



CONCISE COMMUNICATION

Erythema nodosum-like eruption in coronavirus disease 2019: A case report and literature review of Asian countries

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Abstract

In the worldwide coronavirus disease 2019 (COVID-19) outbreak, skin manifestations were seen in COVID-19 patients. We report a case in which a COVID-19 patient developed cutaneous lesions that were diagnosed as erythema nodosum-like lesions, which were associated with COVID-19. Nasopharyngeal swab polymerase chain reaction (PCR) confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Histopathologically, extensive inflammation was seen from the epidermis to the fat tissue. An organized thrombus and disrupted inner elastic lamina were seen in an intradermal vessel. These findings suggest septal panniculitis with cutaneous polyarteritis nodosa. The results of PCR using the specimen of skin lesion was negative. The patient took non-steroidal anti-inflammatory drugs and the skin lesion improved in 3 weeks. To characterize the skin eruption, we reviewed previous reports on COVID-19 (confirmed by the detection of SARS-CoV-2 infection) from Asian countries. The type of eruption and timing of its appearance in this case seemed rare. Differences in skin manifestations between Western and Asian countries were noted.

KEYWORDS

coronavirus disease 2019, erythema nodosum, race, severe acute respiratory syndrome coronavirus 2, thrombosis

1 | INTRODUCTION

In December 2019, cases of pneumonia that showed a poor prognosis were reported in China. A novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was isolated from infected patients and the disease was termed coronavirus disease 2019 (COVID-19). Case reports describing skin manifestations of COVID-19 patients have been accumulating in the literature. Consistent with the prevalence of COVID-19, reports on the skin manifestations reported in Asian countries are still rare and the characteristics are unclear.

We report a patient with COVID-19 who developed cutaneous lesions presenting with erythema nodosum (EN). EN-like lesions in COVID-19 patients are rare and the histopathology has never been

shown.¹⁻³ Since the contribution of the detection of SARS-CoV-2 in a nasopharyngeal swab to the development of a skin eruption is controversial, we have reviewed the cases of previous patients in whom SARS-CoV-2 positivity was confirmed. Thrombus has been suggested to be a characteristic finding in COVID-19 skin eruptions. Since the prevalence of COVID-19 was significantly different among countries, we compared the types of skin eruptions in different racial regions.

2 | CASE REPORT

A previously healthy 30-year-old woman was admitted to our hospital with fever that had persisted for 6 days. A skin lesion appeared

on her left ankle 4 days before the onset of fever and dry cough and spread to her extremities over a 3-day period. She had pain in both knee and ankle joints. She saw a doctor at a nearby general hospital; however, she had multiple skin lesions and after obtaining nasopharyngeal swabs, a diagnosis of COVID-19 was confirmed by real-time reverse transcription polymerase chain reaction (PCR), and she was referred to Gunma University Hospital. She denied any drug intake before the admission to our hospital. There was no significant family history or past medical history. A physical examination revealed the following findings: body temperature, 37.2°C; heart rate, 104 b.p.m.; and SpO₂, 98% (room air). There was no dysgeusia or dysosmia. Numerous indurated painful erythema was present on the bilateral lower legs (Figure 1a). Some lesions had a purple-red dark center surrounded by pale erythema, resembling a target lesion (Figure 1b). There was no enanthem. The results of a laboratory examination were as follows: white blood cell count, 6900/mL (normal,

4000–9600); platelet cell count, 245 000 (160 000–350 000), fibrin/fibrinogen degradation products (<4.0 µg/mL), D-dimer, 0.5 µg/mL (<1.0 µg/mL); and C-reactive protein, 4.09 mg/dL (<0.3). Computed tomography showed no findings to suspect COVID-19. In a histopathological examination, a low-power view showed perivascular cellular infiltration in the upper dermis, and vascular injury and cellular infiltration around a sweat gland were seen in the lower dermis. Mild cellular infiltration was also seen in the fat tissue (Figure 2a). A high-power view showed slight spongiosis, basal cell vacuolation, and mild perivascular lymphocytic infiltrate (Figure 2b). There was a prominent cellular infiltration around the eccrine glands (Figure 2c). An organized thrombus was seen in an intradermal vessel (Figure 2d). Elastica van Gieson staining revealed a disrupted inner elastic lamina (Figure 2e). Partial septal lymphocytic infiltration was seen in the fat tissue. These findings suggest septal panniculitis with cutaneous polyarteritis nodosa. We diagnosed her as having an

