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The Cutaneous Manifestations Associated with COVID-19: A review

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ABSTRACT

Importance: As the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic spreads, increasing cases of dermatologic manifestations of the disease continue to be reported.

Observations: In this general review of the case reports, case series, and other systematic reviews on this subject, several patterns of cutaneous lesions have been compiled. These include viral exanthems, papulovesicular, pernio-like, vasculopathy-related, and other miscellaneous rashes.

Conclusions and Relevance: While clinical observations and subjective cases of rashes associated with SARS-CoV-2 are important to furthering our research and study of this viral disease, we as clinicians must be cautious in attributing causation with correlation. Continued research and study are needed before we can attribute a source for these dermatologic manifestations.

Keywords: Dermatology, Rash, Cutaneous, morbilliform, viral exanthem, pernio, chilblains, urticaria, varicelliform, SARS-CoV-2, COVID-19, Coronavirus Disease 19

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Severe acute respiratory syndrome coronavirus 2, (SARS-CoV-2), the virus responsible for Coronavirus Disease 2019 (COVID-19) was first recognized in December of 2019 in the City of Wuhan in Hubei province, China.[1] In the time since the first reported case, COVID-19 has become a global health crisis reaching the level of a pandemic, and clinicians are grappling with task of treating a virus that is not fully understood as of yet. The most common symptoms are cough, fever, and shortness of breath, and it is now known that the virus accesses the host cells through the protein angiotensin-converting enzyme 2 (ACE2), found abundantly in the lungs, amongst many other tissues.[2] Most testing has been done utilizing a nasopharyngeal sample and a reverse transcriptase polymerase chain reaction (RT-PCR) test.

As the virus has spread, emerging reports of pathophysiology, new symptoms and complications, and preliminary basic science findings continue to be published. Included amongst the emerging cases and associated symptoms are those of cutaneous findings in relation to COVID-19 infection. Here, we hope to offer a general review of the cutaneous findings that have been published to date.

As has been done in other papers on this topic,[3-8] broad categories have been used to organize the various cutaneous findings reported in association with COVID-19. These categories are viral exanthema (which includes maculopapular and urticaria), papulovesicular, pernio-like, vasculopathy, and miscellaneous.

Viral exanthema

One of the most mentioned cutaneous finding was that of a viral exanthem rash. Language used to describe this rash ranged from “maculopapular”, “viral exanthem” “macular” to “erythematous rash”, with many variations in between. Some descriptions tended more towards petechial, however these were also included within this category.

While many cases described primarily maculopapular or morbilliform rashes,[9-13] there was some overlap in certain reports, describing both a viral exanthem but also using morphology reminiscent of urticaria or wheals.[14] Unfortunately, most cases did not report presence of dermatographism. A case from France described an “erythematous and edematous non-pruritic annular, circinate fixed plaques involving the upper limbs, neck, abdomen, palms, and sparing the face and mucous membranes”, which the authors note histologically resembled a classic viral exanthem.[15] The authors state that unlike other viral associated urticaria, these plaques were fixed and non-pruritic. Another similar case from Italy details a maculopapular and urticarial rash in a postpartum female confirmed to have COVID-19.[16] At least one paper mentioning a maculopapular rash reported that their patient subsequently did have reactivation of Epstein Barr virus (EBV), which can occur during viral illness.[17] Whether or not reactivation of EBV may play a role in the appearance of some of these rashes remains unknown.

A case from Thailand details how a patient with a petechial rash was initially misdiagnosed with Dengue and then found to be SARS-CoV-2 positive, with the rash thus being attributed to COVID-19 infection.[18] In another report from Madrid, a 48-year-old male presented with a petechial rash involving the popliteal fossae and anterior thighs, with no involvement of the mucosae, and was found to be SARS-CoV-2 positive. The authors mention that the clinical picture resembled the peri flexural petechial exanthem of parvovirus B19.[19] While described slightly differently, several other cases noted a macular/petechial rash with similar involvement of flexural surfaces. [20,21] One of these cases described the rash as being reminiscent of symmetrical drug related intertriginous and flexural exanthema (SDRIFE), which is typically associated with reactions to drugs but has also been seen with viral infections, such as parvovirus B19. Histologically, the case mentioned from Diaz-Guimaraens had overlap features with that of pityriasis rosea, with mounds of parakeratosis, mild spongiosis, and extravasated red blood cells.

