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Review

COVID-19 gone bad: A new character in the spectrum of the hyperferritinemic syndrome?

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ABSTRACT

The severe form of COVID-19 share several clinical and laboratory features with four entities gathered under the term "*hyperferritinemic syndromes*" and including macrophage activation syndrome (MAS), adult-onset Still's disease (AOSD), catastrophic anti-phospholipid syndrome (CAPS) and septic shock. COVID-19 systemic inflammatory reaction and *"hyperferritinemic syndromes"* are all characterized by high serum ferritin and a life-threatening hyper-inflammation sustained by a cytokines storm which eventually leads to multi-organ failure. In this review, we analyze the possible epidemiological and molecular mechanisms responsible for hyper-inflammation in patients with severe COVID-19 and we underline the similarities between this condition and *"hyperferritinemic syndromes"* which would allow considering severe COVID-19 as a fifth member of this spectrum of inflammatory conditions.

1. Introduction

The umbrella term "*hyperferritinemic syndromes*" encompasses four clinical conditions, including macrophage activation syndrome (MAS), adult-onset Still's disease (AOSD), catastrophic anti-phospholipid syndrome (CAPS), and septic shock, all characterized by high serum ferritin and a life-threatening hyper-inflammation sustained by a cytokines storm which eventually leads to multi-organ failure [1]. In March 2020, the World Health Organization declared COVID-19, the disease-associated to the novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak, a pandemic. A significant amount of COVID-19 patients is currently experiencing severe interstitial pneumonia possibly ending up with acute respiratory distress syndrome (ARDS) and systemic inflammatory response syndrome (SIRS). This severe form of COVID-19 shares several clinical and laboratory features with the four entities mentioned above and currently included in the definition of "*hyperferritinemic syndromes*" [2]. This concept may guide and support therapeutic choices as all these entities respond to a similar approach consisting of anti-inflammatory and immunomodulatory agents such as glucocorticoids, IVIg, cyclosporin, IL-1 and IL-6 inhibition [1,2]. Plasmapheresis or IL-18 blockade may be considered as well [1,3]. Some preliminary results confirm the beneficial effects of Tocilizumab in COVID-19 [4] and current recommendations [5] advocate its use in those patients evolving toward the most severe stage of illness characterized by an extra-pulmonary systemic hyper-inflammation [6].

The idea of a third later stage of COVID-19 as the dramatic result of an overwhelming cytokine storm [7] is strengthened by the observation of the increased level of different molecules including IL-1β, IL-1RA, IL-7, IL-8, IL-9, IL-10, fibroblast growth factor (FGF), granulocyte-macrophage colony-stimulating factor (GM-CSF), IFNγ, granulocyte-colony stimulating factor (G-CSF), interferon-γ-inducible protein (IP10), monocyte chemoattractant protein (MCP1), macrophage inflammatory protein 1 alpha (MIP1A), platelet-derived growth factor (PDGF), tumor necrosis factor (TNFα) and vascular endothelial growth factor (VEGF) [8,9]. Especially in severe cases, IL-2, IL-7, IL-10, G-CSF, IP10, MCP1, MIP1A, and TNFα seem to be extremely high [8,9] and significant elevation of IL-6 in non-survival patients has been described [10].

2. Clinical, laboratory and autoptic similarities: COVID-19 *vs* hyperferritinemic syndromes

The main clinical and laboratory features characterizing patients with hyperferritinemic syndromes are described in Table 1 and compared with COVID-19 severe manifestations. As already mentioned, in addition to cytokine profile, other features make COVID-19 similar to the members of the hyperferritinemic syndromes, at least in some of their stages: lymphopenia, reduced NK number and activity, abnormal

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Table 1
Clinical and laboratory abnormalities of «hyperferritinemic syndromes» and patients with COVID-19 severe infection (modified from Rosario C. et al. [1]).

