


## ORIGINAL ARTICLE

# Cutaneous manifestations of coronavirus disease 2019 patients in Japan

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## Abstract

Some patients with coronavirus disease 2019 (COVID-19) develop skin manifestations. There may be regional and racial differences in the frequency and type of COVID-19-associated skin manifestations. There are, however, few reports on skin manifestations in COVID-19 patients in Asia, including Japan. We retrospectively investigated the frequency, type, and clinical course of skin manifestations in Japanese patients with COVID-19. From 22 February 2020 to 16 August 2021, 738 Japanese patients (median age 59 years, 55% male) with laboratory-confirmed COVID-19 on polymerase chain reaction or antigen tests were admitted to our hospital. We mainly admitted patients with mild to moderate severity who had symptoms such as cough, fever, and oxygen demand but did not require mechanical ventilation. A total of 2.8% (21/738) of the COVID-19 patients treated at our hospital were diagnosed with viral eruptions caused by COVID-19. Of the 21 patients, 19 developed erythematous papules, and two developed urticaria. There were no cases of pernio-like lesions, known as COVID toes. The median duration from the onset of other COVID-19 symptoms to the development of skin manifestations was 9 days. This study revealed that approximately 2–3% of Japanese patients with COVID-19 developed COVID-19-associated viral eruptions, most of which were erythematous papules.

## KEYWORDS

coronavirus disease 2019, cutaneous manifestation, Japan, severe acute respiratory syndrome coronavirus 2, skin

## 1 | INTRODUCTION

Novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) infection, named coronavirus disease 2019 (COVID-19), is spreading worldwide. According to the first extensive report from China on the clinical manifestations of COVID-19 patients, fever and cough were the main symptoms, while only two of 1099 patients (0.2%) presented with a skin rash.<sup>1</sup> Therefore, skin symptoms in COVID-19 patients did not initially receive special attention. However, a report from Italy by Sachdeva *et al.* on skin manifestations in patients with COVID-19 changed this situation. Their

analysis of 88 patients with COVID-19 reported that as many as 20% developed various skin symptoms. This study contributes to the controversy regarding the high incidence of skin symptoms in COVID-19 patients.<sup>2</sup>

Since that report, there have been an increasing number of reports of COVID-19-associated skin manifestations worldwide. Analyzing the frequency and characteristics of the different skin manifestations is in progress. However, there is still no unified view, and one reason for this is that there may be regional and racial differences in COVID-19-associated skin manifestations. We believe it is necessary to evaluate COVID-19-associated skin rashes by race

and country. We previously reported that 4.9% (3/69) of our patients had COVID-19-associated viral eruption.<sup>3</sup> However, this was a small number of cases, but there have been few reports on COVID-19 skin manifestations in Japanese patients, and the analysis has not progressed.

Therefore, we collected data from COVID-19 patients treated at the authors' hospital who presented with skin manifestations and analyzed the frequency and types of skin manifestations among a large cohort of 738 Japanese patients with COVID-19.

## 2 | METHODS

### 2.1 | Analysis of our hospital cases

This was a single-center, retrospective study. The hospital to which the authors belong started accepting COVID-19 patients in February 2020. We mainly admitted patients with mild to moderate severity who had symptoms such as cough and fever, shortness of breath, and oxygen demand but did not require mechanical ventilators. We provided further treatment, including ventilator management, when patients became critically ill in our hospital. From 22 February 2020 to 16 August 2021, we accepted 758 patients with laboratory-confirmed COVID-19 by polymerase chain reaction (PCR) or antigen tests. Of these, 738 were Japanese nationals. We enrolled these Japanese patients in this study and collected their data retrospectively from electronic medical records (MegaOak online imaging system, NEC). Among these patients, we analyzed COVID-19 patients who developed new skin manifestations during the disease period at our hospital. These do not include atopic dermatitis, chronic urticaria, and other skin conditions predating their COVID-19 infection. Our dermatologists, including the authors, diagnosed suspected COVID-19-associated viral eruption by referring to actual examinations, medical record descriptions, and photographs. It is difficult to distinguish between viral eruption and drug eruption since multiple drugs are used in the treatment of COVID-19. We ruled out the possibility of drug eruption if there was no recent new drug use and if the skin rash improved without drug changes during the disease. If the drug was changed or discontinued during the disease, the diagnosis was made based on a comprehensive judgment of the characteristics and the course of the skin rash and the type of drug used. We analyzed the frequency of COVID-19-associated viral eruptions, patient sex, age, timing and duration of skin manifestation, clinical types of skin manifestations, drugs used against COVID-19, drugs used against skin manifestations, and symptoms other than skin manifestations. In statistical analysis, the medians are reported for continuous variables. Categorical variables are summarized as frequencies (percentages).

