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COVID-19 and cutaneous vasculopathy: what is known?

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Background:The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of the coronavirus disease 2019 (COVID-19) pandemic and possesses a tropism for multiple organs.

Method:In this systematic review, we put together all relevant papers to assess the link between COVID-19 infection and acral lesions (particularly chilblain-like lesions) and to determine whether these lesions can be put together in a spectrum of manifestations.

Result: Skin manifestations of COVID-19 vary, ranging from mostly acral chilblain-like, livedoid lesions or ischemia and necrosis to vesicular eruptions, maculopapular lesions, urticaria, oral or periorbital lesions, and drug eruptions.

Conclusion: A great deal of scientific evidence have focused on the peculiar erythematous and purpuric violaceous acral lesions in young and healthy individuals resembling chilblains (pernio), leading the scientific community to investigate the association between these lesions and SARS-CoV-2. Furthermore, this is suggestive that some COVID-19 skin manifestations like livedo reticularis and acral ischemia and necrosis might share dermatopathologic features with thrombophilic states.

Keywords: COVID-19, SARS-CoV-2, vasculopathy, chilblains, retiform purpura

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INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has recently emerged to cause the coronavirus disease 2019 (COVID-19) pandemic. As a multiorgan infection, COVID-19 has variable presentations ranging from fever, fatigue, myalgia, headache, diarrhea, dry coughs, and dyspnea to severe pneumonia, acute respiratory distress syndrome, and multiple organ failure [1,2].

Before the COVID-19 outbreak, studies on the cutaneous manifestations of other coronaviruses were sparse owing to the shorter periods of outbreaks. However, some authors addressed a link between these coronavirus strains and cutaneous chief complaints [3,4]. For example, Chesser *et al.* [4] reported a healthy child who presented with progressive purpura and extremity swelling preceded by a mild cough and bilateral non-exudative conjunctivitis. Common differential diagnoses were ruled out and finally, the patient was diagnosed with acute hemorrhagic edema of infancy (AHEI) induced by coronavirus NL63. The patient experienced a recurrence three weeks after the initial presentation. Both episodes resolved by supportive care.

During the early days of the COVID-19 pandemic, perhaps due to the lack of dermatology consultations, the cutaneous manifestations were neglected. For example, skin manifestations were

reported only at a rate of 0.2% in the first Chinese cohort study [1]. However, in Recalcati's later study, cutaneous manifestations were reported in 20.4% of cases, representing a turning point for drawing attention to the skin manifestations of COVID-19, which can mimic various conditions; this finding also raised transmission concerns [5]. Primary skin manifestations of COVID-19 include erythematous rashes or patchy exanthematous red rashes, morbilliform exanthema, maculopapular rashes, urticaria and acute urticaria, acro-ischemic lesions (chilblain-like or pernio-like lesions), digital ischemia, digitate papulosquamous lesions, chickenpox-like blisters, varicella-like exanthema, pruritic papulovesicular lesions, petechial skin rashes, acute hemorrhagic edema, livedo reticularis, symmetrical pruritic papules, conjunctivitis and eyelid dermatitis, malar eruption, and rashes in infants of COVID-19-positive mothers [6].

Meanwhile, the mass media, as well as the medical literature, became filled with information regarding peculiar erythematous and purpuric violaceous acral lesions in young and healthy individuals resembling chilblains (pernio) [7-9]. Thereafter, an ongoing effort was dedicated to identify the association between chilblain-like lesions and SARS-CoV-2, as well as other skin manifestations to collate a uniform picture.

In this review, we sought to put together all relevant papers until the time of our drafting to perceive the link between COVID-19 infection and livedo reticularis, acral ischemia/necrosis, and chilblain-like lesions. Furthermore, we aimed to understand whether these lesions can be put together in a spectrum of manifestations.

MATERIALS AND METHODS

This systematic review was designed and conducted in June 2020 to compile evidence regarding the vasculopathic entity of COVID-19. We searched for the relevant keywords in the titles and abstracts of articles in the Medline/PubMed, Scopus, Embase, Web of Knowledge, and Google Scholar (for gray literature) databases to identify the published target studies from first publications in December, 2019 to June 14, 2019. Additionally, the references of systematic reviews and meta-analyses were manually searched in order to encompass all relevant articles. Moreover, non-English studies were included. The articles were collected in EndNote X9 (Clarivate Analytics, USA) and the duplicates were automatically discarded, publications before December 1, 2019 also being excluded. The search queries are presented in Table 1.

All targeted statistics were entered into a checklist prepared in the form of a spreadsheet. This checklist included: first author's name, country, number of cases, chief complaint, past medical history, prognosis, drug history, time of skin manifestations' appearance relative to generalized symptoms, dermatology description, involved region, laboratory data (routine tests, PCR, serology tests, coagulation tests, etc.), and biopsy data.

RESULTS & DISCUSSION

1. Livedo reticularis, necrosis and acral ischemia

The first cases of livedo reticularis were reported in the study of Manalo *et al.*, who described two mildly ill patients with transient lesions, one with concurrent hematuria [10]. They postulated that livedo reticularis might be a part of a spectrum of manifestations that include acrocyanosis at its extreme. Manalo *et al.* stated that *"low grade disseminated intravasvular coagulation (DIC)"* and *"microthromboses in non-cutaneous origins"* are responsible for livedo reticularis. Zhang *et al.* [11] reported seven cases of critically ill COVID-19 patients who had acrocyanosis. All of them had abnormal coagulation panel results and five of them expired.

