was indistinguishable from those in the delayed presentations. In early-onset cases, histopathology showed moderate epidermal spongiosis and perivascular lymphocytic infiltrate with eosinophils in the dermis, whereas the analysis of the delayed lesions showed perivascular lymphocytic infiltrate and histiocytes amongst collagen fibres without mucin deposits.

Numerous patients with COVID-19 pneumonia displayed atypical targetoid lesions (Fig. 1e), with histopathological features of erythema multiforme, around 20 days after respiratory symptoms onset. Although the lesions appeared when COVID-19 treatment had commenced in all cases, given the dramatic increase of frequency, we believe that the underlying mechanism is a delayed immune response to the virus.

Palpable purpura lesions (Fig. 1c) were more frequent in middle-aged patients during recovery from severe COVID-19. We noticed a surprising increase in atypical clinical presentations of small vessel leukocytoclastic vasculitis: two patients displayed palpable purpura lesions along with an atypical polymorphic papulovesicular eruption (Fig. 1d), and one patient showed an urticarial exanthem.

In patients who had initiated pharmacological treatment, we cannot reliably link the dermatological symptoms to a single causative mechanism. Histopathology is not conclusive for either causes, and skin lesions like the aforementioned have been reported as side effects in most frequent COVID-19 treatments.

Pseudo-chilblain (Fig. 1a,b) were more commonly found in young patients with mild respiratory symptoms, and the timing of the onset was highly variable. Although RT-PCR test was negative in most cases, pseudo-chilblain have been related to COVID-19 due to the unusual increase in incidence during warm springtime coinciding with the pandemic.[1,3] The histopathological examination revealed different patterns. Most of them showed focal vacuolar degeneration of the basal layer and regenerative changes in the epidermis, with perivascular lymphocytic cuffs in the dermis, involving sweat glands, along with thrombi in some of them. One sample revealed perivascular neutrophilic cuffs with noticeable swollen endothelium and epidermal necrosis. As pointed out before,[4] clinical and histopathological features are similar to chilblain lupus erythematosus, with additional evidence of intense platelets aggregation. Therefore, these lesions might be caused by a mixed mechanism including cellular immune response and prothrombotic state trigged by the virus.

Although the age distribution in our sample is similar to those reported in overall COVID-19 patients,[5] the mortality rate (0%) is far lower and the proportion of affected females is higher in our cohort. Such trend amongst the study population is mirrored in previous COVID-19 skin manifestations series.[1] Thus, we think that cutaneous signs of the infection are more frequent in women and appear to be associated with a better prognosis. Therefore, the dermatological indicators in COVID-19 may act as prognostic factors and heralding signs and henceforth guide diagnostic and isolation protocols for affected patients.

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Conflicts of interest

Dr. Rubio-Muniz, Dr. Puerta-Peña, Dr. Falkenhain-López, Dr. Arroyo-Andrés, Dr. Agud-Dios, Dr. Rodriguez-Peralto, Dr. Ortiz-Romero and Dr. Rivera-Díaz have nothing to disclose.

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References

1 Galván Casas C, Català A, Carretero Hernández G *et al*. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. *Br J Dermatol* 2020. [Epub ahead of print]. http://doi.org/10.1111/bjd.19163

2 Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. *J Eur Acad Dermatol Venereol* 2020; **34**: e212–e213.

3 Recalcati S, Barbagallo T, Frasin LA *et al*. Acral cutaneous lesions in the time of COVID-19. *J Eur Acad Dermatol Venereol* 2020. [Epub ahead of print]. http://doi.org/10.1111/jdv.16533

4 Kolivras A, Dehavay F, Delplace D *et al*. Coronavirus (COVID-19) infection-induced chilblains: a case report with histopathological findings. *JAAD Case Rep* 2020; **6**: 489–492.