	Severe COVID-19 *	Septic shock	AOSD	MAS	CAPS
Hyperferritinemia	+ +	+ +	+ + +	+ + +	+ +
Ferritin range (ng/ml)	> 300 (300–5000)	> 300 (300–5000)	> 300 (even > 5000)	> 300 (even > 10,000)	> 300 (300–5000)
Hypercytokemia	+ + +	+ + +	+ + +	+ + +	+ + +
Infection as trigger	+ + +	+ + +	+ +	+ +	+ +
Fever	+ + +	+ + +	+ + +	+ + +	+ +
Multi organ involvement	+ + +	+ + +	+ + +	+ + +	+ + +
ARDS	+ + +	+	+	+	+
Hepatomegaly	NR	rare	+ +	+ +	NR
Splenomegaly	NR	rare	+ +	+ +	NR
Hemophagocytosis	NR	+	+	+ + +	NR
Trombocytopenia	+/−	+	−	+	+
Anaemia	+	+	+	+	+
Leukopenia	+ +	+	−	+ +	NR
Low/absent NK activity	+	+	+	+	NR
Sol IL-2R > 2400 U/ml	+	+	+	+	NR
Hyper TG	NR	+	−	+ +	NR
Abnormal Liver function	+ +	+ +	+ +	+ +	+ +
Coagulopathy	+ +	+ +	+	+ +	+ + +
ESR/CRP (↓↑)	+ + + (↑ESR ↑CRP)	+ + + (↑ESR ↑CRP)	+ + + (↑ESR ↑CRP)	+ + (↓ESR ↑CRP)	+ + (↑ESR ↑CRP)

Legend: * [54,65–67]; ARDS = acute respiratory distress syndrome; NK = natural killer; Sol IL-1R = soluble interleukin-2 receptor; TG = triglycerides; ESR = erythrocytes sedimentation rate; CRP = C-reactive protein.

liver function tests, coagulopathy and of course hyperferritinemia [1,11].

Hyperferritinemia is the hallmark of the "*hyperferritinemic syndromes*" and along the last decade, increasing evidence supports the idea that high circulating ferritin may not only reflect an acute phase response but also play a critical role in inflammation [12]. Ferritin is a major intracellular iron storage protein and the ratio between its two subunits, H and L, may differ depending on tissue type and physiologic status of the cell [13]. H-ferritin seems to display not only an immunomodulatory function [14,15] but also a pro-inflammatory activity culminating with the induction of the expression of different inflammatory mediators, including IL-1β [16]. Hyperferritinaemia characterizes several autoimmune diseases [17] where it may play a pathogenetic role on the ground of its immunomodulatory properties [12]. The origin of circulating serum ferritin during inflammatory conditions is still debated. *In vitro* experiments demonstrated that ferritin might be actively secreted by hepatocytes [18] as well as by macrophages through a non-classical pathway [19]. Thus, it is likely that in "*hyperferritinemic syndromes*" macrophage activation could actively contribute to ferritin production. In line with this hypothesis, in a previous study, we demonstrated that in AOSD ferritin serum levels are not only correlated with disease activity, but also with macrophage activation [20]. Interestingly, in a very recent study describing a cohort of 39 hospitalized patients with COVID-19, ferritin serum levels were found significantly correlated with disease severity [21]. Besides an active secretion, during the inflammatory reaction, a major component of serum ferritin derives by cellular death and, in particular, by hepatic cells death. Once released, ferritin loses part of the inner iron content giving rise to extremely high serum levels of "free iron" [22]. It seems that the excess of circulating "free iron" detectable during severe inflammatory conditions, can deteriorate the inflammatory reaction with the particular ability to induce a marked pro-coagulant state [22]. This capacity is related to changes in the morphology of red blood cells and fibrin induced by "free iron" able itself to favor the production of hydroxyl radical [22]. Oxidative stress on red blood cells and fibrin can induce the production of dense clots responsible for stroke development [23]. Due to the capacity of iron chelation to taper the inflammatory response through a reduction of ROS production and to promote an anti-viral activity, the utility of this therapeutic approach in patients with SARS-CoV-2 infection has been recently addressed [24]. A clinical trial on the use of Desferal (Deferoxamine, a medication able to bind iron in case of "iron overdose") is currently ongoing in IRAN in patients with mild to severe COVID-19 infection (NCT04333550).