Table 1. Search strategy in PubMed for articles published from December, 2019 to June, 2020

#1. (Chilblain[Title/Abstract]) OR Chilblain-like[Title/Abstract]) OR Pernio[Title/Abstract]) OR Pernio-like[Title/Abstract]) OR Toe$[Title/Abstract]) OR Acral[Title/Abstract]) OR Livedo$[Title/Abstract]) OR necrosis[Title/Abstract]) OR ischemia[Title/Abstract]) OR vascul$[Title/Abstract])
#2. (COVID-19[Title/Abstract]) OR SARS-CoV-2[Title/Abstract]) OR Corona$[Title/Abstract]) OR nCoV-2019[Title/Abstract])
#3. (#1 AND #2)

In the same context, Magro and co-workers [12] reported five critically ill COVID-19 patients, four of whom developed retiform purpura in their hospital course. After observing vascular complement deposits in both normal and involved skin, the researchers linked the occlusive thrombogenic micro-vasculopathy in the lung and/or skin organ systems to the extreme activation of both alternative and lectin-based complement pathways.

Thomas [13], in a commentary article, stated that mechanisms other than DIC may contribute to the appearance of small vessel occlusions among non-critically ill COVID-19 patients since coagulopathies are much more prevalent among, or even limited to, those with severe disease. The author put forward two explanations. First, by the fact that a moderate increase in inflammatory cytokines has been observed in mild COVID-19 cases [2], she proposed that this can theoretically promote thrombogenesis. Secondly, she emphasized that since the *"COVID-19 cell entry mechanism"* is through the angiotensin converting enzyme 2 (ACE2) receptor [14], the COVID-19-ACE2 interaction may result in both indirect and direct thrombus formation; activation of the renin-angiotensin system followed by platelet aggregation as the indirect pathway and endothelial dysfunction modulated by the expression of the ACE2 protein on endothelial cells as the direct mechanism. Moreover, she expressed that further studies on the role of the *"complement system, antiphospholipid antibodies, and endothelial cell tissue factors"* are necessary to learn more about coagulation-linked skin manifestations among non-critically ill COVID-19 patients.

Soon after, the authors of the original work [10] responded to the mentioned commentary by Thomas [15]. They argued that a great deal of evidence points to a thrombophilic state. It is known that the D-dimer level in non-critically ill patients can be elevated to a similar extent relative to critically ill patients [1]. Also, they addressed a study by Zhang *et al.* [16] that showed the presence of antiphospholipid antibodies in severe cases of COVID-19. The authors suggest that tissue biopsies could better elucidate the pathophysiology of livedo reticularis.

Later, Llamas-Velasco *et al.* [17] described the histopathological characteristics of the livedo reticularis and acrocyanosis of a patient who was under intensive care due to COVID-19 pneumonia complicated by diabetic ketoacidosis. The result of the skin biopsy was a slightly necrotic upper epidermis, dilated blood vessels filled with hyaline thrombi in the papillary dermis, perivascular neutrophil infiltrates, focal fibrinoid necrosis, and sweat gland necrosis with intact eccrine ducts. In addition, the patient was also diagnosed with a known thrombophilia risk factor, a heterozygous mutation of factor V Leiden. In a similar patient who was discharged after COVID-19 pneumonia resolution, Bosch-Amate *et al.* [18] reported thrombi in small-sized vessels of the superficial and mid-dermis, featuring IgM, C3, fibrinogen, and C9 deposits. In general, these findings might imply extensive endothelial dysfunction, complement pathway activation, or another immune-mediated mechanism that might be a skin manifestation of a systemic coagulopathy linked to COVID-19 [18,19].

During the current COVID-19 pandemic, the mass media and medical literature have been biased toward the so-called "self-limiting, acral chilblain-like lesions" among asymptomatic or pauci-symptomatic young patients, which do not account for the true acral ischemic lesions due to thrombophilia that were discussed above. Interestingly, Balestri *et al.* [20] presented an elderly but asymptomatic COVID-19 patient with acral ischemia, which progressed to necrosis 20 days after a negative COVID-19 test. The authors concluded that acral ischemia might not exclusively be a primary manifestation of COVID-19, but rather it could also share a similar mechanism with chilblain-like lesions, i.e., a secondary delayed immune-mediated reaction to the virus.

2. Chilblain-like lesions

We believe that the first cases of chilblain-like lesions were reported by Estébanez *et al.* [7] (a 24-year-old female, Spain), Alramthan and Aldaraji [8] (two 27- and 35-year-old females in Qatar with a history of travel to the U.K.), and Mazzotta *et al.* [9] (a case-series). Mazzotta *et al.*'s paper implied an epidemic of self-limiting vasculitis in the hands and feet among asymptomatic children and adolescents, which co-occurred with the COVID-19 pandemic in a specific region. They concluded that it is a mild form of thrombogenic vasculopathy associated with COVID-19, whose severe forms had been described in critically ill patients with ischemic and

ecchymotic lesions of the fingers and toes [11,16,21].

An overall picture of chilblain-like lesions is as follows: (1) red-to-violaceous macules and dusky and purpuric plaques, which can be blistering or necrotic; (2) dissociation between chilblain lesions and the classical winter outbreak; (3) temporal relationship with the COVID-19 pandemic and co-occurrence with peaks in a number of cases of COVID-19; (4) young and asymptomatic or pauci-symptomatic patients; (5) lack of history of chilblains, cold exposure, Raynaud's phenomenon, or collagen vascular diseases; (6) acral involvement with feet affected more than the hands; (7) cough and fever precede the onset of the lesions by a few weeks; (8) predominantly negative COVID-19 PCR or serology results; (9) positive history of close contact with a confirmed or suspicious COVID-19 patient or a healthcare worker who did not need to be hospitalized; (10) no COVID-19 pneumonia or serious complications; (11) resolution within days without treatment or treatment only for itch or pain relief; (12) some family clustering; and (13) should be considered as contagious until a better understanding of the etiopathology of these lesions.

Since asymptomatic and pauci-symptomatic patients observe quarantine at home, skin biopsies have not been performed in almost all cases with chilblain-like lesions. Kolivras *et al.* [22] yielded the first histopathology report of a chilblain-like lesion, which we will be discussed later.

