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A Looking Beyond the Cutaneous Manifestations of Covid 19- Part 1: The Clinical Spectrum - A Review

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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Review Article

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ABSTRACT

Ever since the first case of Covid 19 pneumonia-like condition was reported from Wuhan, China, researchers were seriously engaged in uncovering evidence of the involvement of organs other than the lung, like kidney, heart, brain, liver and gut. From the dermatologists, world over, specifically from UK, USA, France and Italy etc., reports of Cutaneous involvement in Covid 19 started to pour in, since April - May of 2020. From the localised and benign cutaneous lesions-like Covid toes to moderately severe exanthematous rashes like the morabilliform and vesicular rashes, to more severe, livedoid /necrotic and haemorrhagic rashes were reported. The last group in particular, was associated with underlying potentially fatal pathological conditions like hypercoagulable state and disseminated intravascular coagulation (DIC).These types of cutaneous lesions could be clinically the fore-runner of the underlying pathological states and indicate grave prognosis. Such cases need intensive care management, not because of the skin lesions but for the fatal underlying processes which cause them. In many instances of less severe to moderately severe manifestations as mentioned above, the link to Covid 19, is more circumstantial than direct, as most of them are negative for SARS CoV 2 virus. The one reason for attributing some of these lesions to Covid 19, was due to the fact that they were observed at the height of the Covid 19 epidemic in the countries concerned. Even some researchers expressed doubt, that some of the exanthematous lesions of Covid 19 could be due to an independent seasonal virus or due to the

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coexistence of another concurrent viral disease. The latest report of the coexistent CMV viral infection in Covid 19 patient in April 2020 (Damiano D'Ardes, Andrea Boccatonda, et al.) would support the possibility simultaneous of dual infection. Yet another view was that it could be a delayed manifestation or an epiphenomena of Covid 19. Dengue-like and Kawasaki disease- like lesions were cited as examples of how Covid 19 could mimic other potentially serious diseases. Understandably, all the cutaneous lesions could not be considered on the same footing and hence the necessity to eschew any cavalier approach to any dermatological manifestation that turns up in the context of Covid 19 infection. An attempt was made to review and present the clinical spectrum of cutaneous manifestations of Covid 19, reported till date in the literature, in this part of the article. It was planned to discuss the pathology and pathogenesis of the cutaneous manifestations of Covid 19 in part 2, that would follow.

Keywords: Covid toes; dengue-like rash; kawasaki disease-like lesions; multi system inflammatory syndrome.

1. INTRODUCTION

The first case of the cutaneous manifestations of COVID -19 was reported in the early April 2020 by the dermatologists of France. On 18th April, another case from Belgium was reported in the American journal of Dermatology. Dermatologists in Italy and France first noticed these skin lesions, especially, the chilblain- like lesions at the height of the epidemic in their countries, followed by those from Europe and America. Since then, there was sudden surge in the reporting of the cases similar to frostbite or pernio, among kids in the areas severely affected by Covid-19. Several types of skin lesions were described, since the initial report by Recalcati [1]. Cutaneous lesions with laboratory-confirmed COVID-19 were described in two Chinese cohorts [2,3]. Diversity of clinical appearance of cutaneous manifestations in the course of COVID-19.Was reported by Guarneri C, Venanzi Rullo E, et al .[4] In April of 2020, from the United Kingdom pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 [PIMS-TS] in children similar to incomplete Kawasaki disease (KD) was reported.[5] Since then, there had been increasing reports of similarly affected children in other parts of the world.The various cutaneous manifestations of Covid 19 were reviewed by several authors. [6,7,8,9,] Some of the reviews were from the hospitalized cases [10] and others from the non-hospitalized patients [11]. American Academy of Dermatology (AAD) COVID-19 Task Force launched an online COVID19 dermatology registry,[12] where a record of the reported Covid 19 related cutaneous manifestations was maintained. There were several studies that were contributory to our understanding of the cutaneous lesions of Covid 19, a few of which were quoted here. Galván Casas C.Català A. Carretero Hernández G et al. [13], collected data between 3rd April to 16 April 2020, during the peak of the epidemic in Spain and after exclusions, created a data base of 375 cases. They classified the overall cutaneous manifestations into 5 groups and indicated their relative incidence. The overall mortality is put around 2.9%. Sachideva et al. [14] reviewed eighteen articles and three additional cases, reported apart from the relative incidence of various skin manifestations, and other interesting observations regarding the time of onset of symptoms of the disease and time taken for healing. "The timing appearance of skin lesions ranged from 3 days before to 13 days after diagnosis, and 12.5% at diagnosis or onset of COVID-19 symptoms, while 69.4% after the COVID-19 diagnosis. Of these, 74.0% developed cutaneous pathology within 7 days, and 6.0% reported lesions after 7 days. Of the 50 cases with reported healing times, 100% healing of cutaneous lesions, occured within 10 days. Of these 48.0% of lesions healed within 7 days and 50.0% of lesions healed after 7 days". Jia JL, Kamceva M et al 2020) [15] reviewed all articles published between December 31st, 2019 and May 3, 2020. A total of 997, cases from 64 countries with skin manifestations related to COVID-19 were analysed and published. Key un Tang et al reviewed 14 studies with 228 confirmed cases of Covid 19 and published their findings [16].