5 Chen T, Dai Z, Mo P *et al*. Clinical characteristics and outcomes of older patients with coronavirus disease 2019 (COVID-19) in Wuhan, China (2019): a single-centered, retrospective study. *J Gerontol A Biol Sci Med Sci* 2020. [Epub ahead of print]. http://doi.org/10.1093/gerona/glaa089

DOI: 10.1111/jdv.16734

Two cases of cutaneous eruptions due to CoVID-19 infection in Singapore: new insights into the spectrum of clinical presentation and histopathology

Dear Editor,

The dermatological manifestations of CoVID-19 infection (CI) are variable, including livedo/necrosis, pseudochillblains, vesicular (monomorphic vesicles unlike varicella), urticarial and

maculopapular subtypes.[1] We report the cutaneous manifestations of two Han-Chinese patients in Singapore with CI and highlight their instructive features.

Case 1 is a 43-year-old man with CI who developed truncal and limb rashes 12 days after onset of respiratory symptoms. Drug history was non-contributory. Examination revealed erythematous, blanchable, non-follicular papules on his trunk (Fig. 1a), proximal thighs and intertriginous areas including bilateral axillae (Fig. 1b) and groin. Additionally, non-follicular pinpoint pustules were admixed within the intertriginous areas (Fig. 1c). There was no acral involvement.

Skin biopsy of a papule from Case 1 demonstrated spongiotic and interface dermatitis, with superficial perivascular infiltrate of predominantly lymphocytes (Fig. 2a), and focal erythrocyte extravasation without vasculitis (Fig. 2b). An area showed tight perivascular cuff consisting of lymphocytes and infrequent plasma cells, in association with intraluminal neutrophilia (Fig. 2c). There were no viral cytopathic or herpetic changes seen.

He was diagnosed with a papulopustular exanthem secondary to CI, which resolved with topical corticosteroids within 7 days.

Case 2 is a 75-year-old woman with severe CoVID pneumonia developed purpuric plaques on her abdomen and back (Fig. 1d) 15 days after her respiratory symptoms. The patient was not coagulopathic, and there was no peripheral eosinophilia. She had received four days of lopinavir–ritonavir (Kaletra) prior to her rashes, which was discontinued thereafter. Nikolsky sign was negative, and there was no mucositis. A skin biopsy was not performed. She was diagnosed with a purpuric exanthem from CI. There was complete clearance with topical corticosteroids when she was discharged 10 days later.

Reports of CI-related cutaneous manifestations have largely emerged from Europe and North America. Similar reports from Asia have been disproportionately low despite the infection being first discovered on this continent. Indeed, the incidence of rashes was 0.2% amongst a cohort of 1099 patients in China.[2] Correspondingly, there is a paucity of clinicopathologic and photographic descriptions of such eruptions within this demographic.

We describe two Han-Chinese patients in Singapore with CI who developed distinctive rashes. Case 1 highlights the novel non-acral papulopustular morphology that has not been described hitherto, further broadening the phenotypic spectrum of CI-related exanthems. Whilst petechial eruptions have been described,[3,4] florid purpuric exanthem with ecchymotic areas is rare. We opine that the rash was unlikely Kaletra-induced in Case 2 as a four-day latency without prior exposures is relatively short for type 4 hypersensitivity

