Correspondence

Comment on "Chronic spontaneous urticaria exacerbation in a patient with COVID-19: rapid and excellent response to omalizumab"

Dear Editor,

With or without systemic symptoms, widespread urticaria/urticaria-like lesions are among the earliest reported cutaneous signs in association with coronavirus disease 2019 (COVID-19) that has a variable prognostic value.[1] Despite that, few data are available on the therapeutic ladder of urticaria in COVID-19 patients. Second-generation antihistamines, in an up-titrated dosing up to fourfold, were mostly prescribed with satisfactory results.[2] Omalizumab (OMZ) can be used as a third line for refractory cases.[3]

Recently, Criado *et al.*[4] published in the *International Journal of Dermatology* a case of a middle-aged COVID-19 woman with an unremitting chronic spontaneous urticaria (CSU) with angioedema who had shown significant improvement of not only urticarial lesions but also systemic signs of the disease, with monthly injections of 300 mg of omalizumab (OMZ) for three sessions. We agree with this interesting observation. Earlier, we had suggested that OMZ may be tried for treatment of urticaria and vascular lesions manifested in COVID-19 patients, with possible mitigation of the risk of acute respiratory distress syndrome through inhibition of proinflammatory mediators.[5] Interestingly, plasmacytoid dendritic cells (pDC) in asthmatic and in CSU patients were demonstrated to produce type I interferon after OMZ treatment.[6] Gill *et al.*[7] noticed that OMZ had restored type I interferons, namely interferon-α (IFN-α), responses to both rhinovirus and influenza. Restoring type I interferon-mediated innate immune response helps to initiate a powerful antiviral immune response[6] to inhibit SARS-CoV-2 replication, and eventually limiting dissemination of the infection at an early stage of disease.[8] Dursun *et al.*[9] noticed an increased rate of pityriasis rosea and Kawasaki disease in patients who presented to dermatology outpatient clinics during the COVID-19 pandemic. The authors attributed that to coronavirus triggering of HHV-6 (i.e. endogenous viral reactivation of HHV-6 by SARS-CoV-2 infection). Dreyfus observed that HHV-6 reactivation and gene expression could play a role in CSU pathogenesis in OMZ-dependent CSU who had evidence of past infection with HHV-6 and serology.[10] Dreyfus thought that long-term OMZ therapy may be required to decrease HHV-6 titers.[10] Interestingly, OMZ has been used safely for CSU continuously for up to 25 months, according to a recent study from Turkey.[11] An antiviral potential of OMZ may stand behind its mechanism of action in treatment of respiratory viral infections, including SARS-CoV-2, and secondary activated endogenous viruses, such as HHV-6, that are involved in the pathogenesis of CSU or chronic viral urticaria.[7,9,10] García-Gil *et al.*[12] recently reported a child with COVID-19 who had acro-ischemia. The child showed elevated D-dimer (4231 μg/l) and IgE level (1570 U.L/ml). Further studies or accumulating cases may assist in reaching the precise mechanism of action of OMZ as a therapeutic option for cutaneous and systemic signs of COVID-19. On the other hand, Hayakawa *et al.*[13] recommended lymphocyte transformation tests be considered in any COVID-19 patient presenting with cutaneous manifestations to rule out the possibility of drug sensitization. Jimenez-Cauhe *et al.*[14] observed that the presence of enanthem, particularly the petechial pattern, is a strong suggestive clue of viral etiology rather than a drug reaction.

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