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## Vascular skin manifestations in patients with severe COVID-19 in intensive care units: a monocentric prospective study

**Background:** Various skin manifestations have been reported during the coronavirus disease 2019 (COVID-19) pandemic. Among these are acral vascular skin lesions in non-severe patients, but few studies have focused specifically on patients with severe COVID-19 admitted to the intensive care unit (ICU). **Objectives:** We aimed to assess the frequency of acral vascular skin manifestations (AVSM) in patients admitted to the ICU based on systematic dermatological examination. **Materials & Methods:** We conducted a clinical, observational and prospective study in the ICU of Lille University Hospital (France). All adult patients with RT-PCR-confirmed severe acute respiratory syndrome-related coronavirus-2 (SARS-CoV-2) infection were included on May 5<sup>th</sup> and 6<sup>th</sup>, 2020. **Results:** A total of 39 patients with severe COVID-19 were examined (34 males and five females; median age: 61 [55-59]). We observed AVSM in 11/39 patients (28%) including five with acral necrotic lesions, three with haemorrhagic blisters, one with acral live-doid rash, and one with erosive distal lesions. Chilblain or chilblain-like lesions were not seen, unlike ambulatory or non-severe patients described in the literature. There was no difference regarding the median length of stay in the ICU, initial symptoms of COVID-19 or baseline characteristics, except for a lower BMI in patients with AVSM. All patients had biological coagulation abnormalities (e.g. higher levels of fibrinogen or D-dimers), but there was no difference between patients with and without AVSM. **Conclusion:** AVSM are infrequent and heterogenous and seem to be non-specific to patients with severe SARS-CoV-2, and possibly unrelated to COVID-19. The pathophysiology of AVSM described during the COVID-19 pandemic is not fully elucidated.

**Key words:** SARS-CoV-2, COVID-19, coronavirus, vascular skin manifestations, chilblain, intensive care unit

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Coronavirus disease 2019 (COVID-19) became a pandemic infection within three months. Multiple skin manifestations were reported in ambulatory patients such as purpuric-rash, urticarial, erythema-multiforme-like and maculopapular rash [1]. Among them, acral vascular skin lesions were described in non-severe patients, but it remains unclear whether these lesions are really associated with COVID-19 due to the lack of specificity of COVID-19 serologic tests at the beginning of the pandemic [2]. Chilblain-like lesions are frequently described in large cohorts as well as in a Spanish cohort, in which 19% of 375 patients with COVID-19 presented with such lesions [3]. Nevertheless, only one study focused specifically on skin manifestations in patients with severe COVID-19 admitted to the intensive care unit (ICU) [4]. We hypothesized that severe patients could have skin manifestations due to coagulation disorders associated with COVID-19, such as increased D-dimers and a hypercoagulation state [5, 6]. Thus, various vascular manifestations should be observed [7], however, the frequency of acral

vascular skin manifestations, specifically in severe patients, is still unknown and the occurrence of chilblain lesions in severe patients is not yet described. We therefore aimed to assess the frequency of acral vascular skin manifestations in patients with severe COVID-19 admitted to the ICU based on systematic dermatological examination.

### Materials and methods

We conducted a clinical, observational and prospective study in the ICU of Lille University Hospital (CHU Lille, France). All adult patients who had a positive reverse transcriptase polymerase chain reaction (RT-PCR) for SARS-CoV-2 and hospitalized in the ICU at the time of the study were included. A control group with asymptomatic or mild cases of COVID-19, not requiring hospitalization, and severe patients without COVID-19 were not included. Patients were prospectively examined on May 5<sup>th</sup> and May

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6<sup>th</sup>, 2020. Systematic skin examination was performed by a trained team of three senior dermatologists during these two consecutive days. Demographic features, past medical history, treatments, clinical data and outcome, 15 days after examination, were recorded. The primary endpoint was the frequency of acral vascular manifestations (including chilblains or chilblain-like lesions, necrotic or purpuric lesions, haemorrhagic blisters or livedoid rash) at the time of the study (irrespective of the length of stay in the ICU and the severity status of COVID-19). Secondary endpoints aimed to compare patients with and without acral manifestation regarding demographic features, clinical data, COVID-19 initial symptoms and severity data of intensive care management. There was no control group (*i.e.* patients without COVID-19) due to practical considerations.