In light of the fact that patients with type I interferonopathies can develop chilblains [23-25] and its expression correlates with age [26], one possible explanation for this emerging chilblain-like manifestation in young and healthy patients could be the acute COVID-19-induced upregulation of IFN genes, which would be host-protective. This increase in IFN-I level results in chilblain-like microangiopathy. Furthermore, acrocyanosis in serious COVID-19 cases, mostly in older patients with underlying diseases, might be due to a delayed or insufficient IFN-I gene overexpression followed by a cytokine storm [27]. Cordoro *et al.* [28] also emphasized *"effective IFN-I expression"* as a cause of these lesions in healthy children but, according to negative cold agglutinin and cryoglobulin results in their cases, claimed that chilblain-like lesions are likely to be inflammatory rather than thromboembolic. Andina *et al.* [29] counterpoised this hypothesis and mentioned that chilblain is an uncommon finding in other viral infections in these age groups and there is a lack of reports of chilblains in patients treated with recombinant interferons. In addition, the authors suggested that neurovascular instability might play a role in the development of this skin manifestation because COVID-19 can cause neuropathy [30,31].

Recalcati *et al.* [32] looked for acral chilblains among 107 older hospitalized COVID-19 patients with acute respiratory syndrome. Only three patients with acral lesions (one foot thrombosis; two acrocyanosis) were found and none of the lesions resembled chilblains. The authors concluded that while chilblain-like lesions could be linked to COVID-19, reliable serology tests might better explain the etiology of this distinct manifestation. Moreover, Andina *et al.* [29] correctly addressed the fact that PCR has been shown to have low sensitivity among children requiring hospital admission (11.2%) [33].

Romaní *et al.* [34] and Piccolo *et al.* [35] reported the first serology studies of cases with chilblain-like lesions, which apparently clarified Recalcati's assumption, i.e., the viral load and circulating antibodies are below the detection threshold during the occurrence of chilblain-like lesions. Romaní *et al.* reported that the serology test was negative in all five patients with chilblain-like lesions tested for rapid serology. On the other hand, Piccolo *et al.* asserted that among those six tested for serology, two patients had positive results and at the same time were positive for the swab test. Romaní and colleagues stated that the etiology of the lesions remain unknown and cautioned that the serology tests have low sensitivity in this context. It is evident that some viruses (e.g., parvovirus B19) can give rise to atypical acro-syndromes [36]. However, as an example, Colonna *et al.* [37] showed that their cases were negative for parvovirus B19, cytomegalovirus (CMV) and the Epstein-Barr virus (EBV). In addition, parvovirus B19 mostly involves children of early school age. Nonetheless, immediate COVID-19 PCR tests and reliable serology tests in a large group of these young individuals with chilblain-like lesions might be able to elucidate this association. In this context, the first-in-class study by Papa *et al.* [38] reported more than ten pediatric patients with chilblain-like lesions who were positive for IgG against SARS-CoV-2 (indicating a previous infection), but further information

about the cases was not provided. At that time, the scientific community was waiting for upcoming studies screening a large sample of patients with chilblain-like lesions with concomitant COVID-19 PCR and serology results.

Overall, as López-Robles [39] stated that from an epidemiological perspective, *"a link between COVID-19 and chilblain-like lesions is very susceptible."* A recent study by Saenz Aguirre *et al.* [40] suggested that a correlation between these lesions and the number of days in quarantine should be studied, modulated by factors like lack of sun exposure, decreased vitamin D levels, and prolonged barefoot exposure to cool floors. They said while acral lesions flared up 25 days after confinement, they had not registered any cases with chilblain-like lesions in April.

After initial reports, studies with a remarkable number of cases with chilblain-like lesions appeared in the medical literature, reasserting that this pattern could be a convalescent-phase cutaneous reaction to COVID-19 [28,41]. In a retrospective study, de Masson *et al.* [42] reviewed all documented cases with cutaneous manifestations that were linked to COVID-19. They showed that chilblain-like lesions were very common (106 out of 277 patients). They restated that *"the presence of microthrombi in chilblain patients is consistent with the altered coagulation status observed in severe COVID-19 patients"* [43].

According to histopathology findings from different studies, chilblain-like lesions of COVID-19 are characterized by diffuse, dense, perivascular, and peri-eccrine infiltrates of lymphocytes in the superficial and deep dermis, as well as the hypodermis, without neutrophil infiltration [22,28,29,32,42,44,45]. Other findings were variable between different studies; interestingly, some authors found intravascular fibrin microthrombi [29,37,42,45-47] (absent from the Cordoro *et al.* [28] and Kolivras *et al.* [22] studies), endothelial change or degeneration and red cell extravasation [32,37,45,47,48] (absent from the Locatelli *et al.* study [44]), or lymphocytic vasculitis [28,45,49]. Taking together, these findings might implicate a vasculitis spectrum. In other organs, viral inclusion bodies and mononuclear infiltrates were found in endothelial cells [50].

To our knowledge, five studies have reported direct immunofluorescent (DIF) microscopy among patients with chilblain-like lesions, yielding further knowledge toward the pathogenesis. Initial results by Kolivras *et al.* [22] and Cordoro *et al.* [28] were unremarkable. El Hachem *et al.* [45] showed granular C3 deposits in the walls of few isolated dermal vessels in 9 out of 11 patients. Kanitakis *et al.* [47] showed varying IgM, IgA, and C3 vascular deposits in 14 out of 17 cases. The authors mentioned that this noticeable and specific pattern was yet to be been reported for autoimmune-mediated chilblains [51] or idiopathic chilblains [52]. Notably, immunohistochemistry revealed dominant T-lymphocytes [45-47] and CD123 [45,47,48] expressions on dendritic cells (DCs).