Table 1. Viral exanthem rashes reported in association with Covid-19 infection

Sex, Age	Geographic region	Rash Morphology	Initial day of skin findings	Other symptoms	Medications	Suspected vs. confirmed infection	Biopsy results	Day of rash resolution	Author, Publication year
F, 71	Milan, Italy	Pruritic, Maculopapular rash on trunk	N/A	Fever, productive cough, dyspnea	Lopinavir/ritonavir, hydroxychloroquine, ceftriaxone.	Confirmed	N/A	N/A	Sachdeva et al,[1] 2020
F, 77	Milan, Italy	Maculopapular rash (morbilliform) of trunk and macular "hemorrhagic" rash of LE	5	cervical lymphadenopathy, fever, cough	Lopinavir/ritonavir, hydroxychloroquine, Low molecular weight heparin	Confirmed	N/A	N/A	Sachdeva et al,[1] 2020
M, 20	New York, New York	Morbilliform exanthem of trunk and extremities, sparing the face. Non pruritic	NA	Fever, pneumonia	N/A	Confirmed	N/A	N/A	Hunt et al,[2] 2020
F, 64	Colmar, France	Erythematous rash involving antecubital fossa, trunk, axillary folds (reminiscent of Symmetrical drug related intertriginous flexural exanthema, SDRIFE)	4	Fever, fatigue	Paracetamol	Confirmed	N/A	9	Mahe et al,[3] 2020
M, 60	New York, New York	Scattered erythematous macules coalescing into papules on the back, bilateral flanks, groin, and proximal lower extremities, diagnosed to be a viral exanthem.	3	Low grade fever, myalgias, fatigue, mild cough.	N/A	Confirmed	Punch biopsy revealed mild perivascular infiltrate of mononuclear cells surrounding superficial blood vessels. The epidermis had scattered foci of hydropic change with minimal acanthosis, spongiosis, and foci of parakeratosis.	N/A	Rivera-Oyola et al,[4] 2020
M, 39	Marseille, France	Erythematous and edematous non-pruritic annular, circinate fixed plaques involving upper limbs, neck, abdomen, palms and sparing the face and mucous membranes	1	Fever	Hydroxychloroquine	Confirmed	Predominantly superficial perivascular infiltrate of lymphocytes without eosinophils, papillary dermal edema, subtle epidermal spongiosis, mild lymphocytic exocytosis, lichenoid and vacuolar interface dermatitis, with occasional dyskeratotic keratinocytes in the basal layer. No virally induced cytopathic alterations. DIF negative. Compatible with viral exanthemata	7	Amatore et al,[5] 2020
M, N/A	France	Digitate scaly thin plaques involving the lateral trunk, thighs, upper arms, shoulders, and back. The lesions on the back, shoulders, and upper arms were papular. Reminiscent of pityriasis rosea.	8	Fatigue, fever, dyspnea, respiratory distress	N/A	Confirmed	Foci of spongiosis with focal parakeratosis in the epidermis and a few rounded spongiotic vesicles containing aggregates of lymphocytes and Langerhans cells. A moderate lymphohistiocytic infiltrate was present in the superficial dermis and was associated with papillary dermal edema.	N/A	Sanchez et al,[6] 2020
F, 37	Milan, Italy	Erythematous maculopapular lesions of the trunk, neck, and face. Also, nummular erythematous urticaria-like lesions of the lower extremities. No pruritus noted.	3	Fever, cough, myalgias, arthralgia	N/A	Confirmed	N/A	8	Paolino et al,[7] 2020

M, 38	Madrid, Spain	Slightly pruritic Confluent erythematous macules, papules, and petechiae in a symmetric perifluxural distribution affecting the buttocks, popliteal fossae, proximal anterior thighs, and lower abdomen	3	Fever, pleuritic chest pain, dyspnea	Hydroxychloroquine, lopinavir-ritonavir, azithromycin. Dipropionate cream and loratadine for rash	Confirmed	Superficial perivascular lymphocytic infiltrate with abundant red cell extravasation and focal papillary edema, along with focal parakeratosis and isolated dyskeratotic cells. No thrombotic vasculopathy present.	8	Diaz-Guimaraens et al,[8] 2020
M, 27	Tehran, Iran	Erythematous scaly annular plaque on left forearm followed several days later by a generalized papular and plaque type lesions that occurred all over the trunk and upper extremities. Lesions were pruritic.	3	Low grade fever, fatigue, gastroenteritis, and anorexia	Cetirizine	Suspected	N/A	N/A	Ehsani et al,[9] 2020
NA	Bangkok, Thailand	Petechiae rash	N/A	respiratory distress	N/A	Confirmed	N/A	N/A	Joob et al,[10] 2020
F, 57	Paris, France	Diffuse fixed erythematous blanching maculopapular rash on the trunk and limbs and a burning sensation on the palms.	2	Fever, dry cough	paracetamol	Confirmed	Slight spongiosis, basal cell vacuolation and mild perivascular lymphocytic infiltrate. PCR on whole skin biopsy for SARS-CoV-2 was negative.	14	Ahouach et al,[11] 2020
M, 58	Randolph, New Jersey	Erythematous macules arranged in a morbilliform pattern on the legs, thighs, forearms, arms, shoulders, back, chest, and abdomen. These lesions aggregated into confluent erythematous patches larger than 10 cm on the back, abdomen, and chest.	3	Cough, pain in legs and hands.	Azithromycin and benzonatate. Triamcinolone cream.	Confirmed	N/A	5	Najarian et al,[12] 2020
F, 84	Madrid, Spain	Erythematous-purpuric coalescing macules in the flexural regions (axilla). Mildly pruritic.	11	Pneumonia, N/A	Hydroxychloroquine, lopinavir-ritonavir	Confirmed	N/A	N/A	Jimenez-Cauhe et al,[13] 2020
F, 32	Madrid, Spain	Generalized pruritic morbilliform rash, sudden onset, cephalocaudal spread. Involved the face, neck, thorax, abdomen, buttocks, extremities. No palmoplantar or mucosa involvement.	6	Fever, myalgia, asthenia	IV corticosteroid, antihistamine	Confirmed	N/A	10	Avellana Moreno et al,[14] 2020
F, 59	Milan, Italy	Erythematous macules on the arms, trunk, and lower limbs.	3	Bilateral interstitial pneumonia	Lopinavir-ritonavir, heparin, levofloxacin	Confirmed	Superficial perivascular dermatitis with slight lymphocytic exocytosis. In the mid dermis, a small thrombus in a vessel was present. Swollen thrombosed vessels with neutrophils, eosinophils, and nuclear debris were distributed in the dermis	8	Gianotti et al,[15] 2020
F, 89	Milan, Italy	Exanthem of the trunk and arms.	7	Fever, cough	Ceftriaxone, azithromycin	Confirmed	Superficial perivascular dermatitis with cuffs of lymphocytes surrounding blood vessels in a vasculitis pattern. In the mid dermis, there were extravasated red blood cells from damaged vessels.	15	Gianotti et al,[15] 2020

F, 67	Bolognia, Italy	Pruritic, erythematous confluent blanching rash with undefined margins, mainly on neck, trunk, back and proximal extremities.	30	Fever, dyspnea	hydroxychloroquine, omeprazole, piperacillin/tazobactam, and remdesevir	Confirmed	Slight superficial perivascular lymphocytic infiltrate, extremely dilated vessel in the papillary and mis dermis	37	Zengarini et al,[16] 2020