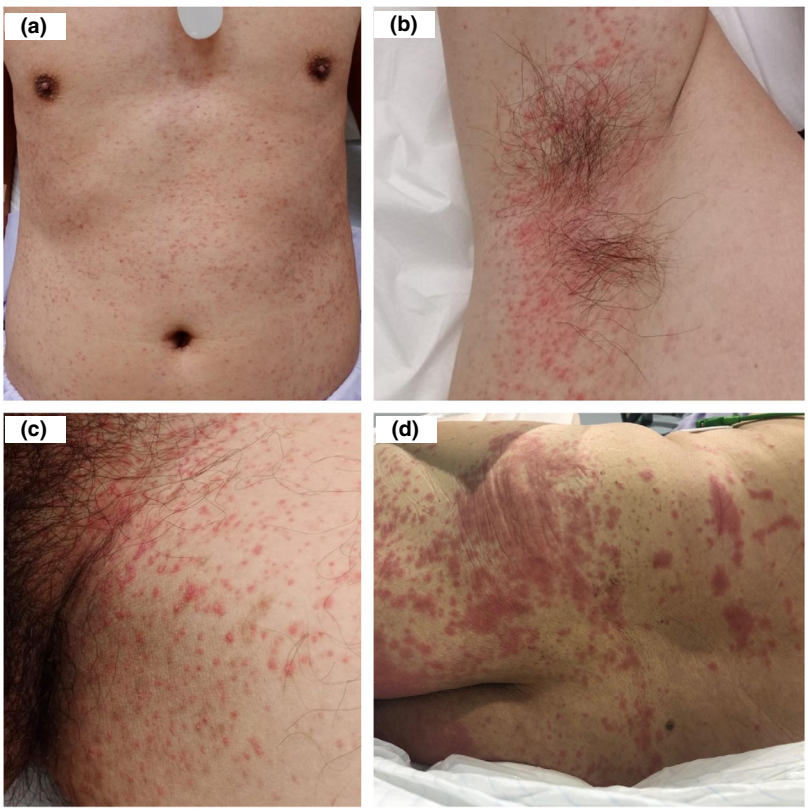

Figure 1 Clinical Photographs of Case 1 (a–c) and Case 2 (d). (a) Blanchable non-follicular erythematous papules on the trunk. (b) Erythematous non-follicular papules coalescing within the right axillary region. (c) Erythematous non-follicular papules and pustules affecting the left thigh and left groin. (d) Purpuric, ecchymotic plaques on the back of Case 2.

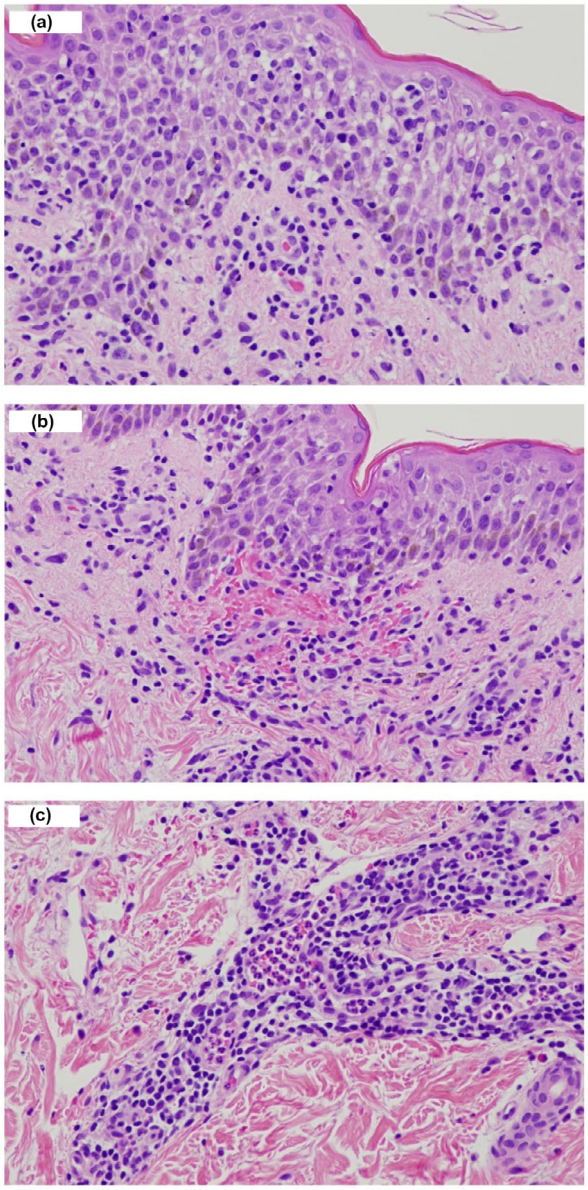

Figure 2 Histopathological findings in Case 1. (a) Spongiosis with lymphocytic exocytosis, basal vacuolar alteration and superficial perivascular lymphocytic infiltrate. (haematoxylin and eosin, magnification 100×). (b) Focal area of red cell extravasation in the absence of frank necrotizing vasculitis. (haematoxylin and eosin, magnification 100×). (c) Coat-sleeve anomaly demonstrated by a tight and dense cuff of lymphocytes and plasma cells around a superficial dermal blood vessel, with intravascular neutrophils. (haematoxylin and eosin, magnification 400×).

