagnosis of COVID-19 without confirmatory laboratory investigations. Information on confirmed cases of COVID-19 was extracted from the study if it reported both suspected and confirmed cases. Our search included articles in different languages, which had translations available. The exanthems were divided into broad clinical categories of (1) generalised maculopapular or morbilliform eruption (2) varicella-like or vesicular lesions (3) vascular ischaemic lesions or chilblains (4) acute urticaria and (5) others. We only included established viral exanthems known to be associated with respiratory symptoms in prominent dermatology and virology textbooks for comparison with COVID-19.[1-3]

RESULTS

Literature review identified 406 reported cases of COVID-19 with cutaneous signs meeting the inclusion criteria (Table 1). The most common type of manifestations (Table 2) are (1) a generalised maculopapular or morbilliform presentation (39.7%), (2) vascular lesions

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Table 1 Summary of the reported cases of the cutaneous manifestations of COVID-19

Type of study	Region	Author	COVID-19 positive patients	Morphology	Location	Age of the patient	Timing of onset in relation to respiratory symptoms	Histological diagnosis
CS	Italy	Recalcati *et al.*[6]	18	Erythematous lesions (14), widespread urticaria (3), varicella-like vesicles (1)	Trunk	NR	At the onset of symptoms (8), after hospitalisation (10)	NR
CS	Canada	Sachdeva *et al.*[22]	3	Maculopapular lesions resembling Grover disease (1), morbilliform lesions (1), papulovesicular eruption (1)	Trunk (1), trunk and hips (1), trunk and legs (1)	71, 77, 72	More than 10 days after symptoms (1), 5 days after symptoms(1), 4 days after symptoms (1)	NR
CS	Italy	Marazano *et al.*[23]	22	Varicella-like papules	Trunk and limbs, no facial or mucosal involvement	60 (median age)	Median latency period of 3 days after the onset of symptoms	Y
CR	Belgium	Kolivaras *et al.*[24]	1	Violaceous, infiltrated plaques on an erythematous background	Dorsal aspect of toes and lateral sides of the feet	23	3 days after onset of symptoms	Y
CR	USA	Najarian *et al.*[25]	1	Morbilliform	Legs, thighs, forearms, arms, shoulders, back, chest, abdomen	58	1 day after symptoms	NR
CR	Iran	Kamali Aghdam *et al.*[26]	1	Cutaneous mottling	NR	15 days	2 days after symptoms	NR
CR	France	Henry *et al.*[27]	1	Urticaria	Hands, face and feet	27	2 days before onset of symptoms	NR
CS	China	Zhang *et al.*[28]	2	Urticaria	NR	57 (median age)	NR	NR
CR	Spain	Estebanez *et al.*[29]	1	Confluent erythematous-yellowish papules	Heel	28	14 days after diagnosis	NR
CR	France	Mahe *et al.*[30]	1	Erythematous lesions	Antecubital fossa, then to the trunk and axillary folds	64	4 days after symptoms	NR
CR	USA	Hunt[31]	1	Morbilliform	Trunk and extremities with sparing of the face	20	6 days after symptoms	NR
CR	Thailand	Joob *et al.*[32]	1	Erythema with petechiae	NR	NR	NR	NR
CS	China	Zhang *et al.*[21]	7	Acro-ischaemia including finger/toe cyanosis, skin bulla and dry gangrene	Extremities	59 (median age)	Median latency period of 19 days after onset of symptoms	NR