Sex, Age	Geographic region	Rash Morphology	Initial day of skin findings	Other symptoms	Medications	Suspected vs. confirmed infection	Biopsy results	Day of rash resolution	Author, Publication year
M, 71	Mons, Belgium	Extensive acute urticaria	1	Weakness, fever, hypoxemia, unilateral ankle pain, chest pain, atrial fibrillation, constipation	Bilastine	Confirmed	N/A	N/A	van Damme et al,[17] 2020
F, 39	Mons, Belgium	Generalized pruritic urticarial rash which started on forearms and spread diffusely.	2	Fever, chills, myalgia, headache, rhinorrhea, dry cough, dyspnea, anosmia, ageusia.	Bilastine	Suspected	N/A	N/A	van Damme et al,[17] 2020
F, 27	Orleans, France	Disseminated pruritic erythematous plaques with involvement of the face and acral surfaces diagnosed as urticaria	N/A	Odynophagia, arthralgia, chills, chest pain, fever	Paracetamol and antihistamines	Confirmed	N/A	N/A	Henry et al,[18] 2020
F, 60	New York, New York	Sudden onset, pruritic urticarial plaques of the trunk, head, upper and lower extremities	9	Low grade fever, myalgias, fatigue, mild cough, lower abdominal discomfort, and loose stools	Fexofenadine	Confirmed	N/A	N/A	Rivera-Oyola et al,[4] 2020
M, 61	Madrid, Spain	Urticarial exanthem consisting of confluent, edematous and erythematous papules on the thighs, arms, and forearms. Mildly pruritic.	0	Asymptomatic	Antihistamine	Confirmed	N/A	7	Quintana-Castanedo et al,[19] 2020
F, 32	Madrid, Spain	Urticariform rash, involving trunk and extremities	6	N/A	Hydroxychloroquine, azithromycin, oral antihistamine	Confirmed	Perivascular infiltrate of lymphocytes, some eosinophils and upper dermal edema.	10	Fernandez-Nieto et al,[20] 2020

Abbreviations: F, female; M, male; N/A, not available; Coronavirus Disease 2019 (Covid-19)

Table 2. Papulovesicular rashes reported in association with Covid-19 infection

Sex, Age	Geographic region	Rash Morphology	Initial day of skin findings	Other symptoms	Medications	Suspected vs. confirmed infection	Biopsy results	Day of rash resolution	Author, Publication year
F, 72	Milan, Italy	Papulovesicular, pruritic rash of inframammary folds, trunk, and hips.	4	Headache, arthralgia, myalgia, fever.	N/A	Confirmed	N/A	10	Sachdeva et al,[1] 2020
M, 75	Rome, Italy	Diffuse Papulovesicular lesions (predominance papules) on the trunk with no itching.	12	Fever, asthenia, hypogeusia, hyposmia	N/A	Confirmed	N/A	17	Marzano et al,[21] 2020
M, 57	Milan, Italy	Diffuse Papulovesicular lesions (predominance vesicles) on the trunk with mild itching.	5	Fever, cough, coryza, headache, hyposmia, hypogeusia, weakness	N/A	Confirmed	N/A	9	Marzano et al,[21] 2020
M, 59	Milan, Italy	Scattered papulovesicular lesions (predominance papules) with mild itching on the trunk	7	Fever, cough, pharyngodynia, headache, weakness	N/A	Confirmed	N/A	22	Marzano et al,[21] 2020
F, 56	Brescia, Italy	Scattered papulovesicular lesions (predominance vesicles) with pain on the trunk	3	Fever, cough, coryza, headache, weakness	N/A	Confirmed	N/A	18	Marzano et al,[21] 2020
M, 28	Bolognia, Italy	Diffuse papulovesicular lesions, predominance papules with itching on the trunk	4	Fever, cough	N/A	Confirmed	N/A	11	Marzano et al,[21] 2020
M, 45	Biella, Italy	Scattered papulovesicular lesions (predominance papules) with no itching on the trunk.	6	Fever, diarrhea, nausea	N/A	Confirmed	N/A	16	Marzano et al,[21] 2020
M, 72	Brescia, Italy	Scattered papulovesicular lesions (predominance vesicles) with no itching on the trunk and limbs	N/A	Fever, cough, coryza, headache, dyspnea	N/A	Confirmed	N/A	N/a	Marzano et al,[21] 2020
M, 83	Cremona, Italy	Scattered papulovesicular lesions (predominance vesicles) with no itching on the trunk	2	Fever, dyspnea	N/A	Confirmed	N/A	7	Marzano et al,[21] 2020
M, 61	Milan, Italy	Diffuse papulovesicular lesions (predominance vesicles) with mild itching on the trunk	2	Fever, cough, dyspnea, coryza, headaches, weakness	N/A	Confirmed	N/A	6	Marzano et al,[21] 2020
M, 29	Brescia, Italy	Scattered papulovesicular lesions (predominance vesicles) with mild itching of the trunk	1	Fever, cough, weakness	N/A	Confirmed	N/A	13	Marzano et al,[21] 2020
M, 65	Brescia, Italy	Scattered papulovesicular lesions (predominance papules) with burning on the trunk.	2	Fever, cough, dyspnea, coryza, headaches, weakness	N/A	Confirmed	N/A	15	Marzano et al,[21] 2020
M, 44	Brescia, Italy	Scattered papulovesicular lesions (predominance vesicles) with burning and itching, on the trunk	3	Fever, cough, coryza, headache, weakness	N/A	Confirmed	N/A	11	Marzano et al,[21] 2020
M, 75	Cremona, Italy	Scattered vesicular lesions (predominance of vesicles) with no itching on the trunk and limbs	0	Fever, dyspnea	N/A	Confirmed	N/A	8	Marzano et al,[21] 2020