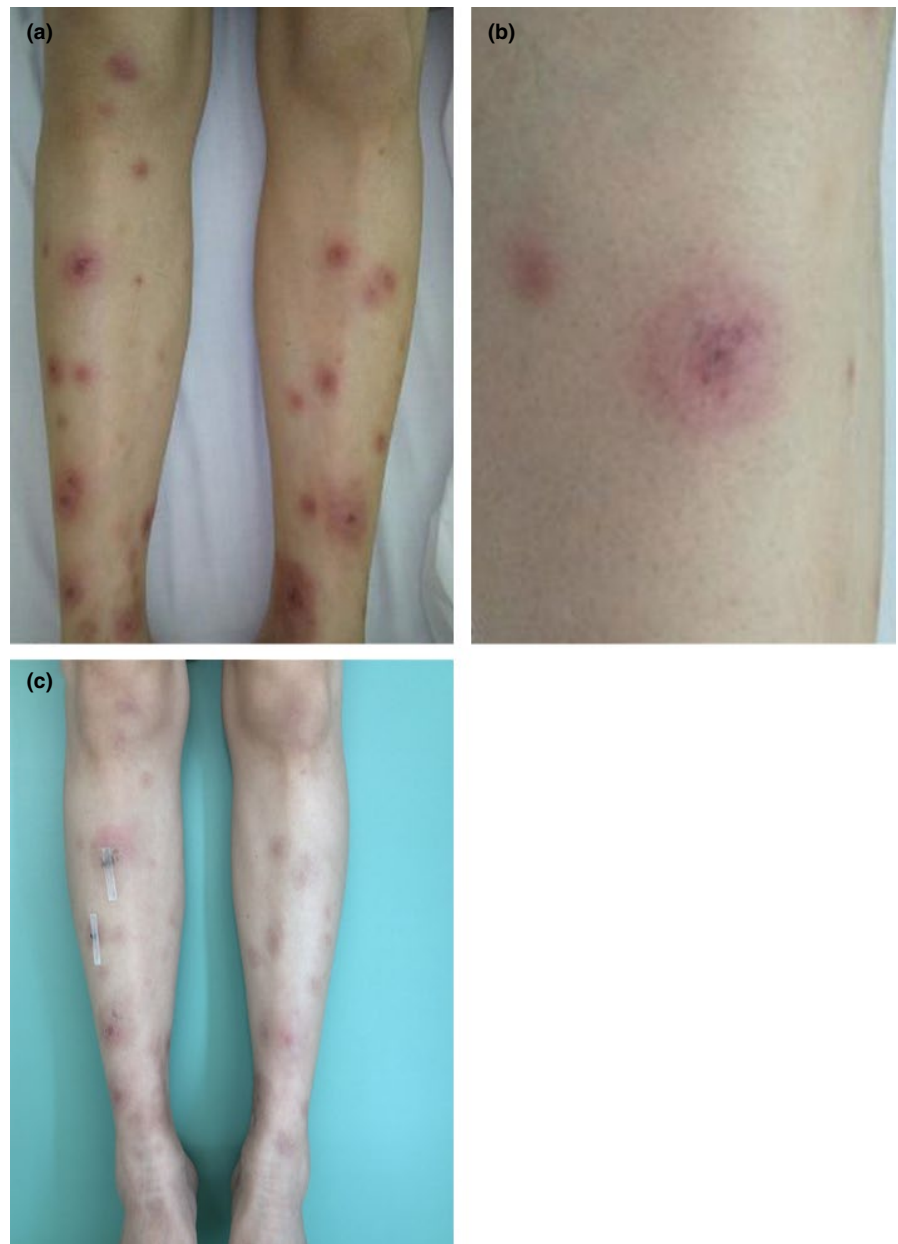


FIGURE 1 Clinical features. (a) Indurated reddish erythema were seen on both legs. (b) Purple-red dark center and surrounding pale erythema. (c) Only pigmentation remained in 3 weeks