Table 1 *Continued*

Type of study	Region	Author	COVID-19 positive patients	Morphology	Location	Age of the patient	Timing of onset in relation to respiratory symptoms	Histological diagnosis
CS	USA	Manalo *et al.*[33]	2	Transient non- pruritic blanching unilateral livedoid patch resembling livedo reticularis (1) Unilateral asymptomatic eruption resembling livedo reticularis (1)	Lower limbs	67, 47	7 days after symptoms (1), 10 days after diagnosis (1)	NR
CS	France	Bouaziz *et al.*[34]	14	Maculopapular eruption (4), chicken pox-like vesicles (2), urticaria (1), vascular lesions including cherry angiomas (6), livedo (1)	Generalised	NR	Few days after onset of symptoms, except cherry angiomas which occurred 21 days later	NR
CS	Belgium	Damme *et al.*[35]	2	Acute urticaria	Generalised	71, 39	A day before onset of symptoms (1), concomitantly with symptoms (1)	NR
CR	Iran	Ehsani *et al.*[8]	1	Pityriasis rosea	Trunk	27	3 days after onset of symptoms	NR
CS	Spain	Fernandez *et al.*[36]	24	Small papules, vesicles and pustules	Disseminated vesicular lesions (18) localised vesicular eruption (6)	40 (median age)	Median latency of 14 days after symptoms	Y
CR	Indonesian	Gunuwan[37]	1	Pruritic urticaria	face	51	5 days after symptoms	NR
CS	Spain	Miriam Morey-Olive´ Mar ıa *et al.*[38]	2	Maculopapular lesions (1) Acute urticaria (1)	Trunk and neck, spreading to palms and hands (1), started on the face then spread to extremities, sparing palms and soles (1)	6 years and 2 months	16 days after symptoms (1), at the onset of symptoms (1)	NR
CR	Spain	Moreno *et al.*[39]	1	Morbilliform	Generalised spread including folds and scalp, respecting the palmo-plantar region and mucosa	32	6 days after symptoms	NR
CR	Spain	Quintana-castanedo *et al.*[5]	1	Acute urticaria	Thighs, arms and forearms, sparing palms and soles	61	Cutaneous manifestation was the only symptom	NR
CS	Spain	Suarez-valle *et al.*[40]	3	Acro-ischaemic lesions	Toes only (2) toes and soles (1)	NR	17, 24, 28 days after symptoms	Y

Table 1 *Continued*

Type of study	Region	Author	COVID-19 positive patients	Morphology	Location	Age of the patient	Timing of onset in relation to respiratory symptoms	Histological diagnosis
CS	France	Adele de Masson *et al.*[41]	7	Acral ischaemic lesions	Toes	27 (median age)	NR	Y
CR	France	Ahouach *et al.*[42]	1	Diffuse fixed erythematous blanching maculopapular lesions	Limbs and trunk, with burning sensation over the palms	57	At the onset of symptoms	NR
CR	Kuwait	Alramthan *et al.*[4]	2	Red-purple papules (1); diffused erythema in the subungual area of the right thumb in the 2nd patient	On the dorsal aspect of fingers bilaterally	27, 35	Asymptomatic patients with skin lesions as the chief complaint	NR
CR	France	Amatore *et al.*[15]	1	Erythematous and oedematous non-pruritic annular fixed plaques	Upper limbs, chest, neck, abdomen and palms, sparing the face and mucous membranes	39	AT the onset of disease	NR
CS	Spain	Andina *et al.*[10]	1	Chilblains	Toes	12 (median age for the series)	Mean of 16 days after initial symptoms	Y
CS	Mexico	Cepeda-Valdes *et al.*[43]	2	Urticaria	Shoulders, elbows, knees and buttocks	20, 50	After respiratory symptoms	NR
CS	Spain	Fernandez *et al.*[44]	2	Acral lesions	Distal aspect of toes and fingers	NR	Median latency of 9.2 days for the series	NR
CR	Italy	Genovese *et al.*[45]	1	Erythematous papules and few vesicles	Trunk	8	6 days after onset of symptoms	NR
CS	USA	Kalner *et al.*[46]	2	Dusky red, non-pruritic, non-blanching periorbital dyschromia	Periorbital region	43, 50	2 days prior to the onset of symptoms	NR
CR	Italy	Locatelli *et al.*[11]	1	Erythemato-oedematous, partially eroded macules and plaques	Dorsal aspect of the hand	16	3 days after dysgeusia and mild diarrhoea	Y
CR	Turkey	Naziroğlu *et al.*[47]	1	Urticaria	Generalised	53	Cutaneous manifestation was the only symptom	NR
CS	USA	Rivera-Oyola *et al.*[48]	2	Erythematous macules coalescing into papules (1) large, disseminated, urticarial plaques (1)	Back, bilateral flanks, groyne, and proximal lower extremities (1), trunk, abdomen, head, and upper and lower extremities (1)	60 , 60	3 days after symptoms (1), 9 days after symptoms (1)	Y