F, 51	Brescia, Italy	Scattered papulovesicular lesions (predominance of vesicles) with pain on the trunk	4	Fever, cough, dyspnea, coryza, headaches, weakness	N/A	Confirmed	N/A	12	Marzano et al,[21] 2020
F, 62	Brescia, Italy	Scattered papulovesicular lesions (predominance of papules) with burning on the trunk	2	Fever, cough, coryza, headache, weakness	N/A	Confirmed	N/A	13	Marzano et al,[21] 2020
M, 25	Siena, Italy	Diffuse papulovesicular lesions (predominance of vesicles) with itching on the trunk and limbs	5	Cough, hyposmia, hypogeusia	N/A	Confirmed	N/A	11	Marzano et al,[21] 2020
F, 90	Cremona, Italy	Scattered papulovesicular lesions (predominance of vesicles) with no itching on the trunk	1	Fever, cough, dyspnea, coryza, headaches, weakness	N/A	Confirmed	N/A	7	Marzano et al,[21] 2020
F, 69	Brescia, Italy	Scattered papulovesicular lesions (predominance of papules) with no itching on the trunk	N/A	Fever, cough, dyspnea, coryza, hyposmia, hypogeusia, headaches, weakness	N/A	Confirmed	N/A	N/A	Marzano et al,[21] 2020
M, 65	Naples, Italy	Diffuse papulovesicular lesions (predominance of papules) with mild itching on the trunk	2	Fever, cough	N/A	Confirmed	N/A	11	Marzano et al,[21] 2020
M, 80	Brescia, Italy	Scattered papulovesicular lesions (predominance of vesicles) with no itching on the trunk and limbs	N/A	Fever, dyspnea	N/A	Confirmed	N/A	N/A	Marzano et al,[21] 2020
M, 43	Milan, Italy	Scattered papulovesicular lesions (predominance of vesicles) with mild itching of the trunk	0	Fever, myalgia	N/A	Confirmed	N/A	11	Marzano et al,[21] 2020
F, 8	Milan, Italy	Scattered papulovesicular lesions (predominance of papules) with no itching on the trunk	3	Fever, cough	N/A	Confirmed	N/A	10	Marzano et al,[21] 2020
F, 8	Milan, Italy	Papulovesicular skin eruption bilaterally and symmetrically on the trunk. The lesions were initially erythematous papules which evolved to superficial vesiculation and crust formation.	3	Cough, fever	N/A	Confirmed	N/A	7	Genovese et al,[22] 2020
M, 57	Milan, Italy	Widespread pruritic eruption of erythematous macules and papules. Grover's-like (vesicles, crust)	0	Fever, headache, cough.	Levofloxacin, hydroxychloroquine.	Confirmed	Superficial perivascular vesicular dermatitis. Focal acantholytic suprabasal clefts, dyskeratotic and ballooning herpes-like keratinocytes observed. A patchy band-like infiltration with occasional necrotic keratinocytes and minimal lymphocytic satellitosis were present. In the dermis, the vessels were swollen, with dense lymphocyte infiltration, mixed with rare eosinophils. Within the epidermis, a nest of Langerhans cells were also observed.	10	Gianotti et al,[15] 2020

Abbreviations: F, female; M, male; N/A, not available; Coronavirus Disease 2019 (Covid-19)

Table 3. Pernio-Like rashes reported in association with Covid-19 infection

Sex, Age	Geographic region	Rash Morphology	Initial day of skin findings	Other symptoms	Medications	Suspected vs. confirmed infection	Biopsy results	Day of rash resolution	Author, Publication year
F, 27	Qatar	Erythematous-purpuric papules on dorsal aspect of fingers bilaterally (chilblains)	N/A	None	N/A	Confirmed	N/A	N/A	Alramthan et al,[23] 2020
F, 35	Qatar	Erythematous-purpuric papules on dorsal aspect of fingers bilaterally, diffuse erythema of subungual right thumb (chilblains)	N/A	None	N/A	Confirmed	N/A	N/A	Alramthan et al,[23] 2020
N/A	Madrid, Spain	Acral-ischemic rounded reddish-purple plaques, sharply defined, no retiform borders. Affected toes.	17	Atypical bilateral pneumonia	N/A	Confirmed	Intraepidermal vesicle with ischemic necrosis on roof, containing preserved cell outlines without nuclei, and reticular changes. Acute inflammatory infiltrate and dermal vessel dilation.	31	Suarez-Valle et al,[24] 2020
N/A	Madrid, Spain	Acral-ischemic rounded reddish-purple plaques, sharply defined, no retiform borders. Affected toes.	24	Atypical bilateral pneumonia	N/A	Confirmed	Intraepidermal vesicle with ischemic necrosis on roof, containing preserved cell outlines without nuclei, and reticular changes. Acute inflammatory infiltrate and dermal vessel dilation.	38	Suarez-Valle et al,[24] 2020
N/A	Madrid, Spain	Acral-ischemic rounded reddish-purple plaques, sharply defined, no retiform borders. Affected toes.	28	Atypical bilateral pneumonia	N/A	Confirmed	Intraepidermal vesicle with ischemic necrosis on roof, containing preserved cell outlines without nuclei, and reticular changes. Acute inflammatory infiltrate and dermal vessel dilation.	42	Suarez-Valle et al,[24] 2020
M, 15	Bilbao, Spain	Chilblains-like lesion on toes and heel, pruritic	N/A	Asymptomatic	Hydroxychloroquine, azithromycin, heparin	Suspected	N/A	N/A	Landa et al,[25] 2020
F, 15	Bilbao, Spain	Chilblains-like lesion of the finger, heels, tender to palpation	7	Nasal Congestion, diarrhea	N/A	Suspected	N/A	N/A	Landa et al,[25] 2020
F, 23	Bilbao, Spain	Chilblains-like lesion to toes, mildly pruritic	21	Fever, headaches, pruritus	N/A	Suspected	N/A	N/A	Landa et al,[25] 2020
M, 44	Bilbao, Spain	Chilblains-like lesion to toes, tender to palpation	10	Pharyngitis	N/A	Suspected	N/A	N/A	Landa et al,[25] 2020
M, 91	Bilbao, Spain	Chilblains-like lesion of toe	21	N/A	N/A	Confirmed	N/A	N/A	Landa et al,[25] 2020
F, 24	Bilbao, Spain	Chilblains-like lesion of the toes, tender to palpation	N/A	N/A	N/A	Confirmed	N/A	N/A	Landa et al,[25] 2020
M, 26	Italy	Hardened, erythematous plaques of the heels with a burning sensation	N/A	Asymptomatic	None	Suspected	N/A	N/A	Tosti et al,[26] 2020
F, 16	Italy	Erythematous plaques of both heels which were moderately painful	14	phayngodynia	Emollients, paracetamol	Suspected	N/A	N/A	Tosti et al,[26] 2020
F, 18	Italy	Erythematous plaques of the extensor surface of the toes and erythematous papules of the heels. Pruritic and painful.	N/A	Asymptomatic	Emollients, paracetamol	Suspected	N/A	N/A	Tosti et al,[26] 2020
M, 48	Italy	Hardened, erythematous plaques of the extensor surfaces of the toes bilaterally consistent with acrocyanosis.	10	headache, low grade fever, asthenia.	Paracetamol	Suspected	N/A	N/A	Tosti et al,[26] 2020

