We are aware that our three cases are not enough to establish a cause–effect relationship between EGR and vaccine; however, it is important to report any new post-marketing reaction and reassure patients about the transience of this clinical manifestation in the vaccination setting. Further studies are desirable to enlighten the pathogenesis.

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Conflict of interest

None declared.

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Data Availability Statement

Data regarding this study are available upon request to the corresponding author.

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Prevalence and patterns of cutaneous manifestations in 1245 COVID-19 patients in Japan: a single-centre study

Dear Editor,

Cutaneous manifestations of COVID-19 are classified into five patterns: pseudo-chilblains vesicular eruptions urticarial lesions maculopapules and livedo/necrosis.[1] The prevalence of cutaneous manifestations varies widely from 0.2% of cases in China to 20.4% of cases in Italy.[2] Therefore the collection of dermatological information by country is important. We present two representative hospitalized COVID-19 cases and discuss the prevalence and patterns of cutaneous manifestations in Japan.

Case 1: An 89-year-old Japanese woman with moderate COVID-19 was treated with oral favipiravir from days 6 to 15 after COVID-19 onset. At day 18 she presented with pruritic erythematous papules on the body and livedo reticularis-like lesions on the legs (Fig. 1a and 1b). The skin rashes had mostly disappeared spontaneously by day 22. A drug-induced lymphocyte stimulation test (DLST) was negative for favipiravir.

Case 2: A 60-year-old Japanese man was admitted for severe COVID-19. A generalized skin rash developed on day 3 of favipiravir treatment (Fig. 1c). Histopathology showed vacuolar degeneration and scattered dyskeratosis (Fig. 1d). Drug eruptions were ruled out by DLST and oral challenge test.

We conducted a retrospective observational single-centre study to investigate the prevalence of cutaneous manifestations associated with COVID-19. Overall 1245 inpatients at Sapporo City General Hospital from January 2020 to June 2021 were extracted. This study was approved by the institutional ethics committee of our institute (R3-060-869).

The median age was 68 years (range: 0–105) and 53.7% of cases were male. All but two patients were Japanese (one Han Chinese and one Canadian). The average hospital stay was 14.0 ± 8.8 days. The distribution of COVID-19 severity was as follows (Fig. 2): mild (176 cases 14.1%) moderate (433 cases 34.8%) severe (368 cases 29.6%) and critical (268 cases 21.5%).

The prevalence of cutaneous manifestations was 0.56% (7/1245 cases three females and four males). The cutaneous manifestations were maculopapules in five cases erythema multiforme in two cases and livedo in one case. The average time from COVID-19 onset to cutaneous lesion appearance was 16.7 days and the average duration of lesions was 9.3 days.

Next we performed a literature search of the PubMed database for articles in English about cases of COVID-19 with cutaneous manifestations between December 2019 and September 2021 (accessed on 30 September 2021) and we added nine Japanese cases. The most frequent cutaneous manifestations were maculopapules (12/16 75.0%) followed by erythema multiforme

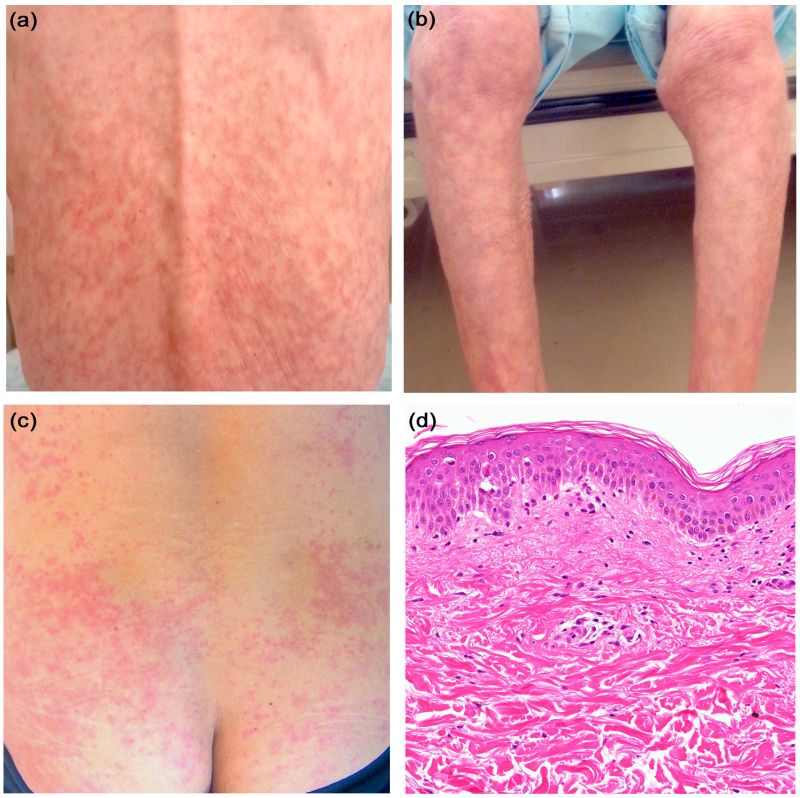

Figure 1 (a, b) Case 1: pruritic erythematous papules on the body and livedo reticularis-like lesion mainly on the lower legs. (c) Case 2: multiple erythematous papules, mainly on the buttocks, some of which form a targetoid lesion. (d) Histopathology of Case 2. Scattered dyskeratosis and vacuolar degeneration at the dermoepidermal junction are seen (H&E staining, original magnification ×200).