2. DISCUSSION

2.1 Three Clinical Pheno Types

Basing on the multiplicity of morphology of the lesions, the different epidemiological settings in

which they were presented, the severity and prognosis etc., the author proposed 3 phenotypic clinical presentations of the cutaneous manifestations of the Covid 19. This perspective may help the clinician to have a basic idea and anticipate the type of skin rash under a given set of conditions. However these clinical types are not water-tight compartments and clinical overlap between groups is possible. Thus a middle aged person might have severe infection associated with increased mortality and an old aged patient could have a more benign clinical course with favourable outcome. Any particular rash may occur, cutting across the age barriers. With these limitations, the characteristics of the 3 phenotypic group characteristics were considered below.

The classification of various types of cutaneous lesions found in the literature and their comparative relative incidence are shown respectively in Table 2 and Table 3.

2.2 Clinically Recognized Cutaneous Lesions in Covid 19

2.2.1 The acral lesions

2.2.1.1 The Covid toe or Chilbain Like Lesions (CLL)

There were several reports in the literature on chilblain-like lesions occurring during Covid 19 infection [17-20]. 80 out of 318 cases in the American Academy of Dermatology/International League of Dermatologic Societies registry developing lesions after the onset of other COVID-19 symptoms. This finding is similar to data from Spain, where 42 out of 71 patients developed lesions after other symptoms .Covid toe is a fanciful name, given to a frostbite like (CLL) /pereniosis like lesion seen on toes and sometimes on fingers. Both have share the same clinical and histological features hearing Covid 19 acral lesions the frostbite perineo like lesions.

2.2.2 CLL- some facts

- Tend to affect younger patients and pediatric groups
- Less severe disease.
- The pseudo-chilblain pattern frequently appears late in the evolution of the COVID-19 disease (59% after the onset of the other symptoms)
- Lasted longer (mean duration 12·7 days),
- May be associated with purpuric areas, affecting the hands and feet.
- They are usually asymmetrical.
- May cause pain (32%)
- Show itching. (30%).
- May show Vesiculation, pustulation, ulceration and haemorrhages some cases.
- They have been described across the age spectrum in patients with confirmed or suspected COVID-19, in the absence of cold exposure or underlying conditions associated with pernio.

2.2.3 Is CLL, due to Covid 19?

The debate is still on, with dermatologists all over the world, taking sides. The occurrence of Covid toe in young asymptomatic patients who tested negative for SARS CoV 2 (see vide infra) is the point raised by those who do not consider the Covid 19 link. The protagonists maintain that such cases represent atypical cases of Covid 19 as seen in young Italians, at the height of the epidemic Yet others, documented with clinical photographs, histological pictures showing frostbite-like pathology with clinico-pathological correlation. Neither CDC nor WHO seems to have made any comment, on this matter till date. The histopathological features of Dense superficial and deep lymphocytic infiltrate, marked Sub -epidermal oedema, lymphocytic perivascular Infiltrate within the dermis and sometimes extending to the sub cutis,are points similar to chilblains suggesting a possible link between the two. This was thought to represent "lymphocytic vasculitis", The most characteristic finding in chilblains in 47% of cases was the association of edema and reticular dermis infiltrate that showed a perieccrine reinforcement. 52% of cases showed necrotic keratinocytes in the epidermis**.** It could also be perhaps due to seasonal virus of the region unrelated to Covid 19 or may be due to concurrent co-infection with other infections. A short discussion on these lines follows vide infra.

2.2.4 Pernio-like lesions may represent a postviral or delayed-onset process

There are several case reports of patients with pernio-like lesions testing positive for either immunoglobulin M (IgM) or immunoglobulin G (IgG) for SARS-CoV-2 infection and negative for polymerase chain reaction (PCR), possibly indicating a later stage in the disease process [21].

Table 1. The group characteristics

	Feature	The first group	The second group	Third group
1	Age group	Paediatric	Middle aged	Older age
2	Lesions	Acral lesions	Truncal lesions	Whole body
3	Lesion Type	Mostly chilblain-like	Morbilliform / vesicular	Haemorrhagic/ Levidoid
4	Severity	Less	Moderate	Extremely high
5	Treatment	Spontaneous healing	Symptomatic treatment	Hospital/ICU treatment
6	Symptoms	Asymptomatic / Paucisymptomatic	Mildly symptomatic	Severely symptomatic
7	SARS virus	Negative	Positive/ Negative	Positive
8	Thrombotic/ Embolic lesions	No	Not seen	Commonly seen
9	Management	Treated on OPD basis	OPD/Hospitalization	Hospitalization/ ICU
10	Prognosis	Good	Good	Guarded
11	Outcome	Good	Good	Could be fatal in some.
12	Comorbidities	Nil	May/ may not be present	Usually present