We conducted this study based on the guidelines from the Declaration of Helsinki and obtained approval from the Institutional Review Board of Toyonaka Municipal Hospital (no. 2021-10-03). The requirement for informed consent was waived via the opt-out method on our hospital website.

## 2.2 | Review of literature

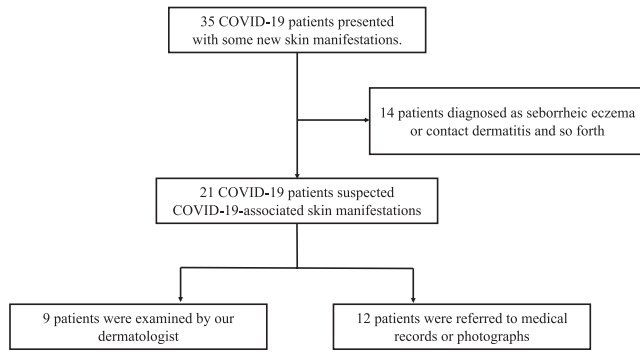
To analyze the occurrence of COVID-19-associated viral eruptions in Japan, we collected cases of viral eruptions in Japanese COVID-19 patients using PubMed, Google Scholar, and the Ichushi website (a Japanese article search site) to search for literature published between December 2020 and 31 August 2021. The following search terms were used: ([Coronavirus] or [COVID-19] or [SARS-CoV-2] and [skin] or [cutaneous] or [rash] or [maculopapular] or [exanthem]). We conducted the same search in Japanese. We determined the eligibility of each paper from the title and abstract. All observational studies, including case reports and case series, were included; review articles and commentaries were not included. We selected only the cases in Japan from among the papers. We also performed an extensive manual search of the reference lists of the relevant papers and reports. From the included studies, we extracted the following information: author, patient age, sex, clinical features of skin manifestations, symptoms other than skin symptoms, the term from the onset of other COVID-19 symptoms to the development of skin manifestations, duration of skin manifestations, drugs used against COVID-19, and drugs used against skin manifestations.

## 3 | RESULTS

### 3.1 | Analysis of our hospital cases

Seven hundred and thirty-eight Japanese patients with COVID-19 were treated in our hospital during the study period; 407 (55%) were male and 331 (45%) were female. The patients ranged in age from 0 to 99 years, with a median of 59 years. Seven hundred and thirteen patients (97%) had symptoms such as cough and fever due to COVID-19. A total of 342 patients (46%) took dexamethasone for COVID-19 treatment. Thirty-five (4.7%) of the COVID-19 patients treated at our hospital presented with some new skin manifestations. Of the 35 cases, we diagnosed 14 as seborrheic eczema or contact dermatitis and so forth after examination by dermatologists and after reviewing the photographs in the medical records. Thus, we suspected that the skin manifestations were viral eruptions caused by COVID-19 in the other 21 cases. Of the 21 cases, our dermatologists, including the authors, examined nine patients and referred them to the medical records or photographs for a diagnosis in the other 12 cases. [Figure 1](#) shows the flow chart of patient enrollment to analyze COVID-19-associated skin manifestations.

