

Cutaneous manifestations of coronavirus disease 2019 in 458 confirmed cases: A systematic review

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ABSTRACT

Background: The coronavirus disease 2019 (COVID-19) pandemic has affected the whole world for a short span of time. As it is a novel virus, its manifestations have been slowly revealed. Cutaneous manifestations of COVID-19 have gradually been reported from different regions of the world. However, their significance in diagnosis, as well as predicting prognosis, remains to be established. **Objective:** This review describes the cutaneous manifestations of COVID-19 patients from diverse regions with the aim of highlighting any important associations. **Methods:** A literature search was conducted using “PubMed” for original articles, case series, and case reports using the search terms “cutaneous manifestations” and “skin manifestations” in combination with “COVID-19” published up to 31 May. **Results:** Nine original research articles and 35 case series or case reports were identified, including 458 confirmed COVID-19 cases. The ratio of male to female patients was 0.94, and the patients’ age ranged from 2 months to 84 years. In 10% of cases, skin lesions appeared before systemic manifestations. The most common cutaneous manifestation was macular/maculo-papular rash (42.5%), followed by acute urticaria (17.9%), vesicular rash (15.3%), pseudo-chilblain or acral purpuric lesions (15.1), and livedo-reticularis (4.4%). The majority of reported cases were located in Spain, Italy, and France. These manifestations do not seem to be sex-, age-, or country-specific. **Conclusion:** It is necessary to conduct worldwide registries and prospective studies to assess the true incidence of cutaneous manifestations of COVID-19 and to streamline their categorization based on their pathogenesis. There appears to be no specific manifestation at present, but a high index of suspicion can help in the diagnosis of patients presenting with cutaneous lesions as the first manifestation.

Keywords: Chilblains, COVID-19, cutaneous manifestations, livedo reticularis, maculo-papular, urticarial

Introduction

The World Health Organization on March 13, 2020 declared coronavirus disease 2019 (COVID-19) to be the cause of a pandemic.^[1] Although it predominantly affects the respiratory system, there are increasing reports of new manifestations, including diarrhea, anosmia, and dysgeusia. The recent literature

shows a surge in reports of the cutaneous manifestations seen in COVID-19. These range from varicella-like eruptions, acute urticaria, chilblain-like lesions, and maculopapular exanthem to livedo reticularis. The incidence of cutaneous manifestations in COVID-19 has varied widely in the limited studies reported to date, ranging from as low as 0.2% to as high as 20.4%.^[2,3] In sick patients, cutaneous manifestations probably remain undocumented or overlooked due to other demanding issues. This review aims to discuss the reported manifestations of COVID-19. These might attain diagnostic or prognostic significance with the passage of time as we get better documentation and insight into their incidence as well as pathogenesis.

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Received: 15-05-2020

Revised: 14-06-2020

Accepted: 15-07-2020

Published: 30-09-2020

Access this article online

Quick Response Code:



Website:
www.jfmpc.com

DOI:
10.4103/jfmpc.jfmpc_872_20

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How to cite this article: Jindal R, Chauhan P. Cutaneous manifestations of coronavirus disease 2019 in 458 confirmed cases: A systematic review. J Family Med Prim Care 2020;9:4563-9.

Methods

A literature search was conducted using “PubMed” for original articles, case series, and case reports using the search terms “cutaneous manifestations” and “skin manifestations” in combination with “COVID-19” published up to 31 May. The inclusion criteria were studies reporting cutaneous manifestations in confirmed cases published in the English language. Exclusion criteria were studies reporting suspected cases, review articles, and cutaneous manifestations attributed to drug hypersensitivity or use of personal protective equipment and hand hygiene practices. Two reviewers independently reviewed the abstracts and full text. A manual search of the reference lists of relevant papers and reports was performed to identify additional studies. Data regarding authors, region, number of participants, cutaneous manifestations, and time of onset with respect to systemic features were extracted.