Despite the fact that more studies progressively were added to the medical literature, the relationship between these acral lesions and COVID-19 testing is yet to become clear. For example, in the cohorts of Docampo-Simón *et al.* [53] (39 patients) and El Hachem *et al.* [45] (19 patients), COVID-19 PCR tests were negative but the median duration between skin lesion appearance and testing was 12 and 22.2 days, respectively. As we discussed previously, the virus becomes undetectable in the upper respiratory airways after 6-11 days [54], and if we assume chilblain lesions to be a late cutaneous manifestation, the window period would be further extended. Moreover, mild cases of COVID-19 might not have an abrupt antibody response and all of this may raise the question about the proper relative timing of serology studies in such patients [55,56]. Of note, El Hachem *et al.* [45] showed that the capillaroscopic features of these lesions in COVID-19 was more severe (for example the presence of microhemorrhages) than idiopathic chilblains [57] and that IgA against the S1 domain of the SARS-CoV-2 spike protein was positive in six and borderline in three patients, *"which strongly suggest an association between chilblain-like lesions and COVID-19"*. Similarly, a 35-year-old woman in the report of Santonja *et al.* [58] and seven patients in the Colmenero *et al.* [59] study had chilblain-like lesions and were negative for COVID-19 PCR and IgM/IgG serology tests but were positive for the SARS-CoV/SARS-CoV-2 spike 1A9 protein. It should be noted that IgA is a marker of respiratory infections and a trigger of mucosal and non-mucosal inflammation [60,61]; hence, these three observations might emphasize strong mucosal protection that simultaneously attenuates the IgG response in the healthy targets.

Finally, Colmenero *et al.* [59] recently detected coronavirus-like particles and tubulo-reticular inclusion bodies within the cytoplasm of endothelial cells on electron microscopy for a patient with chilblain-like lesions, which strongly suggests an association between COVID-19 and these lesions. Moreover, CD61, a marker of microthrombi, was positive in four out of seven cases, showing that SARS-CoV-2 may induce widespread endothelial dysfunction to cause a group of skin manifestations.

Some recent studies have linked chilblain-like lesions to thrombophilic states (i.e., increased D-dimer and decreased fibrinogen levels) and described a spectrum of COVID-19 manifestations ranging from chilblain-like lesions among asymptomatic or pauci-symptomatic adolescents and livedo reticularis to severe acrocyanosis and dry gangrene among critically ill patients. Suarez-Valle *et al.* [62] presented three hospitalized patients with bilateral COVID-19 pneumonia who developed chilblain-like lesions. Interestingly, the D-dimer level and fibrinogen level were abnormal in three and two of the patients, respectively. Cordoro *et al.* [28] reported that among their six patients with chilblain-like lesions, three of them simultaneously had livedo reticularis involving the flexor surfaces of the forearms, the dorsal hands, and/or the dorsal feet. Several studies [29,37,42,45-47] reported fibrin thrombi in the skin biopsies of chilblain-like lesions. In addition, 9.2% of 318 patients of the AAD (American Academy of Dermatology) registry who presented with chilblain-like lesions had acrocyanosis [49]. As we discussed this association before, it appears that ACE2 receptor expression on endothelial cells might be the common trigger of these vascular lesions [46]. Notably, many authors mentioned that acro-ischemia was not the reason for dermatologic consultations in their patients, implying that it is a "neglected" issue with a probably higher prevalence than what is detected. In a letter to the editor [63] by Rokea el-Azhary, it was emphasized that *"the vascular lesions clinically evident in the skin must be related to what is going on systemically."* Furthermore, the author added that Mayo Clinic physicians are now instructed to examine the hands and feet of COVID-19 patients for lesions and, if present, must perform a skin biopsy, send a thrombophilia panel, and immediately test for COVID-19 for undiagnosed or new cases. In addition, in the AAD registry paper, chilblain-like lesions were proposed to be a COVID-19 testing indication, both for PCR as well as the serology panel [49] (Table 2, 3).

CONCLUSION

In conclusion, the medical literature strongly confirms an association between SARS-CoV-2, chilblain-like lesions, and other thrombotic occlusive vascular lesions, to the extent that periorbital dyschromia (probably secondary to thrombophilia) is said to be an early sign of COVID-19 preceding other systemic symptoms [75] and that the red half-moon nail sign is a late immune-mediated skin manifestation [76]. However, the exact molecular pathogenesis is still unknown. It appears that chilblain-like lesions and acro-ischemia are not unusual manifestations, but the puzzle remains as to the association between these lesions and a thrombophilic state. More data are needed to understand the exact roles of the virus, endothelial dysfunction, ACE2 receptor, complement system, immune complexes, cytokine levels, T-lymphocytes, DCs, thrombophilia, and autoantibodies in the cutaneous manifestations of COVID-19. In addition, the presence of other unknown etiologies is still on the table; for example, a question that remains unanswered is the reason why no such lesions have been reported in many other endemic areas with this infection in spite of the fact that the medical society is well aware of these distinct skin manifestations.

Conflict of interest: None declared.