reaction. Moreover, resolution was expedient and precisely mirrored the patient's recovery from CI and inability to detect CI from her respiratory secretions.

Notably, we have not encountered CI-related dermatoses which are conventionally precipitated by cooler temperatures (e.g. pseudochillblains and livedo), which have been reported in European centres.[1] We hypothesize that geographically determined climatic variations contribute to variability in cutaneous manifestations. Moreover, genetic differences between Caucasians and Asians may ultimately influence the incidence and repertoire of cutaneous responses to CI.

From a dermatopathological viewpoint, the coat-sleeve appearance seen in case one, typified by a tight superficial perivascular lymphoplasmacytic infiltrate, is a new finding in the histology of CI dermatoses. Coat-sleeving, archetypal in erythema annulare centrifugum and secondary luetic disease, may be a unique histopathological finding in CI (in addition to microthrombi[5] and superficial dermal vessel ectasia[6]), which can point the clinician to the diagnosis of CI. This is especially when it is encountered with other non-specific histological findings compatible with a viral exanthem.

Our observations underscore the different morphologies of CI-related cutaneous eruptions in South East Asia and showcase, for the first time, a non-acral papulopustular eruption with its associated coat-sleeve infiltrate histologically.

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Author contributions

Dr(s) Wen Yang Benjamin Ho, Chee Hian Tan, Llewelyn Yi Chang Tan, Bundele Manish Mahadeorao, Dingyuan Wang and Hua-Liang Joel Lim contributed equally to this manuscript and had full access to the above data. All of the authors above take full responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of interest

Dr Wen Yang Benjamin Ho, Dr Dingyuan Wang, Dr Llewelyn Yi Chang Tan, Dr Bundele Manish Mahadeorao, Dr Chee Hian Tan and Dr Hua-Liang Joel Lim have nothing to disclose.

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References

1 Galván Casas C, Català A, Carretero Hernández G *et al.* Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. *Br J*

Dermatol 2020. https://doi.org/10.1111/bjd.19163. [Epub ahead of print]
2 Guan WJ, Ni ZY, Hu Y *et al*. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020; **382**: 1708–1720.
3 Joob B, Wiwanitkit V. COVID-19 can present with a rash and be mistaken for dengue. *J Am Acad Dermatol* 2020; **82**: e177.
4 Diaz-Guimaraens B, Dominguez-Santas M, Suarez-Valle A *et al*. Petechial skin rash associated with severe acute respiratory syndrome coronavirus 2 infection. *JAMA Dermatol* 2020; https://doi.org/10.1001/jamadermatol.2020.1741. [Epub ahead of print]
5 Gianotti R, Zerbi P, Dodiuk-Gad RP. Clinical and histopathological study of skin dermatoses in patients affected by COVID-19 infection in the Northern part of Italy. *J Dermatol Sci* 2020; **98**: 141–143.
6 Zengarini C, Orioni G, Cascavilla A *et al*. Histological pattern in Covid-19 induced viral rash. *J Eur Acad Dermatol Venereol* 2020; https://doi.org/10.1111/jdv.16569. [Epub ahead of print]

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A generalized purpuric eruption with histopathologic features of leucocytoclastic vasculitis in a patient severely ill with COVID-19