F, 28	Valencia, Spain	Erythematous-yellowish papules which progressed to indurated pruritic plaques of the bilateral heels.	13	Dry cough, nasal congestion, fatigue, myalgias, arthralgias, diarrhea, ageusia, anosmia.	Paracetamol	Confirmed	N/A	N/A	Estebanez et al,[27] 2020
M, 23	N/A	Many violaceous, infiltrated, and painful plaques on an erythematous background on the dorsal aspect of the toes and the lateral sides of the feet.	3	Low grade fever and dry cough	N/A	Confirmed	Superficial and deep lichenoid, perivascular, and perieccrine infiltrate of lymphocytes, with occasional plasma cells. No vacuolar alteration along basal layer of epidermis, with scattered necrotic apoptotic keratinocytes, which were occasionally present in the superficial layers of the epidermis. The basement membrane zone was smudged, and there was papillary dermal fibrin confined near the ulcer edge. No pallor/edema of papillary dermis. The infiltrate was dense and lichenoid in the papillary and superficial reticular dermis, and deeper dermis had tightly cuffed perivascular and perieccrine distribution.	N/A	Kolivras et al,[28] 2020
F, 16	Ciudad Real, Spain	Red-violet plaques of the bilateral feet with pruritus, swelling, and pain with ambulation	N/A	Fever, nausea, dizziness, abdominal pain, cough, dyspnea, headache, dry eyes.	Acetaminophen, topical emollients	Confirmed	N/A	N/A	Nirenberg et al,[29] 2020
F, 11	Milan, Italy	5-10 mm dusky erythematous macules with indistinct borders on the lateral margin of the feet and dorsal surface of the right first three toes. On the left foot, the plantar surface of the first and fourth toe were erythematous-cyanotic and slightly atrophic. The dorsal surface of the third and fourth toe had erythematous plaques. The lesions became edematous and painful.	N/A	Headache, rhinitis	None	Suspected	N/A	N/A	Colonna et al,[30] 2020
F, 6	Monza, Italy	8-10 mm erythematous, edematous rounded macular lesions with indistinct borders and central erythematous-cyanotic area on bilateral plantar surface of feet. Lesions were pruritic and moderately painful.	10	Fever, localized pain on soles.	none	Suspected	N/A	13	Colonna et al,[30] 2020
M, 5	Milan, Italy	Chilblain-like lesions, several rounded macules and patches on bilateral plantar feet and right hand.	4	Fever, pneumonia	Systemic antibiotics (NOS)	Suspected	N/A	7	Colonna et al,[30] 2020
F, 11	Milan, Italy	5-15 mm erythematous plaques on lateral margin of the left foot and dorsal surface of the left second, third, and fifth toes.	0	Fever, localized pain on soles.	none	Suspected	Dense lymphocytic perivascular cuffing and periadnexal infiltration. Signs of vasculitis were evident in small or medium sized vessels with endothelial cell swelling and erythrocyte extravasation. Fibrin thrombus was evident in superficial capillary vessels.	N/A	Colonna et al,[30] 2020
F, 16	Valencia, Spain	Violaceous erythema over distal joins of hands	N/A	N/A	N/A	Suspected	N/A	N/A	Torres-Navarro et al,[31] 2020
M, 16	Valencia, Spain	Acral erythema with red papules and orange hue	N/A	N/A	N/A	Suspected	N/A	N/A	Torres-Navarro et al,[31] 2020

Abbreviations: F, female; M, male; N/A, not available; Coronavirus Disease 2019 (Covid-19)