Table 2. Classification of the skin lesions seen in Covid 19

Predominantly Acral distribution			Predominantly Truncal distribution		
	Common	**Variants**	**Common**		**Others**
A	Frostbite like / Perineo like / Chilblain like / Covid toes	With or without associated vesiculation pustulation and ulceration.	**A**	Pityriasis Rosea-like (maculopapulosquamous lesions)	Grover's disease like rash
B	Plaques on toes and fingers		**B**	Vesicular lesions EMF like lesions Chickenpox like lesions	Kawasaki like rash
C	Ischemic lesions (Acral ischemia)		**C**	Morbilliform rash	Herpes zoster cases
			D	Urticarial type of lesions	Dengue-like rash.
			E	Livedoid /necrotic lesions	

Table 3. Incidence of types of skin lesions in Covid 19 infection

	Lesion Type	Reported Incidence		
		Galván et al.	Sachideva et al.	Jia JL
1	Pseudo-chilblain	19%	15.38%	41.1%
2	Vesicular eruptions	9%	34. 7%	10.1%
3	Urticarial lesions	19%	9 .4%	21.8%
4	Maculopapules	47%	36.1 %	23.1 %
5	Livedoid or necrosis	6%	2.6%	2.3%
6	Petechiae			
7	Lesions on the trunk		69.4%	
8	Acral lesions		19.4%	

2.2.5 Concurrently present another seasonal virus behind the skin lesions of Covid 19?

Many of the truncal lesions and Covid toe cases negative/positive for SARS CoV 2 mimic seasonal bacterial, virulent mycoplasma lesions giving suspicion to some of the manifestations may be unrelated to the SARS CoV 2. This point is entertained by more than one researcher. No attempt has been made to characterise any other concurrent viral infection behind some of the SARS CoV. Instead, shelter is taken under terms such as “atypical presentation" circumstantial evidence due to occurrence at the height of Covi 19 pandemic. The first case of a concurrent Epstein bar virtual infection in Covid 19 patient is reported [22].

2.2.6 Persistence of positive test for SARS CoV2 virus in Covid toe

There is increasing evidence that pernio-like lesions could , in some cases, appear while patients were still PCR-positive for the virus, which has potential implications for infectivity and viral spread [23] In the American Academy of Dermatology/International League of Dermatologic Societie’s registry study, of 318 cases from eight countries, 14 of these cases were PCR positive. In an Italian study that screened 22 patients presenting with pernio-like lesions, (26 percent) were PCR positive for SARS-CoV-2 [24].The finding of PCR positivity is not universal [25] and not all new-onset pernio during the COVID-19 epidemic was necessarily related to COVID-19.

2.2.7 Persistent CLL with concurrent positivity to SARS2 virus

A. G Locatelli E. Robustelli Test P. Vezzoli A. Carugno (May 2020) [26] reported a case of persistent CLL with concurrent positivity to SARS2 virus with histopathological evidence. It is hinted that the pausi-symptomatic cases like the one described, ould pose public health problem and hence the importance of screening persistent CLL cases for the virus.

2.2.8 Covid toe cases testing negative for the Covid 19 virus

Persistently negative for SARSCoV2: Iin Covid toe and other Truncal lesions reported by several authors [27-31]

It is possible false-negative rates may be higher in minimally symptomatic persons. Recent cases of acral perniosis are unrelated to SARS-CoV-2 infection directly and instead represent a temporally associated epiphenomenon that is not yet fully understood. May represent a response to subclinical infection or a convalescent-phase reaction, given the uncertain relationship to SARS-CoV 2.

Asymptomatic/pauci-symptomatic pediatric Covid toe patients [32,33,34]: The cause might be due to probably healthy children having a robust initial IFN-1 immune response to infetion that produces transient cold-like symptoms or no symptoms at all, and which may both protect from progressive infection and precipitate inflammatory perniosis.

2.2.9 The time of onset of skin lesions

Since exposure, ranged from 3 days before to 13 days after diagnosis. And 12.5% at diagnosis or onset of COVID-19 symptoms, while 69.4% of COVID-19 diagnosis of these 74.0% developed cutaneous pathology within 7 days, and 6.0% reported lesions after 7 days. Of the 50 cases with reported healing times:

100% healing of cutaneous lesions, within 10 days. Of these 48.0% of lesions healed within 7 days and 50.0% of lesions healed after 7 days".

2.2.10 Clustering of Covid toe cases

Kelly M. Cordoro Sean D. Reynolds [35] described six healthy adolescents—three siblings per family from two unrelated families—presented within a 48-hour period in April, 2020, with acral perniosis-like lesions in the context of over 30 similar patients . Skin biopsies performed on each of the six patients demonstrated near identical histopathological findings to those of idiopathic perniosis, with a lymphocytic inflammatory infiltrate without evidence of thromboembolism or immune complex vasculitis. While SARS-CoV-2 polymerase chain reaction was negative, testing was performed 1-2 weeks after URI symptoms or sick contact exposure. Another observed feature is occurence of clusters of Covid toe cases. The significance of this observation is not known. These authors opine that these skin findings represent a convalescent-phase cutaneous reaction to SARS-CoV-2 infection Such clusters were reported in Australia [36] and China [37] during unusually cold periods. Such clusters were also seen during viral and mycoplasma infections. [35] described such cluster in two unrelated siblings in warmer climate.While clusters of perniosis cases had been reported in Australia and parts of China during unusually cold periods, perniosis had also clustered in association with viral and bacterial infection including Mycoplasma. Cold agglutinins and cryoglobulins produced in response to viral infection were hypothesized as a cause of post□infectious perniosis.