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Table 2. Characteristics of studies reporting livedo reticularis, necrosis and acral ischemia

Author	Country	Population	Chief complaint	PMHx	Progress	Excluding drug eruptions	Skin manifestations		Dermatology description	Involved region	Further explanation and comments
							At onset	After other sign and symptoms			
Zhang et al.[11]	China	7 (4 men, 3 women; median age: 59 y/o)	Common symptoms: fever, cough, dyspnea, and diarrhea – acrocyanosis	3 of them had underlying comorbidities	5 cases expired	-	-	7	Acrocyanosis	Finger and toe cyanosis, skin bulla and dry gangrene	↑D-dimer, ↓fibrinogen, ↑FDP, and ↑PT - 4 patients definitely diagnosed with DIC - a median time of 12 days from acrocyanosis to death
Manalo et al.[10]	USA	Case 1 (male, 67 y/o)	Transient livedo reticularis after low-grade fever, coryza and cough without dyspnea	NA	Discharge	-	1	0	Non-pruritic blanching unilateral livedoid patch (netlike exanthem)	Right anterior thigh	Livedo disappeared after 19 hours, concurrent gross hematuria lasted 24 hours; generalized weakness; hospitalized for 6 days
		Case 2 (female, 47 y/o)	mild headache, sinus pressure, anosmia, and low-grade fever	Celiac, Hashimoto's thyroiditis and portal vein thrombosis	Recovery	-	0	NA	Incidental, unilateral livedo reticularis	Right leg	Livedo disappeared after 20 minutes when complete clinical convalescence of COVID-19 symptoms had been achieved
Magro et al.[12]	NA	Case 1 (male, 62 y/o)	Acute severe hypoxemia	CAD, DM, HF, HCV and ESRD	Expiration	-	-	-	-	-	Bx of normal-appearing skin showed significant vascular deposits of C5b-9 within dermal capillaries; ↑INR
		Case 2 (male, 32 y/o)	Progressive fever and cough	OSAS and anabolic steroid use	Ventilator dependent	-	0	1	Retiform purpura with extensive surrounding inflammation	Buttocks	Bx of involved area same as above case; thrombogenic vasculopathy, extensive necrosis, ↑INR, ↑D-dimer, and ↑complements (CH50, C4 and C3)
		Case 3 (female, 66 y/o)	Fever, cough, diarrhea, and chest pain	Neg.	Ventilator dependent, coma	-	0	1	Dusky purpuric patches	Palms and soles, bilaterally	Bx of normal-appearing skin same as case 1; occlusive arterial thrombus without inflammation, thrombogenic vasculopathy, ↑Cr, ↓platelet, and ↑D-dimer

Table 2. Continued

Author	Country	Population	Chief complaint	PMHx	Progress	Excluding drug eruptions	Skin manifestations		Dermatology description	Involved region	Further explanation and comments
							At onset	After other sign and symptoms			
		Case 4 (female, 40 y/o)	Dry cough, fever, myalgia, diarrhea, and progressive dyspnea	Neg.	Ventilator dependent	-	NA	NA	Purpuric reticulated eruptions (livedo racemosa)	Chest, legs and arms	Small thrombi within venules of the deep dermis without vasculitis; vascular complement deposits in both normal and involved area; ↑INR, ↑D-dimer
Llamas-Velasco et al.[17]	Spain	Male, 61 y/o	SARS-CoV-2 pneumonia sign and symptoms, diabetic ketoacidosis, livedoid purple lesions along with acrocyanosis	DM	Partial skin lesion improvement after 17 days – ventilator dependent - extubated	Yes	0	1	Purple ischemic digits and livedo reticularis in fingertips and volar and dorsal areas of both feet and hands	Second and fourth distal phalanges of the right hand, and milder lesions on the second, fourth and fifth digits of the left hand	Hospitalized with severe bilateral pneumonia complicated with diabetic ketoacidosis; biopsy was taken; ↑fibrinogen, ↑D-dimer levels, leukopenia, & heterozygous factor V Leiden mutation
Conforti et al.[19]	Italy	Female, 62 y/o	COVID-19 pneumonia, transient livedo reticularis	HTN, DM	Hospitalized	Yes	0	1	Non-itchy livedoid patches	Trunk and face	Positive COVID-19 PCR
Bosch-Amate et al.[18]	Spain	Female, 79 y/o	General symptoms, livedoid lesions on legs	NA	Hospitalized and discharged, recovered skin lesions after discharge	NA	0	1	Painful retiform purpuric-violaceous patches with some hemorrhagic blisters and crusts	Both legs	Biopsy was taken; ↑ESR and CRP, leukopenia, ↑D-dimer, & positive COVID-19 PCR
Balestri et al.[20]	Italy	Female, 74 y/o	Painful and progressive livedoid macules on hands	Chronic venous leg ulcers, CHF and AF	Home stay, recovery	Yes	1	0	Blanching of fingers, dusky red macules, digital infarcts, & ischemic necrosis	Hands	Positive COVID-19 PCR

Abbreviations: y/o, years old; CAD, coronary artery disease; DM, diabetes mellitus; HF, heart failure; HCV, hepatitis C virus infection; ESRD, end stage renal disease; HTN, hypertension; OSAS, obstructive sleep apnea-hypopnea syndrome; AF, atrial fibrillation; CHF, congestive heart failure; Neg, negative; NA, not available; FDP, fibrin degradation products; PT, prothrombin time; DIC, disseminated intravascular coagulation; Bx, biopsy; Cr, creatinine; INR, international normalized ratio; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; PCR, polymerase chain reaction

Table 3. Characteristics of studies reporting chilblain-like lesions in COVID-19 patients

