




SHORT PAPER

Cutaneous manifestations of the Coronavirus Disease 2019 (COVID-19): A brief review

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Email: doctorjenny1@163.com**Abstract**

COVID-19, first appeared in December 2019 in Wuhan, China, has been spreading quickly throughout the world. We reviewed the evidence on cutaneous manifestations of COVID-19 based on PubMed database. The searching strategy was (COVID* or coronavirus*) and (dermatol* or skin* or cutaneous*). The publication time was limited to 2019 onward. After independent review by two authors, 14 studies with 228 confirmed cases were included in the analysis. A total of 60 patients developed skin rashes, and the age ranged from 8 to 84. Exanthematous eruptions potentially related to COVID-19 infection were highly variable and heterogeneous. Skin lesions mainly appeared erythematous, urticarial, and vesicular (chicken pox-like or varicelliform). Petechiae rash, livedo reticularis, and reactivation of oral HSV-1 were also observed in single cases. Newly reported eruptions like vascular lesions and peculiar (perniosis-like) skin lesions caused concern among dermatologists. Exanthems were widely distributed and were primarily located on the trunk. Associated symptoms, latency time, treatment, and prognosis were also carefully summarized. This study reviewed the recently published COVID-19 studies with skin manifestations, which may pave the way for further research.

KEYWORDS

coronavirus, COVID-19, cutaneous manifestations, review, skin

1 | INTRODUCTION

Coronavirus Disease 2019 (COVID-19) has been spreading quickly throughout the world since its first appearance in December 2019 in Wuhan, China. World Health Organization (WHO) declared a pandemic condition in March, with the confirmed case number gradually rising to 2 626 321 globally by April 25th, 2020. Common clinical features of this virus infection inside and outside of the respiratory system include fever, cough, headache, diarrhea, fatigue, headache, and myalgia.¹ Dermatological symptoms are reported sporadically, and the roles of skin lesions in early recognition and disease progression have

not been extensively studied. In this short review, we will present evidence on cutaneous manifestations and relevant implications in the context of COVID-19, which may highlight dermatological aspects and help dermatologists understand the disease.

2 | METHODS

The literature search using the following search strategy was conducted on Pubmed database on April 25th, 2020 to identify eligible articles: (COVID* or coronavirus*) and (dermatol* or skin* or cutaneous*). The publication time was limited to 2019 onward. A total of 170 papers were identified by the initial search. Two reviewers independently reviewed the abstracts and full-texts. Reports on the range

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of cutaneous manifestations associated with COVID-19 were included in this review.

3 | RESULTS

Overall, 16 studies with 256 confirmed COVID-19 cases were included in the final analysis. A total of 88 patients developed skin rashes, and the age ranged from 8 to 84. Of the 50 patients with determined gender, 27 (54%) were males and 23 (46%) were females. The only prospective study showed that 5 (4.9%) patients in France presented with cutaneous manifestations associated with infections,² which was lower than the rate of occurrences of skin rashes in a previous retrospective study (20.4%, 18 out of 88; Table 1).³

Exanthematous eruptions potentially related to COVID-19 infection were highly variable. Skin lesions mainly appeared erythematous, urticarial, and vesicular (chicken pox-like or varicelliform).¹⁻¹² Petechiae rash,¹³ livedo reticularis,¹⁴ and reactivation of oral herpes simplex virus type 1 (HSV-1)² were also observed in single cases. Newly reported eruptions like vascular lesions and peculiar (perniosis-like) skin lesions caused concern among dermatologists.^{15,16} Exanthems were widely distributed and were primarily located on the trunk. Patients often presented with other clinical symptoms during the disease course, including fever, cough, headache, weakness, coryza, dyspnea, and other respiratory problems.^{1,5,7-14} The latency time from systemic symptoms to exanthem ranged from -2 to 21 days, and lesions of three patients were detected during the prodromal or sub-clinical phase.^{1,8,11} Thirteen patients remained asymptomatic across the entire observation period except for peculiar lesions, red-purple papules, and additional erythematous.^{4,16}