Table 4. Vasculopathy rashes reported in association with Covid-19 infection

Sex, Age	Geographic region	Rash Morphology	Initial day of skin findings	Other symptoms	Medications	Suspected vs. confirmed infection	Biopsy results	Day of rash resolution	Author, Publication year
F, 70	Chicago, Illinois	Gradually worsening mottled duskiness of the right hand second, third, and fourth phalanges and nailbeds. Cool to palpation	19	Fever, chills, dyspnea, headache, malaise, ARDS	Tocilizumab, kaletra/ribavirin, cefepime, vancomycin, hydroxychloroquine, azithromycin, cefdinir, ceftriaxone, oral vancomycin, and metronidazole. Heparin drip, topical nitroglycerin.	Confirmed	N/A	N/A	Schultz et al,[32] 2020
M, 43	Chicago, Illinois	Ischemic changes, duskiness of middle and small fingertips. Digital ischemia.	N/A	Dyspnea, cough, chest pain, fatigue, diarrhea, decreased urine output	Tocilizumab, kaletra/ribavirin, cefepime, vancomycin, hydroxychloroquine, azithromycin, tobramycin, ceftriaxone, piperacillin/tazobactam, fluconazole, oral vancomycin, and metronidazole. Heparin, topical nitroglycerin.	Confirmed	N/A	N/A	Schultz et al,[32] 2020
M, 32	New York, New York	Retiform purpura with extensive surrounding inflammation on buttocks.	N/A	Fever, cough, ventilator dependence	Hydroxychloroquine, azithromycin, remdesivir.	Confirmed	Thrombogenic vasculopathy accompanied by extensive necrosis of the epidermis and adnexal structures, including the eccrine coil. There was a significant degree of interstitial and perivascular neutrophils with prominent leukocytoclasia. Immunohistochemistry showed striking deposition of C5b-9 within the microvasculature.	N/A	Magro et al,[33] 2020
F, 66	New York, New York	Dusky purpuric patches on palms and soles bilaterally	19	Fever, cough, diarrhea, chest pain, ventilator dependence	Hydroxychloroquine, enoxaparin.	Confirmed	Superficial vascular ectasia and occlusive arterial thrombus within deep reticular dermis, absent inflammation. Extensive vascular deposits of C5b-9, C3d, and C4d were observed throughout the dermis, with marked deposition in an occluded artery.	N/A	Magro et al,[33] 2020
F, 40	New York, New York	Mildly purpuric reticulated eruption on chest, arms, and legs consistent with livedo racemosa.	N/A	Fever, dry cough, myalgias, diarrhea, ventilator dependence.	N/A	Confirmed	Modest perivascular lymphocytic infiltrate in the superficial dermis along with deeper seated small thrombi within rare venules of the deep dermis. Absence of clear vasculitis. Significant vascular deposits of C5b-9 and C4d were observed.	N/A	Magro et al,[33] 2020

Abbreviations: F, female; M, male; N/A, not available; Coronavirus Disease 2019 (Covid-19)

Table 5. Miscellaneous rashes reported in association with Covid-19 infection

Sex, Age	Geographic region	Rash Morphology	Initial day of skin findings	Other symptoms	Medications	Suspected vs. confirmed infection	Biopsy results	Day of rash resolution	Author, Publication year
F, 6 months	N/A	Kawasaki disease, mucocutaneous findings: prominent tongue papilla, blanching polymorphous, maculopapular rash, edema of hands and lower extremities	2	Fever, fussiness, limbic sparing conjunctivitis	IVIG, high dose ASA	Confirmed	N/A	N/A	Jones et al,[34] 2020
F, 43	New York, New York	Dusky red, non-pruritic, non-blanching periorbital dyschromia	0	Fever, cough, pharyngitis, muscle weakness, myalgias, dyspnea	Alclometasone dipropionate 0.05% ointment	Confirmed	N/A	N/A	Kalner et al,[35] 2020
M, 50	New York, New York	Dusky red, non-pruritic, non-blanching periorbital dyschromia	0	Fever, dyspnea, myalgias, syncope	N/A	Confirmed	N/A	N/A	Kalner et al,[35] 2020
F, 63	Madrid, Spain	Erythematous papules on the upper trunk that progressively turned to erythematous violaceous patches with a dusky center, and a pseudo vesicle in the middle. Lesions were markedly coalescing in the back and spread to the face and limbs within 1 week, no involvement of palms and soles.	19	N/A	Lopinavir-ritonavir, hydroxychloroquine, azithromycin, corticosteroids, ceftriaxone	Confirmed	Normal basket weave stratum corneum, mild to moderate spongiosis in the epidermis. The dermis revealed dilated vessels filled with neutrophils, extravasation of erythrocytes, and lymphocytic perivascular and interstitial infiltrate	N/A	Jimenez-Cauhe et al,[36] 2020
F, 77	Madrid, Spain	Erythematous papules on the upper trunk that progressively turned to erythematous violaceous patches with a dusky center, and a pseudo vesicle in the middle. Lesions were markedly coalescing in the back and spread to the face and limbs within 1 week, no involvement of palms and soles.	16	N/A	Lopinavir-ritonavir, hydroxychloroquine, azithromycin, corticosteroids	Confirmed	Normal basket weave stratum corneum, mild to moderate spongiosis in the epidermis. The dermis revealed dilated vessels filled with neutrophils, extravasation of erythrocytes, and lymphocytic perivascular and interstitial infiltrate	N/A	Jimenez-Cauhe et al,[36] 2020
F, 58	Madrid, Spain	Erythematous papules on the upper trunk that progressively turned to erythematous violaceous patches with a dusky center, and a pseudo vesicle in the middle. Lesions were markedly coalescing in the back and spread to the face and limbs within 1 week, no involvement of palms and soles.	24	N/A	Lopinavir-ritonavir, hydroxychloroquine, azithromycin, corticosteroids, ceftriaxone	Confirmed	Normal basket weave stratum corneum, mild to moderate spongiosis in the epidermis. The dermis revealed dilated vessels filled with neutrophils, extravasation of erythrocytes, and lymphocytic perivascular and interstitial infiltrate	N/A	Jimenez-Cauhe et al,[36] 2020
F, 69	Madrid, Spain	Erythematous papules on the upper trunk that progressively turned to erythematous violaceous patches with a dusky center, and a pseudo vesicle in the middle. Lesions were markedly coalescing in the back and spread to the face and limbs within 1 week, no involvement of palms and soles.	19	N/A	Lopinavir-ritonavir, hydroxychloroquine, azithromycin	Confirmed	Normal basket weave stratum corneum, mild to moderate spongiosis in the epidermis. The dermis revealed dilated vessels filled with neutrophils, extravasation of erythrocytes, and lymphocytic perivascular and interstitial infiltrate	N/A	Jimenez-Cauhe et al,[36] 2020