Results

Nine original research papers [Table 1] and 35 case series/case reports that met the inclusion criteria were analyzed for this review [Table 2]. All studies were published between February 2020 and May 2020. The highest number of publications were from Spain (13), Italy (11), and France (5). The rest were from China, Kuwait, Russia, Indonesia, Belgium, Mexico, Poland, and the United States of America.

There were 458 patients with confirmed COVID-19 with cutaneous manifestations. For studies reporting both confirmed and suspected cases, only confirmed cases were included in the analysis. The age of patients ranged from 2 months to 84 years. Because of the heterogeneity among studies, the mean age could not be calculated as some studies reported mean age while others reported median age. However, the maximum number of patients was in the 50–70 years age group. Data regarding sex were available for 412 patients. Of these, 200 (48.6%) were male and 212 (51.4%) were female. Information about the onset of cutaneous signs and symptoms with respect to systemic manifestations, including fever, cough, malaise, and respiratory distress, was available for 433 patients. Cutaneous lesions developed after, simultaneously with, and before the onset of systemic features in 212 (48.9%), 172 (39.7%), and 42 (9.7%) patients, respectively. Seven patients (1.6%) had only cutaneous manifestations and were otherwise asymptomatic.

The most common cutaneous manifestation observed was macular/maculo-papular exanthem in 195 (42.5%) patients. In most cases, it was generalized. Acute urticaria was reported in 82 (17.9%), vesicular/varicella-like rash in 70 (15.3%), chilblain/pernio-like lesions in 69 (15.1%), and livedo reticularis in 20 (4.4%) patients. Vesicular lesions were localized in a few patients and generalized in others. Livedo reticularis was transient and was present for less than a day in some patients, while in others it persisted for weeks. Less commonly

reported manifestations include erythema multiforme (6), panniculitis (3), cutaneous hyperesthesia (2), small vessel vasculitis (1), and purpuric lesions (2). Reactivation of herpes simplex virus was reported in four patients and herpes zoster in two patients.

Analysis of the available data revealed that the age of patients with pseudo-chilblain lesions ranged from 16 years to 74 years, with most patients in their 5th to 6th decade. No sex-related predilection was noted. However, Casas *et al.* reported that young patients presented more commonly with such lesions.^[4] Similarly, for vesicular lesions, there appeared to be no sex-related predilection and a substantial proportion of patients were in their 5th or 6th decade. Casas *et al.* and Giorgi *et al.* reported an association between cutaneous manifestations and the severity of COVID-19 infection.^[4,5] Both reported that diffuse petechiae, dependent purpura, and acral ischemia/necrosis are associated with severe disease with coagulation defects. Casas *et al.* reported livedo reticularis in older patients and vesicular rash in middle-aged patients.^[4]

Discussion

The true incidence of cutaneous manifestations is difficult to ascertain due to the lack of large-scale prospective studies. The current literature reveals a wide disparity in the incidence of cutaneous manifestations, ranging from 0.6% to 20.4%.^[3-5,9-11] Whether this reflects geographical variation or erroneous documentation remains to be seen. The likelihood of identifying skin changes are high if the primary care team involves a dermatologist. The analysis of 458 reported cases found an almost equal number of male and female patients (male: female = 0.94), ruling out sex as a risk factor. Cutaneous lesions appeared after systemic features in close to half of the cases. However, in 11.3% of patients, cutaneous lesions were the presenting manifestation, with 1.6% of patients being otherwise asymptomatic. Thus, a high index of suspicion can help in the diagnosis of this subset, which, if missed, could increase the spread of COVID-19.

The literature on cutaneous manifestations in COVID-19 is growing, and a few recent large case series have tried to classify them systematically. Casas *et al.* in a multi-center study from Spain, including 375 patients, categorized cutaneous findings into five sub-groups: pseudo-chilblain-like lesions, other vesicular eruptions, urticarial lesions, other maculo-papular exanthems, and livedo reticularis/necrosis.^[4] The limitation of their study was the inclusion of suspected as well as confirmed cases.

