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Cutaneous, skin histopathological manifestations and relationship to COVID-19 infection patients

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Abstract

COVID-19 diseases have been a nationwide pandemic condition. However, cutaneous, skin histopathological manifestations of COVID-19 infection are not well described. Our study aims are to present heterogeneous cutaneous, histopathological manifestations in COVID-19 patients, to investigate the possible relationship between cutaneous manifestations and histopathological features in COVID-19 infection. We performed a systemic review in PubMed database and Chinese medical journal search engines which were wangfang.data (http://www.wanfangdata.com.cn/), Science China (http://www.cnki.net/) until June 17th, 2020. Search terms "COVID-19," "SARS-Coronavirus-2" and "Coronavirus" were used in combination with "cutaneous," "rash," "skin," "dermatology." Seventy-five papers were included with confirmed COVID-19 infection. The most frequent cutaneous manifestation of COVID-19 present was erythema, nearly 38.4%. Trunk was the most affected location, presenting in 51.4% patients. Rash occurred before onset of other symptoms was in 5.3% patients. Seventy-seven patients were received treatments. Rash was dismissed in 49% patients, improved in 21.2% patients ranged from 0 to 17 days. The histopathological examination present in 39 patients. Skin is one of target organs affected by COVID-19 infection. Cutaneous manifestations should be paid more attention. It can help doctors diagnose COVID-19 infection in prodromal stage, understand progression, and determine prognosis of COVID-19 infection.

KEYWORDS
COVID-19, cutaneous manifestations, histopathology, SARS-CoV-2

1 | INTRODUCTION

Coronavirus is a big family which can damage respiratory system. Previous epidemics or pandemics of coronavirus were severe acute respiratory syndrome (SARS) in 2002 and Middle East respiratory syndrome (MERS) in 2012. Since 8, December 2019, a novel kind of coronavirus pneumonia was reported. Right now, the novel coronavirus infected diseases spread more than 200 countries around the world. The virus is known as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2, COVID-19).[1]

COVID-19 is a single-stranded RNA virus from the coronaviridae family. The genetic sequence of COVID-19 shows more than 80% familiar with SARS-CoV, and more than 50% with MERS-CoV.[2] COVID-19 originates in bats, and can infect humans, bats, and wild animals.[3] COVID-19 has 5 to 7 days incubation period (range from 2 to 14 days). Symptoms may appear from 2 to 14 days.[4] Mortality is nearly 2.2% to 2.79%,[5] contrasting with 9.65% fatality of SARS, 34.5% fatality of MERS.[6] The mortality is high in patients over 65 years with comorbidities, such as diabetes, hypertension, cardiovascular involvements, or cancer. The frequent symptoms at onset are fever, cough, fatigue, anosmia, myalgia, dyspnea, acute respiratory distress syndrome (ARDS), sputum production, headache, hemoptysis, diarrhea.[7-9] COVID-19 can damage multi-systems, such as respiratory system, central nervous system,

gastrointestinal tract, hematological system, cardiovascular system, urinary system, skin.

Cutaneous manifestations are heterogeneous. Some patients presented with more than one kind of cutaneous lesions.[10] Atypical symptoms could result in misdiagnoses, delayed diagnoses, and virus transmission. Cutaneous and skin histopathological manifestations have been poor described. Because of high contagious, widespread of COVID-19 diseases, negative swab or PCR tests, we tried to find out if COVID-19 diseases had signaled eruptions during prodromal, illness or decline periods. In the study, we performed a retrospective observational worldwide study of cutaneous manifestations and histopathology and their relationship in COVID-19 infection (CI) patients from December 2019 to June 17th, 2020.

2 | METHODS

We collected previously published literatures on cutaneous manifestations and histopathology of CI diseases through Chinese medical journal search engines which were wangfang.data (http://www.wanfangdata.com.cn/), Science China (http://www.cnki.net/) and PubMed database, since onset of current COVID-19 epidemic to June 17th, 2020. Search terms "COVID-19," "SARS-Coronavirus-2" and "Coronavirus" were used in combination with "cutaneous," "rash," "skin," "dermatology." Studies written in Chinese and English about cutaneous symptoms, histopathology of COVID-19 were included. The studies that did not mention cutaneous lesions with confirmed CI or did not include related information or did not write in English or Chinese were excluded.

