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LETTER TO THE EDITOR

Development of toxic epidermal necrolysis in a coronavirus disease 2019 patient with recurrence of positive SARS-CoV-2 viral RNA

Dear Editor,

This case report involves an 81-year-old woman with coronavirus disease 2019 (COVID-19) who was initially treated with azithromycin, hydroxychloroquine, and ciclesonide inhalation and recovered after respiratory management in the intensive care unit. A loop-mediated isothermal amplification assay for the detection of SARS-CoV-2 at 28 and 35 days after onset and polymerase chain reaction (PCR) testing on day 33 showed negative results. A 0.8 mg/kg/day dose of prednisolone (40 mg/day) was administrated against secondary organizing pneumonia (SOP) from day 28 onward, and antimicrobial drugs were also administrated as required.

On day 40, she developed widespread erythematous lesions and subsequently presented with fever. The sputum culture tested positive for methicillin-resistant *Staphylococcus aureus*, *Escherichia coli*, *Enterococcus faecalis*, and *Candida albicans*. Furthermore, PCR testing for SARS-CoV-2 was positive again, 44 days after the first onset of COVID-19. Computed tomography showed exacerbation of severe acute respiratory distress syndrome (ARDS). Erythematous lesions rapidly expanded and were diagnosed as erythema multiforme, related to either the most recently administrated antibiotics (cefmetazole from day 23 to 30 and ampicillin from day 35 to 40) or infectious agents. Although high-dose i.v. immunoglobulin

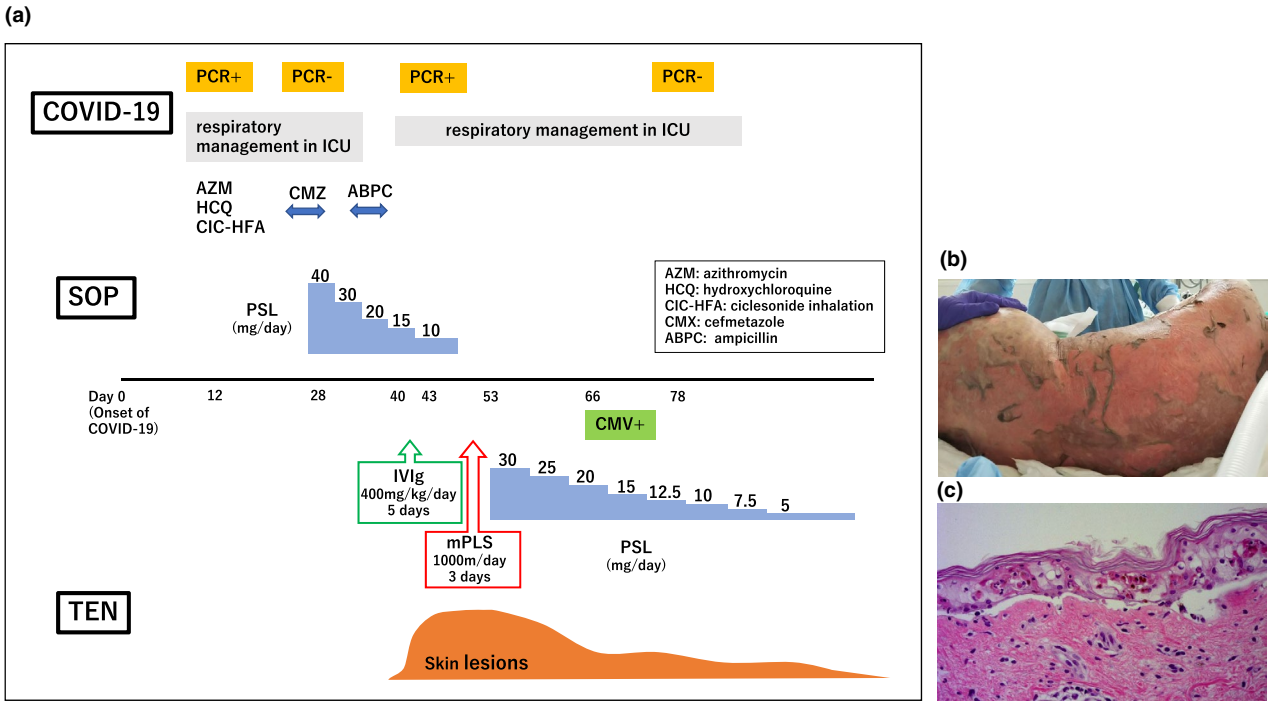

FIGURE 1 (a) Clinical course of coronavirus disease 2019 (COVID-19) and toxic epidermal necrosis (TEN). (b) Clinical appearance of the patient after the diagnosis of TEN. The widespread coalescent macules developed into large blisters and desquamation. (c) Histopathological examination (hematoxylin–eosin, original magnification ×200). There were subepidermal bullae with widespread epidermal necrosis and apoptotic keratinocytes. Abbreviations: ABPC, ampicillin; AZM, azithromycin; CIC-HFA, ciclesonide inhalation; CMV, cytomegalovirus; CMZ, cefmetazole; HCQ, hydroxychloroquine; ICU, intensive care unit; IVIg, i.v. immunoglobulin; mPSL, methylprednisolone; PCR, polymerase chain reaction; PSL, prednisolone, SOP, secondary organizing pneumonia

was administrated taking into account her infectious state, she developed toxic epidermal necrolysis (TEN) (Figure 1). Steroid pulse therapy was administrated followed by a 0.6 mg/kg/day dose of prednisolone, and the patient's skin lesions and respiratory and circulatory conditions improved.

Cutaneous manifestations in COVID-19 patients have been reviewed and, as a differential diagnosis, drug-induced reactions should be considered.[1] There have been only two case reports of TEN[2,3] in COVID-19 patients, and both were considered to be drug-induced. Our patient developed recurrence of ARDS with re-positive SARS-CoV-2 RNA at the onset of the erythematous lesions and it was difficult to rule out the cutaneous manifestation triggered by COVID-19. Furthermore, the drug-induced lymphocyte stimulation test for cefmetazole and ampicillin was negative. However, other medications during her clinical course might have been related.

Upon developing TEN, the prednisolone dose for SOP was tapered from 40 to 15 mg/day for 16 days, and the patient recovered from both the viral infection and immunosuppression caused by prednisolone and she was considered to be under immune reconstitution. Immune reconstitution inflammatory syndrome (IRIS) develops in HIV-infected populations when the immune response recovers following antiretroviral therapy. It has also been recognized in HIV-negative immunocompromised patients. In the dermatological field, drug-induced hypersensitivity syndrome has been considered to represent a prototype of non-HIV IRIS and draft diagnostic criteria for non-HIV IRIS have been proposed.[4] In addition, Sueki *et al.*[5] reported two cases of TEN during the tapering of systemic corticosteroid therapy and described the implications for non-HIV IRIS. We assume that TEN development in our case can also be described as non-HIV IRIS. Incidentally, reactivation of cytomegalovirus was detected on day 68 (negative for human herpesvirus 6 and Epstein–Barr virus). In this case, it was not possible to determine whether recurrence of positive SARS-CoV-2 RNA virus had any relationship with IRIS. However, we plan to take our experience into consideration and continue further investigations.

CONFLICT OF INTEREST

None declared.

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