COVID-19 SPECIAL FORUM

Toxic epidermal necrolysis and co-existent SARS-CoV-2 (COVID-19) treated with intravenous immunoglobulin: '*Killing 2 birds with one stone*'

Editor

Toxic epidermal necrolysis (TEN) is classified as severe cutaneous adverse reaction. It can be induced by drugs, infection and malignancy or can be idiopathic.

We present a 62-year-old man of Indian origin with a widespread, tender, erythematous maculopapular eruption and targetoid lesions on the palms and soles. He had a history of multiple myeloma and a stem cell transplant in 2008. He was recently started on amoxicillin for a suspected lower respiratory tract infection and lenalidomide, septrin and allopurinol 6 weeks prior to presentation due to a relapse of the myeloma. The rash evolved into large areas of flaccid blistering (over 30% of the body surface area) with severe mucosal involvement (Fig. 1a), and a diagnosis of TEN was made.

The patient also had a fever and cough and was tested COVID-19-positive with a normal chest X-ray. His investigations showed CRP 55 mg/L, ferritin 240 ug/L, D-dimer 2218 ng/L, lymphocytes 0.5 × 10*9/L and neutrophils 2.3 × 10*9/L at this stage. A skin biopsy confirmed the diagnosis of incipient TEN (Fig. 2a,b). At this stage, his SCORTEN was 3. He was given supportive treatment, and intravenous immunoglobulin (IVIG) was started at 2 g/kg for 3 days. This led to a rapid attenuation of the TEN and no further progression of his COVID-19 (Fig. 1b).

The most likely culprits of TEN in this case were septrin, allopurinol or lenalidomide (all drugs were stopped) due to the temporal association. The mechanism of drug-induced TEN is type IV hypersensitivity which requires days to weeks of disease onset after exposure to antigen.[1] The most important and effective therapeutic measure is withdrawal of the offending drug.

Our patient was at high risk of having a poor outcome with COVID-19, with risk factors of male gender, Asian origin, hypertension, diabetes mellitus and multiple myeloma. His mortality rate from TEN was calculated at 32%, but in reality, it was much higher from the presence of SARS-CoV-2 infection. Thus far, there are no reported cases of SARS-CoV-2 and toxic epidermal necrolysis but of various other skin presentations.[2]

Immunoglobulin therapy contains highly purified immunoglobulins, especially IgG, natural antibodies that can recognize and neutralize various exogenous antigens. They play a role in modulating the natural and adaptive immunity by inducing anti-inflammatory effects.[3] IVIG may also inhibit T-cell activation, IL-6 and TNF-α and therefore may have a role in the attenuation of the cytokine storm seen in COVID-19.[4]

Reports have shown that IVIG may be beneficial for critically ill COVID-19 patients.[3,5,6,7] The acute and viraemic phases seen in COVID-19 infection manifest with a rise in neutrophils, creatinine, urea, ferritin, D-dimer and IL-6, a presumed reduction in B cells[7] with the risk of multi-organ failure. The acute phase is induced by an inflammatory storm, particularly with IL-6, which IVIG may affect.[4]

Critically ill patients with COVID-19, who were given IVIG at a dose of 0.3–0.5 mg/kg/day for 5 days within the first 48 hours after admission, could significantly reduce the 28-day mortality rate.[6] Another study supports the use of high dose of IVIG (2 g/

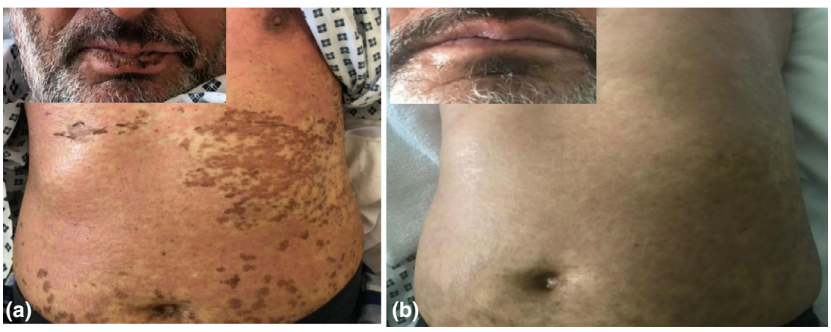

Figure 1 Patient at time of presentation (a) with a widespread, erythematous, crusted, rash affecting the lips and the oral mucosa and (b) after treatment with IVIG with re-epithelialization of skin.

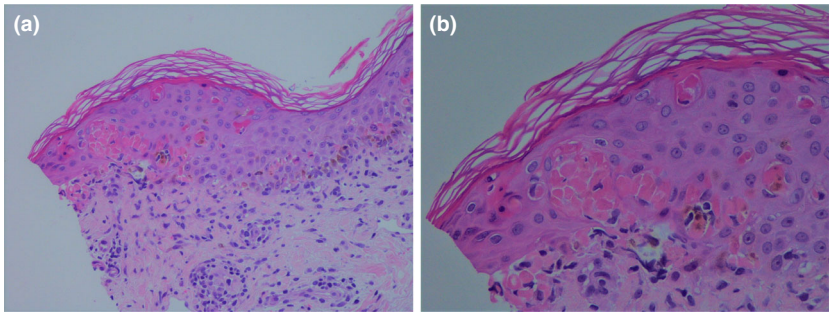

Figure 2 H&E × 200 image showing apoptotic keratinocytes occupying almost the entire thickness of the epidermis, resembling TEN (a) and H&E × 400 image showing the TEN-like area in more detail (b).

kg given over 2–5 days) in COVID-19.[3] In children with atypical Kawasaki disease and COVID-19 exposure, high dose of IVIG (2 g/kg) was successfully given in the first 24 h.[8]

We postulate that the IVIG may have had a role in reducing the severity of disease from COVID-19, as well as switching off the TEN. We propose that high dose of IVIG (2 g/kg) may have a role in improving disease outcome from COVID-19 by modulating the hyperinflammatory phase and cytokine storm seen in this disease. However, further studies are needed.

Acknowledgement

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

Conflict of interest

The authors declare that there are no conflicts of interest related to this article. Dr Saha, Dr D'Cruz, Dr Paul, Dr Healy, Dr Collins, Dr Charles, Dr Sahu and Dr Fonia have nothing to disclose.

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Comment on 'Drug reaction with eosinophilia and systemic symptoms syndrome in a patient with COVID-19': involvement of herpesvirus reactivations and adverse drug reactions in diverse cutaneous manifestations and overall disease severity of COVID-19

Dear the Editor,

We have read with great interest the publication by Herman *et al*.,[1] which reported occurrence of drug reaction with eosinophilia and systemic symptoms (DRESS), also known as drug-induced hypersensitivity syndrome (DiHS), in a COVID-19 patient: the patient developed DiHS/DRESS 17–18 days after starting azithromycin and hydroxychloroquine. The