Abbreviations: F, female; M, male; N/A, not available; Coronavirus Disease 2019 (Covid-19)

Several cases reviewed also mentioned COVID-19 positive patients who appeared to have a rash similar in appearance to pityriasis rosea.[17,22]

Several rashes were described as purely urticarial.[23-25] Pruritus was a common associated symptom. Interestingly, many of the cases had relatively mild COVID-19 related symptoms, with one case of a 27 year old female whose presenting symptom was disseminated urticaria prior to onset of other symptoms of COVID-19, such as fever, chills, and pleuritic chest pain.[24] Another such patient was a 61 year old male from Madrid, Spain, who was essentially asymptomatic but was confirmed to be positive with SARS-CoV-2 on PCR.[26] Histological findings of this case included perivascular infiltrate of lymphocytes, some eosinophils, and upper dermal edema. A more complete outline of the articles reporting a viral exanthem rash are summarized in Table 1.

Papulovesicular

While less common, vesicular or papulovesicular rashes have been reported in association with COVID-19. Almost all the cases involved the trunk, with associated symptoms ranging from pain, to a burning sensation, to pruritus. Most of these cases were paucisymptomatic regarding COVID-19 systemic symptoms. In a paper summarizing results from Barcelona and Rome, vesicular eruptions were also documented.[27] From their Rome data, 2 of the 130 patients (1.5%) experienced isolated herpetiform lesions on the trunk, described as vesicles with erythematous halos and pruritus. One such patient did have serum crust formation. One patient from Barcelona experienced numerous vesicular lesions on his back 8 days after diagnosis with COVID-19.[27] There was no information on whether the lesions were biopsied or if other herpes viruses were ruled out.

A case series from eight Italian dermatology units looked at 22 patients with confirmed COVID-19 who experienced a varicella-like rash.[28] They documented no new medications within 15 days of the rash for all patients. Unfortunately, only 7 patients were able to provide a biopsy. The general histology findings were reported as a basketweave hyperkeratosis, with a slightly atrophic epidermis, vacuolar degeneration of the basal layer with multinucleate, hyperchromatic keratinocytes and dyskeratotic cells, with absence of an inflammatory infiltrate. Interestingly, another report from Milan, Italy, detailed a rash “reminiscent of Grover’s disease” with very similar findings on pathology,[10] described as a superficial perivascular vesicular dermatitis with focal acantholytic suprabasal clefts and dyskeratotic and ballooning herpes-like keratinocytes. A patchy band-like infiltration with occasional necrotic keratinocytes and minimal lymphocytes were present. In the dermis, the vessels were swollen, with dense lymphocyte infiltration, mixed with rare eosinophils. The articles reporting a papulovesicular rash are summarized in Table 2.

Pernio

The cutaneous finding that seems to have had the most attention in social media and recent publications is the pernio-like rash. Pernio, also synonymous with chilblains, is typically a cold-sensitive inflammatory disorder with discoloration of acral skin, usually attributed to exposure to cold and wet conditions.[29] The pathogenesis is unknown but thought to be vascular, with some association to cryoglobulins and cold agglutinins, and even bacterial and viral infections.

From the reports we reviewed, the average patient age for this skin finding in association to COVID-19 is much younger, presently most commonly in children and young adults. Morphological descriptions range from erythematous-purpuric papules and plaques to erythematous-yellowish papules, usually located on the toes, heels, and feet and sometimes occurring on the fingers as well. One observed case described a rash in a 28 year old female as erythematous plaques of the bilateral feet and offered a differential of urticaria vs urticarial vasculitis, however the description falls more in line with the pernio category.[30] Associated symptoms were tenderness, burning, or pruritus. Some patients also

had livedo reticularis reported on the upper and lower extremities.[31] The prognosis tended to be favorable, as most patients had relatively mild symptomatology and required little to no medical intervention.[32]

Many of these lesions appeared either in asymptomatic individuals or in patients who endorsed mild URI symptoms weeks prior. In a retrospective review of 22 children and adolescents with chilblains-like lesions seen in the peak of the COVID-19 pandemic in Madrid, Spain, most patients were found to be SARS-CoV-2 negative on PCR testing. [32] Although negative SARS-CoV-2 testing was seen frequently in the pernio case reports, it was argued that many patients had exposure to sick contacts and perhaps the PCR test was administered too late, thus, it was still reasonable to credit or associate COVID-19 with the rash.[33-36] From the cases that were able to obtain histology specimens, the findings tended to support the diagnosis of pernio.[32]

Unlike the other cutaneous findings reviewed, there were many more attempts at explaining the possible pathophysiology for the acral pernio-like lesions. Earlier reports tended to hypothesize that systemic coagulopathy may be responsible for the lesions.[3,37] Some authors support an involvement of interferons,[31,38] such as interferon I, while other authors discredit this hypothesis and err on the side of skepticism.[32] The former argue that patients with type I interferonopathies experience pernio-like lesions and that, perhaps a robust type I interferon response to viral infection in younger, healthier patients may contribute to pernio-like eruptions. Others hypothesize that the pernio lesions may due to an immune vasculitis[35] or be a late manifestation of COVID-19,[39] as they were observed weeks after the peak of infectivity was reached in their country. Thus, the lesions may be due to antigen-antibody immunology processes when viral load and infectivity is low, partially explaining why some patients tested negative for SARS-CoV-2.[34] However, some argue that the rash likely has nothing to do with COVID-19 infection and is due to the social distancing and stay-at-home orders in place, which may make individuals less active and prompt them to stay indoors.[36] This in turn may increase their exposure to cooler temperatures, making them susceptible to pernio. The summary of articles reporting a pernio rash are reviewed in Table 3.