Coagulopathy is one of the main complications occurring in hospitalized patients with severe COVID-19. Despite prophylaxis with low molecular weight heparin, the occurrence of cardiovascular stroke is extremely high, in some cases in the form of a diffused intravascular coagulopathy (DIC). In a Chinese cohort from Wuhan, DIC occurred in about 6.4% of patients who died (n = 109) for severe COVID-19 [25]. Acro-ischemia is one of the most frequent presentations of this complication being associated with a significant rate of death [26]. Intrestingly, DIC is also a major complication the other hyperferritinemic syndromes including AOSD [27], MAS [28], sepsis [29] and, of course, CAPS. Inflammation induces increased coagulation by two different effects: by activating the cascade coagulation system and by down-regulating the anti-coagulant mechanisms [29]. The endothelial cell and platelet activation occurring in CAPS is a key contributor to the genesis of a "thrombotic storm" [30] and in this setting, it is remarkable the role of infections as triggers of the disease [31]. It is of note that three Chinese COVID-19 patients admitted to ICU and presenting thrombotic events tested positive for anticardiolipin IgA antibodies as well as anti–β2 glycoprotein I IgA and IgG antibodies [32].

However, as noted by Mc Gonagle D and coll, the increased vascular coagulation occurring in COVID-19 patients is more close to a lung centric pulmonary intravascular coagulopathy (PIC) rather than a classical DIC [33]. This peculiar presentation seems related to a MAS-like intra-pulmonary inflammation. Indeed, although severe COVID-19 has several abnormal laboratory parameters similar to MAS, the lack of other features, such as the classical organomegaly, is remarkable, leading to suppose a hyper-activation of the immune system mainly confined to the lung parenchyma [33].

Further similarities between "hyperferritinemic syndromes" and SARS-CoV-2 severe infection are revealed from the few autopsies on COVID-19 patients reported so far. Macroscopic features in autopsies include pleurisy, pericarditis, lung consolidation, pulmonary edema [34]; microscopic findings include diffuse alveolar damage with inflammatory infiltrates composed mainly by monocytes and macrophages, but minimal lymphocytes infiltration, and multinucleated giant cells alongside large atypical pneumocytes [11,35]. Cardiac involvement in the form of myocarditis has been also described [36]. Similarly, pleurisy, pericarditis and myocarditis have been largely described in patients with AOSD and MAS [37,38]. Some recommendations and guidelines to safely perform autopsies in COVID-19 patients have been published [39] but the literature on this aspect is still poor even if

