



REVIEW

Time of Onset of Selected Skin Lesions Associated with COVID-19: A Systematic Review

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Received: March 3, 2021 / Published online: April 2, 2021
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ABSTRACT

Introduction: Distinct skin lesions associated with coronavirus disease 2019 (COVID-19) have been described, but data regarding their time of onset during the COVID-19 course are scant. Our objective was to systematically review the studies reporting the time of onset of selected skin lesions with respect to the reported onset of the COVID-19 core symptoms.

Methods: A comprehensive search of studies published before 21 January 2021 was

performed on MEDLINE via PubMed database using a predefined strategy to identify relevant articles.

Results: Out of 354 references, 87 were selected, reporting a total of 895 patients with skin lesions associated with COVID-19. The most frequent pattern was exanthema ($n = 430$, 48%), followed by vascular ($n = 299$, 33%), urticarial ($n = 105$, 12%) and others ($n = 66$, 7%). Skin lesions occurred more frequently in the first 4 weeks from the COVID-19 onset ($n = 831$, 92%), whereas prodromal or late lesions were rarer ($n = 69$, 8%). The urticarial and exanthema patterns were more frequent in the first 2 weeks. About the vascular pattern some differences were noted among its subtypes. Livedoid lesions occurred mainly in the first 2 weeks, while chilblain-like lesions between weeks 2 and 4. Purpuric/petechial lesions were equally distributed during the first 4 weeks. Several skin manifestations did not fall into the pattern classification, including erythema multiforme, generalized pruritus, Kawasaki disease and others.

Conclusion: The diversity in the time of onset of skin lesions as well as their polymorphic nature likely reflects the diversity of the pathogenetic underlying mechanisms.

PROSPERO database registration number: CRD42021236331.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s13555-021-00526-8>.

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Keywords: Chilblain; COVID-19; Livedo; Purpura; SARS-CoV-2; Urticaria; Varicella; Weal

Key Summary Points

The most frequent patterns of skin manifestations associated with COVID-19 were exanthema, followed by vascular and urticarial lesions.

Skin lesions occurred more frequently during the first 4 weeks after COVID-19 onset, whereas prodromal or late sequelae were rarer.

The diversity in the time of onset of skin lesions as well as their polymorphic nature likely reflects the diversity of the pathogenetic underlying mechanisms.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article, go to <https://doi.org/10.6084/m9.figshare.14319707>.

INTRODUCTION

Although coronavirus disease 2019 (COVID-19) is best known for causing fever and respiratory symptoms, it is also associated with different extrapulmonary manifestations [1, 2]. A population-based framework of the spectrum of different manifestations associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been proposed recently by Datta SD et al., who describes three main phases of the disease: acute (within 2 weeks of the COVID-19 onset), post-acute (week 2–4) and late (after week 4) [3]. The acute phase is clinically characterized by the core COVID-19 symptoms related to active viral replication and initial host response including fever, cough, dyspnoea, myalgia, headache, anosmia and dysgeusia; the post-acute phase is driven by the hyperinflammatory illness

leading to gastrointestinal, cardiovascular, respiratory, neurological, musculoskeletal and mucocutaneous symptoms; the late phase is associated with cardiovascular, pulmonary, neurological and psychological sequelae [4]. Dermatologic manifestations associated with SARS-CoV-2 infection are polymorphic, and they have been classified in distinct patterns, including the exanthema (varicella-like or papulo-vesicular, and morbilliform rash), vascular (chilblain-like, purpuric/petechial and livedoid lesions) and urticarial pattern (Fig. 1) [5, 6]. Although there is a growing literature amplifying the current knowledge on their clinical features, pathophysiological mechanisms and therapeutic management, data on their time of onset during the course of COVID-19 are scant. The objective of this study is to systematically review the studies reporting the time of onset of selected skin lesions with respect to the beginning of the reported onset of the COVID-19 core symptoms.

