Funding sources
None declared.

Data availability statement
Data available within the article or its supplementary materials.

A. Lepekhova,* E. Grekova, O. Olisova, E. Dunaeva, S. Ali, I. Maximov, N. Teplyuk
Department of Dermatology and Venereology, Sechenov University, Moscow, Russia
*Correspondence: A. Lepekhova. E-mail: anfisa.lepehova@yandex.ru

References
1 Schmidt E, Zillikens D. Pemphigoid diseases. *Lancet* 2013; **381**: 320–332.
2 Liu Y, Sawalha AH, Lu Q. COVID-19 and autoimmune diseases. *Curr Opin Rheumatol* 2021; **33**: 155–162.
3 Kasperkiewicz M. COVID-19 outbreak and autoimmune bullous diseases: a systematic review of published cases. *J Am Acad Dermatol* 2021; **84**: 563–568.
4 Kridin K, Schonmann Y, Weinstein O, Schmidt E, Ludwig RJ, Cohen AD. The risk of COVID-19 in patients with bullous pemphigoid and pemphigus: a population-based cohort study. *J Am Acad Dermatol* 2021; **85**: 79–87.
5 Joly P, Horvath B, Patsatsi A *et al*. Updated S2K guidelines on the management of pemphigus vulgaris and foliaceus initiated by the European academy of dermatology and venereology (EADV). *J Eur Acad Dermatol Venereol* 2020; **34**: 1900–1913.
6 Murrell DF, Daniel BS, Joly P *et al*. Definitions and outcome measures for bullous pemphigoid: recommendations by an international panel of experts. *J Am Acad Dermatol* 2012; **66**: 479–485.
7 Duca A, Piva S, Focà E, Latronico N, Rizzi M. Calculated Decisions: Brescia-COVID Respiratory Severity Scale (BCRSS)/Algorithm. *Emerg. Med Pract* 2020; **22**: CD1–CD2.
8 Kasperkiewicz M, Schmidt E, Fairley JA *et al*. Expert recommendations for the management of autoimmune bullous diseases during the COVID-19 pandemic. *J Eur Acad Dermatol Venereol* 2020; **34**: e302–e303.
9 Zhang Y, Li B, Ning B. The comparative immunological characteristics of SARS-CoV, MERS-CoV, and SARS-CoV-2 coronavirus infections. *Front Immunol* 2020; **11**: 2033. https://doi.org/10.3389/fimmu.2020.02033.
10 Di Altobrando A, Patrizi A, Bardazzi F. Should SARS-CoV-2 influence immunosuppressive therapy for autoimmune blistering diseases? *J Eur Acad Dermatol Venereol* 2020; **34**: e295–e297.

DOI: 10.1111/jdv.18118

A rare case of reactive granulomatous dermatitis during COVID-19: a possible role of cephalosporine and potential mechanisms

Editor

Patients with COVID-19 present with a wide variety of cutaneous manifestations.[1] However, granulomatous lesions arising during or after COVID-19 infection are rare[2] and particularly reactive granulomatous dermatitis (RGD)[3] has not been reported. Here, we report a case of COVID-19 with a diffuse dermal infiltrate of epithelioid histiocytes possibly triggered by drug that resolved shortly.

A 61-year-old man with type 2 diabetes, hypertension and chronic renal failure requiring haemodialysis presented with headache, dry cough, and fever (38.5°C) for 2 days and SARS-CoV-2 polymerase chain reaction (PCR) test was positive. Computed tomography scan of the chest showed ground-glass opacities and bilateral lung involvement. Significant laboratory findings were as follows: white blood cell count, 7900/mm^3; lymphocyte count, 800/mm^3, platelet count, 128 000/mm^3; and C-reactive protein, 8.75 mg/dL. He was started on dexamethasone 6.6 mg, heparin 10 000 U and favipiravir 1200 mg. Ceftriaxone 1000 mg was introduced empirically. The course of medications, clinical events, and therapies is shown in Fig. 1. On day 19, he developed neutropenic fever (39°C), elevated transaminase levels and an absolute neutrophil count decreased to 0 cells/mm^3. He was treated with granulocyte colony-stimulating factor (G-CSF) (300 μg/day for 3 days) and cefepime for 2 days, which was replaced by meropenem, as a maculopapular-erythematous to violaceous rash developed on the trunk and extremities (Fig. 2a and b). Histopathology showed a diffuse dermal infiltrate composed of lymphocytes and epithelioid histiocytes expressing CD163 (Fig. 2c, d and f). The majority of the infiltrates were CD3$^+$T cells admixed with abundant CD163$^+$ epithelioid histiocytes. Multinucleate giant cells were not present in most specimens. Bone marrow biopsy showed multiple non-necrotizing granulomas composed of CD163$^+$ epithelioid cells (Fig. 2e). After cessation of ceftriaxone, cefepime, and G-CSF,[4] the skin lesions rapidly and completely resolved over the following 2 weeks. Lymphocyte transformation test showed positive reactions to both ceftriaxone (Stimulation Index, 7.32) and cefepime (2.82). There was no recurrence during the 3-month follow-up period.