Among 738 patients with COVID-19, 21 patients had skin manifestations suggestive of COVID-19-associated viral eruptions. This number represents 2.8% of all COVID-19 patients in our hospital. The 21 patients ranged from 0 to 81 years, with a median of 45 years, and there were 11 males and 10 females. In terms of skin manifestations, 19 cases were erythematous papules and two cases were the urticarial type. There were no pernio-like lesions, papulovesicular type, livedo reticularis, or necrotic lesions. The time from the onset of other COVID-19 symptoms to the development of skin



**FIGURE 1** A flow chart of patient enrollment

manifestations ranged from 0 to 21 days, with a median of 9 days. The duration of skin manifestations ranged from 3 to 14 days, with a median of 9 days. For the treatment of the skin manifestations, three (14%) patients received topical moisturizers, seven (33%) received topical steroids, one (5%) received topical crotamiton, three (14%) received oral antihistamines, three (14%) received topical steroids and antihistamines, one (5%) received topical crotamiton and antihistamines, one (5%) received an unspecified ointment that she initially had, and two (10%) had no specific treatment. A summary of patient characteristics, treatment for COVID-19, and skin manifestations is shown in Table 1. Information on these 21 patients is given in Table 2, and more detailed information is given in Table S1 and Appendix S1. We obtained informed consent from patients or their guardians for publication of the photographs of skin manifestations.

### 3.2 | Review of literature

In Japan, 12 cases of COVID-19-associated viral eruptions have been reported thus far.<sup>4,5,6-12</sup> These reports are summarized in Table S2. The total number of cases of COVID-19-associated viral eruption in Japan was 33, including the 21 patients we saw. The patients ranged in age from 0 to 83 years. The median age was 48 years and the mean age was 42.8 years. There were 17 males and 16 females included in the review. The types of skin manifestations and their respective rates of occurrence were as follows: erythematous papules in 27 cases (82%), urticarial in three patients (9%), pernio-like lesions in two cases (one case combined with erythematous papules) (6%), papulovesicular type in zero patients (0%), livedo reticularis in one case (combined with erythematous papules) (3%), and others (erythema nodosum, toxic epidermal necrolysis[TEN]) in two patients (6%). Two patients with pernio-like lesions, known as COVID toes, have been reported in Japan, but one patient had systemic sclerosis as the primary disease.<sup>11</sup> Pernio-like lesions in patients with no underlying disease are still rare, with only one case reported in Japan. There was one case each of TEN and erythema nodosum.<sup>4,10</sup> The median time from the first symptom to the skin manifestations were 10.5 days, respectively, from 0 to 40 days. The duration of the skin manifestations ranged from 3 to 26 days, with a median of 9 days. A

**TABLE 1** Summary of patient age, sex, and treatment for COVID-19 and skin manifestations

Characteristics	Patients suspected COVID-19-related eruption
Age, median (average)	45 (37.1)
Male sex, n (%)	11 (52)
Type of skin manifestations	
Erythematous papules, n (%)	19 (90)
Urticaria, n (%)	2 (10)
Pernio-like lesions, n (%)	0 (0)
Papulovesicular type, n (%)	0 (0)
Livedo reticularis, or necrotic lesions, n (%)	0 (0)
Time of appearance of skin manifestations, median/average (days)	10/11.2
Duration of the skin manifestations, median/average (days)	9/10
Drugs used against COVID-19	
Dexamethasone, n (%)	7 (33)
Favipiravir, n (%)	8 (38)
Hydroxychloroquine, n (%)	2 (10)
Remdesivir, n (%)	2 (10)
Ciclesonide inhalation, n (%)	3 (14)
Drugs used against skin manifestations	
Topical steroids, n (%)	10 (48)
Topical crotamiton, n (%)	7 (33)
Topical moisturizer, n (%)	2 (10)
Oral antihistamines, n (%)	3 (14)
Other symptoms than skin manifestations	
Fever, n (%)	20 (95)
Cough, n (%)	13 (62)
Dyspnea, n (%)	8 (38)
Smell and taste disorder	1 (5)
Diarrhea, n (%)	4 (19)
Nasal discharge, n (%)	1 (5)
Chest pain, n (%)	4 (19)
Sputum, n (%)	1 (5)
Sore throat, n (%)	1 (5)

summary of age, sex, and skin manifestations of Japanese patients with COVID-19-associated viral eruption is shown in Table 3.