Author	Country	Population	Chief complaint	PMHx	Progress	Excluding drug eruptions	Skin manifestations		Dermatology description	Involved region	Further explanation and comments
							At onset	After other sign and symptoms			
Estébanez et al. [7]	Spain	1 (female, 24 y/o)	Dry cough, nasal congestion, fatigue, myalgia & arthralgia without fever followed by diarrhea, ageusia & anosmia, then skin rash	Neg.	Home stay	Yes (skin rash started 10 days after last dose of paracetamol)	0	1	Pruritic, confluent erythematous-yellowish papules coalesce into plaques	Bilateral heels	DDx: urticaria, urticarial vasculitis, idiopathic plantar hidradenitis, & neutrophilic dermatosis; no response to topical corticosteroids
Alramthan et al. [8]	Qatar	2 (female, 27 and 35 y/o)	Skin rash	Neg.	NA	Yes	2	0	Red-purple papules, one with diffuse erythema in the right thumb's subungual area	Dorsal aspect of fingers bilaterally	Normal laboratory findings; asymptomatic
Mazzotta et al. [9]	Italy	NA (children and adolescents)	Itching and burning rash; difficulty and pain in joint movement	Neg.	Self-limiting in 12-20 days	-	NA	0	Initial multifocal and often asymmetric erythema, evolved to infiltration, exudation, ecchymosis or necrosis (mostly feet)	Feet and/or hands	Same skin manifestations in siblings but not in parents (in 10% of patients); no other signs and symptoms; rarely flu-like symptoms
Kolivras et al. [22]	Belgium	Case 1 (Male, 23 y/o)	Low-grade fever, dry cough & acute-onset plaques on the toes and lateral aspect of the feet	Psoriasis		Yes	1	0	Numerous violaceous, infiltrated, and painful plaques on an erythematous background	Dorsal aspect of the toes and the lateral sides of the feet	Within normal limits or negative laboratory findings – biopsy was taken
Romaní et al. [34]	Spain	12 (4 males and 8 females, age ranged 7-46 y/o)	Purpuric acral lesions	-	Resolution	-	12	0	Erythematous purpuric purple lesions with edema sometimes blistering and crusted	Fingers, toes, palmar or plantar surfaces, or heels	Lesions' sensation ranged from itchiness to burning or pain – PCR for COVID-19 was negative for all - normal or negative routine laboratory findings
Recalcati et al. [32]	Italy	14 (11 children with mean age 14.4 y/o, 3 young adults with mean age 29 y/o; female:male of 8:6)	Fever, cough and skin lesion	Neg.	Resolution	Yes	14	0	Acral eruption of erythemato-violaceous papules and macules, sometimes bullous evolution or digital swelling	Feet (8 cases), hands (4 cases), both sites (2 cases)	Mild itchiness (3 cases), no familial history of COVID-19-related symptoms, normal or negative routine laboratory findings; COVID-19 PCR sent in five cases and all were negative; skin biopsy was taken

Table 3. Continued

Author	Country	Population	Chief complaint	PMHx	Progress	Excluding drug eruptions	Skin manifestations		Dermatology description	Involved region	Further explanation and comments
							At onset	After other sign and symptoms			
Piccolo et al. [35]	Italy	63 (male: female of 0.83; median age of 14 y/o)	Gastrointestinal symptoms (11.1%), respiratory symptoms (7.9%), fever (4.8%), & rash on extremities (100%)	Autoimmune disorders (6), familial or personal history of coagulopathies (4), Wolf-Parkinson-White (1), peripheral neuropathy (1), drug allergy (1)	NA	NA	In most cases, systemic symptoms preceded cutaneous findings		Out of 54 patients: erythematous-edematous lesions (57.4%), blistering lesions (42.6%)	Feet (85.7%), Both feet/ hands (7%) and hands alone (6%)	COVID-19 tests: PCR only for 11 patients (17.5%), positive in 2 cases (3.2%); serology only in 6 cases (9.5%), positive in the 2 patients that also were positive swab Test for other etiologies: 10 patients (15.9%), Mycoplasma pneumoniae in one case Pain in 27%, itchiness in 27%, both pain/itchiness in 20.6%; stable lesions (79.4%), relapsing lesions (14.3%), quick resolution (6.3%)
Landa et al. [64]	Spain	Case 1 (male, 15 y/o)	Asymptomatic, multiple skin lesions, slight itchiness	Asthma	Recovery	NA	1	0	Lesions initially were erythematous and palpable and 1 week later became purpuric or crusted	Toes and heels	Chilblain-like lesions
		Case 2 (female, 15 y/o)	Skin lesions, mildly painful (1 week before had nasal congestion and mild diarrhea)	NA	Recovery	NA	1	0		Fingers and heels	
		Case 3 (female, 23 y/o)	Slightly itchy lesions (3 weeks before had fever and headache)	NA	NA	NA	1	0		Toes	
		Case 4 (male, 44 y/o)	A slightly painful lesion (following a sore throat)	NA	NA	NA	0	1		Toe	
		Case 5 (male, 91 y/o)	An asymptomatic cutaneous lesion	NA	Hospitalized; recovery	NA	0	1		Toe	
		Case 6 (female, 24 y/o)	Painful skin lesions	NA	NA	NA	0	1		Toes	
Fernandez-Nieto et al. [41]	Spain	95 (49 M and 46 F, mean of 23.4 y/o [range 2-56])	Red to violet acral macules, plaques and nodules	NA	NA	Yes	NA	NA	Red to violet acral macules, plaques and nodules	Feet (76.8%) and hands (34.7%)	25% with COVID-19 symptoms; mean duration of skin lesions was 9.2 days (range 3 to 24)
Abril-Pérez et al. [65]	Spain	Male, 13 y/o	Purpuric acral macule and papules	NA	NA	Yes	1	0	Purpuric acral macule and papules	Toes of both feet	Normal laboratory findings
Torres-Navarro et al. [66]	Spain	2 (16 y/o M and 16 y/o F)	Lesions on the fingers	NA	Recovery	NA	2	0	Violaceous-red erythema or papule	Distal joints of fingers	Normal or negative results of thorough laboratory work-up