Our patient's clinical course was noteworthy. First, his granulomatous lesions resolved rapidly over 2 weeks after drug cessation. Second, our patient's history of SARS-CoV-2 infection was likely a predisposing factor for the development of granulomatous lesions. No previous studies have detailed the unique constellation of clinical features observed in our patient. Given the atypical clinical presentations, it is appropriate to use the unifying umbrella term, RGD.[3] An association between RGD and COVID-19 has not been previously reported, but it is not surprising, considering the involvement of CD14$^+$16$^+$ proinflammatory monocytes producing IL-6 in COVID-19. The detrimental role of CD14$^+$16$^+$ proinflammatory monocytes in the pathogenesis of COVID-19 is only beginning to be understood: the temporal population shift from CD14$^+$16$^-$ classical monocytes to CD14$^+$16$^+$ intermediate or proinflammatory monocytes expressing CD163 in COVID-19 patients are associated with progression to severe disease.[5–7] This shift may share numerous features

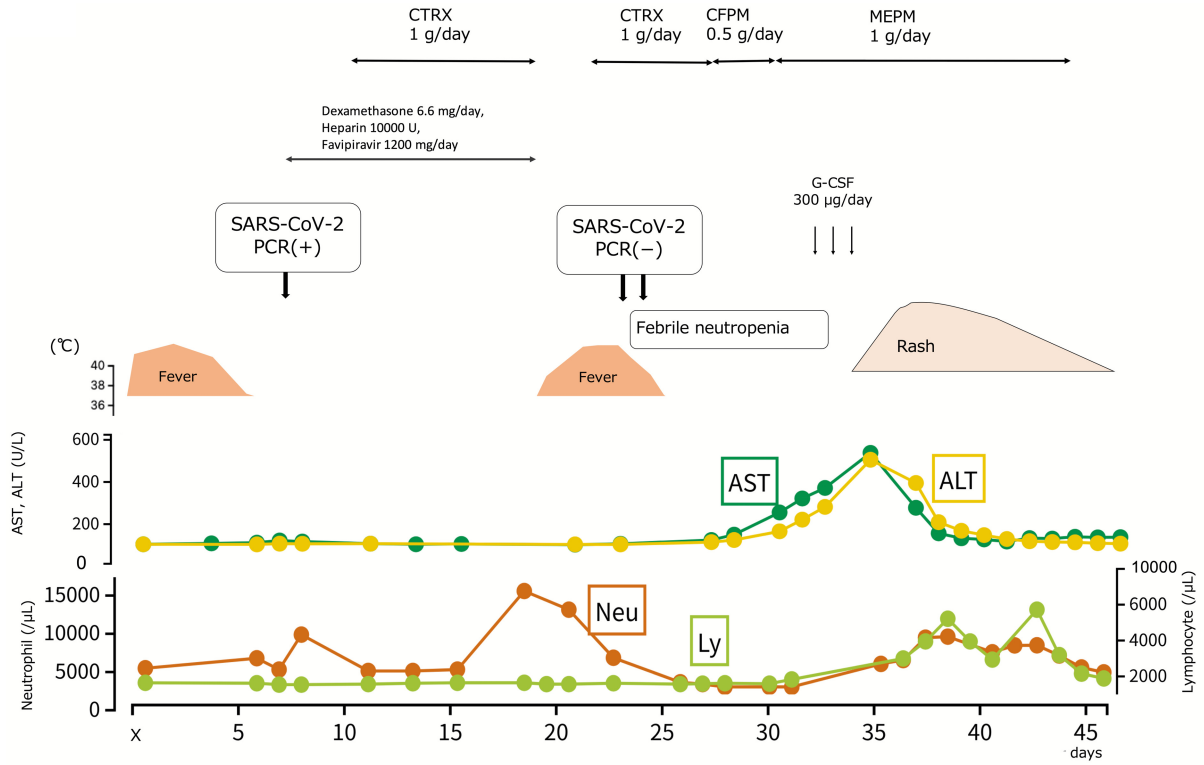

Figure 1 Clinical course of a patient who developed granulomatous drug reactions 4 weeks after onset of COVID-19. CTRX, ceftriaxon; CFPM, cefepime; MEPM, meropenem.