Of the nine patients receiving medications, four patients received conservative drug therapy for exanthem.^{1,5,6,9} Oral antihistamines contributed to clinical and symptomatic improvement in two patients with urticaria.^{1,6} Local corticosteroids were given to a patient with erythematous-yellowish papules, however, these papules progressed into hardened and pruritic erythematous plaque 3 days later despite the treatment.⁵ Another patient with confluent erythematous patches and worsening dermatitis demonstrated a good response to triamcinolone 0.1% cream.⁹ These agents were used in combination with systemic drugs for infectious complications and symptoms. Five patients receiving treatment for symptoms of COVID-19 infection had no specific agents for skin rashes. Based on the recorded clinical outcomes in four of five patients, rash improved or disappeared within a few days spontaneously.^{10,11} Among nine patients receiving treatments,^{1,5-7,9-11} two presented with rash before^{1,11} while six developed skin eruptions following drug administration.^{5-7,10,11}

4 | DISCUSSION

Recently, Recalcati and colleagues reported the cutaneous manifestations of COVID-19 infection in Italy and asked for more papers to confirm and better understand the pattern of skin involvement with

COVID-19.³ As the disease became pandemic globally, additional evidence has been constantly emerging. Therefore, we conducted a study to briefly review the ongoing research advances.

For COVID-19 treatment, one possible treatment option was the combination of anti-viral medicine (hydroxychloroquine and lopinavir/ritonavir) with antibiotics (azithromycin, levofloxacin, and ceftriaxone). Supporting therapy of paracetamol or benzonatate could also be performed. However, only four case reports mentioned medicine usage for skin symptoms, including oral antihistamines and local corticosteroids.^{1,5,6,9} Antihistamines and corticosteroids are commonly used as anti-inflammation and anti-allergic agents, but they will increase the risk of infection as well. This paradox may restrict the usage of these medicines, especially in COVID-19 patients. Policies and guidelines for the treatment of COVID-19 were different among countries, and some researchers refused to give any treatments for asymptomatic patients or those with mild symptoms because the symptoms may spontaneously remiss after several days.

The pathogenesis of cutaneous manifestations remains unknown and may be extremely different among these researches. Mottling, livedo reticularis, petechiae rash, purpura, chilblain, and other vascular signs could be associated with a series of thrombotic events such as disseminated intravascular coagulation (DIC), hyaline thrombus formation, acral ischemia, and thrombocytopenia.^{4,14,15} Immune dysregulation, vasculitis or neoangiogenesis might also be associated with lesions' pathophysiology.¹⁵ In other cases, skin rash may be directly induced by virus infection as is common in other viral diseases, for example, dengue, rubella, and measles. However, differential diagnosis of exanthematous eruption is problematic since drug eruptions and viral exanthems share considerable similarities.¹⁰ Recalcati preliminarily excluded the skin lesion from the usage of a novel drug by analyzing the medication history of patients.³ Raffaele Gianotti provided histopathological evidence by biopsy, finding viral particles in the cutaneous blood vessels in patients with COVID-19 infection.¹¹ Recently, Recalcati raised a hypothesis that peculiar lesions that were unreported in previous literature may represent late clinical manifestations of COVID-19 infection among young healthy individuals. To clarify the underlying mechanisms, large-scale prospective studies with biopsies, serological tests showing antibody response to virus infection and PCR analysis of suspected patients are warranted. Since the time kinetics of skin exanthem and viremia probably vary among different infections, it may be significant to measure blood viral load at different time points (before, during, or after lesions onset), thereby determine the appropriate time of biopsies for molecular identification.