Table 1 *Continued*

Type of study	Region	Author	COVID-19 positive patients	Morphology	Location	Age of the patient	Timing of onset in relation to respiratory symptoms	Histological diagnosis
CS	Spain	Landa *et al.*[49]	2	Acral vascular lesions	Toes	91, 24	Asymptomatic (1), after symptoms (1)	NR
CR	Spain	Mayor-Ibarguren *et al.*[50]	1	Acute leukocytoclastic vasculitis	Lower legs, feet and toes	84	4 weeks after symptoms	Y
CR	Italy	Rossi *et al.*[51]	1	Generalised maculopapular lesions	Trunk, limbs, legs, face	34	Fever and cutaneous lesions only	NR
CS	Spain	Galvan *et al.*[14]	234	Pesudo-chilblain (29), vesicular (17), urticarial (49), maculopapular (122), livedo/necrosis (17)	Trunk and limbs	Pseudo-chilblain (median age: 32), vesicular (median age: 45), urticarial median age: 49), maculopapular (median age: 55), livedo/necrosis (median age: 63)	Pseudo-chilblain (occurred later in the disease), vesicular (occurred during the course of the disease), urticarial and maculopapular lesions (happened at the same time), livedo/necrosis (late sign)	NR
CS	8 countries (USA, UK, Canada, France, Italy, Mexico, The Netherlands and Iran)	Freeman *et al.*[52]	23	Pernio-like lesions	Foot (20), hand (7)	NR	Before symptoms (4), after symptoms (11), at the onset of symptoms (3), no other symptoms (5)	NR
CR	Russia	Olisova *et al.*[53]	1	Erythematous lesions and purpura	Upper eyelid, eyebrow and temple region	12	3 days after symptoms	NR
CR	Portugal	Calvao *et al.*[54]	1	Petechial lesions that evolved into haemorrhagic bullae and necrotic plaques	Hands and feet	81	After respiratory symptoms	Yes
CR	Spain	Bosche-amate *et al.*[55]	1	Reticular purpura	Lower legs	79	7 days after symptoms	Yes
CR	UK	Klimach *et al.*[56]	1	Multiple erythematous, tender papules, macular lesions with associated scattered petechiae	Feet and legs	13	1 days after symptoms	NR
CR	Belgium	Verheyden *et al.*[57]	1	Symmetric livedo reticularis	Trunk and thighs	57	At onset of symptoms	NR
CR	France	Giudice *et al.*[58]	1	Acute necrosis	Bilateral leg and foot	83	After respiratory symptoms	NR
CS	Turkey	Dertlioğlu *et al.*[59]	5	Erythematous lesions	Trunk (4), feet (1)	32, 42, 29, a teenager, 10-month old	After respiratory symptoms (3), cutaneous lesions as the only complaint (2)	NR

CS: case series; CR: case report; NR: not reported.

Table 2 Proportion of analysed case reports and case series of various cutaneous manifestations observed in COVID-19 positive patients

Type of exanthem associated with COVID-19	Cases (n = 406)	Percentage (%)
Acral ischaemic lesions or chilblains	84	20.2
Varicella-like or vesicular lesions	67	16.5
Generalised maculopapular or morbilliform	161	39.7
Urticaria	65	16.0
Livedo reticularis	21	5.20
Others		
Pityriasis rosea	1	0.20
Petechial eruption	1	0.20
Confluent erythematous-yellowish papules	1	0.20
Cutaneous mottling	1	0.50
Periorbital dyschromia	2	0.50
Leukocytoclastic vasculitis	1	0.20
Reticular purpura	1	0.20

manifesting as acral ischaemic lesions or chilblains (20.2%) (3) varicella-like lesions (16.5%) and (4) an acute urticarial reaction (16.0%). The acral lesions affected the toes more commonly than fingers and the vesicular and maculopapular lesions tend to be widespread and usually seen on the trunk, face and neck. There is significant heterogeneity in the timing of onset of the exanthems and the respiratory symptoms. Some reports have suggested that the cutaneous manifestation was the only symptom of COVID-19 in some patients (1.7%).[4,5] A histopathological diagnosis was included in 11 (23%) studies.