with monocyte responses in severe drug eruptions characterized by sequential reactivations of herpesviruses, that is drug-induced hypersensitivity syndrome (DiHS)[8]/drug reactions with eosinophilia and systemic symptoms (DRESS). Granulomatous inflammation has also been reported to occur as a manifestation of DiHS.[9] However, some distinction between RGD and DiHS could be made: RGD differs from DiHS due to its rare association of viral reactivation and its complete resolution after cessation of offending drugs, which support our diagnosis of RGD and elevated transamidase levels and multiple drug hypersensitivity[10] are also consistent with DiHS, but not with RGD. Thus, it can be speculated that RGD develops as an indirect consequence of SARS-CoV-2 infection via exaggerated monocyte activation. Although in our case granulomatous infiltrates resolved rapidly and did not progress to organ damage, long-term monitoring of patients with both diseases is needed.

Acknowledgement

The patients in this manuscript have given written informed consent to the publication of their case details.

Funding source

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflicts of interest

The authors have no conflicts of interest to declare.

Data availability statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

A. Aoki, M. Yamane, Y. Aoyama*

Department of Dermatology, Kawasaki Medical School, Kurashiki, Okayama, Japan

*Correspondence: Y. Aoyama. E-mail: ymaoyama@med.kawasaki-m.ac.jp

References

1 Freeman EE, McMahon DE, Lipoff JB *et al.* The spectrum of COVID-19–associated dermatologic manifestations: an international registry of 716 patients from 31 countries. *J Am Acad Dermatol* 2020; **83**: 1118–1129.

2 Monte-Serrano J, García-Gil MF, García-García M, Casas-Flecha I, Matovelle-Ochoa C, Ara-Martín M. Granuloma annulare triggered by SARS-CoV-2 infection: immunohistochemical staining. *Dermatol Ther* 2021; **34**: e14897. https://doi.org/10.1111/dth.14897.

3 Rosenbach M, English JC. Reactive granulomatous dermatitis a review of palisaded neutrophilic and granulomatous dermatitis, interstitial granulomatous dermatitis, interstitial granulomatous drug reaction, and a proposed reclassification. *Dermatol Clin* 2015; **33**: 373–387.