Several effective measures have been taken in hospitals across China to control the spread of COVID-19 and ensure public health. Services of dermatology outpatient department and surgery in Peking Union Medical College were postponed where only emergency operations were conducted. Meanwhile, to meet the patients' medical requirements and to reduce the capacity of skin clinics, we provided follow-ups and free dermatological consultations through telephone and social media, particularly for patients with severe autoimmune diseases and those receiving biologics and chemotherapeutics. We

TABLE 1 Articles on cutaneous manifestations of the Coronavirus disease 2019 (COVID-19)

Author and year	Study design	Number of patients	Age and gender	Coronavirus diseases 2019 manifestations	Treatment for Coronavirus diseases 2019	Skin manifestation	Days after the onset of Coronavirus diseases 2019 symptoms	Location of the skin symptoms	Treatment for dermatology symptoms	Clinical outcome of the skin manifestation
Fernandez-Nieto and colleagues, 2020	Retrospective, case report	1	32, female	Unavailable	Hydroxychloroquine and azithromycin	Urticiform	6	Unavailable	Oral antihistamines	Clinical and symptomatic improvement
Anwar Alramthan and colleagues, 2020	Retrospective, case series	2	27, female; 35, female	Asymptotic	None	Red-purple papules and additional erythematous	Unavailable	Dorsal aspect of fingers bilaterally	Unavailable	Unavailable
Andrea Estébanez and colleagues, 2020	Retrospective, case report	1	28, female	Dry cough, nasal congestion, fatigue, myalgias, and arthralgias without fever	Paracetamol for 4 d	First pruritic lesions and then confluent erythematous-yellowish papules	14	Both heels	Local corticosteroids	Lesions persisted and became erythematous plaques that both hardened and became pruritic
Diane Henry and colleagues, 2020	Retrospective, case report	1	27, female	Odynophagia but chills, chest pain, fever, moderate lymphopenia, rise of C reactive protein after 2 d	Paracetamol	Diffuse arthralgia and pruritic disseminated erythematous plaques eruption, confirmed with urticaria	2 d before	Particular face and acral involvement	Antihistamines	Slow improvement
Beuy Job and colleagues, 2020	Retrospective, case report	1	Unavailable	Low platelet count, respiratory problems	Unavailable	Petechiae rash	Unavailable	Unavailable	Unavailable	Unavailable
Juan Jimenez-Cauhe and colleagues, 2020	Retrospective, case report	1	84, female	Bilateral pneumonia	Hydroxychloroquine and lopinavir/ritonavir	Erythematopurpuric, millimetric, coalescing macules	11	Flexural regions, mildly pruriginous and mainly located in the peri-axillary area	Unavailable	Unavailable
Giovanni Genovesi and colleagues, 2020	Retrospective, case report	1	8, female	Fever, mild cough, and thrombocytopenia	None	Forty erythematous papules and few vesicles scattered, resembling varicella-like exanthem	6	Bilaterally and symmetrically on the trunk	None	Subsided in 7 d
Raffaele Gianotti and colleagues, 2020	Retrospective, case series	3	59, female; 89, female; 57, male	Fever and cough	lopinavir-ritonavir, heparin and levofloxacin; ceftriaxone and azithromycin; levofloxacin; and hydroxychloroquine	Erythematous macules; exanthem; pruritic eruption of erythematous macules and papules	3; 7; 2 d before	arms, trunk and lower limbs; trunk and arms	None	Spontaneously improved
Antoine Mahe and colleagues, 2020	Retrospective, case report	1	64, female	Fever, asthenia, and cough	Oral paracetamol	Erythematous rash	4	First both antecubital fossa, then extended to the trunk and axillary folds	None	Rash disappeared 5 d after its beginning
Iviansan F. Minalto and colleagues, 2020	Retrospective, case report	2	67, male; 47, male	Fever, nasal congestion, postnasal drip, and cough, gross hematuria and generalized weakness, a mild headache, sinus pressure, anosmia, and fever	Unavailable	Nonpruritic blanching unilateral livedoid patch; unilateral asymptomatic rash, resembling livedo reticularis	7; 10	Right anterior thigh	Unavailable	Resolved or disappeared
Marzano and colleagues, 2020	Retrospective, observational study	22	Median age of 60, male	Most observed with fever (95.5%), cough (72.7%), headache (50%), weakness (50%), coryza (45.5%), dyspnea (40.9%), and other symptoms	Unavailable	Varicella-like papulovesicular exanthem and mild/absent pruritus	3 d of median (range from -2 to 12 d)	Scattered in most cases (72.7%) and diffuse in 6 cases (27.3%), constant trunk involvement	Unavailable	Unavailable