Pseudo-chilblain-like eruptions are described as erythema and edema with few vesicles or pustules with or without purpura over the hands and feet. Casas *et al.* reported this in 19% of their patients.^[4] These were reported to occur in younger patients with less severe disease and manifested late during the course of the disease. On average, these lasted for 12.7 days. Alramthan *et al.* and Recalcati *et al.* reported similar findings in two and

Table 1: Original articles reporting cutaneous manifestations of COVID-19

Study	Country	Number of cases with cutaneous manifestations	Gender	Age (years)	Onset of symptoms No. of patients (time)	Pseudo-chilblain/ pernio like/acral necrosis	Vesicular/ varicella like	Maculo-papular exanthem	Urticarial	Livedo reticularis	Others (no. of patients)
Casas <i>et al.</i> ^[4]	Spain	234	113 (M) 121 (F)	56.38 (mean)	9 (before) 147 (simultaneously) 77 (after)	29	17	122	49	17	-
De Giorgi V <i>et al.</i> ^[5] (n=678)	China, Italy	53	32 (M) 21 (F)	55.9 (mean)	23 (before) 30 (after)	-	2	37	14	-	-
Nieto <i>et al.</i> ^[6]	Spain	24	6 (M) 18 (F)	40.5 (median)	2 (before) 3 (simultaneously) 19 (after)	-	24	-	-	-	-
Freeman <i>et al.</i> ^[7]	Multinational (8 countries)	23	12 (M) 11 (F)	41 (median)	4 (before) 3 (simultaneously) 11 (after) 5 (asymptomatic)	23	-	-	-	-	-
Marzano <i>et al.</i> ^[8]	Italy	22	16 (M) 6 (F)	60 (median)	After 3 day median latency	-	22	-	-	-	-
Recalcati <i>et al.</i> ^[3] (n=88)	Italy	18	NA	NA	8 (simultaneously) 10 (after)	-	1	14	3	-	-
Guarneri <i>et al.</i> ^[9] (n=125)	Italy	13	NA	NA	NA	3	-	2	2	-	Panniculitis (3) HSV reactivation (3)
Zhang <i>et al.</i> ^[10] (n=140)	China	2	NA	NA	NA	-	-	-	2	-	-
Moyano <i>et al.</i> ^[11] (n=1177)	Spain	8	4 (M) 4 (F)	72.2 (mean)	After 27.6 days mean latency	-	-	8	-	-	-

“n” is the number of COVID-19 confirmed cases reported in the study

one patient, respectively.^[3,17] They described them as red-purple papules over the dorsal aspect of the fingers. Estebanez *et al.* reported a similar presentation in Spain, where a patient with COVID-19 developed erythematous, yellow papules and plaques over the heels during the convalescent period (12 days after testing positive) that resolved without treatment.^[26] Small vessel occlusion similar to that seen in the autopsies of lung specimens could be the underlying pathology behind this cutaneous presentation. This is potentiated by visualizing hyaline thrombi in microvessels of the skin in the histopathology of such lesions.^[17]

Varicella-like vesicular eruptions were one of the first manifestations reported in COVID-19 patients. Recalcati *et al.* reported chickenpox-like vesicles in one of their 18 patients and Tammaro *et al.* in two patients.^[3,18] Marzano *et al.* reported a large series of 22 patients with varicella-like exanthem from Italy.^[8] These developed after a median latency period of three days after the onset of systemic features. These lesions were scattered in 72.7% of patients and diffuse in 27.3% of patients. The trunk was almost always involved, and the face and mucosae

were spared. In seven patients in whom a biopsy was performed, it was reported to be consistent with viral infection. Casas *et al.* described such lesions in 9% of their patients. The important differentiating point is that these vesicles are monomorphic, unlike varicella, where polymorphic vesicles are seen. These lesions were seen more commonly in middle-aged patients with intermediate disease severity, and developed even before the onset of fever and cough and lasted for an average of 10.4 days.^[4] Similar eruptions were reported in an 8-year-old girl who had a history of varicella infection. Five days later, she and her family members tested positive for COVID-19.^[34] The varicella-like eruptions could be coincidental as they resemble lesions produced by other parvoviruses.