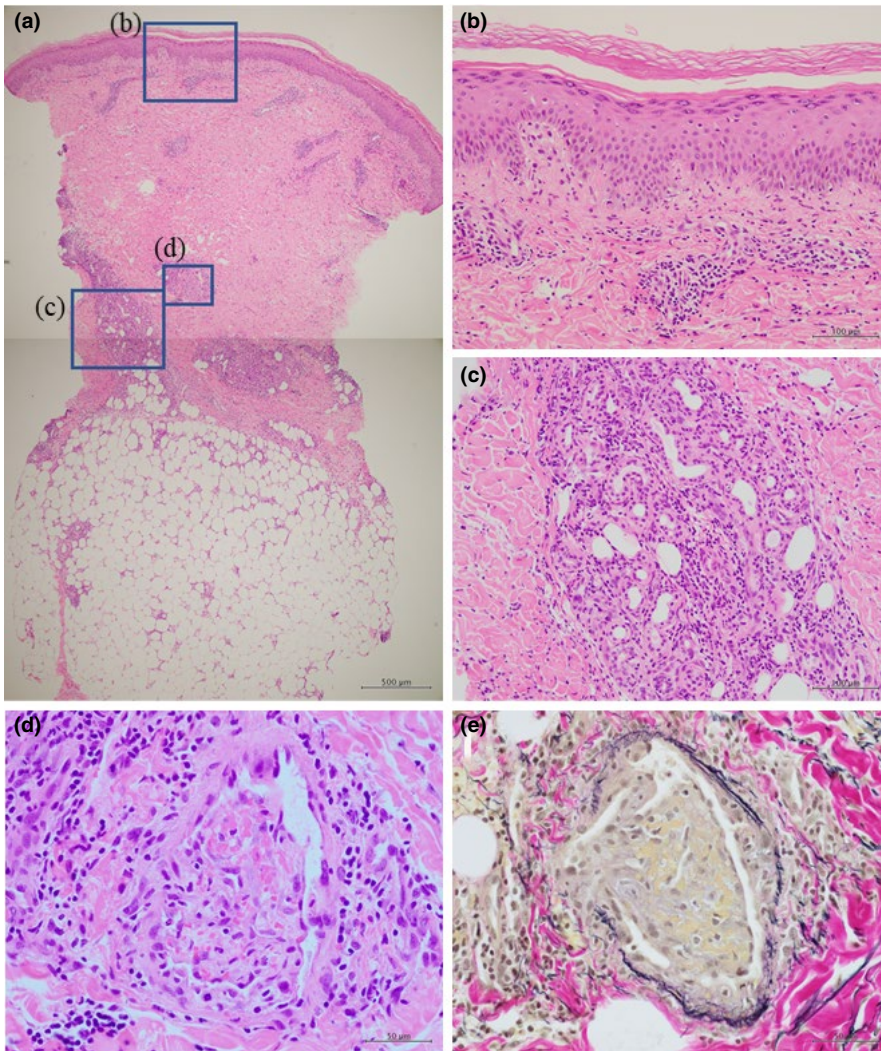


FIGURE 2 Histopathological features. (a) A low-power view showed perivascular cellular infiltration in the upper and mid-lower dermis. Mild cellular infiltration was seen in the fat tissue (hematoxylin-eosin [HE], original magnification $\times 20$; bar = 500 μm). (b) Mild vacuolar change and perivascular mononuclear cellular infiltration were seen (HE, $\times 200$; bar = 100 μm). (c) Dense monocellular infiltration was seen around the eccrine gland (bar = 100 μm). (d) An organized thrombus was seen in an intradermal vessel (HE, $\times 200$; bar = 50 μm). (e) The inner elastic lamina was disrupted (elastica van Gieson, $\times 200$; bar = 50 μm)

EN-like eruption which showed septal panniculitis with cutaneous polyarteritis nodosa pathologically, associated with COVID-19. The result of PCR using a whole-skin biopsy specimen was negative for SARS-CoV-2. She was given loxoprofen sodium hydrate and acetaminophen to reduce her symptoms. While her fever resolved quickly, her dry cough continued for 2 weeks. The eruption and arthralgia improved within a few days. After 3 weeks, the eruption site showed pigmentation (Figure 1c).

3 | DISCUSSION

In this report, we described a rare case of COVID-19 patient with EN-like eruption. So far, only three cases of EN-like rash have been reported.¹⁻³ Two of three reports demonstrated the clinical appearance; however, the histopathology was unclear.^{2,3} Notably, our case showed venous thrombosis in the dermis, which is frequently seen in COVID-19.⁴ Whether the skin eruption was a hallmark of the COVID-19 infection is important. Our case showed skin manifestations 4 days before the onset of general symptoms. Van Damme *et al.*⁵ reported two patients with acute urticaria as the first

manifestations of COVID-19 infection, and Casas *et al.*⁶ reported that 6% of the patients presented skin eruption before the general symptoms. The average incubation period of COVID-19, which is the time between exposure to the virus and the onset of symptoms, is approximately 5 days;⁷ however, it can be up to 14 days. It is possible that the EN-like lesion seen in our patient represents an early skin manifestation of COVID-19.