This observational study was indexed in the French National Commission on Informatics and Liberties (CNIL) and the management of patients was not modified by the study protocol. The statistical analysis was carried out by the Biostatistics Department of Lille University Hospital using XLSTAT 2018 software, Addinsoft Inc, USA. Qualitative variables were described by numbers and percentages. The quantitative variables were described by mean and standard deviation in the case of normal distribution, verified using a Shapiro-Wilk test, or by median and interquartile (*i.e.* 25<sup>th</sup> and 75<sup>th</sup> percentiles) in the opposite case. Comparison of frequencies was performed using the chi-square test and Fisher exact test. Comparison of the distributions was performed using the Kruskal-Wallis test when comparing three groups or using the Mann-Whitney test for the comparison of two groups. Statistical significance at  $p < 0.05$  was considered.

## Results

A total of 39 SARS-CoV-2 patients were examined. The demographic and clinical features are shown in [table 1](#). There were 34 males and five females. Median age was 61 (55-59) years. Obesity (body mass index [BMI]  $> 30 \text{ kg/m}^2$ ) and severe obesity (BMI  $> 35 \text{ kg/m}^2$ ) were present in 51.2% (20/39 patients) with a mean BMI of  $31.6 \pm 6.1 \text{ kg/m}^2$ . Only one patient was actively smoking and six patients had stopped smoking. There was no difference between the two groups of the study. At baseline, 33 and 38 patients suffered from fever and cough/dyspnoea, respectively. Among them, six patients described diarrhoea and three had anosmia at the beginning of COVID-19. There were no obvious dermatological lesions recorded in the initial medical observation. Global median length of stay for all patients in the ICU was 35 (21-41) days and median duration of invasive mechanical ventilation was 35 (28-38) days. The mean delay between the first symptoms of COVID-19 and admission to the ICU was  $7.7 \pm 4.2$  days. We recorded, at the time of dermatological examination, a total of seven thromboembolic events such as pulmonary embolism or deep venous thrombosis, two myocardial infarctions and one acute brain ischemia. Extra-corporeal membrane oxygenation was ongoing for two patients. All patients had biological coagulation abnormalities such as higher levels of fibrinogen or D-dimers, but there was no difference between the two groups of patients ([table 1](#)). We did not

observe significant abnormalities between the two groups concerning coagulation factors, such as factor II, V, VIII, anti-thrombin III or prothrombin levels. We recorded nine patients who were tested for antinuclear antibodies and three for anti-phospholipid antibodies; only one patient showed positive levels of antinuclear antibodies and one for anti-phospholipid antibodies.

Viral reactivation status was assessed by RT-PCR and we identified six patients with EBV reactivation (viral load  $> 320 \text{ UI/mL}$ ), one of whom presented with acral skin manifestation. Three patients with CMV reactivation status (viral load  $> 305 \text{ UI/mL}$ ) were recorded, but no skin manifestations were observed in these patients. We recorded six deceased patients, 17 patients continuously hospitalized in the ICU and 15 patients hospitalized under standard care 15 days after examination.

Regarding the primary endpoint, we observed acral vascular skin manifestations in 11 patients (28%) including five patients with acral necrotic lesions, three patients with haemorrhagic blisters ([Figures 1, 2](#)), one patient with acral livedoid rash and one patient with erosive distal lesions. Chilblains (characterized by red or violet macules, plaques and nodules localized at the toes or fingers) or chilblain-like lesions were not observed. The median number of involved fingers was 2 (2-4). Skin biopsy was not performed. Among these 11 patients, two patients suffered from two types of acral manifestations with distal necrotic lesions and erosive lesions and one patient with necrotic lesions and ungual haemorrhages. Three patients presented with haemorrhagic ungual lesions located on the cuticula area ([figure 3](#)). Only one patient had a previous medical history of autoimmune disease, but none had a known medical history of acral vascular manifestations (such as Raynaud phenomenon or chilblains). We did not observe any other skin manifestations in this severely affected population. Vasoactive drugs had been administered to 21 patients (54%) and stopped in 11 patients (28%) at the time of the study. Among the 10 patients who had received vasoactive drugs, nine patients presented with acral skin manifestations and four patients were being weaned off the drug. Among the 39 patients examined, 21 had negative SARS-CoV-2 RT-PCR with a mean delay of  $14 \pm 9$  days. Among the patients with acral manifestations, six patients had negative PCR, with a mean delay of  $14 \pm 9$  days before dermatological examination. For patients with acral skin manifestations, the median duration of hospitalization in the ICU was 37 (32-44) days and the median duration of COVID-19, from first symptoms to dermatological examination, was 49 (41-52) days. Concerning the comparison between the two groups ([table 1](#)), we noticed that there was no difference regarding the median duration of hospitalization in the ICU. The median BMI of patients with acral skin manifestations was lower ( $33.8 [28.1-37.6]$  versus  $27.8 [25.2-29.4]$ ). There was no difference between our groups regarding initial symptoms of COVID-19 infection or baseline characteristics (excepted for BMI).