## 4 | DISCUSSION

In the present study we found that 2.8% (21 out of 738) of Japanese patients with COVID-19 had skin manifestations suspicious for COVID-19-associated viral eruption. There are few reports of COVID-19-associated viral eruptions in Japan. Only two reports mention skin manifestations in COVID-19 patients in Japan.

TABLE 2 Information on COVID-19 patients presenting skin manifestations in the authors' hospital

Case	Age (years)	Sex	Features of skin manifestations	The time from the first symptom to the skin manifestations(days)	Duration of skin manifestations (days)	Drugs used against COVID-19	Drugs used against skin manifestations
1	24	Male	Multiple erythematous papules with mild infiltration of the extremities and trunk, edematous erythema of face	8	9	Ciclesonide inhalation, Favipiravir, Hydroxychloroquine	Topical steroids, Oral antihistamines
2	81	Female	Multiple erythematous papules with mild infiltration of the upper limb.	20	7	Ciclesonide inhalation	Topical crotamiton, Oral antihistamines
3	54	Male	Multiple small erythematous papules with slight infiltrates on the abdomen	9	8	Ciclesonide inhalation, Favipiravir, Hydroxychloroquine	Topical steroids, Oral antihistamines
4	31	Male	Multiple erythematous papules of the anterior chest	2	Unknown	None	Topical steroids
5	38	Female	Multiple erythemas of the brachium and thigh	5	Unknown (Gradually improved)	None	Topical crotamiton
6	0	Female	Multiple erythemas of the face and anterior chest	Unknown	Unknown (Gradually improved)	None	External medicine unknown
7	4	Male	Multiple erythemas of the trunk	14	Unknown (Gradually improved)	None	Topical moisturizer
8	0	Male	Multiple erythemas with slight infiltrates on the right upper eyelid	9	Unknown (Gradually improved)	None	none
9	32	Female	Multiple erythematous papules of the axilla and groin	9	Unknown	None	Topical steroids
10	1	Female	Multiple erythemas of the chest and abdomen	Unknown	Unknown	Dexamethasone, Tulobuterol patch, Expectorant	None
11	74	Female	Multiple erythemas of the face and trunk	14	9	Favipiravir, Dexamethasone	Topical steroids
12	78	Female	Multiple small erythemas of the face and neck and trunk and brachium	17	Unknown	Favipiravir, Dexamethasone	Oral antihistamines
13	49	Male	Erythemas of the neck and chest and limbs	17	Unknown	Favipiravir, Dexamethasone	Topical steroids
14	61	Male	Multiple erythematous papules of the chest and abdomen and limbs	13	13	Favipiravir	Topical steroids
15	47	Female	Multiple erythemas on the abdomen and joint part of limbs	0	Unknown	None	Topical steroids
16	46	Male	Urticaria of the abdomen and limbs	7	4	Favipiravir, Dexamethasone, Antitussive	Topical steroids, Oral antihistamines

(Continues)

TABLE 2 (Continued)

Case	Age (years)	Sex	Features of skin manifestations	The time from the first symptom to the skin manifestations(days)	Duration of skin manifestations (days)	Drugs used against COVID-19	Drugs used against skin manifestations
17	52	Female	Multiple erythemas of the superior limbs	8	3	Favipiravir, Dexamethasone	Oral antihistamines
18	8	Female	Multiple small erythemas on the trunk and joint part of limbs	11	Unknown	None	Topical steroids
19	45	Male	Urticaria of the superior limbs and thigh	13	Unknown	Remdesivir	Oral antihistamines
20	55	Male	Multiple erythemas of the neck and brachium	6	Unknown	Remdesivir, Dexamethasone	Topical moisturizer
21	0	Male	Scattered erythematous macules of the neck and brachium	4	14	None	Topical moisturizer