Acute urticaria as a manifestation of COVID-19 has been reported quite widely. Recalcati *et al.* first described cutaneous findings in three of their patients.^[3] Casas *et al.* reported acute urticaria in 19% of patients.^[4] It is widespread and involves the palms. Urticaria develops simultaneously with systemic features, such as fever and cough, and resolves after an average of 6.8 days.

Table 2: Case reports and case series reporting cutaneous manifestations of COVID-19

Study	Country	No. of cases	Gender	Age (years)	Onset of lesions (days)	Pseudo-chilblain/ pernio like/ acral necrosis	Vesicular/ varicella like	Maculo-papular exanthem	Urticarial	Livedo reticularis	Others (no. of patients)
Zhang <i>et al.</i> ^[12]	China	7	4 (M) 3 (F)	59 (median)	Median 19 days (after)	7	-	-	-	-	-
Gianotti <i>et al.</i> ^[13]	Italy	5	NA	NA	NA	-	-	4	-	-	-
Hedou <i>et al.</i> ^[14]	France	5		NA	1 patient (before) 4 patient (after)	-	-	2	2	-	HSV-1 reactivation (1)
(n=103) Jimenez-Cauhe <i>et al.</i> ^[15]	Spain	4	4 (F)	66.75 (mean)	Mean 19.5 days after	-	-	-	-	-	Erythema multiforme like (4)
Sachdeva <i>et al.</i> ^[16]	Italy	3	3 (F)	71 72 77	NA, 4 days after 4 days after	-	-	1	2	-	-
Alramthan <i>et al.</i> ^[17]	Kuwait	2	2 (F)	27 35	Asymptomatic	2	-	-	-	-	-
Tammaro <i>et al.</i> ^[18] (n=130)	Italy	2	NA	NA	NA	-	2	-	-	-	-
Van Damme <i>et al.</i> ^[19]	Belgium	2	1 (M) 1 (F)	71 39	Same day Same day	-	-	-	2	-	-
Manalo <i>et al.</i> ^[20]	Atlanta	2	1 (M) 1 (F)	67 47	7 days (after) 10 days (after)	-	-	-	-	2	-
Janah <i>et al.</i> ^[21]	Morocco	2	2 (M)	17 29	15 days (after) 12 days (after)	-	-	-	-	-	Erythema multiforme (2)
Morey-Olive <i>et al.</i> ^[22]	Spain	2	1 (M) 1 (F)	6 2 months	16 days after, same day	-	-	1	1	-	-
Elsaia <i>et al.</i> ^[23]	Egypt	2	1 (M) 1 (F)	68 60	2 days before, same day	-	-	-	-	-	Herpes zoster (2)
Cepeda-Valdes <i>et al.</i> ^[24]	Mexico	2	2 (F)	50 20	Same day Same day	-	-	-	2	-	-
Krajewski <i>et al.</i> ^[25]	Poland	2	1 (M) 1 (F)	40 40	Same day Same day	-	-	-	-	-	Cutaneous hyperesthesia (2)
Estebanez <i>et al.</i> ^[26]	Spain	1	1 (F)	28	13 days after	-	-	-	-	-	Erythematous papuloplaques over heels (1)
Nieto <i>et al.</i> ^[27]	Spain	1	1 (F)	32	6 days after	-	-	-	1	-	-
Moreno <i>et al.</i> ^[28]	Spain	1	1 (F)	32	6 days after	-	-	1	-	-	-
Amatore <i>et al.</i> ^[29]	France	1	1 (M)	39	Same day	-	-	-	1	-	-
Joob <i>et al.</i> ^[30]	Thailand	1	NA	NA	NA	-	-	-	-	-	Patchial rash (1)
Ehsani <i>et al.</i> ^[31]	France	1	1 (M)	27	3 days after	-	-	-	1	-	-
Paolino <i>et al.</i> ^[32]	Italy	1	1 (F)	37	3 days after	-	-	1	-	-	-
Olisova <i>et al.</i> ^[33]	Russia	1	1 (F)	12	3 days after	-	-	-	-	-	Purpuric rash over face (1)
Genovese <i>et al.</i> ^[34]	Italy	1	1 (F)	8	5 days before	-	1	-	-	-	-
Henry <i>et al.</i> ^[35]	France	1	1 (F)	27	2 day before	-	-	-	1	-	-
Dominiguez-Santas ^[36]	Spain	1	1 (F)	71	7 days after	-	-	-	-	-	Small vessel vasculitis (1)
Gracia-Gil <i>et al.</i> ^[37]	Spain	1	1 (M)	51	3 days after	1	-	-	-	-	-
Gunawan <i>et al.</i> ^[38]	Indonesia	1	1 (M)	51	5 days after	-	-	-	1	-	-
Mahe <i>et al.</i> ^[39]	France	1	1 (F)	64	4 days after	-	-	1	-	-	-
Hunt <i>et al.</i> ^[40]	USA	1	1 (M)		Same day	-	-	1	-	-	-

