

**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.<sup>3</sup> 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.<sup>8</sup>

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.

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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.*,<sup>1</sup> 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

benefits shortly after starting these drugs appeared to be minor, whereas the long-term immune dysregulation was significant. DiHS/DRESS is a life-threatening multiorgan system reaction induced by a limited number of the causative drugs with the immunosuppressive potential and are characterized by sequential occurrence of herpesvirus reactivations.<sup>2,3</sup> Here, we provide a brief insight into the similarities and differences in the clinical manifestations of COVID-19 and DiHS/DRESS. DiHS/DRESS can mimic virally related diseases including Epstein–Barr virus- and cytomegalovirus-induced infectious mononucleosis, parvovirus B19 infection, dengue virus infection and Kawasaki disease.<sup>2</sup> In DiHS/DRESS, even after drug withdrawal, resolution of symptoms in one organ is often followed by a stepwise development of other organ failures, such as gastroenteritis, interstitial pneumonia, limbic encephalitis and myocarditis.<sup>2</sup> Such clinical variability in the presentation and course could be mediated by sequential occurrence of herpesvirus reactivations. Initial expansions of regulatory T cells (Tregs) and their subsequent exhaustion provide a mechanism for why herpesviruses can be sequentially reactivated at the acute~subacute phases (3–40 days after onset) and why the patients have severe complications/sequelae:<sup>4</sup> a gradual loss of Treg function could increase the risk of developing widespread collateral tissue damage.<sup>2–4</sup> In DiHS/DRESS, the pathogenic cascade triggered by drug damages many organs from the skin to the brain, as shown in COVID-19 patients. During the disease process in COVID-19 as well as DiHS/DRESS, a variety of clinical symptoms may develop later depending on the herpesvirus reactivated. Indeed, diverse clinical symptoms in DiHS/DRESS have been also reported as COVID-19-related cutaneous manifestations without confirming viral or drug aetiologies; they include erythema multiforme, varicella, herpes zoster, pityriasis rosea, Kawasaki disease and urticaria,<sup>5–7</sup> in which herpesviruses, such as varicella-zoster virus (VZV) and human herpesvirus 6 (HHV-6), have been suggested to play a role. A recent report also describes co-reactivation of herpes simplex virus-1 and VZV in a critically ill COVID-19 patient.<sup>8</sup> Because HHV-6 has been shown to be associated with chronic spontaneous urticaria, herpesvirus reactivations including HHV-6 could be involved in diverse cutaneous manifestations previously attributed to SARS-CoV-2. If so, antiviral agents may ameliorate severe COVID-19 symptoms when used as adjuncts to putative anti-COVID-19 agents. In addition, adverse drug reactions (ADRs) could have contributed to the diverse cutaneous manifestations. In support of this, a recent report describe 5.84-fold higher incidence rate of severe ADRs in COVID-19 patients;<sup>9</sup> and we have recently reported a COVID-19 patient who developed typical COVID-19-associated cutaneous manifestations,<sup>10</sup> symmetrical drug-related intertriginous and flexural exanthema, in which ‘multiple drug hypersensitivity’ not only to the causative drug but also to other drugs used for COVID-19 was

demonstrated by lymphocyte transformation tests.<sup>10</sup> Such ‘multiple drug hypersensitivity’ was typically observed in the acute~subacute phases of DiHS/DRESS, at which time Treg function becomes impaired.<sup>4</sup> Most reports, however, demonstrated cutaneous manifestations of COVID-19 without performing screening tests for herpesvirus reactivation and ADRs. Thus, severe COVID-19 symptoms appear to be driven by a complex interplay involving reactivations of latent herpesviruses, antiviral immune responses and drug-driven immune responses, as demonstrated in DiHS/DRESS. Patients who experienced herpesvirus reactivations and ADRs are more likely than those without them to have a more severe disease course; the combination of these factors could result in COVID-19-associated multiorgan failures. Accurate assessment of the patient’s viral infection status and a possibility of ADRs is highly required. The aetiology of severe COVID-19 symptoms may be multifactorial.

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## Why are chilblains underreported in Nordic countries during the COVID-19 pandemic? An analysis of Google Trends

Dear Editor,

An unusual number of cases of chilblains has mainly been reported in Southern Europe (Italy, Spain, France)<sup>1</sup> and in the United States<sup>2</sup> during the COVID-19 pandemic. However, the link of causality between those two events remains debated.<sup>3,4</sup> Herman *et al.*<sup>4</sup> suggested that confinement and lockdown restrictions with decreased physical activity, increased time spent in sedentary positions, use of recreation drugs and remaining barefoot or in socks at home may be related to the symptoms. In Northern Europe, Finland (7871 declared cases on 23 August 2020) and Norway (10 197) suffered less infections than Sweden (86 068).<sup>5</sup> As confinement has not been applied in Nordic countries, it is of interest to know whether there has also been an increase of chilblains cases in those countries. To our knowledge, there are no reports published thus far. We used Google Trends (GT) to investigate whether there were notable variations in searching for information related to chilblains, before and during the COVID-19 pandemic, between Northern and Southern Europe.

We analysed the data generated through GT for relative search volumes (RSV) of the word ‘chilblains [disease]’, worldwide and in six countries (Italy, Spain, France, Norway, Finland, Sweden) from 1 January 2016 to 23 August 2020. We also evaluated RSV for ‘COVID toes’. The methodology has been described in a previous study.<sup>6</sup>

Worldwide searches for ‘chilblains’ display a striking regularity with yearly peaks in January/February. Smaller but regular

peaks occur also every July and match searches from the Southern Hemisphere during austral winter (Fig. 1a). The peak in January 2020 was less high compared to previous years, possibly because of exceptional warm temperatures this winter.<sup>7</sup> Two additional peaks occurred around April/May 2020 and July 2020. The pattern in Italy and in Spain is strikingly similar with notable peaks every December/January and almost no search the rest of the year. A resumption in April and May 2020 is notable. France displayed a similar pattern, although a background noise of searches occurs also in springs (Fig. 1b). In Nordic countries, winter peaks are notable too; however, the patterns are not as clear-cut as for Italy and Spain. Peaks in April and May 2020 are also visible in Norway and Sweden (Fig. 1c). Peaks in May and July 2020 usually matched with ‘COVID toes’ searches (*data not shown*).

There may be several reasons for the paucity of reports of chilblains in Nordic countries: low prevalence of infection in the general population compared to other countries, low prevalence of infection among the young,<sup>8</sup> underreporting of cases and failure to consult for symptoms that are not severe. The search peaks in spring 2020 may be related to patients with symptoms and indicate that the same symptoms occurred elsewhere in Europe. However, peaks matched also ‘COVID toes’ key word, so we cannot rule out an artificial increase of searches on Google and other Web search engines in relation to news coverage over the Internet of this new phenomenon.

To conclude, Nordic countries have not imposed strict confinement to population as in Southern Europe and there are currently no reports of chilblains ‘outbreaks’ during this period. This could indirectly point towards a link between confinement and chilblains. However, there have been searches for ‘chilblains’ in Spring 2020 on GT in northern Europe. Nordic dermatologists should gather and report their cases of chilblains during the COVID-19 pandemic, so we could evaluate whether chilblains are a global phenomenon that occurred in countries that did not confine as well.

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