



Secondary hemophagocytic lymphohistiocytosis, HScore and COVID-19

Giuseppe G. Loscocco^{1,2}

Received: 21 May 2020 / Accepted: 26 May 2020 / Published online: 30 May 2020
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To the Editor,

In a Letter to the Editor published online on May 12 on International Journal of Hematology [1], Prof Takami exposed, competently, the possibility to treat secondary hemophagocytic lymphohistiocytosis (sHLH) in COVID-19 patients with low-dose etoposide. In this paper are described many intriguing links about the role of cytokines, hyperinflammation and macrophage activation in these patients. The main point, as speculated by the author, is the potential use of low-dose etoposide to restore immunological homeostasis by depleting activated Cytotoxic T lymphocytes (CTLs) and suppressing their production of inflammatory cytokines, which reduces the activity of macrophages and leads to the elimination of activated macrophages and SARS-CoV-2-infected cells by newly activated CTLs. This interesting hypothesis is based (as written by the author) on a recent report by Mehta and colleagues [2] in which “all 35 patients with severe COVID-19 showed hemophagocytosis on bone marrow (BM) aspirates, cytopenia of two or more lineages, and increased serum ferritin levels (≥ 2000 ng/mL)”. I believe that the message of this Correspondence published in Lancet last March, has been misinterpreted by the author. This paper concluded that all patients with severe COVID-19 should be screened both for a hyperinflammatory state using laboratory tests (e.g. ferritin, decreased platelet count or erythrocyte sedimentation rate) and for HScore to identify the subgroup of patients for whom immunomodulating/immunosuppressive therapies as steroids, immunoglobulin, cytokine blockers (e.g. anakinra or tocilizumab) and JAK

inhibitors could improve survival. This is a point of view—a proposal—of a panel of experts but, in this study, there are no documented and reported real sHLH cases. Therefore, “35” does not represent the number of patients with HLH, as written by Prof. Takami, but the points (according to the HScore) both for a ferritin level between 2000 and 6000 ng/mL and for documented hemophagocytosis on BM aspirate (Table 1) [3]. To date, to the best of my knowledge, no cases of sHLH have been described in COVID-19 patients on BM. It was only supposed and, in support of this hypothesis there are many interesting studies, including those of Prof. Takami on the possible role of etoposide. Conversely in a more recent paper [4], the use of HScore for COVID-19 patients has been questioned. After highlighting some HScore limitations regarding temperature, leukopenia (the score does not distinguish between neutropenia and lymphocytopenia), hyperferritinemia (in early phase ferritin levels rarely reach the HScore threshold of 2000 ng/mL) and the lack of published data on hypertriglyceridemia, splenomegaly, hepatomegaly and BM hemophagocytosis, the authors recommend against the use of HScore due to a potential lack of sensitivity. Given these considerations, during the acute phase of severe COVID-19 infection, hyperinflammation state and hypercytokinemia probably reflect more an acute respiratory distress syndrome (ARDS) damage of pulmonary compartment rather than a systemic macrophages activation, the hallmark of sHLH. Many hypotheses, based on some theories, have been suggested by scientists from all over the world in this pandemic. It is a terrible and complex historical period that fully involves our lives. Collective efforts are needed to hope that these hypotheses can lead to some effective treatments under the process of bench-to bedside (and back) research.

✉ Giuseppe G. Loscocco
giuseppeloscocog@gmail.com

¹ CRIMM, Centro di Ricerca e Innovazione per le Malattie Mieloproliferative, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy

² Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy

Table 1 Clinical and laboratory parameters of the HScore with the corresponding points

Clinical/laboratory parameters	Points
Temperature (°C)	
< 38.4	0
38.4–39.4	33
> 39.4	49
Organomegaly	
None	0
Hepatomegaly or splenomegaly	23
Hepatomegaly and splenomegaly	38
Number of cytopenias ^a	
One lineage	0
Two lineages	24
Three lineages	34
Triglycerides (mmol/L)	
< 1.5	0
1.5–4.0	44
> 4.0	64
Fibrinogen (g/L)	
> 2.5	0
≤ 2.5	30
Ferritin (ng/mL)	
< 2000	0
2000–6000	35
> 6000	50
Serum aspartate aminotransferase (U/L)	
< 30	0
≥ 30	19
Hemophagocytosis on bone marrow aspirate	
No	0
Yes	35
Known immunosuppression ^b	
No	0
Yes	18

HLH hemophagocytic lymphohistiocytosis

^aDefined as either haemoglobin concentration of 9.2 g/dL or less, a white blood cell (WBC) count of 5000/mm³ or less, or platelet count of 110.000/mm³ or less

^bHIV positive or receiving long-term immunosuppressive therapy (glucocorticoids, cyclosporine, azathioprine etc.)

Compliance with ethical standards

Conflict of interest The author declares no conflict of interest.

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