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SARS-CoV-2 asymptomatic infection in a patient under treatment with dupilumab

Dear Editor,

We have read with great interest the letter of the European Task Force on Atopic Dermatitis on SARS-CoV-2 infection and atopic dermatitis published in JEADV (March 2020)[1] in which the authors state: 'Targeted treatment selectively interfering with type-2 inflammation such as dupilumab is not considered to increase the risk for viral infections and might thus be preferred . . .in a situation such as COVID-19 pandemic'.[1]

We would like to report the case of a 72-year-old man affected by severe atopic dermatitis (histologically ascertained), who is under treatment with dupilumab since November 2019, with excellent clinical results.

At the beginning of SARS-CoV-2 pandemic in Italy, although he was totally asymptomatic for COVID-19, as all the other residents in Vo' Euganeo, a small town near Padua, in the so-called 'Vo' Red Zone' (i.e. restricted area), he was tested with nasopharyngeal swab for SARS-CoV-2 detection and resulted positive.

After 20 days of isolation period, the nasopharyngeal swab for SARS-CoV-2 resulted again positive. After 20 more days of isolation, he was tested positive for the third time. Three weeks later, the nasopharyngeal swab for SARS-CoV-2 was finally negative. Notwithstanding the risk factors (i.e. age >65 years and male gender), our patient throughout all this period (9 weeks) remained totally asymptomatic for COVID-19, in good general condition and free of atopic dermatitis.

It would seem that treatment with dupilumab, similarly to other antibodies targeting pro-inflammatory cytokines (e.g. adalimumab, infliximab, ustekinumab, secukinumab and guselkumab), does not worsen the condition of patients infected by SARS-CoV-2 or increase the risk of infection by SARS-CoV-2,[2–7] possibly because these antibodies neutralize individual mediators of the inflammation cascade rather than leading to broad immunosuppression.[8]

However, of course, more robust clinical data are needed in order to evaluate the safety of dupilumab and of other biologics in patients infected by SARS-CoV-2.

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'Toxic erythema' and eosinophilia associated with tocilizumab therapy in a COVID-19 patient

Dear Editor,

Since the new fatal pneumonia was identified in December 2019 in Wuhan, China, the WHO declared the infection a health emergency of international concern.

The novel ss-RNA ß-coronavirus (SARS-CoV-2) spreads through airborne and direct contagion; virulence is high in the elderly and in patients with diabetes, chronic pulmonary, cardiovascular and neoplastic diseases. SARS-CoV-2 ssRNA is recognized by intracellular pattern recognition receptors (PRRs), which trigger NF-kB – the master regulator of inflammation – and interferon regulatory factors (IRFs). These regulators induce type I interferon (IFN-α/β) production, along with a series of acute-phase cytokines, mainly TNF-α/ß, IL-1ß and IL-6, powerful mediators of Th1-like inflammatory response.[1,2] IL-6 acts both locally, to activate lymphocytes, and systemically, to induce fever and production of acute-phase proteins. IL-6 has been recognized as one of the most accurate biomarkers predictive of death in clinical sepsis.[3] The main pathogenic mechanism related to COVID-19 is the cytokine storm, characterized by massive release of pro-inflammatory cytokines and chemokines that characterize highly aggressive fatal forms.[2] Characteristic findings are leukopenia and lymphocytopenia. Chest CT shows typical diagnostic patterns of ground-glass opacities and bilateral patchy shadowing.[2] Severe forms are also characterized by neutrophilia, increase in D-dimer and IL-6 serum levels; the latter marker is a main culprit of the cytokine storm and is considered a strong negative prognostic factor. In COVID-19-related cytokine storm, tocilizumab – a humanized monoclonal antibody targeting IL-6 cytokine receptor – has been proposed as effective biological treatment and is currently being evaluated in large-scale RCTs (NCT04346355).

A 70-year-old man was admitted to the Emergency Department of 'Policlinico Umberto I' in Rome, for the recent onset of dry cough, rising fever (38.4°C), asthenia and dyspnoea. High-resolution CT showed sub-pleural ground-glass opacities and interlobular septal thickening; oxygen saturation was 90.1%. RT-PCR performed on nose and throat swabs, revealed positivity to SARS-CoV-2. The patient started therapy with lopinavir/ritonavir combination, hydroxychloroquine 200 mg twice daily and oxygen supplementation. Despite the medical care, after 7 days clinical conditions and radiological findings had worsened. Blood examinations showed leukocytopenia with lymphopenia, neutrophils and monocytes count increase. Treatment with intravenous tocilizumab 600 mg was then started. Few hours after the administration of the drug, the patient developed an itching generalized cutaneous 'toxic erythema-like' rash. Blood cell count showed severe eosinophilia (2.2×10^9/L) with increasing trend. Methylprednisolone 20 mg twice daily was started. During the following days, COVID-19-related symptoms underwent sensible remission: there was normalization of inflammatory markers and clinical parameters; RT-PCR on swabs became negative. Cell blood parameters returned within normal range, except eosinophil count which raised progressively to 7.8×10^9/L. Despite corticosteroid treatment, the skin rash was still present after 10 days (Fig. 1). Skin eruption and blood eosinophilia integrate two criteria for the diagnosis of drug reaction with eosinophilia and systemic symptoms syndrome (DRESS), and their persistence after withdrawal of suspect drug is typical of DRESS; however, the rapid onset and absence of internal organ involvement are not consistent with such diagnosis.[4] Unfortunately, skin biopsy and allergological tests could not be performed due to safety concerns.