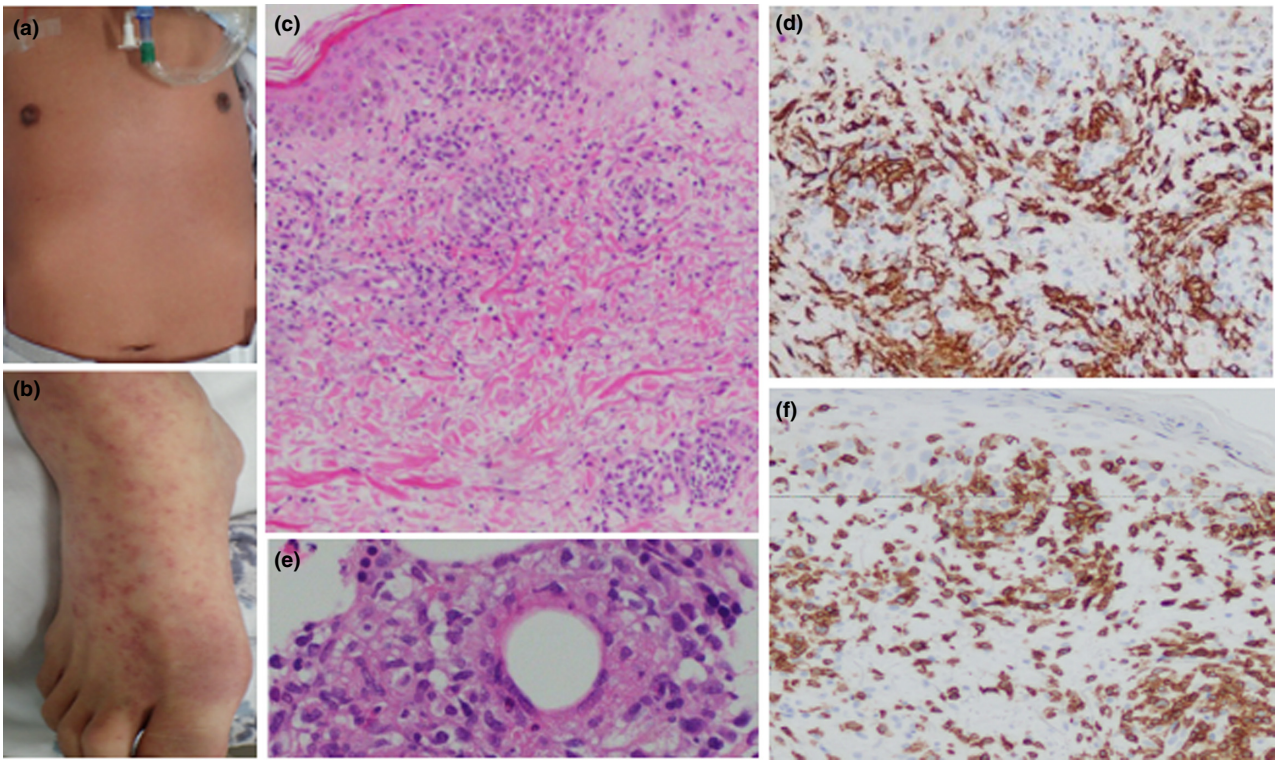

Figure 2 Clinical manifestations and histopathology of a skin biopsy from violaceous erythema. (a) Diffuse erythema without erosion involving the trunk. (b) Violaceus plaques were diffusely distributed on feet. (c) Histopathology of a skin biopsy. Hematoxylin and eosin staining. ×100. (d) Immunohistochemical staining for CD163. ×200. (e) Histopathology of bone marrow biopsy. Hematoxylin and eosin staining. ×400. (f) Immunohistochemical staining for CD3. ×200.

4 Álvarez-Ruiz S, Peñas P, Fernández-Herrera J, Sánchez-Pérez J, Fraga J, García-Díez A. Maculopapular eruption with enlarged macrophages in eight patients receiving G-CSF or GM-CSF. *J Eur Acad Dermatol* 2004; **18**: 310–313.
5 Zhang D, Guo R, Lei L *et al*. Frontline Science: COVID-19 infection induces readily detectable morphologic and inflammation-related phenotypic changes in peripheral blood monocytes. *J Leukocyte Biol* 2020; **109**: 13–22.
6 Bao L, Deng W, Huang B *et al*. The pathogenicity of SARS-CoV-2 in hACE2 transgenic mice. *Nature* 2020; **583**: 830–833.
7 Boumaza A, Gay L, Mezouar S *et al*. Monocytes and macrophages, targets of severe acute respiratory syndrome coronavirus 2: The clue for coronavirus disease 2019 immunoparalysis. *J Infect Dis* 2021; **224**: 395–406.
8 Ushigome Y, Mizukawa Y, Kimishima M *et al*. Monocytes are involved in the balance between regulatory T cells and Th17 cells in severe drug eruptions. *Clin Exp Allergy* 2018; **48**: 1453–1463.
9 Fernando SL, Henderson CJ, O'Connor KS. Drug-induced hypersensitivity syndrome with superficial granulomatous dermatitis-a novel finding. *Am J Dermatopathol* 2009; **31**: 611–613.
10 Hayakawa J, Takakura H, Mizukawa Y, Shiohara T. COVID-19-related cutaneous manifestations associated with multiple drug sensitization as shown by lymphocyte transformation test. *J Eur Acad Dermatol* 2020; **34**: e779–e781.

DOI: 10.1111/jdv.18119

Haemorrhagic bullous pyoderma gangrenosum following COVID-19 vaccination

Dear Editor,

Pyoderma gangrenosum (PG) is a destructive, inflammatory, neutrophilic dermatosis and often associated with an underlying systemic disease. PG is characterized by a rapidly progressive ulcer with a purulent, necrotic base and a raised, violaceous, undermined border developing from the breakdown of painful nodules or pustules.[1,2] Clinical variants of PG include ulcerative, bullous, pustular, vegetative and peristomal.[1,2] There have been various cutaneous reactions reported after COVID-19 vaccination. However, to our knowledge, there has been no COVID-19 vaccination-associated PG reported.

A 46-year-old otherwise healthy male presented with fever (38.4°C) and painful blisters on the extremities for 5 days. He had received the first-dose ChAdOx1 nCov-19 (Oxford-AstraZeneca) vaccination 2 weeks before presentation. Dermatologic examination revealed numerous haemorrhagic blisters on his hands, elbows, knees, legs and feet and scattered necrotic ulcers