In the SARS-CoV-2 outbreak, five well-characterized patterns of skin manifestation were described in Spanish COVID-19 patients: (i) pseudo-chilblain; and (ii) vesicular, (iii) purpuric, (iv) urticarial, and (v) maculopapular eruptions.⁶ In Italy, among 88 patients with a confirmed diagnosis of COVID-19 who had not used any new medicine in the 15 previous days, 20.4% developed skin manifestations, including an erythematous rash (16%), widespread urticaria (3%), and chickenpox-like vesicles (1%).⁸ Recently, a case series from an international registry from the American Academy of Dermatology and International League of Dermatological Societies has been published.⁹ One hundred and seventy-one confirmed cases of COVID-19 from 31 countries were included. The most common morphologies were morbilliform (22%), pernio-like (18%), urticaria (16%), macular erythema (13%), vesicular (11%), papulosquamous (9.9%),

TABLE 1 Clinical characteristics of coronavirus disease 2019 from Asian countries

Clinical characteristics	All patients (n = 38)	Disease severity	
		Non-severe (n = 22)	Severe (n = 16)
Age, median (range), years	47.9 (17–88)	41.3 (22–88)	55.9 (38–75)
Age group, n (%)			
0–14 years	0 (0)	0 (0)	0 (0)
15–49 years	19 (50.0)	14 (63.6)	5 (31.3)
50–64 years	12 (31.6)	6 (27.3)	6 (37.5)
≥65 years	7 (18.4)	2 (9.1)	5 (31.3)
Country, n (%)			
India	15 (39.4)	13 (59.1)	2 (12.5)
China	7 (18.4)	0 (0)	7 (43.8)
Japan	6 (15.8)	4 (18.2)	2 (12.5)
Thailand	5 (13.2)	2 (9.1)	3 (18.8)
Indonesia	3 (7.9)	2 (9.1)	1 (6.2)
Singapore	2 (5.3)	1 (4.5)	1 (6.2)
Male sex, n (%)	25/38 (65.8)	16/22 (72.7)	9/16 (56.3)
Cutaneous manifestation, n (%)			
Maculopapular	13 (34.2)	9 (40.9)	4 (25.0)
Acral ischemia	7 (18.4)	0 (0)	7 (43.8)
Urticarial eruption	6 (15.8)	6 (27.2)	0 (0)
Purpuric eruption	4 (10.5)	1 (4.6)	3 (18.8)
Vesicular eruption	0 (0)	0 (0)	0 (0)
Pseudo-chilblain-like eruption	2 (5.3)	1 (4.6)	1 (6.2)
Others	6 (15.8)	5 (22.7)	1 (6.2)
Timing of dermatological changes, n (%)			
Before general symptoms	1/16 (6.2)	1/8 (12.5)	0/7 (0)
After general symptoms	15/16 (93.8)	7/8 (87.5)	7/7 (100)

and retiform purpura (6.4%). In this study, it was reported that the pernio-like lesions showed a mild disease course, whereas retiform purpura was observed in patients with more severity.

The COVID-19 pandemic has occurred worldwide; however, the prevalence among countries has varied.¹⁰ It is well known that the number of COVID-19 patients in Asian countries was much lower in comparison to Europe and the USA.¹⁰ The prevalence of skin symptoms in Thailand (2.5%) and China (0.2%) was lower in comparison to that in Italy (20%).^{8,11,12} A meta-analysis revealed that the prevalence of skin manifestations in Europe was 6.6%, while that in Asia was 0.2%.¹³ The reason for the low prevalence of COVID-19 skin lesions in Asia is unknown. Based on these results, there might be significant differences in the patterns of skin

manifestations among races. Although these studies included large numbers of patients, the details of the skin manifestations are unknown. We therefore searched the PubMed database for COVID-19 cases that involved skin lesions using the following terms: COVID19, SARS-CoV-2, and skin/cutaneous manifestation. The patients are listed in Table 1. Case reports were collected from Asian countries. The diagnostic criteria used to determine the severity of COVID-19 was based on the clinical spectrum of SARS-CoV-2 infection in the National Institutes of Health. According to this analysis, we selected 37 COVID-19 cases in which skin lesions were clearly described in patients who were positive for SARS-CoV-2. These cases were reported from Asian countries (China, India, Thailand, Indonesia, Singapore, and Japan). Our case was added to this collection. The mean age was 48.9 years (range, 17–88). The sex ratio (male : female) was 25:13. With the exception of our case, skin lesions appeared after the onset of general symptoms in all cases. The skin manifestations were as follows: maculopapular (n = 13, 34.2%), acral ischemia (n = 7, 18.4%), urticarial eruption (n = 6, 15.8%), purpuric eruption (n = 4, 10.5%), pseudo-chilblain-like eruption (n = 2, 5.3%), and others. There were no cases in which skin rash appeared before systemic symptoms and in which the patient showed erythema nodosum-like skin rash, as was observed in our case.

The skin manifestations of COVID-19 in Asian countries differed from those in the European Union (including Italy, Spain, and France) and USA. Our study revealed that pernio-like eruption, which was frequently reported in Europe, was not common in Asian countries. Some genetic basis for increased coagulation after SARS-CoV-2 infection might be involved.

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CONFLICT OF INTEREST

None declared.

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