Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Cytokine storm syndrome in severe COVID-19

Dear Editor,

we read with interest the article by McGonagle et al., which has been recently published on this Journal [1]. This article highlights the role of pro-inflammatory cytokines in inducing pneumonia and cytokine storm syndrome in patients with severe coronavirus disease 2019 (COVID-19) [1]. We agree with the Authors with the relevance of development of cytokine storm syndrome in these patients, since it is associated with a high mortality rate [2].

The term cytokine storm syndrome accommodates the observation that multiple inflammatory causes may result in a clinical picture resembling sepsis [2], clinically characterised by continuous fever, multiorgan failure, hyperferritinemia, and, potentially, death [2,3]. Different aetiologies are consequently recognised, either iatrogenic, inflammatory, or infectious, in inducing this syndrome, which may be considered the common end point of the overwhelming massive systemic inflammation [3]. Considering iatrogenic trigger, a cytokine storm syndrome may be induced by cancer immunotherapy [4]. This is one of the most important adverse event of these therapies, as shown by T cell-engaging therapies and CD19-targeted CAR T cells [4]. As far as the inflammation is concerned, the haemophagocytic lymphohistiocytosis (HLH) represents a prototype of cytokine storm syndrome, characterised by hyperinflammatory response leading to organs damage [5]. HLH has traditionally been classified into primary and secondary forms [6]. The primary forms of HLH are those related to genetic abnormalities leading to deficiency in cytotoxic cell function, concerning perforin or molecules associated with perforin vesicular transport and release [7]. The secondary forms of HLH may be triggered by infections, cancer, or inflammatory diseases. Secondary form of HLH, which occurs in the context of rheumatic diseases is generally termed macrophage activation syndrome (MAS) or rheuma HLH [7]. The typical hallmark of all these forms of HLH is the presence of hemophagocytes, activated macrophages which are engulfed by hematopoietic cells [5]. Although this histological feature could be elusive, the peripheral blood bi- or pan-cytopenia, depending from haemophagocytosis and severe cytokine-mediated inflammation, are key laboratory markers inducing the suspicion of HLH [5–7].

During COVID-19, a virally induced cytokine storm syndrome occurs in more aggressive patients, who are characterised by severe lung involvement, probably associated with a specific genetic susceptibility [8–10]. In the article by Mc Gonagle et al. [1], following as already proposed in sepsis [11], the Authors define this clinical phenotype as MAS-like syndrome, but two of the main features of primary or secondary HLH, the hemophagocytosis and the peripheral blood bi- or pan-cytopenia have been not clearly demonstrated in COVID-19 [5–7,12]. The reports from Wuhan suggested that patients developing severe COVID-19 showed an isolated lymphopenia [13,14], and personal observations from patients enrolled in our study, including SARS-CoV2 infected patients developing severe lung involvement, confirm this finding in the context of neutrophilia [NCT04332913]. On the contrary, thrombocytopenia and anaemia are identified in the large majority of adult cases with HLH, frequently associated with severe anaemia or neutropenia [5,7,12]. These data suggest the need of future efforts to fully classify this clinical hyper-inflammatory picture.

As other conditions leading to the clinical phenotype of cytokine storm syndrome, severe COVID-19 is characterised by elevated levels of IL-6. In addition to the mechanisms described in article of Mc Gonagle et al. [1], IL-6 could have a role in prompting the cytokine storm syndrome by inducing a cytolytic dysfunction. In fact, the exposure to high levels of IL-6, as observed in severe COVID-19, inhibits natural killer (NK) cell-cytotoxicity and down-regulates the expression of perforin and granzyme B [15]. This leads to a failure of cytotoxic T lymphocytes or NK cells to kill target cells by perforin/granzyme-induced apoptosis, thus prolonging the survival of target cells and enhancing the antigen stimulation, with consequent overproduction of pro-inflammatory cytokines [15–17]. The enhanced antigen presentation leads to a repeated and persistent IFN-γ dependent activation of toll like receptors, which, in turn furtherly suppresses cytolytic function and exaggerates activities of cytotoxic T lymphocytes and macrophages [18–20]. Taking together all these observations, a defect in granule-mediated cytotoxicity could be postulated as a further mechanism facilitating the cytokine storm syndrome in patients with severe COVID-19, who are characterised by a decrease of NK cells [21,22]. In addition, this pathogenic mechanism may allow us to consider COVID-19 as part of large disease spectrum, including severe sepsis, secondary HLH, systemic inflammatory response syndrome, and multiorgan dysfunction syndrome, all characterised by hyper-inflammatory activation and a specific dysfunction of cytotoxic T cells and NK cells [23]. A better understanding of the pathogenesis of severe COVID-19 may improve the therapeutic strategy of these patients [24].

Presently, data deriving from available studies and observations from the frontline do not allow, in our opinion, to define the severe COVID-19 as a MAS-like syndrome, lacking of at least two of the main signs of the disease. Probably, during COVID-19, we observe a virally induced cytokine storm syndrome, leading to a clinical picture in which some features are common with other diseases characterised by this massive release of cytokines, independent of the pathogenic trigger [25]. Thus, it could be suggested that SARS-Cov2 is another possible cause of cytokine storm syndrome. In conclusion, a deeper knowledge of the pathogenic mechanisms, the genetic background, and the inflammatory pathways of the host are still needed before fully categorise the hyper-inflammatory clinical picture of COVID-19.

Authors contributions

All the authors meet all criteria for authorship in the ICMJE Recommendations, since all authors made substantial contributions to the conception or design of the work, the acquisition and interpretation

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Declaration of Competing Interest

The authors declare that they have no conflicts of interest for this work.

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