We analyzed the following variables: gender, age, onset of symptoms, contacts with potentially infected relatives, clinical manifestations, comorbidities, skin symptoms, types and location of lesions, tests for SARS- CoV-2 (Swabs, PCR, IgM, IgA, IgG), treatments, outcome, region, previous histology (allergy to drugs or food, drugs intake, if the same rash occurred before, autoimmune-related diseases history). Patients with autoimmune-related diseases, drug eruptions, or with history of the same eruptions were excluded.

Not every article could present all characteristics that were content with our study. For each characteristic, the number in table was referred to the variable data in the published articles.

3 | RESULTS

224 articles were evaluated. A total of 75 studies including 198 patients with confirmed CI from December 2019 to June 17th, 2020 were included in our study. These patients were confirmed by nasopharyngeal swab, COVID-19 IgM, IgG antibodies, COVID-19 virus RT-PCR, or radiologic diagnosis. Twenty-one countries reported cutaneous manifestations of CI. There are China, Spain, Italy, France, UK, American, Indonesia, Singapore, Turkey, Iran, Kuwait, Mexico, Morocco, Brazil, Thailand, Switzerland, Japan, Poland, Portugal, Belgium, and Russia.

The ages of patients were ranged from 15 days to 91 years. 141 patients were determined gender. 70 (49.6%) patients were male and 71 (50.4%) patients were female. The latency time from systemic symptoms to exanthema occurring ranged from −17 days to 1 month (Table 1). Meanwhile, 102 patients present lesions after other symptoms ranged from 1 day to 1 month. The most frequent lesion was erythema in 38.4% patients, following by urticarial lesions in 13.6% patients. Chilblain-like lesion was in 20 (10.1%) patients. Trunk was the most common affected area, almost in 51.4% CI patients, following by extremities in 66 (35.7%) patients. 2 (1.1%) patients had skin hypersensitivity.

Eight patients were asymptomatic across the entire observation time except for lesions. Pain and itching were found in 11 (12.9%), 47 (55.3%) patients, respectively. Pain with itching occurred in 2 (2.4%) patients. Burning was found in 4 (4.7%) patients.

Twenty-one patients were treated for cutaneous involvements. Fifteen patients received oral antihistamines. Topical corticosteroid was given to 10 patients. Rash improved or disappeared in several hours to 21 days, based on the reported of 151 patients. Rash worsened in 9 patients. Eleven patients died (Table 2).

4 | DISCUSSION

On March 11th, 2020, World Health Organization declared COVID-19 was a pandemic viral infection. Rightnow, the confirmed cases were more than 8 million globally by June 17th.

COVID-19 attacks alveolar epithelial cells through angiotensin-converting enzyme 2 (ACE2) which is ACE of isozyme, as well as cellular receptor for COVID-19, mainly found in cardiovascular, kidney, testes, lung, colon, and other organizations.[11] ACE2 plays an important role in incising Ang II to generate Ang1-7, which antagonizes Ang II-induced vascular smooth muscle contraction, cell proliferation, exudation of neutrophils, macrophages and fibrinous, vascular inflammation, loss of pulmonary ventilation function and trouble of maintaining oxygenation.[12,13]

Interleukin (IL)-6 is one of main pro-inflammatory factors resulting in cytokine storm, enhancing vascular permeability, weakening organ function. Elevation of IL-6 level was found in severe, critically ill COVID-19 patients, as a biomarker for severity assessment.[14]

Some blood inflammatory factors, such as D-dimer, CRP are thought to be responsible with coagulation abnormalities.[15] Severe COVID-19 pneumonia is accompanied with elevation of D-dimer, fibrinogen, coagulation function. Because of cytokine storm trigger of virus which could induce coagulation and microthromb,[16] D-dimer may relate with poor prognosis.[17]

Virus particles are found in cutaneous blood vessels in CI patients. Viral interaction with keratinocytes, which may result in a spectrum of clinical and histological manifestations.[18] Variable lesions may be impacted by immune dysregulation, vasculitis, vessel thrombosis, neoangiogenesis.