2.2.11 Simultaneous presence of multiple types of lesions in a patient

Sarah Young, and Anthony P. Fernandez [38] presented a case of Covid 19 with multiple types of cutaneous lesions differing in morphology and occurring simultaneously was reported in a 68-year-old critically ill man with COVID-19 who had a morbilliform rash on his trunk acral purpura reminiscent of perniosis and an ulcerated, purpuric plaque with retiform/livedoid borders on his buttocks. A biopsy from the abdomen shows groups of apoptotic keratinocytes in the epidermis, suggestive of a viral exanthema. A biopsy from the buttocks showed features consistent with a thrombotic vasculopathy.

2.2.12 Demonstration of viral particle in lung and acral capillaries

Our understanding of the pathogenesis of these lesions was still under evolution, though it appears to be a primarily inflammatory process. [39,40,41,42]

The demonstration by immuno-histochemistry and electron microscopy of the virus causing severe acute respiratory syndrome (SARS-CoV-2), in endothelial cells of lesional skin biopsies in a small series of pediatric patients suggests a virus-induced, vascular injury as a potential pathogenic mechanism [43]

3. TRUNCAL LESIONS

3.1 Exanthematous Morbilliform Rash

77.8% In an Italian cohort had an erythematous/morbilliform eruption. Several Spanish groups have also reported morbilliform eruption with one case accompanied by focal purpura. Several case series, a morbilliform rash predominantly involving the trunk were reported as the most common cutaneous manifestation of COVID-19.[44,45,46,47] The rash was noted either at the disease onset or, more frequently, after hospital discharge or recovery. In some cases it was perifollicular and associated with scaling and confluence, which might cause it to be mistaken for pityriasis rosea (pityriasis rosea - like lesions) [48]. They heal in 7 to 10 days time requiring symptomatic treatment.Treated on OPD basis and prognosis is good.

3.2 Vesicular Rash

EMF like lesions,chicken pox like lesions are described in Covid 19 patients . Increased incidence of Herpes Zoster is also reported.

3.2.1 EMF-like lesions

Antonio Torrelo David Andina, Carlos Santonj [49] reported chilblain-like lesions along erythema multiforme (EMF), 3 of them were negative to SARS-CoV2.Immunohistochemistry for SARS-CoV/SARS-CoV-2 spike protein showed granular positivity in endothelial cells and epithelial cells of eccrine glands in 2 biopsies. All patients were pauci- symptomatic and the outcome was good.

J Jimenez-Cauhe et al. [50] described 4 case of EMF -like lesions in Covid 19 patients.

Consisting of erythemato-violaceous patches with a dusky centre, and a pseudo-vesicle in the middle, involving upper trunk, back face and limbs but not palms and soles. Typical target lesions and palatal macules and petechial are also reported by a few patients. Histologically-normal basket-weave stratum corneum, and mild to moderate spongiosis in epidermis, dermis showing dilated vessels filled with neutrophils, extravasation of red blood cells, and lymphocytic perivascular and interstitial infiltrate. resolution occurred within 2-3 weeks of corticosteroid treatment targetoid lesions in Covid 19 reported by Amatore F, Macagno N, Mailhe Met al (2020) [51] and Amatore F, Macagno N, Mailhe Met al [52]

3.2.2 Chicken pox like lesions

22 case of RT-PCR positive Covid 19 cases were reviewed by Angelo Valerio Marzano, Giovanni Genovese, and Piergiacomo Calzavara-Pinton et al. [53]. The details are tabulated below.

AV, Genovese G, Fabbrocini G, et al described an exanthem of chickenpox like rash in a Covid epidemic of 22 patients [54]

3.2.3 Rash resembling Grover's disease

Gianotti R, Zerbi P, Dodiuk-Gad RP [55] reviewing histopathological feature of various types of skin lesions seen in Covid 19, described a case of maculopapuar rash resembling Grovers disease- like feature. diffuse maculopapular eruptio.n involving only the trunk, clinically suggestive for Grover disease. Histopathology showed, in addition to the classic dyskeratotic cells, ballooning multinucleated cells and sparse necrotic keratinocytes with lymphocytic satellitosis. These overlapping features mimicking a viral infection and Grover disease have already been described in patients with simultaneous Grover and Kaposi's varicelliform eruption.

3.3 Acute Urticarial Rash

Recalcati S, reported a few cases of urticaria occurring during Covid 19 infection.D. Henry M. Ackerman E. Sancelme A. Finon E et al reported a case of acute urticaria 3 days before the pt became positive for SARS 2 virus and symptoms began.Recalcati S. noted an increase in IL-6, PCR, and d-dimer [56,57,58] inflammatory factors that are greatly increased during COVID-19 The IL-6 is the possible immunological link between them.