Vasculopathy

One distinction mentioned in the literature that will be reiterated is that there seems to be a clear division between the pernio lesions observed in young, relatively asymptomatic or paucisymptomatic patients who heal with no sequalae, and acro ischemia and necrotic lesions of the extremities witnessed in an older age demographic. The latter present with more severe COVID-19 infection, usually in conjunction with coagulopathy and tend to have a grim prognosis.[4,40,41] This rash was described as plantar plaques, dry gangrene, mottling and duskiness involving the fingers, with digital ischemia frequently occurring. They are typically seen in the setting of a disseminated intravascular coagulation (DIC) picture. These patients are usually hospitalized, require ventilator support, have laboratory abnormalities such as elevated d-dimer and fibrinogen, and require anticoagulation.[40-42]

Attempted explanations of how SARS-CoV-2 infection may predispose to a hypercoagulable state continue to be discussed. One explanation is that the infection induces a cytokine storm, leading to undesirable activation of the coagulation cascade and development of microthrombi.[41] Another explanation for microthrombi formation is through the viral entry ACE2, which promotes platelet aggregation. ACE2 receptors are also located on endothelial cells and viral interaction could cause endothelial damage and, thus, promote thrombus formation.[2,42] Other proposed mechanisms include antiphospholipid antibody production and complement activation.[43]

In a study on 5 cases of severe COVID-19 infection characterized by respiratory failure and purpuric skin lesions, a link to complement mediated microvascular injury and thrombosis was observed.[44] The authors noted that both lung and skin tissue had evidence of deposition of

C5b-9 and C4d in the microvasculature. Interestingly, skin biopsies were taken from both involved and clinically normal sites. There was co-localization of the SARS-CoV-2 spike glycoproteins within the microvasculature of purpuric skin and normal appearing skin. In another patient with no skin involvement, there was still significant vascular deposition of C5b-9 within the dermal capillaries. Vascular deposition of these complement proteins is a key feature of many microthrombotic syndromes, such as catastrophic antiphospholipid antibody syndrome, atypical hemolytic uremic syndrome, purpura fulminans, and severe multi-organ malignant atrophic papulosis.[44] The articles reporting a vasculopathy-related rash are summarized in Table 4.

Miscellaneous

An interesting new pattern of Kawasaki's disease in conjunction with COVID-19 infection has now been reported. Recently, a case of a 6 month old female who had typical Kawasaki's symptoms, including prominent tongue papillae, a blanching polymorphous maculopapular rash, and swelling of the hands and lower extremities, then subsequently tested positive for SARS-CoV-2.[45] There has been previous speculation that Kawasaki's disease may be triggered by an infectious agent[46], largely due to the winter-spring seasonality and reported wave-like epidemic spread within Japan.[45] Increasing case reports of Kawasaki's disease in conjunction with the COVID-19 pandemic continue to be published daily.

In a retrospective study of dermatology consultations from March 5, 2020 to April 15, 2020 in Spain, two cutaneous patterns in relation to COVID-19 infection were observed. One, being the pernio-like rash previously described, and another erythema multiforme (EM) rash observed in 37 out of 132 patients (28%). They describe the rash as rounded erythematous macules with vesicles that tend to coalesce and were smaller than classic EM lesions and had atypical targetoid lesions.[4] Another article detailed 4 hospitalized patients with confirmed SARS-CoV-2 infection. The lesions began as erythematous papules on the trunk which became violaceous with a dusky center and pseudo vesicle formation. Some patients had typical targets and oral mucosa involvement, with palatal macules and petechiae.[47] Histology was consistent with EM.

Two cases from New York detail a dusky red, non-pruritic, non-blanching periorbital dyschromia in patients with confirmed SARS-CoV-2 infection. No histology samples were provided, and no other cutaneous findings were reported. The cases rashes that did not fall within the previously mentioned categories are summarized in Table 5.

Discussion

The vast amount of cutaneous manifestations being linked to COVID-19 is unusual given our knowledge of how other viral illnesses behave. The likelihood that one virus could present with such a variety of clinical patterns is low, as has been discussed by others.[5] Additionally, properly working up each rash and ruling out potential drug reactions or other coinfections was not thoroughly done in many of the reported cases.

Other retrospective observational studies have been able to remark on characteristics of certain rashes such as whether their appearance is early or late within the course of disease.[5] Making general claims from the pooling of cases and case reports is difficult as there has not been universal standard reporting of all relevant aspects of each case.

The way in which clinicians are relaying cases is heterogeneous at best, with unsatisfactory and imprecise language used to describe rash morphology. We understand that in many cases, concern over contagion exposure and contamination has prevented the obtainment of photographs and biopsy samples. However, the proper characterization of dermatological entities often requires sufficient images and histology.

With the widespread use of social media and messaging applications, many dermatologists

and clinicians have turned to these informal modalities to share their observations with one another.[48,49] Data collection at this time is a double-edged sword. Wide dissemination on the topic allows us to discover patterns of disease and new areas of study, but hastily drawn conclusions can attribute correlation where it may not exist. This study, and all articles pertaining to this subject face the limitations associated with reporting in real time for a novel pathogen that we do not fully understand.

With new initiatives, such as the COVID-19 Registry from the American Academy of Dermatology, a more centralized and standardized method of collecting dermatologic findings associated with COVID-19 now exists.[49] In summary, while there have been recurring reports of COVID-19 infection and similar cutaneous entities, it is important to exercise caution in drawing conclusions.[50] More research is needed to study how SARS-CoV-2 may be interacting with the skin, and how a COVID-19 rash is related to clinical outcomes.

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