Cutaneous lesions in CI patients are heterogeneous, such as erythematous maculopapular,[19,20] urticarial,[19,21] chickenpox-like,[22]

TABLE 1 Clinical manifestations of the Coronavirus disease 2019 (COVID-19) until June 17th, 2020[a]

Age (126)	Number	Percent (%)
0-10	8	6.3%
10-20	28	22.2%
21-30	10	7.9%
31-40	12	9.5%
41-50	11	8.7%
51-60	25	19.8%
61-70	21	16.7%
71-80	15	11.9%
81-90	6	4.8%
91-100	1	0.8%
Gender (141)[b]		
Male	70	49.6%
Female	71	50.4%
Clinical syndromes (127)[c]		
Fever	82	64.6%
Cough	64	50.4%
Headache	19	15%
Nasal obstruction/Congestion/ Coryza/Rhinorrhea	14	11%
Fatigue	21	16.5%
Myalgia	13	10.2%
Arthralgias	6	4.7%
Chill	5	3.9%
Chest pain	4	3.1%
Dyspnea	20	15.7%
Nausea/Vomiting/Diarrhea	14	11%
Anosmia/Ageusia	1/4	0.8%/3.1%
Pneumonia/respiratory symptoms	16	12.6%
Asymptotic	8	6.3%
Treatments (77)[d]		
Hydroxychloroquine	22	28.6%
Azithromycin/Ceftriaxone	13/4	16.9%/5.2%
Paracetamol/Acetaminophen/ Leflunomide	7/5/1	9.1%/6.5%/1.3%
Lopinavir/Ritonavir	16/16	20.8%/20.8%
Levofloxacin	3	3.9%
Heparin	12	15.6%
Antihistamine	15	19.5%
Topical corticosteroids	10	13%
Systemic corticosteroids	14	18.2%
IVIG	7	9.1%
Outcome (151)[e]		
Worsening	9	6%
Improved	32	21.2%
Complete resolved	74	49%
Death	11	7.3%

[a]Calculated over 137 patients with known on-set age.
[b]Calculated over 141 patients with known gender.
[c]Calculated over 127 patients with known clinic symptoms.
[d]Calculated over 77 patients with known treatments.
[e]Calculated over 151 patients with known outcome.

TABLE 2 Cutaneous manifestations of the Coronavirus disease 2019 (COVID-19) until June 17th, 2020

Cutaneous manifestations (198)	Number	Percent (%)
Urticarial	27	13.6%
Papulovesicular	21	10.6%
Erythematous papules/ plaques/macules	76	38.4%
Morbilliform	4	2%
Edematous	4	2%
Chicken box-like	3	1.5%
Petechiae	9	4.5%
Chilblain-like/Perniosis-like/Cyanosis/Purpuric	20/1/7/14	10.1%/0.5%/3.5%/7.1%
Livedoid /Necrosis	8/3	4%/1.5%
Dry gangrene	1	0.5%
Ulcer	4	2%
Rash and symptom sequence (131)		
Before other symptoms	7	5.3%
The same time as other symptoms	22	16.8%
After other symptoms	102	77.9%
Locations (185)[a]		
Trunk	95	51.4%
Extremities	66	35.7%
Palms/Finger/Hands	39	21.1%
Toes/Soles/Foot/Plantar	58	31.4%
Face	24	13%
Whole body	4	2.2%
Feelings (85)		
Itching	47	55.3%
Pain	11	12.9%
Pain and Itching	2	2.4%
Burning	4	4.7%

[a]Calculated over 185 patients with known location of lesions.

morbilliform, livedo reticularis,[23] vesicular, chilblain-like lesions,[24] acrocyanosis, petechiae, acral ischemic, dry gangrene. Bouaziz divided lesions into two categories: inflammatory lesions (exanthema, chicken

pox, urticaria), vascular lesions (violaceous macules, livedo, non-necrotic purpura, necrotic purpura, chilblain-like, cherry angioma).[8] However, Marzano suggest dividing livedo reticularis/racemosa and purpura into two isolated types, because the first was vasculopathic origin, comparing with latter as vasculitic pathogenesis.[25]