(Continues)

TABLE 1 (Continued)

Author and year	Study design	Number of patients	Age and gender	Coronavirus diseases 2019 manifestations	Treatment for Coronavirus diseases 2019	Skin manifestation	Days after the onset of Coronavirus diseases 2019 symptoms	Location of the skin symptoms	Treatment for dermatology symptoms	Clinical outcome of the skin manifestation
Sebastiano Recalcati and colleagues, 2020	Retrospective, observational study	18 out of 88	Unavailable	Unavailable	Unavailable	Erythematous rash (77.7%), widespread urticaria (16.6%) and chickentpox-like vesicles (5.6%)	44.4% developed at the onset and 55.6% after the hospitalization	Trunk mostly involved	Unavailable	Remission of itching and healing of lesions in a few days
David J. Najarian and colleagues, 2020	Retrospective, case report	1	58, male	Cough, pain in hands, and lower extremities	Azithromycin and benzonatate	Pruritic, expanding, and worsening dermatitis, erythematous macules, confirmed with morbilliform exanthem	Unavailable	Widespread, on the legs, thighs, forearms, arms, shoulders, back, chest, and abdomen	Triancinolone	Improvement of the dermatitis
Hedou M. and colleagues, 2020	Prospective, pilot study	5 out of 103	Unavailable	Unavailable	Unavailable	Erythematous rash (40%), urticaria (40%) and an oral herpes simplex virus type 1 (HSV-1) reactivation (20%)	Unavailable	Mainly located on the face and the upper body	Unavailable	Disappeared with a median time of 48 h (from 24 h to 6 d)
Sebastiano Recalcati and colleagues, 2020	Retrospective, case series	14	11 children (average age 14.4 y, range 13-18) and 3 young adults (average age 29 y, range 23-39), female-male was 8:6	Asymptomatic (n = 11), cough and fever (n = 3)	Unavailable	Peculiar (pemphig-like): acral eruption of erythematous-violaceous papules and macules, with possible bullous evolution, or digital swelling	3 w before (n = 3)	Located on the feet in 8 cases, on the hands in 4 cases, on both sites in 2	None	Developed into erythematous-papular targetoid lesions in two children; resolved after 2 to 4 w without treatment
Jean David Bouaziz and colleagues, 2020	Retrospective, observational study	14	Unavailable	Respiratory distress; chest pain and cough, fever, anosmia	Unavailable	Inflammatory lesions: exanthema (n = 4), chicken pox like vesicles (n = 2), cold urticaria (n = 1); Vascular lesions: violaceous macules with "porcelain-like" appearance (n = 1), livedo (n = 1), non-necrotic purpura (n = 1), necrotic purpura (n = 1), chilblain appearance with Raynaud's phenomenon (n = 1), eruptive cherry anglioma (n = 1)	Few days after systemic onset	Unavailable	Unavailable	Unavailable
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also conveyed medical knowledge about personal protection, skincare, mental health, and household cleaning to dermatological patients.

A limitation of our research is that we cannot analyze the cutaneous manifestations and disease courses quantitatively due to the relatively large amounts of unavailable and incomparable data. Close attention should be paid to the cutaneous manifestations of COVID-19 in further clinical practice. Some of them may emerge before the onset of COVID manifestations. This may be useful to identify patients or asymptomatic carriers in the risk population. Understanding how COVID-19 present on the skin may help practitioners and patients to recognize and manage the disease. In conclusion, we reviewed the recently published COVID-19 studies with cutaneous manifestations, which may pave the way for further research.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript. Keyun Tang and Yuanzhuo Wang conducted the literature search and wrote the manuscript. Hanlin Zhang and Qingyue Zheng made the table. Rouyu Fang examined and collected the data. Qiuning Sun designed the study, made the analysis and examined the data. The manuscript have been read and approved by all the authors. We have thoroughly read the instructions for authors. The requirements for authorship have been met and each author believes that the manuscript represents honest work.

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