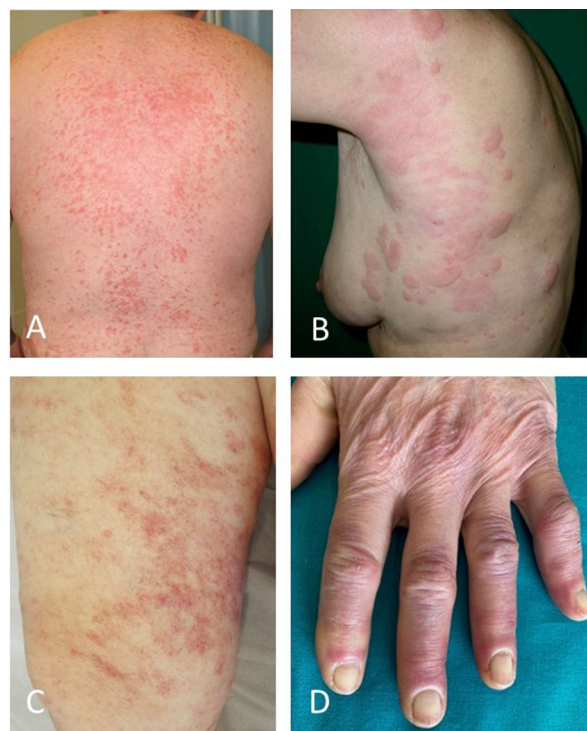


Fig. 1 Selected skin lesions associated with COVID-19; **a** morbilliform rash in the back; **b** urticarial lesions in the chest; **c** purpuric lesions in the thigh; **d** chilblain like lesions in the hand

METHODS

Search Strategy

The study was designed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [7]. The protocol of the study was registered on PROSPERO database (registration number CRD42021236331). Electronic searches were performed on MEDLINE via PubMed database using the following key words: COVID-19, varicella, morbilliform, chilblain, erythema, acropapular, manifestation, lesion, sign, pattern, vesicular, purpuric, petechial, livedoid, weal. The exact string, combining the disease of interest and skin manifestations and its subtype/elementary lesion was as follows: (COVID-19) AND (varicella* OR morbill* OR chilblain OR urticaria* OR erythem* OR acropapul*) AND (manifestation* OR lesion* OR sign* OR pattern* OR vesicul* OR purpuric OR petechial OR lived* OR weal*). Original articles published between 1 January 2020 and 21 January 2021 were included. References of the selected publications were additionally screened for other eligible records.

Selection Criteria

Eligible manuscripts included all the original studies reporting the time of onset of selected skin lesions with respect to the reported onset of the COVID-19 core symptoms (i.e. fever, cough, dyspnoea, myalgia, headache, anosmia and dysgeusia). Skin lesions were then classified in the following patterns: exanthema (varicella-like and morbilliform rash), vascular (chilblain-like, purpuric/petechial and livedoid lesions) and urticarial [4]. Skin lesions not falling within the previously mentioned patterns were classified as 'other'. According to the framework proposed by Datta SD et al., the time of onset of skin lesions was classified as acute (within 2 weeks of COVID-19 onset), post-acute (from week 2 to 4) or late (after week 4) [3]. We have additionally considered a prodromal phase in case skin lesions had been reported before COVID-19 onset, as the first symptom defining

SARS-CoV-2 infection. Non-eligible manuscripts included those not reporting the time of onset of skin lesions or written in a language other than English, expert opinion, literature reviews, meta-analyses and reply letters.

Data Extraction

Two blinded investigators (SDL, FB) independently extracted data by using an extraction form, and a third author (PG) was consulted to resolve any disagreement. Manuscripts were screened by title and abstract. References considered relevant were reviewed in full text and selected or rejected based on the inclusion and exclusion criteria. For each reference, the following features were considered: type of the study, number and gender of the patients, details of skin lesions and the time interval between their onset and the reported onset of the COVID-19 core symptoms (Supplementary Table 1). For each pattern, the number and proportion of cases occurring in the prodromal, acute, post-acute and late phase were estimated.