3.4 Ischemic Acral Lesions

These lesions were confused with chilbain-like lesions and levidoid /necrotic lesions by some authors. Others favour these as distinct entities. Zhang Y, Cao W, Xiao M, et al. [59] in a early analysis from Wuhan, China, reported 7 cases of acral ischemia in critically ill patients with COVID19 pneumonia. The most common manifestations of such ischemia included plantar plaques and acrophytic bruises. Five out of the seven patients died of the disease. Kathryn Schultz et all [60] described two cases of acral ischemia involving two fingers, suggesting that acral ischemia has poor prognosis. Clinical and histopathological features and potential pathological mechanisms of skin lesions in COVID-19. Acral ischemia case that occurred in older pts treated in ICU setup and are fore runners of DIC had fatal outcome. Haemorrhagic turn of the rash rash also occurred in similar conditions and were associated with intravascular thrombosis.

Table 4. Description of chickenpox like lesions

S. No	Feature	Findings
1	Median Age	60 Years
2	Gender	Males – *72.7%*
3	Median time from symptoms to exanthem	3 days
4	Median duration of skin manifestations	8 days
5	**Distribution of lesions**	
	Scattered	*72.7%*
	Diffuse	*27.3%*
6	**Site involved**	
	Trunk	Predominantly
	Limbs	Some cases
	Face / Mucosa	Not involved
7	Mild Itching	*40.9%*
8	Skin Biopsy	Consistent with viral infection

3.5 Livedo-like/Retiform Purpura/Necrotic Vascular Lesions

These lesions were reported in patients with COVID-19 [61,62,63]. Retiform purpura and necrotic vascular lesions were described in three patients with severe pulmonary disease [64]. Histologic and immunohistochemistry studies of skin biopsies revealed a pattern of complement-mediated microvascular injury in both involved and normally appearing skin. Histopathological findings of thrombotic vasculopathy and/or laboratory coagulation alterations had been demonstrated in patients with severe COVID-19 and acral, ischemic lesions [65]. InYoung Kim (2020) reported systematic review of 46 articles with 997 patients from 9 countries with skin manifestations related to COVID-19 , found the incidence of levidoid /necrotic lesions to be 2.3%.

3.6 Dengue-like Rash

Gabriel Yan et al [66] reported 2 cases of COVID-19 patients coinfected with dengue fever in Singapore. Beuy Joob et al [67] described a case from Thailand with petechial rash with low platelet counts, initially thought to be due to dengue. In a few days, the patient developed respiratory symptoms and turned positive for the SARS CoV 2. Di Wu, Jianyun Lu, and Weiyun et al [68] contended on the strength of 3 cases that dengue and SARS CoV 2 might coexist simultaneously, especially where dengue was endemic in counties like Thailand, Singapore, Malaysia and Central America. They advised screening of all cases of either disease for the simultaneous occurrence of both the diseases.

3.7 Like Disease (KD) in Covid -19

Cases resembling Kawasaki disease in children were reported in April-may 2020 from UK, USA, France and China. [69] Cases were being reported from Mumbai, India also recently. The rash and fever bring Covid 19 into differential diagnosis with KD and SARS cov 2 positivity establishes the link between the two. Both share the feature of a systemic arteritis especially involving the coronary arteries. Additionally the KD associated with covid 19, exhibited evidence of multi systemic inflammation involving not only the heart but also lungs, liver, and kidneys etc. So this new disease is named as " Multisystem inflammatory syndrome"(MIS). In children syndrome paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 [PIMSTS], [70] The syndrome appears typically 2 to 3 weeks after the child becomes.

4. CONCLUSION

This article reviewed the reported cases of cutaneous manifestations of Covid 19, in the literature till date. The author introduced three clinical phenotypes which correlate with epidemiological and clinical aspects of the various types of lesions described. It is observed that the serious dermatological manifestations like haemorrhagic; livedoid and necrotic rashes correlate with the degree of severity of the severely ill patients admitted in ICU. Benign lesions like Covid toes, occur late in the course of the disease when patients might turn out to be negative for the SARS CoV2 virus, resulting in lesions appearing to be unrelated to Covid 19. Alternatively it could be a late or epiphenomena as contended by some authors. The other exanthematous lesions like vesicular and morbilliform rash etc could be due to manifestations as seen with any other exanthematous viral diseases or could be more specifically related to the Covid 19 or might be due to coexistence of unrelated seasonal viruses. Future research might shed more light on these aspects.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. J Eur Acad Dermatol Venereol; 2020.
2. Guan WJ, Ni ZY, Hu Y et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708–1720.
3. Zhang J, Dong X, Cao Y et al. Clinical characteristics of 140 patients infected with SARS-Cov-2 in Wuhan, China. Allergy. 2020;395:1607
Available:https://doi.org/10.1111/all.14238.
5 phagen S, Gomez X, Gonzalez-Martinez C, et al. Hyperinflammatory shock in children during COVID-19 pandemic, Lancet.

4. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Hyperinflammatory shock in children during COVID-19 pandemicTheocharis P Hyperinflammatory shock in children during COVID-19 pandemic Lancet. 2020;395(10237):1607.
5. Guarneri CE. Venanzi Rullo R. Gallizzi M. et al Diversity of clinical appearance of cutaneous manifestations in the course of COVID-19. Journal of the European Academy of Dermatology and Venereology; 2020.
6. Matar S, Oulès B, Sohier P, Chosidow O, Beylot-Barry M, Dupin N, Aractingi S. Cutaneous manifestations in SARS-CoV-2 infection (COVID-19): a French experience and a systematic review of the literature. J Eur Acad Dermatol Venereol; 2020. DOI:10.1111/jdv.16775. [Epub ahead of print]. Case series & review. [No methods given, despite description as a systematic review] Available:https://doi.org/10.1111/jdv.16775
7. Zhao Q, Fang X, Pang Z, Zhang B, Liu H, Zhang F. COVID-19 and cutaneous manifestations: A systematic review J Eur Acad Dermatol Venereol; 2020. DOI:10.1111/jdv.16778. [Epub ahead of print]. Systematic review.
8. Bakar Dertlioğlu S. Skin manifestations in COVID-19: A case series of 5 patients from ElazıĞ, Turkey. Dermatol Ther. 2020;30:13932. DOI:10.1111/dth.13932. [Epub ahead of print] No abstract available. Case series. Available:https://doi.org/10.1111/dth.13932
9. Rubio-Muniz CA, Puerta-Peña M, Falkenhain-López D, Arroyo-Andrés J, Agud-Dios M, Rodriguez-Peralto JL, Ortiz-Romero PL, Rivera-Díaz R. The broad spectrum of dermatological manifestations in COVID-19. Clinical and histopathological features learned from a series of 34 cases. J Eur Acad Dermatol Venereol. 2020;1.
10. Askin O, Altunkalem RN, Altinisik DD, Uzuncakmak TK, Tursen U, Kutlubay Z. Cutaneous manifestations in hospitalized patients diagnosed as COVID-19. Dermatol Ther; 2020.
11. Diego Fernandez-Nieto, MD, Juan Jimenez-Cauhe,and Daniel Ortega-Quijano. Characterisation of acute acral skin lesions in nonhospitalized patients: A case series of 132 patients during the COVID-19 outbreak. Am Acad Dermatol. 2020;83(1):61–63.
12. Freeman EE, McMahon DE, Fitzgerald ME, et al. The AAD COVID-19 Registry: Crowdsourcing Dermatology in the Age of COVID-19. J Am Acad Dermatol. 148 Published online; 2020. DOI:10.1016/j.jaad.2020.04.045
13. Galván C, Casas A, Catal G. Carretero Hernández etal: Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. British Journal of Dermatology; 2020.
14. Muskaan Sachdeva, Raffaele Gianotti, Roni P. Dodiuk-Gad: Cutaneous manifestations of COVID-19: Report of three cases and a review of literature. Journal of Dermatological Science. 2020;98(2):75-81.
15. Jia JL, Kamceva M, Rao SA, Linos E, Cutaneous Manifestations o COVID-19: A Preliminary Review, Journal of the American Academy of Dermatology; 2020. DOI:https://doi.org/10.1016/j.jaad.2020.05.059.
16. Keyun Tang et al. Cutaneous manifestations of the Coronavirus Disease 2019 (COVID-19): A brief review. Dermatol Ther; 2020.
17. Alramthan A, Aldaraji W. A case of COVID-19 presenting in clinical picture resembling chilblains disease. First report from the Middle East. Clin Exp Dermatol; 2020. .
18. Kolivras A, Dehavay F, Delplace D et al. Coronavirus (COVID-19) infection-induced chilblains: a case report with histopathological findings. JAAD Case Reports; 2020.
19. Piccolo V, Neri I, Filippeschi C et al. Chilblain-like lesions during COVID-19 epidemic: a preliminary study on 63 patients. J Eur Acad Dermatol Venereol 2020.
20. Landa MD et al.Chilblain-like lesions on feet and hands during the COVID-19 Pandemic. International Journal of Dermatology. 2020;59(1).
21. Papa A, Salzano AM, Di Dato MT, Varrassi G Images in Practice: Painful Cutaneous Vasculitis in a SARS-Cov-2 IgG-Positive Child. Pain Ther; 2020
22. EGarcía-Martínez, Javier & Ester, Moreno-Artero & Sandra, Jahnke. Coinfección por SARS-CoV-2 y virus Epstein Barr. Medicina Clínica; 2020. DOI:10.1016/j.medcli.2020.06.017.