In Italy, the most common lesion is erythematous rash (20%, 18/88), followed by acute urticaria 3.4% (3/88). Trunk is the main involved region. Itching was mild or absent. Our results are consistent with previous reports. The most common eruption was erythematous lesions (76, 38.4%), following by urticaria (27, 13.6%). Trunk was mostly affected lesion, followed by extremities (66, 35.7%). 42.9% patients had symptoms of lesions, such as itching, burning or pain. In Poland, cutaneous hyperesthesia was found in two CI patients. The abnormal hypersensitivity was aggravated by any kind of touch, even clothing, bed. The feeling was alleviated by warm baths.[26]

Cutaneous lesions could be a late manifestation of COVID-19, because of late appearance after peak of infections.[27] In our study, most patients (102, 77.9%) had rash after other symptoms, which may be induced by delayed immune mediated reaction to virus in genetically-predisposed patients[28] or early IFN-I response in young patients, resulting in microangiopathic changes.[29] 6.3% CI patients were asymptotic excepted cutaneous lesions. Long found among 178 laboratory-confirmed CI patients, 20.8% patients were asymptomatic. These asymptomatic CI patients had a longer duration of viral shedding and weaker immune response to COVID-19 than symptomatic patients.[30]

Many investigators took biopsies from CI patients trying to find some clues of the crafty and threaten diseases. Right now, COVID-19 has already been present in epithelial cells of the affected skin.[31]

In our study, 39 patients had biopsy examinations. Variable cutaneous manifestations in patients with CI reflect a spectrum of viral interaction with skin.

Acral lesions (COVID toes) are considered as a continuum ranging from erythematous macules, chilblain-like lesions, to gangrene or digital ischemia.[21] The state of hypercoagulation and disseminated intravascular coagulation were related with elevation of D-dimer, fibrinogen, fibrinogen degradation productions and prolonged prothrombin time.[32] The median time from ischemia in limbs to death in five patients was 12 days.[33] In our study, we found 70 patients with acro-ischemic lesions, including gangrene, livedoid lesions, necrosis, perniosis, cyanosis, petechiae, chilblain-like, bullous, ulcerative, vasculitic, edematous, and erythematous lesions, dyschromia, with mortality of 8.6%.

Chilblain-like lesions (CLL) are different from idiopathic chilblains, idiopathic perniosis. CLL and vesicular lesions might be helpful as epidemiological markers of CI. French dermatologists present three hypotheses of chilblain lesions: another confounding factor than COVID-19; post immunological reaction in asymptomatic forms of COVID-19; special immune anti-viral reaction. Most patients with chilblain-like lesions had mild CI or asymptomatic, which highlighted this type of eruptions resulting in positive prognosis.[34] In our study, we found 20 patients with CLL had symptoms, such as fever, dry cough, dysgenusia, diarrhea, asthenia, shiver, anosmia and headache. All of them had positive outcome.

Histopathological manifestations of CLL are intraepidermal vesicle, vacuolar alteration in basal layer, scattered singly necrotic (apoptotic) keratinocytes, edema of papillary dermis, superficial and deep lymphocytic infiltration in a perivascular and strong perieccrine pattern, with occasional plasma cells, dilated vessels.[18,35] Direct immunofluorescence result was negative.[36] Locatelli present one patient with long lasting CLL 17 days before onset of other symptoms, suggesting long lasting CLL could be carriers of COVID-19 virus.[35]

Histopathological manifestations of perniosis are lymphocytic infiltrate perivascular and perieccrine, lymphocytic vasculitis, without thromboembolism or immune complex vasculitis. Direct immunofluorescence is negative for immunoreactant deposition. In purpura lesion, histopathological manifestations are extensive necrosis of epidermis and adnexal structures, interstitial and perivascular neutrophilia with prominent leukocytoclasia, extravasation of red cells, vascular ectasia, leukocytoclastic vasculitis, small vessel damaged with fibrinoid necrosis, thrombogenic vasculopathy.[31] Immunohistochemical (IHC) showed extensive deposition of C5b-9, C3d, C4d within the microvasculature, normal-appearing skin showed microvascular deposits of C5b-9.[31,37] Petechiae/purpuric lesions are symptom of milder CI.[32] Some researchers found that perniosis, petechiae, chilblain-like lesions were not reported thrombotic vasculopathy.[38] In a research of 375 patients in Spain, Cases found that patients with CLL were less severe pulmonary comparing with patients with livedoid lesions. Vesicular lesions were in early stage of CI, before other symptoms.[39] However, Torres-Navarro considered perniosis-like lesions were induced by cold temperature and immobility.[40]

