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DOI: 10.1111/jdv.16736

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

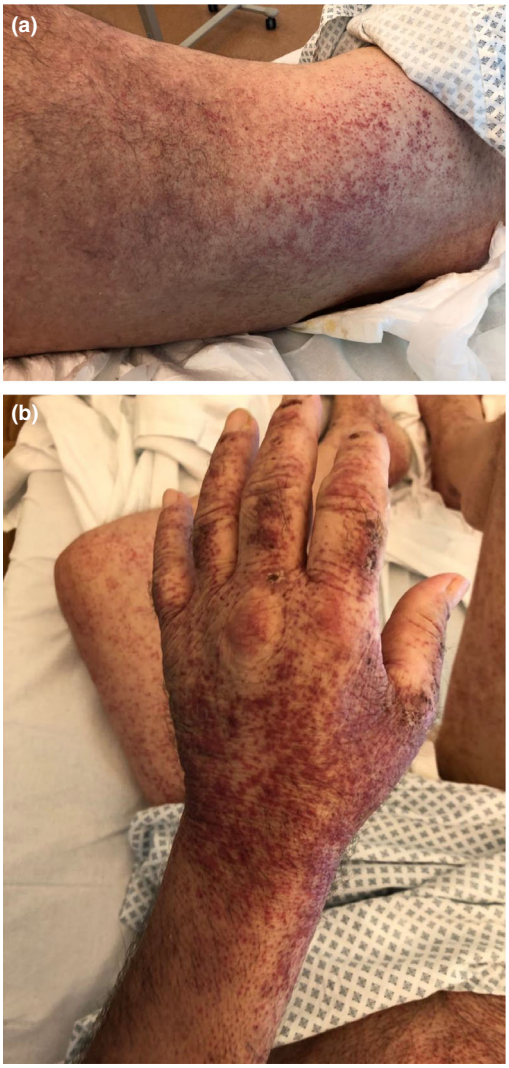

Figure 1 The patient developed a symmetrically distributed maculopapular purpuric exanthema on the trunk (a) and extremities (b).

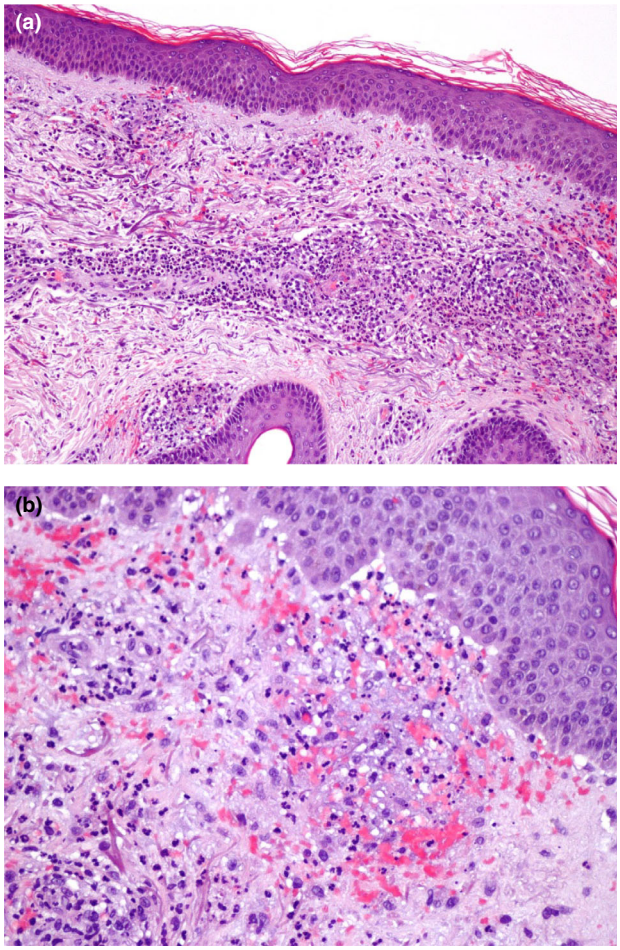

Figure 2 Skin biopsy revealed a dermal perivascular neutrophilic infiltrate (a; Haematoxylin–Eosin, 10×) with sparse leucocytoclasis, red blood cell extravasation and fibrinoid necrosis (b; Haematoxylin–Eosin, 40×).