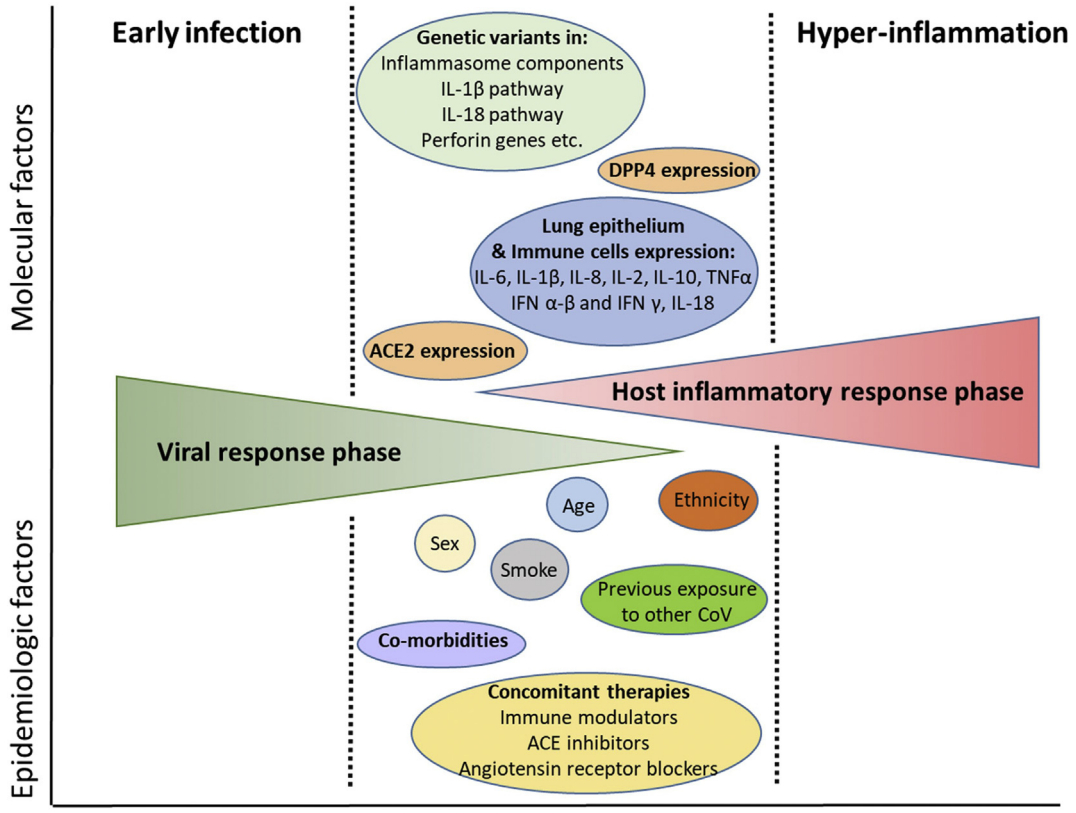

Fig. 1. Molecular and epigenetic factors possibly able to contribute to the evolution of COVID-19 infection toward an exaggerated inflammatory response. Figure modified from Siddiqi HK et al. [7].

pathological aspects are of utmost importance to better understand the extent and type of damage associated with this infection and its possible pathogenesis.

3. Molecular and epigenetic factors implicated in COVID-19 induced systemic inflammation

Why some patients with SARS-CoV-2 infection evolve to a hyper-inflammation state with such a dramatic course while others seem to respond to treatment, is still unknown. The severity of its evolution does not seem exclusively ascribable to viral factors, but probably to host features including different epidemiologic and molecular factors (Fig. 1). Among them, the presence of an age and sex preference is evident with a higher occurrence of severe inflammation especially in elderlies and men [40]. The different lung expression of the ACE2 molecule, the receptor used by COVID-19 to enter cells, could be one of the reasons responsible for a higher prevalence of the severe disease in this specific subset of patients [41]. Accordingly, specific therapies modulating the expression of this receptor such as ACE inhibitors or angiotensin receptor blockers could be considered an additional external factor providing a major risk for patients. Co-morbidities represent an ulterior risk factor for the development of severe COVID-19 systemic inflammation and among them, type II Diabetes is one of the mostly described. To this regard, the increased expression of another receptor named human dipeptidyl peptidase 4 (DPP4), highly expressed in patients with type II Diabetes, might be implicated in the worst disease outcome do to the possible ability of SARS-CoV-2 to infect cells through DPP4 binding, as already described in MERS-CoV infection [42].

Despite the lack of specific data on COVID-19, ethnicity might also have some impact on virus infection outcome. At birth, differences in innate immune response between Caucasian and Asian people have been identified [43]. Macrophages derived from healthy Filipinos and challenged with M. Tuberculosis, demonstrate a lower production of IL-1 and IL-6 as well as higher production of IL-8, compared to Chinese and non-Hispanic white people [44]. Additionally, studies on PBMC from children vaccinated for measles showed race-related variation in the amount of cytokine produced following stimulation [45].

Another fascinating hypothesis supporting the differences in COVID-19 infection outcome is an antibody-dependent enhancement of SARS-CoV2 due to previous exposure to other coronavirus [46]. Indeed, previous contact with other coronaviruses responsible for a boost in immune response before COVID-19 infection could be accountable for the differences in disease severity observed among people.

What is sure right now is that for reasons that still need to be clarified, in some COVID-19 patients there is an over-inflammatory reaction, which strictly reminds the one observed in other inflammatory conditions, such as AOSD, which is a prototype of idiopathic autoinflammatory disorder frequently triggered by infections [47]. Due to similarities with this condition, a genetic predisposition cannot be excluded as well. In AOSD, the presence of rare coding variants in IL-1 related pathways [48] and gene polymorphism associated with IL-18 [49] have been identified. At the same extent, heterozygous mutations related to PRF1 and UNC13D genes, have been linked to a specific subset of MAS patients [50].