Livedoid and necrotic lesions were uncommon, and mostly in elder, severe patients. That may be primary lesions of COVID-19 or related with vascular occlusion.[41] Epidermis was slightly necrotic. In the papillary dermis, dilated blood vessels were filled with hyaline thrombi. Fibrinoid necrosis, endotheliitis, and leukocitoclasia were surrounding some vessels in reticular dermis. Livedo reticularis-like lesions may be induced by accumulation of microthromboses originating from other organs, which reduced blood flow to cutaneous microvasculature system.[23]

Erythema was most common lesion in CI. Histopathological manifestations were not special as follows: dyskeratotic basilar keratinocytes, spongiosis, ballooning necrotic, nest of Langerhans cells, basal vacuolar changes with interface dermatitis, liquefaction and perivascular cell infiltrations, such as histiocytes and neutrophils or rare eosinophilis, with minimal lymphocytic satellitosis. Extravasation of red blood cells, dilated vessels were in the papillary and mid dermis. Small thrombus was in the mid dermis. Microthrombi were not common found in erythematous lesion. Vasculitis was with nuclear debris and a small thrombus.[20,42] Erythema multiform-like lesions are common in children. Non-drug associated erythema multiforme, urticaria caused by COVID-19 might suggest better outcome.[43]

Urticariform rash needed to be differentiated from acute idiopathic urticaria and urticarial drug-induced rash. Eosinophilic cells

blood count may have a major role in COVID-19 diagnosis and prognosis. Du found 80% CI patients had eosinopenia.[44] Urticaria lesions related with eosinophilia could be positive outcome of CI.[43] Histopathological manifestations were present vacuolar-type dermatitis with occasional necrotic keratinocytes, perivascular infiltration of lymphocytes and eosinophils, dermal edema.[21]

In our study, we only found two patients had sequelae of hyperpigment on onset day 10, and 21 respectively. If the sequelae can disappear needs time to tell.

Treatments of CI are combination of anti-viral medicine (hydroxychloroquine, lopinavir/ritonavir) and antibiotics (azithromycin, levofloxacin, ceftriaxone). In our study, we found 24 (31.2%) patients received medicine usage for skin symptoms, such as antihistamine, topical corticosteroids. Most patients were not received medicine for rash, because cutaneous lesions are considered to be self-resolved in several days. Eleven patients were death, whose lesions including diffuse papulovesicular lesions, scattered vesicular, or papulovesicular lesions, acro-ischemia lesions, petechiae, hemorrhagic bullae, necrotic plaques. The ages of death CI patients were from 49 to 80, median age was 65. No children patients were death.

We are still unclear whether cutaneous lesions are secondary consequence of respiratory-related infection or primary infection of the skin. In the future, the more doctors pay attention to cutaneous and histopathological manifestations, the more etiology of CI we will know.

5 | CONCLUSION

We summarized and analyzed cutaneous, histopathological manifestations, and their relationship of CI patients. Cutaneous manifestations are highly variable. We recommend personal, family, medication history, infectious diseases history should be collected carefully. Physical examination should be taken carefully.

Acro-ischemic could be linked to systemic involvements. This may a clue to help clinicians recognize the paucisymptomatic or mildly symptomatic patients. But the livedo-like, purpura, dry gangrene lesions may be a sign from rapidly progressive/life-threatening disease.

In the future, doctors should pay attention to those CI patients who initially only present lesions, unique clinical symptoms, or are asymptomatic and potential carriers of the virus. We also need to study the relationship among COVID-19 unique lesions, organ involvements, and skin histopathology which may be considered as a predictor of increased complications and negative outcomes.

Right now, in the special period of COVID-19, we are facing a whole human disease with a number of unknown questions which need us to explore.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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