## Discussion

In this descriptive study, as observed in the literature, men were more affected by severe COVID-19 in our cohort [8] and we observed only 11/39 patients (28%) with various and

**Table 1.** Population characteristics and disease severity for patients with and without acral skin manifestations. N/A: not applicable. \* $p < 0.05$ .

	patients with acral skin manifestations n=11/39 (28%)	patients without acral skin manifestations n=28/39 (72%)	p
Mean Age (years $\pm$ SD)	63,5 $\pm$ 9,5	59,4 $\pm$ 19	0,36
Gender			
Male	9 (82%)	25 (89%)	0.61
Female	2 (18%)	3 (11%)	
Body mass index (kg/m2)	27,7 $\pm$ 3,3	33,2 $\pm$ 6,3	<b>0,018*</b>
Medical history of autoimmune disease	1 (9%)	2 (7%)	N/A
Medical history of acral skin manifestations	0 (0%)	0 (0%)	N/A
Smoking status	1 (20%)	0 (0%)	N/A
Initial COVID-19 symptoms			
Fever	9 (82%)	24 (86%)	1
Cough/dyspnea	11 (100%)	27 (96%)	N/A
Rhinitis	0 (0%)	0 (0%)	N/A
Diarrhea	1 (9%)	5 (18%)	0,66
Anosmia	1 (9%)	2 (7%)	N/A
Other	3 (27%)	13 (46%)	0,47
Viral reactivating status (PCR)			
EBV	1 (9%)	5 (18%)	0,66
CMV	0 (0%)	3 (11%)	N/A
HHV 6	0 (0%)	0 (0%)	N/A
HHV 7	0 (0%)	0 (0%)	N/A
SARS-CoV-2 disease severity			
Length of stay in the IUC (days)	36,7 $\pm$ 12,3	34 [18-38]	0,14
Duration of COVID-19 (days)	46,2 $\pm$ 10,2	36,6 $\pm$ 15	<b>0,044*</b>
Vasoactive drugs	9 (82%)	12 (43%)	<b>0,028*</b>
ECMO	1 (9%)	1 (3,6%)	N/A
Thrombo-embolic events			
Pulmonary embolism	3 (27%)	4 (14%)	0,38
Myocardial ischemia	2 (18%)	0 (0%)	N/A
Acute brain ischemia	0 (0%)	1 (3,6%)	N/A
Coagulation status			
Activated clotting time (ACT) (x Control)	1,2[1,1-1,7]	1,3[1,1-1,6]	0,89
Prothrombin level (N>65%)	78[61-84]	73[61-82]	0,63
Blood platelets (N>150000/mm3)	304000[256000-346000]	285000[218000-379500]	0,85
D-dimers (N<0,5mg/l)	3.3 [1.6-3.5]	3.2 [1.4-4.7]	0,87
Fibrinogen (N 2-4g/l)	4.6 [4.3-5.1]	6.2 [4.8-7.0]	0,019*
Factor II (N 60-120%)	98.5 [78.0-108.0]	97.0 [91.0-119.0]	0,63
Factor V (N 60-120%)	127.5 [109.0-140.0]	138.0 [118.0-168.0]	0,15
Anti-thrombin III (N 80-120%)	83.0 [67.0-88.0]	85.0 [69.0-99.0]	0,43
Anti phospholipids antibodies (data available n=3)	1/3	2/3	N/A
Nuclear antibodies (data available n=9)	1/9	8/9	N/A
Outcome at D15			
Death	3 (27%)	3 (11%)	0,32
hospitalized in ICU	2 (18%)	9 (32%)	0,073
hospitalized in standard hospitalization	6 (55%)	15 (54%)	0,28