Contd...

Table 2: Contd...

Study	Country	No. of cases	Gender	Age (years)	Onset of lesions (days)	Pseudo-chilblain/ pernio like/ acral necrosis	Vesicular/ varicella like	Maculo-papular exanthem	Urticarial	Livedo reticularis	Others (no. of patients)
Jimenez-cauhe <i>et al.</i> ^[41]	Spain	1	1 (F)	84	11 days after	-	-	-	-	-	Flexural purpuric rash (1)
Andina <i>et al.</i> ^[42]	Spain	1	NA	NA	NA	1	-	-	-	-	-
Locatelli <i>et al.</i> ^[43]	Italy	1	1 (M)	16	3 days after	1	-	-	-	-	-
Conforti <i>et al.</i> ^[44]	Italy	1	1 (F)	62	7 days after	-	-	-	-	1	-
Saenz Aguirre <i>et al.</i> ^[45]	Spain	1	NA	NA	NA	1	-	-	-	-	-
Balestri <i>et al.</i> ^[46]	Italy	1	1 (F)	74	Asymptomatic	1	-	-	-	-	-

"n" is the number of COVID-19 confirmed cases reported in the study.

Patients developing urticaria were found to have severe disease with higher mortality. However, it appears unclear if these urticarial lesions represent a manifestation of COVID-19 itself or are drug-induced as sick patients are on multiple drugs. Viral infections are a known trigger for urticaria, especially in children, and thus is likely to be seen in COVID-19.

Maculo-papular exanthems have been described variably by researchers as erythematous, morbilliform, and purpuric rash. However, all fit the description of maculo-papular rash similar to that seen in other viral exanthems. Casas *et al.* reported different morphologies of maculo-papular rash in 47% of patients. These include pityriasis rosea-like, purpuric, peri-follicular rash with scaling, erythema multiforme-like, and erythema elevatum diutinum-like.^[4] Some patients develop erythematous infiltrated papules over the extremities resembling pseudo-vesicles. Like urticarial lesions, maculo-papular rash is also associated with severe disease and high mortality. These last for a mean of 8.6 days and subside without any post-inflammatory pigmentation.^[4] Underlying lymphocytic vasculitis with red blood cell extravasation and papillary dermal edema exacerbated by complement deposition, as seen in histopathology.^[35]

Occlusive vascular disease can also explain the development of livedo reticularis. Casas *et al.* reported livedo reticularis in older patients with severe disease.^[4] However, age is a poor prognostic factor itself and may be responsible for the higher mortality. Livedo reticularis has been reported as a transient finding in some patients who do not require specific treatment.^[20] A few patients also developed cutaneous necrosis secondary to small vessel thrombosis. Other manifestations include enanthems, purpuric flexural lesions, and reactivation of herpes simplex and varicella zoster virus.

It is difficult to specifically attribute the cutaneous manifestations to COVID-19 to the virus itself because of a lack of histopathological and virological confirmation in most studies. It is even difficult to obtain photographs because of the risk of disease transmission. The findings reported to date may be incomplete, and new manifestations will be added with time. There is a need to develop countrywide registries to maintain

records of cutaneous manifestations. With a better understanding of the pathogenesis of the disease, as well as its cutaneous manifestations, their significance will be clear.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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