DISCUSSION

COVID-19 can present as a syndrome of dry cough, fever, rhinorrhoea, anosmia and fatigue with radiological evidence of bilateral pneumonia seen on chest x-ray and CT chest.[6] Recalcati and colleagues were the first to describe the cutaneous manifestations of COVID-19 infection observed in Italy in 20% of their cohort.[6] Subsequently, new reports have come from many countries confirming the widespread cutaneous signs related to the virus which has been observed sporadically in COVID-19 patients. A recent review by Tang *et al.* analysed 16 studies with 88 confirmed COVID-19 related cutaneous manifestations and concluded that they can be categorised as erythematous, urticarial, and vesicular (chicken pox-like or varicelliform) which most commonly affected the trunk.[7] Some individual reports of a petechial eruption, livedo reticularis, pityriasis rosea and reactivation of herpes simplex virus-1 have also been reported.[8,9] There has also been reports of outbreaks of peculiar perniosis-like acral lesions (chilblains) that have occurred in Spain and Italy amidst the pandemic believed to be a late manifestation of the COVID-19 infection; however, its relevance is questionable as discussed later in the article.[10,11] COVID-19 associated Kawasaki syndrome or paediatric multisystem inflammatory syndrome temporarily associated with COVID-19 (PIMS-TS), also known as multisystem inflammatory syndrome in children (MIS-C) has emerged in Europe and America, with very few cases observed in Asia, especially Japan where the usual incidence is 20 times higher than the Western world.[12] One report recorded significant differences in the COVID-19 triggered Kawasaki disease to the traditional entity, in that COVID-19 was associated with Kawasaki in older children (mean age: 7.5 years) and caused haemodynamic instability in 20% of the affected children as compared to the usual 7%.[12]

According to the analysis done by Tang *et al.*, the latency period between the prodromal clinical symptoms such as cough and fever and cutaneous presentation was −2 to 21 days, with some reports suggesting that the cutaneous manifestation was the only symptom of COVID-19 in otherwise asymptomatic patients.[7,13] The pathogenesis of the skin signs of COVID-19 remains poorly understood and warrants further investigation via large scale prospective studies analysing the serological profile of the antibody response to the infection supported by histopathological diagnosis through biopsies. A study reporting the clinical patterns and sequalae of COVID-19 skin lesions suggested that chilblains affected younger patients, lasted longer and presented later in the disease and were associated with less severe disease.[14] Similar observations have been reported by Andina *et al.* and Recalcalti *et al.*[10,15] In comparison, urticarial and maculopapular lesions occurred earlier in the disease and were associated with more severe COVID-19 disease.[14] Necrotic lesions mainly affected older patients who had severe COVID-19 disease, which is also evident from the data summarised in Table 1.[14]

Given the variety of cutaneous presentations and their timing with respect to stage of disease, it is likely that there are distinct underlying mechanisms potentially including direct endothelial infection, coagulopathy with microthrombosis and immune complex deposition.[16] SARS-CoV-2 virus shows endothelial tropism due to the

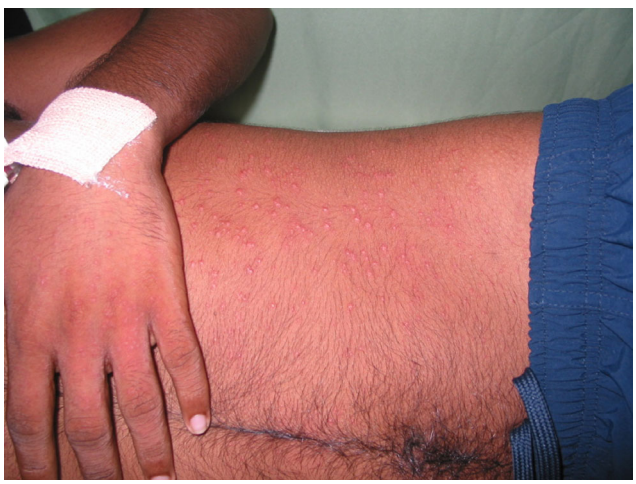

Figure 1 An erythematous maculopapular viral exanthem.