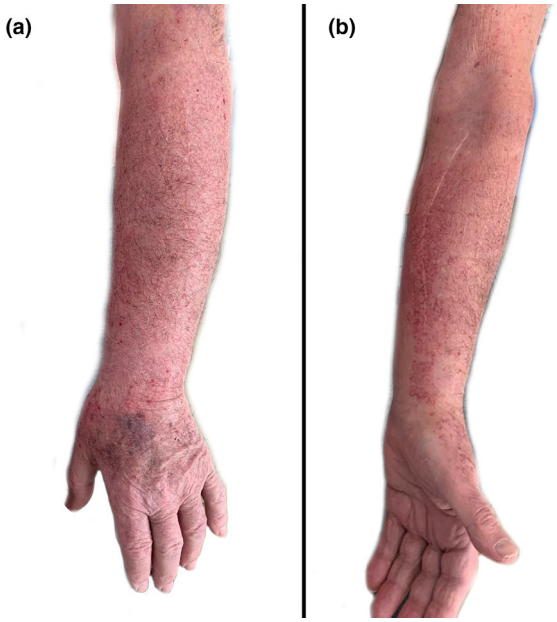

Figure 1 Diffuse erythematous and desquamative eruption following the administration of tocilizumab and persisting with mild improvement after 10 days, when skin examination showed prominent lesions associated with intense pruritus on the upper limbs. Extensor (a) and flexor (b) surfaces of the left forearm are shown.

Tocilizumab is considered a powerful anti-inflammatory agent and safe biological drug, already in use for the treatment of rheumatoid arthritis. It is among the most effective biological drugs in the treatment of COVID-19-related cytokine storm. Regarding adverse reactions to the drug, there are no reported cases of skin rash associated with eosinophilia in COVID-19 patients. Hypereosinophilic reactions in patients under tocilizumab therapy for autoimmune diseases have already been documented in literature.[5] Common findings in these studies were generalized skin manifestations, hypereosinophilia and eosinophilic cutaneous infiltrate on biopsy.[6–10]

In the SARS-CoV-2-era, the appropriate strategy for the treatment of the cytokine storm is a topic of great interest and awareness of unusual side effects, as that in our report, could help physicians to better manage these critical patients.

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Dermatologic surgery training during the COVID-19 era

Dear Editor,

COVID-19, a novel coronavirus, has spread throughout the world. Because of exponential growth, social distancing is a critical strategy to decrease transmission. Thus, educational medical communities from many countries have transitioned to online didactics.[1] Recommendations to cancel all non-urgent visits have been proposed.[2] Our dermatology department has cancelled all elective outpatient visits and surgeries. Consequently, trainees' surgical skills have been severely affected. To continue our educational programme, we have implemented measures to help our trainees continue learning and maintaining surgical skills.

We continued our educational programme with a general review of basic and advanced dermatologic surgery using PowerPoint presentations using a web-based video conferencing tool. Professors share their knowledge and experiences with trainees and answer any questions. Afterwards, professors apply a hypothetical case scenario so the surgical trainee can decide the surgical approach [Mohs micrographic surgery (MMS) or conventional wide-margin excision (WME)] using a simulator bust model (Diaphanous Zsa Zsa, DermSurg Scientific, Dayton, OH, USA).

Residents design multiple flaps and practise surgical skills in a life-like scenario (Fig. 1) and place the simulator akin to how patients are normally positioned for surgery. Then, with a non-permanent marker they draw a hypothetical skin defect. Depending on the size and location of the cancer, they design and discuss different possible reconstruction flaps. Multiple flap designs are then drawn by the trainees to see which is best suited. To reassure complete comprehension, trainees explain the concepts behind every flap and are assessed by their professors. Drawings from conventional surgical markers are easily erased from the bust models with isopropyl alcohol allowing a quick turnaround time for the next case.

The combined use of simulation-based education and digital technologies for dermatologic surgery has been previously reported.[3,4] Nicholas *et al*.[5] carried out a pilot study and reported that learners were receptive to the use of simulators in their dermatologic training after a 2-day surgical symposium. More than 90% of the participants agreed that simulators were helpful. Additionally, more than 75% of the participants agreed that simulators were useful in acquiring, refining, assessing and learning these skills. Notably, 90.9% of the participants thought that training using simulators should be mandatory in their residency programme.

It is important to clarify that this educational experience is new for everyone, and we acknowledge that any recommendations we propose are likely to shift in the coming weeks as the advancement of online medical education evolves. Despite the need to polish and improve the dermatological surgery programme with simulators in our department, our experience indicates that surgical trainees learn to train their minds to consider the different flaps and possible reconstructions with 1-hour weekly practices. Our main goal is that when the COVID-19 contingency ends, our trainees will have the confidence and mental ability to treat patients. We want to emphasize that learning and/or practicing with simulators will never substitute a real patient. We remind our trainees that each patient's case is unique and it is necessary consider the personal history (e.g. smoking, anticoagulants), skin characteristics (elasticity, sun damage), and size and location of the lesion, among others, in order to evaluate the type of surgery (MMS vs. wide-margin excision), surgical margins and reconstruction method for the defect once clear margins have been obtained. While cost and availability of dermatologic surgery professors remain the main limitations,[5] efforts should be made during this contingency to