Matsunaga *et al.* reported that 0.6% (11/1850) and Nozaki *et al.* reported that 2.2% (4/181) of patients developed skin manifestations.<sup>13,5</sup> Skin manifestations in patients with COVID-19 are often overlooked among other severe conditions, and minimum contact with COVID-19 patients to prevent infection or less involving dermatologists could be omitted from reports. In our hospital, 2.8% (21/738) of COVID-19 patients had skin manifestations, which is relatively close to the number reported by Nozaki *et al.* Our study involved dermatologists who examined the patients and analyzed their skin rashes as well as reported by Nozaki *et al.* Based on those reports, we speculated that the incidence of COVID-19-associated viral eruptions in our country was approximately 2–3%.

The erythematous papule type is the most common Japanese COVID-19-associated skin manifestation. Shams *et al.* conducted a systematic review of erythematous papules in COVID-19-associated viral eruption worldwide.<sup>14</sup> They reported that the duration of erythematous papules ranged from 2 to 14 days with a mean of 8 days, and in 97% of cases (242/249), the skin symptoms appeared simultaneously as or after COVID-19 symptoms. The characteristics of erythematous papule manifestations in Japanese COVID-19 patients are similar to those reported by Shams *et al.* On the other hand, the erythematous papule-type is difficult to distinguish between viral eruption, drug eruptions, and other diseases.<sup>15</sup> We ruled out the possibility of other diseases, such as contact dermatitis or seborrheic dermatitis, through examination or evaluation of photographs in the medical record by a dermatologist. In 13 of the 21 cases we experienced, the possibility of drug eruption or another skin rash was very low, so we diagnosed these patients with definite viral eruptions. One case was difficult to differentiate from a sweat rash for the remaining eight cases. For the other seven cases, the possibility of drug eruption was suspected. Therefore, some drugs (especially those started after hospitalization for COVID-19 and drugs to relieve various symptoms caused by COVID-19) were discontinued, making it challenging to differentiate drug eruptions from viral eruptions. It has been reported that favipiravir may cause drug eruptions, but the skin manifestation improves quickly with discontinuation of the drug, averaging 1.75 days.<sup>16</sup> In five out of the seven cases, favipiravir was used to treat COVID-19, but all patients continued to have skin symptoms for a certain period of time after discontinuation, and their skin symptoms improved along with improvement of other symptoms of COVID-19, leading to the diagnosis of COVID-19-associated viral eruptions. The other two cases were also diagnosed as viral eruptions based on comprehensive judgment of the course of the skin manifestation and other factors.

There are regional differences in the frequency and type of skin manifestations in COVID-19 patients. Sameni *et al.*<sup>17</sup> reported in a meta-analysis of skin manifestations in COVID-19 patients who the frequency of skin manifestations tended to be lower in Asian countries than in European countries. Few papers by dermatologists have described the frequency of skin manifestations in COVID-19 patients in Asia. The frequency of COVID-19-associated viral eruption was 2.5% (5/204) in Thailand,<sup>18</sup> and 2.8% in our Japanese cohort. In Japan and Asia, erythematous papules are the most common skin

**TABLE 3** Summary of age, sex, and skin manifestations of Japanese patients with COVID-19-associated viral eruption

Characteristics	Patients suspected COVID-19-related eruption in Japan
Age, median (average)	48 (42.8)
Male sex, n (%)	17 (52)
Type of skin manifestations	
Erythematous papules, n (%)	27 (82)
Urticaria, n (%)	3 (9)
Pernio-like lesions, n (%)	2 (6)
Papulovesicular type, n (%)	0 (0)
Livedo reticularis, or necrotic lesions, n (%)	1 (3)
Others, n (%)	2 (6)
The time from the first symptom to the skin manifestations, median (days)	10.5
Duration of the skin manifestations, median (days)	9

symptoms reported in COVID-19 patients, while pernio-like lesions are infrequent.<sup>4</sup> In our study, 42.7% (315/738) of patients hospitalized during seasons with low temperatures or large temperature differences (October to March), when frostbite is likely to occur, but no pernio-like lesions were observed. In some systematic reviews of skin manifestations in COVID-19 patients, pernio-like lesions were the most common skin symptoms.<sup>19–21</sup> However, these reports include many patients with clinical diagnoses of COVID-19 based on the clinical symptoms. Only 6.7% of patients with pernio-like lesions tested positive for COVID-19 by PCR or serological tests in France.<sup>22</sup> There is a possibility that some of the pernio-like lesions in COVID-19 patients are not caused by COVID-19, which may be related to the influence of COVID toes propagated by the media, especially in Europe and the USA, and the new lifestyle that tends to keep people indoors.