development of COVID-19.[6] Another young patient with severe lung disease showed at first a vasculitic purpura of legs followed by a fleeting erythematous rash.[7] In all these cases, the diagnosis was only made on clinical grounds as skin biopsy was not performed. A symmetric periflexural eruption with confluent erythematous macules, papules and petechiae sparing the inguinal folds, face, palms, soles and mucosa was reported in a 48-year-old man in whom histopathology showed a superficial, perivascular lymphocytic infiltrate with haemorrhages and papillary oedema without sign of vasculitis or thrombotic vasculopathy.[8] On the contrary, a pauci-inflammatory thrombogenic vasculopathy with complement deposition of C5b-9 and C4d in involved purpuric skin and normal skin was described in three patients with lung disease due to COVID-19 pneumonia.[3] Finally, a purpuric, non-blanching, pruritic and painful rash involving the trunk and extremities was observed in a 57-year-old woman. The authors reported that a biopsy specimen showed a vasculitis but no further details were added.[9] Our patient was the first in whom a generalized purpuric eruption showed typical microscopic features of leucocytoclastic vasculitis in the setting of COVID-19. He also had severe lung disease and developed neurological complications. Although we cannot prove it, a central nervous system vasculitis due to invasion of SARS-CoV-2, similar to SARS and MERS viruses, could be hypothesized.[10] In conclusion, this case report illustrates the potential of COVID-19 infections to trigger severe drug-related cutaneous leucocytoclastic vasculitis and possibly systemic vasculitis.

Acknowledgement

The patient in this manuscript has given written informed consent to the publication of his case details.

Conflicts of interest

The authors declare no conflicts of interest.

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DOI: 10.1111/jdv.16737

SARS-CoV, Mers-CoV and COVID-19: what differences from a dermatological viewpoint?

Editor,

Over the past two decades, 3 zoonotic global coronavirus outbreaks have occurred: 1. SARS starting in 2002 in China due to SARS-CoV; 2. MERS starting in 2012 in Saudi Arabia due to MERS-CoV; 3. COVID-19 due to SARS-CoV-2 starting in 2019 in Wuhan, China.[1] Both beta-coronaviruses, SARS-CoV and MERS-CoV, caused a severe disease in most infected people. In fact, as many as 8700 cases were confirmed from 37 countries with 775 deaths for SARS, while 2494 MERS cases and 858 deaths have been reported worldwide in 27 countries. SARS-CoV-2 caused a pandemic that spread across 203 countries in all 5 major continents involving many more cases than its predecessors.[2] Phylogenetic analysis of SARS-CoV-2 indicated that it is related to SARS-CoV (~79%) and MERS-CoV (~50%).[3] Pathological manifestations of COVID-19 greatly resemble what has been seen in SARS and MERS infection and the pathologic findings indicate that a similar cytokine cascade storm plays a critical role in patient rapid death.[4]

However, it is clear now that the epidemic of COVID-19 is different from SARS and MERS. Although presenting symptoms are similar – fever and cough, progressing to pneumonia in severe cases, with poorer outcomes associated with men gender, older age and comorbidities – SARS and MERS were/are much less transmissible but more likely to be severe or fatal than COVID-19. In fact, COVID-19 has a general fatality rate of 3.4% lower than that of SARS (9.6%) and much lower than that of MERS (34.4%)[5] but SARS-CoV-2 caused many more deaths.

As for dermatology, the most relevant difference between COVID-19 and SARS/MERS is the absolute lack of reports of skin manifestations in the latter. Actually, many cutaneous manifestations have been described in association with SARS-COv-2 infection, although their prevalence is controversial ranging from 0.2% in a cohort of 1099 Chinese patients to 20.4% in an Italian study of 88 patients.[8,9]

They include the following: pseudo-chilblain lesions, livedoid or necrotic lesions and vesicular eruptions which appear as the most characteristic ones and urticarial, purpuric and maculopapular eruptions which are the most frequent rashes, albeit less specific.[6,7]

The reasons why there is a robust evidence in the literature of cutaneous manifestations in COVID-19 due to SARS-CoV-2 and not even one report of skin rashes both in SARS-CoV and MERS-CoV infections is unclear. One possible explanation is that the international response to COVID-19 has been more transparent and efficient when compared to the SARS/MERS outbreaks. The rapidly progressing of COVID-19 pandemic has become a global concern stimulating a lot of dermatological researches with many more cases than its predecessors. Another explanation is that a part of these skin manifestations of COVID-19 is not directly related to the virus but to the multidrugs which have been used in a relatively large amount in COVID-19 compared to the therapies used for the previous epidemic of SARS and MERS.[10] In this setting, we cannot rule out that, in view of the greater severity of lung and multiorgan involvement in SARS and MERS, the skin has received less attention or that SARS-CoV and MERS-CoV may have less tropism for the skin than SARS-CoV-2.

There is still much more to know about skin manifestations associated with COVID-19 but unfortunately, we cannot learn from the experience of previous coronavirus epidemics. It is only with this new pandemic that dermatologists are exploring a new chapter whose aim is not only to identify patients or asymptomatic carriers in the risk population throughout skin signs but also to understand whether skin rashes could be a part of a potential transmission route for SARS-CoV-2.

Funding sources

None.

Conflicts of interest

None.

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