Table 3. Continued

Author	Country	Population	Chief complaint	PMHx	Progress	Excluding drug eruptions	Skin manifestations		Dermatology description	Involved region	Further explanation and comments
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Tosti et al. [67]	Italy	4 (two 26 and 48 y/o M and two 16 and 18 y/o F)	Erythematous papules and plaques	One with alopecia areata universalis	Recovery	Yes (only 1 patient with use of oral paracetamol)	2	2	Erythematous papules and plaques	Heels and toes	Also burning sensation, itchiness or pain
de Masson et al. [42]	France	106	-	-	-	-	-	-	Chilblain-like lesions	Acral	28% of cases tested for COVID-19 were positive – 59 patients were negative for past history of similar lesions
López-Robles et al. [39]	Spain	41 (22 M and 19 F, mean of 16 y/o [range 1-74])	Acral erythematous or purplish papules and plaques	Neg.	Recovery	NA	38	3	Acral erythematous or purplish papules and plaques	Mostly feet alone (80%), followed by hands and feet (10%), hands (7%), and ears (2%)	All 19 cases tested for COVID-19 were negative – 6 patients had been in close contact to at least one person with a confirmed diagnosis of COVID-19
Colonna et al. [37]	Italy	Case 1 (Female, 11 y/o)	Mild flu-like symptoms with headache and rhinitis in preceding weeks, 14-day history of lesions on the feet	Neg.	Recovery	Yes	0	1	Several 5-10 mm macules – dusky, erythematous-cyanotic, slightly atrophic, with blurred edges on the plantar surface of the left 1st and 4th toes	Lateral margin of the feet and the dorsal surface of toes	Feeling of coldness and mild pain - parents had cough – the case and her father were negative for COVID-19 PCR – extensive laboratory work-up was normal/negative
		Case 2 (Female, 6 y/o)	Mild intermittent fever and localized pain in the soles; two-day history of vascular lesions on the feet	NA	Recovery	NA	0	1	Erythematous, edematous 8-10 mm round macular lesions with blurred edges and a central erythematous-cyanotic area	Bilateral plantar surfaces	Itchiness and moderate pain, close contact with positive cases in parents, the case and her mother were negative for COVID-19 PCR; slightly ↑D-dimer
		Case 3 (male, 5 y/o)	Fever and cough with radiographic evidence of pneumonia; vascular lesions on the feet and right hand	NA	Recovery	NA	0	1	Several rounded macules with blurred edges, 5-20 mm in diameter	Plantar surface of both feet, as well as the right hand	Parents had cough; the case and his mother were negative for COVID-19 PCR; mild thrombocytosis and monocytosis seen
		Case 4 (female, 11 y/o)	Foot lesions; swelling and difficulty walking; intermittent fever & localized pain	NA	Recovery	NA	0	1	Erythematous and dusky 5-15 mm plaques	Lateral margin of the left foot and the dorsal surface of the left toes	The case and her mother were negative for COVID-19 PCR; biopsy was done; no abnormal laboratory results

Table 3. Continued

Author	Country	Population	Chief complaint	PMHx	Progress	Excluding drug eruptions	Skin manifestations		Dermatology description	Involved region	Further explanation and comments
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Garcia-Lara et al. [68]	Spain	27 (18 M and 9 F, mean of 14.4 y/o)	Chilblain-like lesions; 4% with diarrhea	NA	Stayed home	NA	NA	NA	Chilblain-like lesions	74% feet, 22% hands, 4% both	Two cases with erythema multiforme-like lesions; itchiness (11%); mild pain (22%); mean duration disease of 14.6 days; PCR for 2 cases and serology for 9 cases were negative; 26% of patients had a relative affected by COVID-19 and none were hospitalized
Suarez-Valle et al. [62]	Spain	NA	COVID-19 pneumonia; chilblain-like lesions	NA	Hospitalized & recovered	Yes	0	4	Round 0.5-1 cm red-purple plaques, sharply defined with no retiform borders	Toes in all case and soles in one	↑D-dimer and ↓fibrinogen
Locatelli et al. [44]	Italy	Male, 16 y/o	Transient dysgeusia and mild diarrhea, skin lesions	Neg.	Stayed home	NA	1	0	Multiple erythematoedematous, partially eroded, macules and plaques	Dorsal aspects of the fingers and toe	Confirmed COVID-19, long lasting chilblain-like lesion, normal or negative thorough laboratory work-up results
Andina et al. [29]	Spain	22 (13 M and 9 F, median of 12 y/o [range 6-17])	Mild systemic symptoms in 10 patients; afebrile; erythematous to purpuric macules and violaceous swellings located on the toes, feet, fingers & hands	5 patients with ADHD	Recovery	Yes (lesions less likely to be induced by ADHD drugs)	-	-	Erythemato-violaceous or purpuric macules, sometimes swollen toes with dusky, violaceous discoloration, less commonly dark ischemic areas with superficial blisters	Feet (100%, lateral aspects of the feet, heels) – hands (14%, fingers)	Dermoscopy: violaceous erythema, dilated capillaries, ischemic areas, purpuric dots and hyperpigmentation; pruritus (41%) and mild pain (32%); only 1 case with positive COVID-19 PCR; 1 case with close contact with a confirmed case, 12 cases with probable cases; normal coagulation test results – only 1 case with slightly ↑D-dimer; skin biopsy was done
Cordoro et al. [28]	USA	6 (5 M and 1 F, 12-17 y/o)	Mild symptoms of viral upper respiratory infection (2 cases); acral purpura	Neg.	Recovery	Yes	4	2	Red to violaceous macules and dusky, purpuric plaques, sometimes edematous with overlying superficial bullae and focal hemorrhagic crust	Mid and distal aspects of the toes, heels, soles and feet	Siblings in each family from 2 unrelated families; close contact with adults with mild, transient upper respiratory infection symptoms; itchiness and some tenderness; livedo reticularis in 3 patients; normal or negative complete laboratory tests, except 1 patient with recent positive pharyngeal group A Streptococcus infection, and from one family each child had very subtle, isolated reductions in fibrinogen levels; all PCR and serology tests were negative
Diotallevi et al. [69]	Italy	Female, 12 y/o	Skin lesions	Neg.	Recovery	Yes	1	0	Erythematous-edematous purple lesions	Distal phalanges of all ten toes	Patient and her father had positive COVID-19 PCR
Saenz Aguirre et al. [40]	Spain	74 (42 M and 32 F, median of 14.5 y/o [range 3-100])	Skin lesions	Neg.	Recover	Yes	66.7%	33.3%	erythematous papules or purpuric macules	Feet (95.94%) and hands (8.1%)	Nearly one-third had close contact with confirmed or clinically diagnosed COVID-19 – one out of eleven tests was positive