23. Freeman EE, McMahon DE, Lipoff JB, Rosenbach M, Kovarik C, Takeshita J, French LE, Thiers BH, Hruza GJ, Fox LP, Pernio-like skin lesions associated with COVID-19: a case series of 318 patients from 8 countries.American Academy of Dermatology Ad Hoc Task Force on Covid-19J Am Acad Dermatol; 2020.
24. Guarneri C, Venanzi Rullo E, Gallizzi R, Ceccarelli M, CannavòSP, Nunnari G. Diversity of clinical appearance of cutaneous manifestations in the course of COVID-19. J Eur Acad Dermatol Venereol; 2020.
25. Docampo-Simón A, Sánchez-Pujol MJ, Juan-Carpena G, Palazón-Cabanes JC, Vergara-De Caso E, Berbegal L, Poveda-Montoyo I, Pastor-Tomás N, Mataix-Díaz J, Terencio-Alemany C, Martínez-Torres A, Miralles-Botella J, Blanes-Martínez M, González-Villanueva I, Betlloch-Mas I. Are chilblain-like acral skin lesions really indicative of COVID-19? A prospective study and literature review. J Eur Acad Dermatol Venereol; 2020
26. Locatelli AGE. Robustelli Tes P. Vezzoli et al Histologic features of long lasting chilblain-like lesions in a pediatric COVID-19 patient. Journal of the European Academy of Dermatology and Venereology; 2020.
27. Alramthan A, Aldaraji W. A case of COVID-19 presenting in clinical picture resembling chilblains disease. First report from the Middle East. Clin Exp Dermatol; 2020.
28. Kolivras A, Dehavay F, Delplace D et al. Coronavirus (COVID-19) infection-induced chilblains: a case report with histopathological findings. JAAD Case Reports; 2020.
Available:https://doi.org/10.1016/j.jdcr.2020.04.011. [Epub ahead of print].
29. Piccolo V, Neri I, Filippeschi C et al. Chilblain-like lesions during COVID-19 epidemic: a preliminary study on 63 patients. J Eur Acad Dermatol Venereol; 2020.
Available:https://doi.org/10.1111/jdv.16526 [Epub ahead of print].
30. Recalcati S, Barbagallo T, Frasin LA et al . Acral cutaneous lesions in the Time of COVID-19. J Eur Acad Dermatol Venereol; 2020.
Available:https://doi.org/10.1111/jdv.1653 [Epub ahead of print].
31. Fernandez-Nieto D, Jimenez-Cauhe J, Suarez-Valle A et al. Characterization of acute acro-ischemic lesions in non-hospitalized patients: a case series of 132 patients during the COVID-19 outbreak. J Am Acad Dermatol; 2020.
32. Ivashkiv LB, Donlin LT.Regulation of type I interferon responses. Nat Rev Immunol. 2014;14(1):36- 49
33. Fiehn C. Familial Chilblain Lupus – What can we learn from type I interferonopathies? Curr Rheumatol Rep. 2017;19(10):61.
34. Kolivras A, Dehavay F, Delplace D, et al. Coronavirus (COVID-19) infection induced chilblains: a case report with histopathological findings. JAAD Case Reports; 2020.
35. Cordoro KM, Reynolds SD, Wattier R, McCalmont TH. Clustered cases of acral perniosis: Clinical features, histopathology, and relationship to COVID-19. Pediatr Dermatol. 2020;37(3):419-423.
DOI:10.1111/pde.14227
36. Larkins N, Murray KJ. Major cluster of chilblain cases in a cold dry Western Australian winter. J Paediatr Child Health. 2013;49(2):144-147.
37. Chan YW, Tang WY, Lam W, et al. A cluster of chilblains in Hong Kong. Hong Kong Med J; 2008.
38. Sarah Young, MD, Anthony P. Fernandez, MD, PhD Cleveland Clinic Journal of Medicine; 2020.
39. Masson A, Bouaziz JD, Sulimovic L, Cassius C, Jachiet M, Ionescu MA, Rybojad M, Bagot M, Duong TA, SNDV Chilblains is a common cutaneous finding during the COVID-19 pandemic: A retrospective nationwide study from France. J Am Acad Dermatol; 2020.
40. Andina D, Noguera-Morel L, Bascuas-Arribas M, Gaitero-Tristán J, Alonso-Cadenas JA, Escalada-Pellitero S, Hernández-MartínÁ, de la Torre-Espi M, Colmenero I, Torrelo A Chilblains in children in the setting of COVID-19 pandemic.Pediatr Dermatol. 2020;37(3):406.
41. Recalcati S, Barbagallo T, Frasin LA, Prestinari F, Cogliardi A, Provero MC, Dainese E, Vanzati A, Fantini F Acral cutaneous lesions in the time of COVID-19. J Eur Acad Dermatol Venereol; 2020.
42. Zhang Y, Cao W, Xiao M, Li YJ, Yang Y, Zhao J, Zhou X, Jiang W, Zhao YQ, Zhang SY, Li TS Zhonghua Xue Ye Xue Za Zhi.

Clinical and coagulation characteristics of 7 patients with critical COVID-2019 pneumonia and acro-ischemia]. 2020;41(0):006.