Table 3 Summary of other viral exanthems that present similar to COVID-19[1-3]

Viral URTIs with exanthems	Cutaneous exanthem	Timing of the cutaneous manifestations
Measles (morbillivirus), Fig. 2	Erythematous macules and papules that spread in a cephalocaudal direction	2–4 days after prodrome
Rubella (rubella virus)	Rose-pink macules with cephalocaudal spread	1–5 days after prodrome
Erythema Infectiosum (parvovirus B19 (PVB19))	Bright red macular erythema of the cheeks (slapped cheeks), followed by lacy reticular pattern of macules and papules on the extremities	7–10 days after prodrome
Roseola Infantum (human herpesvirus (HHV) 6B and HHV-7)	Rose-pink macules and papules on the trunk, neck and proximal extremities	3–4 days later
Unilateral laterothoracic exanthem (Epstein–Barr virus, adenovirus and PVB19, HHV-7, parainfluenza)	Morbilliform eruption which is initially unilateral, affecting mainly the axilla and lateral trunk	Few days after the prodrome
Varicella (varicella-zoster virus, VZV)	Erythematous macules and papules on the scalp and face that spread to the trunk and extremities. Lesions evolve into 1–3 mm clear vesicles that evolve into pustules and crust	12 h after the prodrome
Kawasaki disease	Macular and papular erythematous lesions in a morbilliform pattern	Early in the illness
Pityriasis Rosea (multiple causes; HHV-6 and HHV-7, but can also be triggered by hepatitis C, HINI influenza, HHV-8)	Starts with a herald patch (single oval macule) followed by a generalised maculopapular eruption	Herald patch appears 1–20 days before the generalised exanthem
Erythema Multiforme (parapoxvirsuses, HIV, CMV, VZV, hepatitis viruses)	'target-like' lesions, which can involve mucous membranes	Abrupt onset, within 24 h
Human parechoviruses (HPeV −1, 2)	Maculopapular exanthem	Skin signs appear 3 days after febrile illness
Togaviruses (esp. Chikungunya) and bunyavirus haemorrhagic fevers (including Lassa)	Generalised maculopapular petechial exanthem. Often pruritic and may be accompanied by oral or genital aphthous ulceration	2–3 days after onset of fever
Hand, foot and mouth disease (coxsackievirus 16, 4, 5, A7, A9, A10, B2, B5 and enterovirus 71), Fig. 3	Oral lesions begin as erythematous macules and papules on the hard palate, tongue, cheeks and gums then progress to vesicles, which may burst and may form painful ulcers surrounded by a red halo Skin lesions start as erythematous macules or papules which quickly turn into small, grey vesicles surrounded by a red halo	Variable timing, usually early in the illness
Papular pruritic gloves and socks syndrome (PVB19, EBV, CMV, HHV-6, HHV-7, hepatitis B, rubella, measles)	Macular and papular erythema associated with oedema affecting the hands, wrists, feet and ankles. Oral inflammation with petechiae, vesicopustules and ulceration is also common.	Onset of the eruption occurs a few days before fever and malaise
Toxoplasma gondii, 'others' including syphilis, rubella, cytomegalovirus and herpes simplex types 1 and 2 (TORCH) ('Others' now also includes: coxsackie, enteroviruses, PVB19, VZV, HIV, hepatitis B, Zika virus)	Purpura and petechiae associated with oral vesicles and mucosal inflammation if caused due to herpes virus	Variable onset depending on the cause
Zika virus (flavivirus)	Morbilliform or scarlantiniform eruption	Starts on the face on the first day and then spreads to trunk and limbs

cellular distribution of the angiotensin converting enzyme-2 receptor. Direct infection and endothelial activation are likely to explain some of the severe manifestations of COVID-19 including coagulopathy.[16] Furthermore, the deposition of immune complexes on vessels has been implicated in COVID-19 vasculitis with some reports describing leukocytoclastic vasculitis on histopathology.[17]

The cutaneous side effects of medications used to treat COVID-19 such as hydroxychloroquine need to be reported as they can be similar to the cutaneous manifestations of COVID-19.[18] Moreover, the pandemic has resulted in cutaneous signs for up to 97% of the frontline healthcare workers due to the strict personal protective equipment requirements, with the most common eruptions being desquamation, erythema and maceration over the nasal bridge, cheek and face from wearing the N95 facial masks.[19,20]