heterogenous acral skin manifestations. Necrotic lesions were the most frequent (5/11 patients). Interestingly, we did not observe chilblain or chilblain-like lesions as observed in many ambulatory and non-severe patients during the outbreak with suspected COVID-19 [9]. Indeed, chilblains or chilblain-like lesions have frequently been seen in paediatric or adolescent populations with a low rate of confirmed infection [10, 11]. Surprisingly, we only identified acral

manifestations, and no other skin manifestations such as urticarial rash, vesicular eruption as, reported in the retrospective cohort of De Masson *et al.* in non-severe patients [11]. Similarly, purpuric macules and papules were not seen in some case reports of severe patients [12]. We identified necrotic lesions (*i.e.* acro-ischemia) possibly induced by thrombosis. These should not be confused with chilblains or chilblain-like lesions. There was no statistical difference



**Figure 1.** Acral skin necrotic lesions.



**Figure 2.** Haemorrhagic blisters of the feet and toes.



**Figure 3.** Ungual haemorrhage of the cuticula.

between the two groups of patients regarding clinical outcomes. However, we observed that the mean duration of COVID-19 was longer and that more vasoactive drugs were administered to patients with acral skin manifestations, suggesting a higher level of severity of the disease in this group. However, the small number of patients limited the analysis

and the variable length of stay before dermatological examination and the potential role of vasoactive or anticoagulant drugs in the development of acral skin lesions may have introduced possible bias.

A limitation of our study is the absence of non-COVID-19 control patients with severe acute respiratory syndrome,



and the high degree of heterogeneity of patients who were seen at different times during their disease course (due to the design of the study) precluded us from drawing strong conclusions. Our understanding of the pathophysiology of acral vascular lesions observed during the COVID-19 pandemic remains incomplete. We assumed that the hypercoagulability state usually found in severe COVID-19 patients could explain some clinical features such as pulmonary embolism [6, 13]. Indeed, seven patients presented with deep thrombosis in our series, of whom three developed acral lesions. However, an anticoagulant treatment (heparin) was administered to all patients. In a Chinese series from Wuhan, seven severe patients had acro-ischemia lesions with elevated D-dimer, fibrinogen and fibrinogen degradation product [4]. In another study, Zhang *et al.* suggested that antiphospholipid antibodies could be transient in patients with severe COVID-19. The presence of these antibodies is associated with thrombotic events (thus we investigated coagulation abnormalities), however, this is difficult to differentiate from other causes of thrombosis in severe patients [14]. In contrast, Del Giudice *et al.* described catastrophic acute bilateral lower limb necrosis associated with COVID-19 as a likely consequence of both vasculitis and coagulopathy, but antiphospholipid antibodies were absent in this case [15]. In our study, we observed a higher level of some coagulation parameters in all patients, but did not observe significant abnormalities concerning coagulation parameters specifically in the group with acral skin manifestations compared to the group without acral skin manifestations. We are unable to draw conclusions regarding the lesions observed in our study due to the lack of control patients without COVID-19. Concerning chilblain lesions, some authors suggested that a non-optimal type I interferon reaction to SARS-CoV-2 may explain the absence of chilblain lesions, specifically in severe patients in whom an inadequate immune response against SARS-CoV-2 is observed [16, 17].

Furthermore, none of these patients, as well as those in other series, presented with a rash within two weeks, thus a difference in delay or immunological pathways may exist among some series in the literature [18, 19].

We identified some necrotic acral skin manifestations in a homogenous population of SARS-CoV-2-confirmed, severely affected patients in the ICU, contrary to non-hospitalized and non-severe patients. Nevertheless, most studies have focused on a minority of tested patients, the majority of whom were negative (PCR and serological test). Dysfunction of the immune system during non-severe disease has been suspected as an explanation for the absence of detectable antibody [20].

## Conclusion

We have identified various necrotic and haemorrhagic lesions specifically on the cuticula area in patients with severe COVID-19. Acral vascular skin manifestations are infrequent and seem to be non-specific in patients with severe COVID-19, and possibly unrelated to COVID-19, however, we are unable to draw firm conclusions due to the lack of control group. Lastly, our study suggests that chilblain lesions may not be associated with severe, or non-severe COVID-19. ■

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