It remains controversial why the skin manifestations in COVID-19 patients differ by race and country. The situation in Asia, including Japan, clearly deviates from the trends seen around the world, especially in the West, and is most likely due to racial differences or other geopolitical factors. There is a hypothesis that this is due to racial differences in human leukocyte antigen (HLA), the angiotensin-converting enzyme gene, and the type I interferon response.<sup>23–25</sup> Many systematic reviews of COVID-19 skin manifestations have been reported, but almost all included patients were of various races and regions without any distinction between the patients. Racial and geopolitical differences may have a significant impact on the appearance of skin manifestations. Therefore, we believe it is appropriate to analyze COVID-19 skin manifestations by region and race.

There are several limitations to the current study. First, this is a single-center study with a retrospective design. Consequently, the accuracy of the frequency of COVID-19-associated viral eruptions may be lacking. Many more patients may be experiencing skin

symptoms than we have counted. This is because it is difficult to perform detailed skin examinations (including biopsies) on these patients due to infection control measures against COVID-19. We need to judge skin symptoms based mainly on the patients' self-reports. Some patients may not recognize the rash; others may realize it but not pay much attention to it because of more severe symptoms, such as dyspnea. Second, it is possible that the systemic administration of steroids may prevent the appearance of COVID-19-associated viral eruptions when used for the treatment of COVID-19. In fact, among 735 COVID-19 patients treated at our hospital, the incidence of viral eruption was 3.6% (14/394) in the group of patients not using dexamethasone and 2.1% (7/341) in the group of patients using dexamethasone. Of the seven patients who received dexamethasone, only two developed viral eruptions while taking the drug. Although the differences in severity of COVID-19 and frequency of underlying diseases between the groups using dexamethasone and those not using dexamethasone precluded general comparison, it was suggested that dexamethasone may have suppressed the appearance of viral eruptions. Third, there may be an error in the duration of skin manifestations. We reported the duration of the skin manifestations as 3–14 days with a median of 9 days. Nevertheless, some patients were discharged without rash improvement, and these cases were omitted as having an unknown duration. Therefore, the duration of the skin manifestations of COVID-19 is likely to be longer than the results of this study. It is also possible that we did not identify skin manifestations reported to appear relatively late during the COVID-19 course, such as pernio-like lesions.<sup>15</sup> Finally, our hospital was primarily responsible for treating patients with moderate COVID-19 (patients who required oxygen administration but not ventilation), which resulted in a skewed patient population. Most patients with COVID-19 do not require oxygenation and do not warrant hospitalization. These patients do not receive systemic administration of steroids, which could suppress the appearance of skin manifestations. They may also be more susceptible to the formation of skin manifestations because the symptoms are milder than in inpatients. The incidence of skin manifestations in COVID-19 patients in Japan may be higher than in this report or previous reports.

In conclusion, this study suggests that COVID-19-associated viral eruption occurs in approximately 2–3% of Japanese patients and that the type of erythematous papules is the majority. Now that there are racial differences in the frequency and types of skin manifestations in COVID-19 patients, it is necessary to strictly discuss the skin manifestations of COVID-19 by race and country. However, even within the same country, the prevalent variant of the virus has changed. It has also been pointed out that viruses acquire the ability to evade HLA by mutation.<sup>23</sup> There is a possibility that the frequency of skin manifestations in COVID-19 patients and the proportion of each type of skin manifestation will change. We hope that more cases will be collected in Japan and worldwide.

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## CONFLICT OF INTEREST

None declared.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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