



## “Toxic erythema” and eosinophilia associated to tocilizumab therapy in a COVID-19 patient

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Article type : Letter to Editor

### **“Toxic erythema” and eosinophilia associated to 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  $\beta$ -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- $\kappa$ B – the master regulator of inflammation – and Interferon Regulatory Factors (IRFs)<sup>1</sup>. These regulators induce type I interferon (IFN- $\alpha/\beta$ ) production, along with a series of acute phase cytokines, mainly TNF- $\alpha/\beta$ , IL-1 $\beta$  and IL-6, powerful mediators of Th1-like inflammatory response<sup>2,3</sup>. 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<sup>4</sup>. 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<sup>3</sup>. Characteristic findings are leukopenia and lymphocytopenia. Chest CT shows typical diagnostic patterns of ground-glass opacities and bilateral patchy shadowing<sup>3</sup>. 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 dyspnea. 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 exams 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 ( $2,2 \times 10^9/L$ ) 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  $7,8 \times 10^9/L$ . 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<sup>5</sup>. Unfortunately, skin biopsy and allergological tests could not be performed due to safety concerns.

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 to eosinophilia in COVID-19 patients. Hypereosinophilic reactions in patients under tocilizumab therapy for autoimmune diseases have already been documented in literature<sup>6</sup>. Common findings in these studies were generalized skin manifestations, hypereosinophilia and eosinophilic cutaneous infiltrate on biopsy<sup>7-11</sup>.

In the SARS-CoV2-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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The patient in this manuscript has given written informed consent to the publication of their case details.

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**Figure legend**

**Fig. 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 to intense pruritus on the upper limbs. Extensor (a) and flexor (b) surfaces of the left forearm are shown.



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