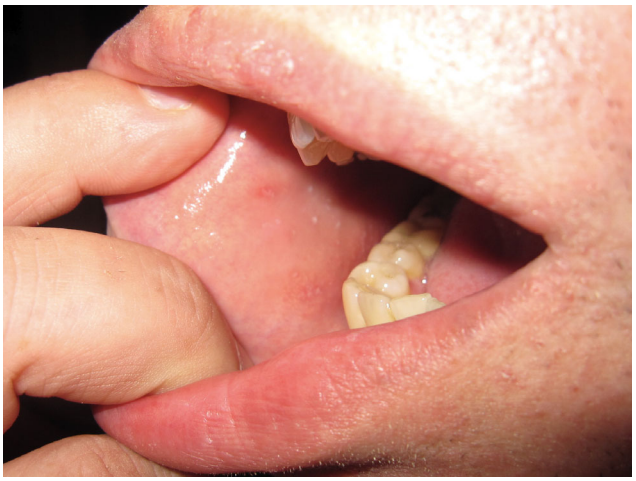

Figure 2 Koplik's spots seen in measles.

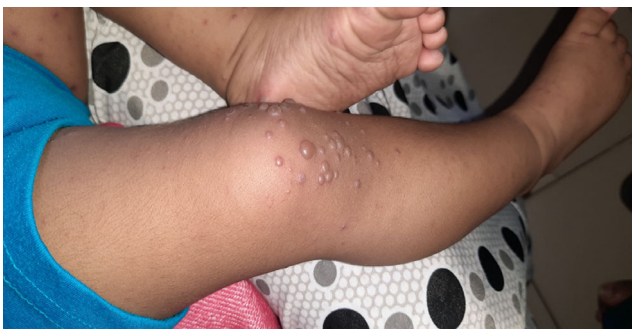

Figure 3 Vesicular eruption seen in hand, foot and mouth disease.

COMPARISON OF COVID-19 WITH OTHER VIRAL EXANTHEMS

The maculopapular (Fig. 1) and morbilliform exanthem is quite commonly observed with other viral infections associated with respiratory symptoms such as infectious mononucleosis, measles, rubella, human immunodeficiency virus (HIV) and roseola, which can also present with a similar prodrome of fever, nasal congestion, cough followed by the skin signs.[1-5] Measles, pityriasis rosea, erythema multiforme and Kawasaki disease are some examples of non-specific viral exanthems that are similar to the reported cutaneous signs of COVID-19.[8,12] The vesicular eruption observed in COVID-19 patients is similar to varicella, hand foot and mouth (HFM) and acute generalised exanthematous pustulosis (AGEP).[1,2] Chilblains, also known as pernio, are quite unusual in other viral upper respiratory tract infections and the mechanism by which SARS-CoV-2 leads to this manifestation is still being investigated. Chilblains can be primary (idiopathic or cold related) or secondary (connective tissue disorders, haematological malignancies, cryopathies, blood hyper viscosities and genetic conditions).[1,2] A study of children from Spain, reported mild symptomatic chilblains as a late manifestation of COVID-19 based on a single case which was positive for COVID-19 via nasopharyngeal swabs.[10] We have not included the patients with chilblains who had negative swab results and thus the prevalence of chilblains may be underrepresented in the summary we have provided. However, given that the PCR result was negative for SARS-CoV-2 in most patients with chilblains, many clinicians question the reliability of this clinical sign in the diagnosis of COVID-19. Other vascular manifestations of COVID-19 such as acro-ischaemic lesion have been reported by Yang *et al.* with a median latency period of 19 days.[21] Table 3 summarises the key similarities and differences between the different viral exanthems (Fig. 2, Fig. 3).[1-5]

CONCLUSION

Viral exanthems provide early diagnostic cues for the clinician. COVID-19 seems to have various cutaneous manifestations, none of which are specific or diagnostic for the disease. It is unclear what proportion of COVID-19 infected patients develop cutaneous manifestations and what pathological mechanisms lead to this. Physicians and dermatologists around the world need to be vigilant about the possibility of COVID-19 as the causative agent of a cutaneous sign in a patient with a viral prodrome, which should prompt testing for COVID-19 where available.

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