Evaluation of Risk Bias

The risk bias was assessed using the tool proposed by Murad et al. [8] Selection, ascertainment, causality and reporting domains were considered. The results of this tool were reported as an aggregate score (ranging from 0 to 8) as the sum of the scores of the eight binary responses. According to this tool, the average aggregate score across the studies was 4.41 ± 0.49 (Supplementary Table 2).

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors. The review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. This research has been conducted in accordance with the Helsinki Declaration. The participants provided consent for the images to be used in this publication.

RESULTS

A total of 354 manuscripts were first identified through the electronic database search. Then, they were screened by title and abstract, and those deemed relevant ($n = 260$) were reviewed in full text and selected based on the inclusion and exclusion criteria. Finally, 87 original manuscripts [9–95] were analysed, and summarized in Table 1. All the articles were retrieved according to the algorithm shown in Fig. 2.

A total of 895 patients with skin lesions associated with COVID-19 were identified (5 patients presented two concomitant patterns). The most frequent pattern was exanthema ($n = 430$, 48%), followed by vascular ($n = 299$, 33%) and then urticarial ($n = 105$, 12%). No acro-papular pattern was reported. Skin lesions occurred more frequently in the first 4 weeks

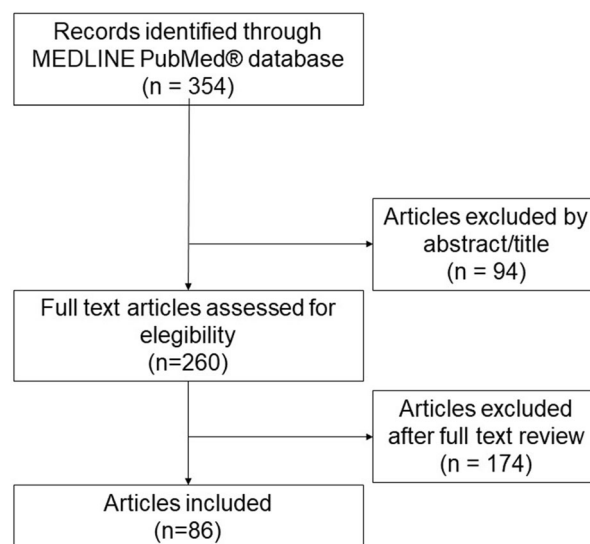


Fig. 2 Literature screening algorithm for articles included in the systematic review

Table 1 Time of onset of selected skin lesions with respect to the reported onset of the COVID-19 core symptoms

Pattern	Skin lesions	Prodromal ^a	Week 0–2 ^a Acute	Week 2–4 ^a Post-acute	Week > 4 ^a Late sequelae	Total, N (%)
Exanthema	Varicella-like papulo-vesicular	12 (8.8)	86 (63.2)	36 (26.5)	2 (1.5)	136 (15.1)
	Morbilliform rash	12 (4.1)	167 (56.8)	113 (38.4)	2 (0.7)	294 (32.7)
Vascular	Chilblain-like	10 (4.4)	46 (20.1)	172 (75.1)	1 (0.4)	229 (33.2)
	Purpuric/petechial lesions	0 (0)	13 (43.3)	17 (56.7)	0 (0)	30 (3.3)
	Livedoid lesions	1 (2.5)	27 (67.5)	11 (27.5)	1 (2.5)	40 (4.4)
Urticaria	Weal	17 (16.1)	83 (79)	4 (3.9)	1 (1)	105 (11.6)
Others	^c	4 (6.2)	40 (61.5)	15 (23.1)	6 (9.2)	65 (7.2)
Total		56 (6.1)	462 (49.4)	368 (43)	13 (1.4)	899 ^b

COVID-19 core symptoms: fever, cough, dyspnoea, myalgia, headache, anosmia and dysgeusia

^a Number of cases and row proportion between brackets are reported

^b 894 total cases (5 cases presented two concomitant patterns)