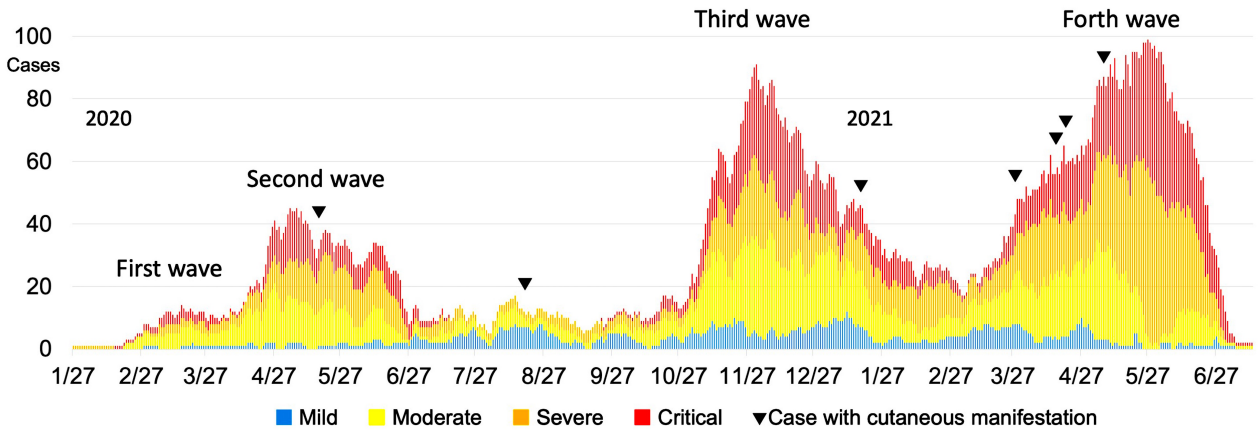

Figure 2 The temporal distribution of COVID-19 inpatients at our hospital. There were four waves: the first from February to March 2020, the second from April to July 2020, the third from November to February 2021 and the fourth from March to July 2021. COVID-19 severity is colour-coded as follows: blue for mild, yellow for moderate, orange for severe and red for critical. The black triangles show cases with cutaneous manifestations. They tended to be more frequent in the fourth wave.

(2/16 12.5%); there was only one case each of pseudo-chilblain and livedo.

Our study highlights that cutaneous manifestations in COVID-19 cases are rarely observed in Japan. A meta-analysis reported a 6.6% prevalence of skin manifestations in Europe and a 0.2% prevalence in Asia (China and Thailand).[2] In Japan one small study reported a 4.3% (3/69) prevalence in mild-to-moderate COVID-19 patients.[3] Since our study included 1245

inpatients for 17 months the prevalence of 0.56% is thought to accurately reflect the clinical situation.

We also reveal that maculopapular lesions are common (75.0%) in Japan. The most common COVID-19-related skin rash was reported to be pseudo-chilblain lesions (40.9%) and 97% of these cases were from Europe or the USA.[4] The differences in cutaneous patterns may owe to a genetic/racial predisposition. The minor allele frequency of the *IFIH1* gene which is common in Caucasians increases the production of type-1 interferons that can induce microangiopathy.[5] The patient age and the observation period might also explain the low frequency of pseudo-chilblains. The median age of pseudo-chilblains is reported to be 16.6–27.2 years and approximately 80% of cases were noticed at more than 2 weeks after onset whereas the figures for our study are median age of pseudo-chilblains of 68 years and mean duration of hospitalization of 14.0 days.[4,6,7]

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Conflicts of interest

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Data availability statement

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

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Erythema multiforme in COVID-19 patients and following COVID-19 vaccination: manifestations, associations and outcomes

Dear Editor:

Erythema multiforme (EM) is a delayed-type hypersensitivity reaction linked to infectious agents in 90% of cases and medications or vaccination in less than 10% of cases.

A 19-year-old male presented with a 48-h history of an itchy rash. Examination revealed erythematous papules and plaques with central dusky erythema and crusting on the bilateral upper extremities. There was no involvement of the palms, soles or oral mucosa. He had no fever, cough or medications. Prednisone 20 mg and cetirizine 10 mg daily were started. After 3 days, he developed fever, shortness of breath and dry cough; and a SARS-CoV-2 test was positive. He was started on remdesivir and dexamethasone. After 5 days, the rash started to improve, and after 2 weeks, it completely resolved.

EM in patients with COVID-19 has been reported in 23 publications (Fig. 1), including 36 cases with 19 males (53%). Four articles reported EM after COVID-19 vaccination (Fig. 1). The details of these manuscripts are summarized in Table 1. Among patients with EM and COVID-19, 16.7% (6/36) patients were less than 18-year old, 19.4% (7/36) patients were 18–40 years old and 63.9% (23/36) patients were more than 40 years old. Eleven patients (30.6%) took no medications before EM; however, 25 patients (69.4%) reported exposure to medications before. Drugs to which patients were exposed before EM were HCQ in 20 cases (55.5%), azithromycin in 14 cases (38.9%) with 13 of them receiving HCQ in addition to azithromycin and lopinavir/ritonavir in 12 patients (33.3%), all in combination with HCQ. EM occurred before any classic COVID-19 symptoms only in 5/36 patients (13.9%), four of them under 23 years. Three patients (8.3%) presented with EM and COVID-19 symptoms simultaneously. However, in most of the patients (78%), EM started after COVID-19 symptoms. Four patients (11.1%) had only mucosal involvement, five patients (13.9%) had mucosal and skin involvement, but most of the patients (27 patients,