43. Colmenero I, Santonja C, Alonso-Riaño M, Noguera-Morel L, Hernández-Martín A, Andina D, Wiesner T, Rodríguez-Peralto JL, Requena L, Torrelo A SARS-CoV-2 endothelial infection causes COVID-19 chilblains: histopathological, immunohistochemical and ultraestructural study of 7 paediatric cases.Br J Dermatol; 2020.
44. de Masson A, Bouaziz JD, Sulimovic L, Cassius C, Jachiet M, Ionescu MA, Rybojad M, Bagot M, Duong TA, SNDV Chilblains is a common cutaneous finding during the COVID-19 pandemic: A retrospective nationwide study from France.J Am Acad Dermatol; 2020.
45. Cutaneous manifestations in COVID-19: a first perspective. Recalcati S. J Eur Acad Dermatol Venereol. 2020;34(5):212.
46. Najarian DJ. Morbilliform Exanthem Associated with COVID-19.JAAD Case Rep; 2020.
47. Sachdeva M, Gianotti R, Shah M, Bradanini L, Tosi D, Veraldi S, Ziv M, Leshem E, Dodiuk-Gad RP. Cutaneous manifestations of COVID-19: Report of three cases and a review of literature. J Dermatol Sci. 2020;98(2):75.
48. Galván Casas C, Català A, Carretero Hernández G. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. Br J Dermatol; 2020.
49. Antonio Torrelo, David MD, Andina MD. Carlos Santonja MD Erythema multiforme-like lesions in children and COVID-19. Pediatric Dermatology. 2020;37(3).
50. J Jimenez-Cauhe et al. Erythema Multiforme-Like Eruption in Patients with COVID-19 Infection: Clinical and Histological Findings. Clin Exp Dermatol; 2020.
51. Amatore F, Macagno N, Mailhe M, et al. SARS-CoV-2 infection presenting as a febrile rash. J Eur Acad Dermatol Venereol; 2020.
Available:https://doi.org/10.1111/jdv.16528
52. Van Damme C, Berlingin E, Saussez S, Accaputo O. Acute urticaria with pyrexia as the first manifestations of a COVID-19 infection. J Eur Acad Dermatol Venereol; 2020.
53. Angelo Valerio Marzano, MD, Giovanni Genovese, and Piergiacomo Calzavara-PintonVaricella-like exanthem as a specific COVID-19–associated skin manifestation: Multicenter case series of 22 patients Am Acad Dermatol. 2020;83(1):280–285.
54. Marzano AV, Genovese G, Fabbrocini G, et al. Varicella-like exanthem as a specific COVID-19-associated skin manifestation: Multicenter case series of 22 patients. J Am Acad Dermatol. 2020;83(1):280-285.
55. Gianotti R, Zerbi P, Dodiuk-Gad RP. (Accepted/In press). Clinical and histopathological study of skin dermatoses in patients affected by COVID-19 infection in the Northern part of Italy. Journal of Dermatological Science.
56. Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. J Eur Acad Dermatol Venereol; 2020.
57. Henry D, Ackerman M, Sancelme E, Finon A, Esteve E. Urticarial eruption in COVID-19 infection. J Eur Acad Dermatol Venereol; 2020.
58. Najarian DJ. Morbilliform Exanthem associated with COVID-19. JAAD Case Rep; 2020.
59. Zhang Y, Cao W, Xiao M, et al. Clinical analysis of seven cases of critical new coronavirus pneumonia complicated with extremity ischemia published online ahead of print; 2020.
60. Kathryn Schultz, Jennifer Moriatis Wolf. Digital Ischemia in COVID-19 Patients: Case Report.. Acro-ischemia: in children. The Journal of Hand Surgery. 2020;45(6):518-522
61. Fernandez-Nieto D, Jimenez-Cauhe J, Suarez-Valle A, Moreno-Arrones OM, Saceda-Corralo D, Arana-Raja A, Ortega-Quijano D. Characterization of acute acral skin lesions in nonhospitalized patients: A case series of 132 patients during the COVID-19 outbreak J Am Acad Dermatol. 2020;83(1):61.
62. Hubiche T, Le Duff F, Chiaverini C, Giordanengo V, Passeron T. Negative SARS-CoV-2 PCR in patients with chilblain-like lesions. Lancet Infect Dis. 2020.
63. Roca-Ginés J, Torres-Navarro I, Sánchez-Arráez J, Abril-Pérez C, Sabalza-Baztán O, Pardo-Granell S, Martínez I Cózar V, Botella-Estrada R,Évole-Buselli M Assessment of Acute Acral Lesions in a

Case Series of Children and Adolescents During the COVID-19 Pandemic JAMA Dermatol; 2020.
64. Herman A, Peeters C, Verroken A, Tromme I, Tennstedt D, Marot L, Dachelet C, Gruson D, Hermans C, Baeck k. Evaluation of Chilblains as a Manifestation of the COVID-19 Pandemic. JAMA Dermatol; 2020.
65. Guarneri C, Venanzi Rullo E, Gallizzi R, Ceccarelli M, CannavòSP, Nunnari G Diversity of clinical appearance of cutaneous manifestations in the course of COVID-19. J Eur Acad Dermatol Venereol; 2020.
66. Beuy Joob et al. COVID-19 can present with a rash and be mistaken for dengue. J Am Acad Dermatol. 2020;82(5):177.
67. Yan G, Lee CK, Lam LTM, et al.Covert COVID-19 and false-positive dengue serology in Singapore. Lancet Infect Dis; 2020.
68. Di Wu, MPH, Jianyun Lu, MPH, and Weiyun et al To alert coinfection of COVID-19 and dengue virus in developing countries in the dengue-endemic area. Control and Hospital Epidemiology. Cambridge University Press.
69. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet. 2020;395(10237):1607.
70. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2. JAMA; 2020.

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