^c Seven erythema multiforme pattern, eight generalized pruritus, four herpes zoster, one herpes simplex virus-1 (HSV-1), three Kawasaki disease, one pityriasis rosea-like, one atypical erythema nodosum, one bullae non-haemorrhagic, four Raynaud's phenomenon, nine dry gangrene with arteriosclerosis, six severe micro-circulatory ischaemia with preserve pulse, two palmar/acral erythema, one leucocytoclastic vasculitis, two acute generalized exanthematous pustulosis (AGEP), one Stevens–Johnson syndrome, one urticarial vasculitis, two pressure-induced ischaemic necrosis in prolonged coma patient, one haematoma, one lichen planus, two contact dermatitis, one psoriasis, one generalized fixed drug eruption, one benign familial pemphigus, one chronic graft-versus-host disease, one stasis dermatitis, one dermatophytosis and one eruptive cherry angioma

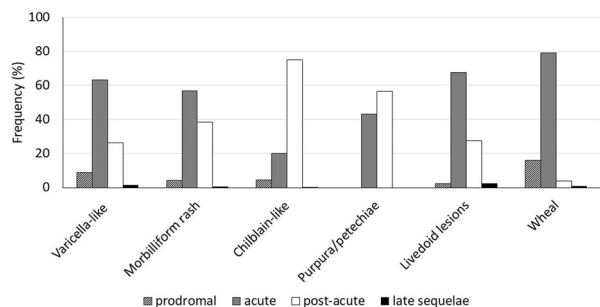


Fig. 3 Histograms reporting the frequency of COVID-19 associated skin lesions classified as prodromal (before COVID-19 onset), acute (within 2 weeks of COVID-19 onset), post-acute (from week 2 to 4) or late (after week 4)

from the COVID-19 onset ($n = 831$, 92%), whereas prodromal or late lesions were rarer ($n = 69$, 8%). The time of onset of the skin lesions differed among the patterns. In particular, the urticarial and exanthema patterns, both varicella-like and morbilliform rash, were more frequent in the acute phase of the infection (within 2 weeks) (Fig. 3). In papers reporting varicella-like lesions, the diagnosis was based either on clinical examination only or after exclusion of true chickenpox by serology [68] or polymerase chain reaction (PCR) analysis of vesicle fluid [34, 54, 61] or histologic examination [10, 40, 58]. About the vascular pattern some differences were noted among its subtypes. In detail, livedoid lesions were predominantly in the acute phase, while the chilblain subtype was more frequent in the post-acute phase (between week 2 and 4). The vascular purpuric/petechial subtype was equally distributed between the acute and post-acute phase. Several skin manifestations reported as associated with COVID-19 did not fall into the pattern classification, including erythema multiforme ($n = 7$), generalized pruritus ($n = 8$), herpes zoster ($n = 4$), HSV-1 virus infection ($n = 1$), Kawasaki disease ($n = 3$), pityriasis rosea-like ($n = 1$), atypical erythema nodosum ($n = 1$), bullae non-haemorrhagic ($n = 1$), Raynaud's phenomenon ($n = 4$), dry gangrene with arteriosclerosis ($n = 9$), severe micro-circulatory ischaemia with preserve pulse ($n = 6$), palmar/acral erythema ($n = 2$), leucocytoclastic vasculitis ($n = 2$), AGEP ($n = 2$), Stevens-Johnson syndrome ($n = 1$), urticarial vasculitis ($n = 1$),

pressure-induced ischaemic necrosis in prolonged coma patient ($n = 2$), haematoma ($n = 1$), lichen planus ($n = 1$), contact dermatitis ($n = 2$), psoriasis ($n = 1$), generalized fixed drug eruption ($n = 1$), benign familial pemphigus ($n = 1$), chronic graft-versus-host disease ($n = 1$), stasis dermatitis ($n = 1$), dermatophytosis ($n = 1$) and eruptive cherry angioma ($n = 1$).