Besides genetic factors, the modulation of the expression of different cytokines both by lung epithelial cells and by innate and adaptive immune cells needs to be taken into account. Regarding IL-1β, it is important to remind that previous studies on SARS-CoV demonstrated the ability of the virus to up-regulate inflammasome activity with consequent capacity to actively increase the production of IL-1β [51]. Due to the similarities between SARS-CoV and SARS-CoV-2 (82% nucleotide sequence homology), it is likely that SARS-CoV-2 displays the same capacity to induce an exaggerated IL-1β mediated response. Thus, the link between COVID-19 induced inflammatory reaction and hyperferritinemic syndromes, such as AOSD or MAS, is immediately

evident being both related to a massive IL-1β systemic release. During MAS, it is also important to remind the role of type II interferon (IFN), which is a crucial mediator of the inflammatory response and whose neutralization looks promising [52]. In this regard, although it is known that type I IFN represents the main anti-viral pathway, studies on SARS-CoV revealed that both type I and type II IFN (alpha-beta and gamma) synergize to inhibit virus replication with a concomitant active virus attempt to reduce such IFN production [53]. Preliminary data from COVID-19 patients suggest how a suppressed IFNγ production by CD4 + T cells is associated with more severe disease [54]. Nonetheless, in the advanced stages of the disease, an over-expression of this molecule may occur, due to a second "wave" of systemic inflammatory reaction similar to MAS. For this reason, a clinical trial evaluating the efficacy of concomitant inhibition of IL-1 (Anakinra) and IFNγ (emapalumab) in severe COVID-19 patients has just started (NCT04324021). However, in patients with COVID-19, a clear distinction between ARDS and MAS is challenging, especially in the first phases of the disease where ARDS represents the main source of IL-6 and IL-1 [33]. Results from Anakinra/Emapalumab trial will surely provide interesting insights on COVID-19 associated "MAS like-syndrome".

Besides IL-1β, the majority of studies published up to now suggests a predominant role of IL-6 in severe COVID-19 inflammatory reaction. In patients with ARDS, the lung epithelium and immune cell hyper-expression of IL-6 is associated with a poor disease outcome [55], as confirmed by a recent study on COVID-19 patients [56]. However, IL-6 is also a crucial regulator of the balance among fibroblasts, macrophages, and epithelial lung cells and is able to participate in the resolution of inflammation [57]. Thus, a prolonged therapeutic blockade of this cytokine and the exact timing to do that needs to be carefully considered [33].

Finally, regarding other epidemiological factors possibly able to influence disease outcome, the use of concomitant immune modulating/immune-suppressive therapies is certainly critical [58]. Interestingly, preliminary observations point out that immunosuppressed heart- transplanted patients present a milder form of COVID-19 during the later stages when the clinical evolution is mediated by the host inflammatory response [59,60]. At the moment, the Italian Society of Rheumatology has organized a national registry to gather information regarding patients with immune-rheumatologic disease infected by SARS-CoV-2 and the European League Against Rheumatism (EULAR) has proposed a similar registry too. Very preliminary results on a large cohort of Italian patients with chronic arthritis treated with immunosuppressive agents (biologic and targeted synthetic DMARDs), showed no increased risk of respiratory or life-threatening complication from SARS-CoV-2 infection. Despite the limited follow-up and the small number of cases that do not allow to draw any conclusion, the results could suggest a possible benefit of immune suppression in these patients, possibly preventing the onset of uncontrolled systemic inflammation [61]. Collection and further analysis of such information will be of great interest for the future.

4. Conclusions

In conclusion, we believe that COVID-19 systemic inflammation is part of the spectrum of hyerferritinemic syndromes. A common pathogenic background is probably underlying to these conditions supporting the use of therapies that target crucial inflammatory mediators. To date, several clinical trials evaluating the efficacy of IL-6 inhibition by Tocilizumab or Sarilumab, and IL-1 inhibition by Anakinra or Canakinmab are ongoing (Clinical trial.gov; EU Clinical Trial Registry; Chinese Clinical trial registry; Iranian Registry of Clinical trials). Response to these therapies, known to display a significant benefit especially in AOSD [62,63] and MAS [64], will further support the hypothesis of a strict pathogenic connection between "*hyperferritinemic syndromes*" and severe COVID-19.

Contributions of each author

R. Priori had the idea, organized and partly wrote the article, and reviewed it.

S. Colafrancesco critically reviewed the literature and wrote most of the article.

C. Alessandri and F. Conti discussed the topic, contributed to the review of the literature, reviewed the article.

Declaration of Competing Interest

The Authors have neither financial interests nor have received financial support or benefits from commercial sources for the work reported on in the manuscript, which could create a potential conflict of interest or the appearance of a conflict of interest with regard to the present work.

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