Table 3. Continued

Author	Country	Population	Chief complaint	PMHx	Progress	Excluding drug eruptions	Skin manifestations		Dermatology description	Involved region	Further explanation and comments
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Mastrolonardo et al. [70]	Italy	38	Skin lesions	NA	Recovery	NA	NA	NA	Multifocal and asymmetric purpuric-ecchymotic and/or chilblain-like lesions	Feet; sometimes hands and ears	All PCR-negative
Eka Putra et al. [71]	Indonesia	Male, 29 y/o	Fever, myalgia, sore throat, dry cough, & skin lesions	NA	Recovery	Yes (less likely)	0	1	Discrete multiple lenticular red papules with a maximum diameter of 3 mm	Fingertips and toe tips	Lymphopenia; ↑CRP
Guarneri et al. [72]	Italy	3 (male, 14-18 y/o)	Chilblain-like lesions	NA	Recovery	NA	NA	NA	Chilblain-like lesions	Feet	All positive for PCR – two of them had close contact with positive cases -
Docampo-Simón et al. [53]	Spain	58 (29 M and 29 F, median of 14 y/o [range 0.25-85])	Chilblain-like lesions	Thrombosis (3.8%), dermatologic condition (13%)	NA	NA	41	11	Chilblain-like lesions	Feet (62.1%), hands (15.5%), both (22.4%)	65.5% without history of contact
El Hachem et al. [45]	Italy	19 (14 M and 5 F, mean of 14 y/o [range 11-17])	Flu-like symptoms (11/19)	Neg.	Recovery	NA	8	11	Swollen erythemato-violaceous roundish macules and purpuric lesions, pustulosis and crusts as well as pain and/or itchiness in some cases	Toes, heels, soles	Normal or negative blood tests, negative PCR and IgG, positive (6) and borderline (3) results for S1 domain of SARS-CoV-2 spike protein IgA; biopsy was done
Kerber et al. [73]	USA	Male, 7 y/o	Both feet: toe pain, pruritus, swelling, & inability to bear weight	NA	NA	NA	1	0	Erythema and mild edema of the dorsal toes and localized violaceous vesicular changes in the plantar side	Toes	Normal or negative blood tests, negative COVID-19 PCR, but positive SARS-CoV-2 IgG antibodies
Ruggiero et al. [74]	Italy	100 (64 M and 36 F, mean of 12.9 y/o [range 0.25-17])	Chilblain-like lesions	NA	NA	NA	84	16	Circumscribed erythematous edematous lesions	Feet (75%), hands, (25%), & face (2%)	One positive case out of 11 patients tested for COVID-19 PCR
Freeman et al. [49]	AAD registry	318 (163 M and 155 F, median of 25 y/o [range 17-38])	Mild general symptoms in 45, chilblain-like lesions	25%	98% recovered, 1.3% hospitalized, 0.6% expired	NA	19	299	Chilblain-like lesions	Feet (94%); hands (15%),	23 positive cases out of 69 patients tested for COVID-19 PCR, 68 with close contact to positive of suspicious cases
Mahieu et al. [46]	France	10 (median of 27 y/o [range 17-38])	Mild general symptoms in two cases; chilblain-like lesions	NA	Recovery	NA	8	2	Erythemato-violaceous, infiltrated papules or macules, bullous evolution in 5	Toes, lateral feet and heel – some of with fingers and soles	Biopsy was done, COVID-19 PCR and serology tests were negative, normal or negative blood tests
Kanitakis et al. [47]	France	17 (11 M and 6 F, mean of 32 y/o [range 15-63])	Mild general symptoms in five cases; chilblain-like lesions	Neg.	NA	NA	12	5	Cutaneous red violaceous, edematous, rarely necrotic, lesions	Toes, feet (heel, soles) and/or the fingers	COVID-19 PCR and serology tests were negative; normal/negative blood tests

Table 3. Continued

Author	Country	Population	Chief complaint	PMHx	Progress	Excluding drug eruptions	Skin manifestations		Dermatology description	Involved region	Further explanation and comments
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Rodríguez-Villa Lario et al. [48]	Spain	Male, 17 y/o	Chilblain-like lesions	NA	NA	NA	NA	NA	Chilblain-like lesions	Toes	↑Serum IgA level; COVID-19 PCR was negative; positive COVID-19 IgG and negative IgM
Santonja et al. [58]	Spain	Female, 35 y/o	Fever, cough, chilblain-like lesions for three weeks	NA	Recovery	NA	1	0	Acral purpuric lesions	Toes	COVID-19 PCR and serology tests were negative, positive for SARS-CoV-2 spike protein IgA, perivascular deposits of C5b9, C3 and C1q
Colmenero et al. [59]	Spain	7 (4 M and 3 F, range 11-17 y/o)	Respiratory and/or GI symptoms; chilblain-like lesions	ADHD in two patients	Recovery	NA	NA	NA	Chilblain-like lesions	Toes and lateral aspects of feet and heels; hands	Normal/negative blood tests; negative COVID-19 PCR but positive for SARS-CoV-2 spike protein IgA; biopsy was done

Abbreviations: y/o, years old; M, male; F, female; GI, gastrointestinal; ADHD, attention deficit hyperactivity disorder; Neg, negative; NA, not available; Bx, biopsy; CRP, C-reactive protein; PCR, polymerase chain reaction; DDx, differential diagnoses

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