DISCUSSION

We classified the time of onset of selected skin lesions associated with COVID-19 according to the framework proposed by Datta et al., who described the acute, post-acute and late phase of SARS-CoV-2 infection [3]. We have additionally considered a prodromal phase because skin lesions have been reported as the first and occasionally the only symptom of SARS-CoV-2 infection [12, 44, 96, 97]. The main finding of the study is that skin lesions occur more frequently in the first 4 weeks from the onset of the reported onset of the COVID-19 core symptoms. We acknowledge that the low number of cutaneous manifestations reported in the late phases could be interpreted as a report bias [98]. Indeed, late sequelae of SARS-CoV-2 infection will be likely reported more extensively in the future [99]. Our findings provide new information to the framework proposed by Datta et al. in which cutaneous manifestations were considered only in the post-acute phase, whereas we found that urticarial and exanthema patterns are more frequently reported in the acute phase of the infection [3]. Moreover, we found that the time of onset of individual patterns is different. Urticarial and exanthema patterns were more frequent in the acute phase, whereas the vascular pattern showed some differences among its subtypes. Livedoid lesions were predominantly in the acute phase, while chilblain-like lesions were more frequent in the post-acute phase. The diversity in the time of onset of skin lesions as well as their polymorphic nature likely reflects the diversity of the pathogenetic underlying mechanisms [100]. Exanthema may result from the haematogenous spreading of the virus through the cutaneous vascular system

and the immunologic reaction to viral particles [101]. Urticarial lesions may reflect the cutaneous expression of angiotensin-converting enzyme 2 as well as the direct stimulation of mast cell degranulation via complement activation [102]. Purpuric and livedoid lesions reflect a complement mediated endothelial injury [103]. The chilblain-like lesions are considered secondary to a delayed immune-mediated response involving the small cutaneous capillaries [104]. Several other muco-cutaneous manifestations that did not fall into the pattern classification have been reported, but we do not have solid arguments to classify them as incidental or linked to COVID-19, because pathogenetic studies are needed. SARS-CoV-2 infection is a complex disease that can favour different types of immunological disorders through various mechanisms that need to be elucidated.

We acknowledge the limitations of our study. Firstly, we have not considered all the muco-cutaneous manifestations associated with COVID-19 reported in literature, but we have selected a priori only a few of them that were the most frequent. We have collected information about their time of onset with respect to the reported onset of the COVID-19 core symptoms, not considering their overall duration, which is, however, poorly reported. The criterion for defining the onset of COVID-19 was not uniform among the articles, and we had to exclude those not clearly detailing the time of onset of skin lesions. Some skin lesions such as chilblain-like lesions were easily identified in the literature review, while others such as livedoid or purpuric lesions may have been overlapping. We were not able to make any inferential statistics on the data collected.

CONCLUSIONS

In conclusion, the diversity in the time of onset of skin lesions associated with COVID-19 as well as their polymorphic nature likely reflects the diversity of the pathogenetic underlying mechanisms. Finally, some proposals for future research may be suggested, including the definition of diagnostic criteria for COVID19 onset

of COVID-19 infection, the identification of time of onset and duration of the different extrapulmonary manifestations associated with SARS-CoV-2 infection as well as their pathophysiological mechanisms and specific therapeutic approach.

ACKNOWLEDGEMENTS

Funding. No funding or sponsorship was received for this study or publication of this article.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authorship contributions. Gisondi Paolo, Di Leo Sara, Bellinato Francesco, Cazzaniga Simone, Piaserico Stefano, Naldi Luigi contributed equally to concept and design of the study. Bellinato Francesco, Di Leo Sara and Cazzaniga Simone performed the statistical analysis. Gisondi Paolo, Di Leo Sara, Bellinato Francesco, Cazzaniga Simone, Piaserico Stefano, Naldi Luigi contributed to draft and revise the manuscript.

Disclosures. Gisondi Paolo, Di Leo Sara, Bellinato Francesco, Cazzaniga Simone, Piaserico Stefano, Naldi Luigi have no conflicts of interest to declare.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors. This research has been conducted in accordance with the Helsinki Declaration. The participants provided consent for the images to be used in this publication.

Data availability. Data are available in the Tables and supplementary Tables attached.

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