Editor,

A 59-year-old man was admitted to hospital for a severe respiratory failure and then intubated due to worsening of his respiratory condition. During his hospital stay, he received multiple empirical broad-spectrum antibiotics (cefepime, piperacillin/tazobactam, linezolid, gentamicin and meropenem plus amikacin). The patient had no known history of drug allergies. A test to detect SARS-CoV-2 by real-time reverse transcription polymerase chain reaction (RT-PCR) assay of a throat swab was positive. Blood cell count showed severe eosinophilia (from 1.3 to 4.60 × 10) that decreased abruptly to 0.47 × 10 after introduction of methylprednisolone 1 mg/kg/day. On day 35 postadmission, while on therapy only with corticosteroids, he developed a symmetrically distributed maculopapular purpuric exanthema on the face, trunk and extremities (Fig. 1a,b). Mucous membranes were spared. No lymphadenopathies were present. Laboratory data including liver function, cryoglobulins, antinuclear antibody, and anti-neutrophil cytoplasmic antibody test results were all normal. A skin biopsy found a superficial and deep perivascular neutrophilic infiltrate (Fig. 2a) with sparse leucocytoclasis, red blood cell extravasation and fibrinoid necrosis of vessel walls (Fig. 2b). The patient's conditions worsened for neurological complications in the form of confusional state and absences.

Drug reaction with eosinophilia and systemic symptoms syndrome (DRESS) was considered in our patient for skin eruption and blood eosinophilia that integrate two criteria for the diagnosis[1]; however, histopathology showing a classical picture of leucocytoclastic vasculitis was not consistent with DRESS. In fact, different histopathologic patterns were described in DRESS including spongiotic, erythema multiforme-like, or lichenoid but no vasculitis.[2] Despite an antibiotic allergy was considered, it is known that severe COVID-19 induces endothelial damage and vasculopathic changes.[3] Although some reports have showed purpuric eruptions as skin manifestations in patients with COVID-19,[4] histopathology was rarely performed and, in any case, leucocytoclastic vasculitis has never been described. A petechial skin eruption resembling dengue fever was described in a COVID-19 patient in Thailand.[5] A morbilliform rash with purpuric features was observed in a 32-year-old woman occurring 6 days after the

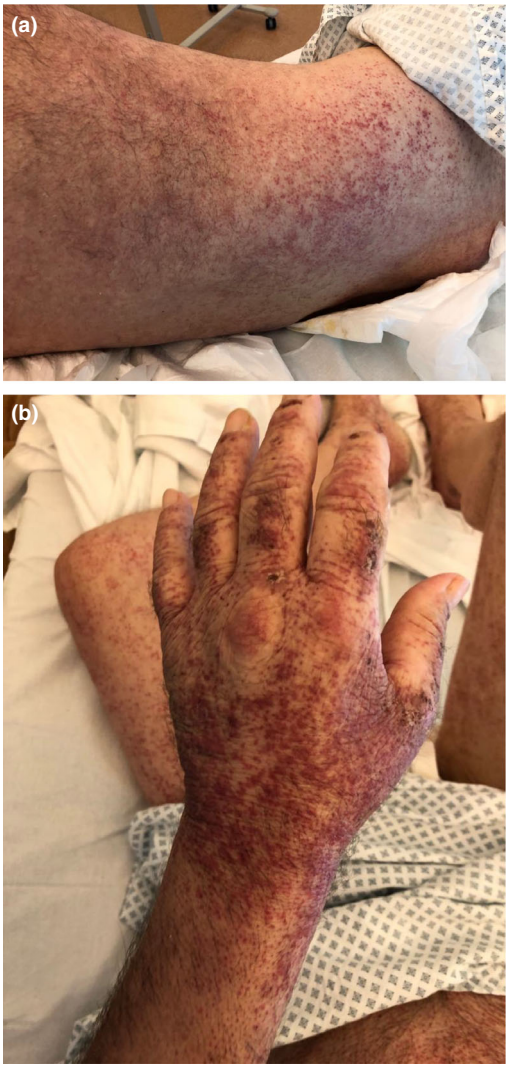

Figure 1 The patient developed a symmetrically distributed maculopapular purpuric exanthema on the trunk (a) and extremities (b).