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Mini Review

Cytokine Storm: A Threatening Challenge for COVID-19 Infected Patients

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Abstract

Cytokine storm (CV) is result of uncontrolled emission of cytokines under stimulation of infective agent. In fatal COVID-19 infection is represented by acute respiratory distress syndrome (ARDS), pneumonia, hypercoagulation and multiorgan dysfunctions. The characteristics of CS are capillaries leakage, tissue edema, which result with organ failure and shock, associated with excessive immune response reaction which is triggered by activation of T-helper 1 reactions. Early detection of interleukin-6 (IL-6) in patients with COVID-19 infection is helpful for early prediction of illness severity. Extracorporeal blood ultrafiltration by hemofilter AN69ST (oXiris®) absorb IL-6, systemic hyperinflammation and coagulopathy and accelerate clinical recover of the COVID-19 patients.

Keywords: *SARS-CoV-2; Acute Respiratory Distress Syndrome (ARDS); Cytokine Storm (CV); COVID-19*

The first infection with the virus 2 (SARS-CoV-2) was reported in China, Wuhan, in December 2019. The infected patients with SARS-coV-2, showed symptoms of fever, dry cough and muscle soreness. 42% of them develop acute respiratory distress syndrome (ARDS) presenting by pneumonia and 61 - 81% of those requiring intensive care. The patients with rapid progression of ARDS and multiple organ failure results in death, rapidly.

The cytokine storm (CS) in fatal COVID-19 is represented by ARDS, coagulation, and multiorgan dysfunctions [1]. Uncontrolled production of cytokines leads to "cytokine storm" - a new term used to denote the uncontrolled release of cytokines under stimulation of infective agent. The lost control of cytokine emission, at local and systemic levels, is the basic mechanism of pathogenesis for CS.

The term CS was first used in scientific papers dating back to 1993 [3]. The use of this term in virus infection research began in 2000 in reports on cytomegalovirus, Epstein-Barr virus, influenza virus, variola virus and severe acute respiratory syndrome corona virus (SARS-CoV) [4]. CS can also occur in non-infectious diseases: in graft-versus-host reaction, multiple sclerosis, multiple organ dysfunction syndrome and pancreatitis [5-8]. This term has become very popular in 2005 in the context of avian H5N1 influenza virus infection [9], as evidenced by the great interest in it am the large number (350,000 hits) of Google searches which yielded more than 3,150,000 hits today. Multiple inflammatory cytokines as response of pathogenic stimulation were realized by innate immune system. These realized cytokines directly combat the virus and recruit additional fast immune responses [10]. The characteristics of CS are that it can often be uncontrolled and manifest with capillaries leakage, tissue edema, which result with organ failure and shock [11]. The cytokines are small proteins (5 - 20 kDa) that are secreted by cells to provide cell signaling and communication [11,12]. The main cytokines which participate in the CS are interferons and interleukins [13]. Chemokines control the cells migration of the immune system and contribute to both innate and adaptive immune system function and development [13-17]. Colony-stimulating factors (CSFs) increase the number of cytokine by increasing macrophages production at a site of inflammation. Chronic inflammatory disease, autoimmune disease and CS develop by excess of Tumor necrosis factors (TNFs) production [15,16].

The CS syndrome is associated with abnormal overreacted reaction of COVID-19 infection with excessive immune response reaction which is triggered by activation of T-helper 1 reactions. This mechanism releases too much proinflammatory cytokines (especially interleukine-6) into circulation. The degree of science today does not yet have an idea and suggestions when this CS begins and what its signs are [18].

Lymphopenia (< 1.0×10^9/L,) is the first predicate sign for the CS [19]. In that case, additional laboratory tests are required: D - dimer, lactate dehydrogenase (LDH), ferritin, C-reactive protein and interleukin - 6 (IL-6). Poor prognosis at an early stage of the disease is recognizable by the elevation/reduction of below mentioned biomarkers: reduced lymphocytes, elevated D-dimer (> 1000 ng/mL), elevated LDH (> 300 IU/mL), elevated ferritin (> 500 ng/mL) and CRP elevation (> 10 mg/L) are crucial makers for definition of Cytokine Storm Score [19,20]. Cytokine network with its flagship IL-6 plays a crucial role as a trigger of inflammation [20]. Increased level of IL-6 and other cytokines lead to T-cell depletion, massive pulmonary inflammation with extensive bronchopneumonia. It counts IL-6 as the stronger predictor of disease severity. The realized cytokine have an important role in the pathogenesis of viral infection [21]. This suggests and imposes it as an imperative to check the blood level of IL-6 a routine blood analysis in patients with COVID-19 infection, with sole purpose of early prediction of illness severity.

Elevated level of the IL-6 increase the likelihood of Covid-19 infection with these mechanisms: need of cathepsin to infect pulmonary epithelial cells, with help of cathepsin L production unregulated by IL-6. This interleukin also likely up regulates expression of the angiotensin converting 2 receptors which the virus utilizes for entry in the cells [23-25]. Silberstein (2020) found strong correlation between the number of deaths and the level of the interleukins in COVID-19 patients [26]. Thrombogenic impact of IL-6 is another factor in increasing of mortality from the virus [23,24]. Vitamin D modulates interleukins, because of that; there is evidence that its deficiency correlated with increased risk of fatal outcome [26].

The cycle induced by interleukin-6 interaction with macrophages and pulmonary epithelium is showed on figure 1.

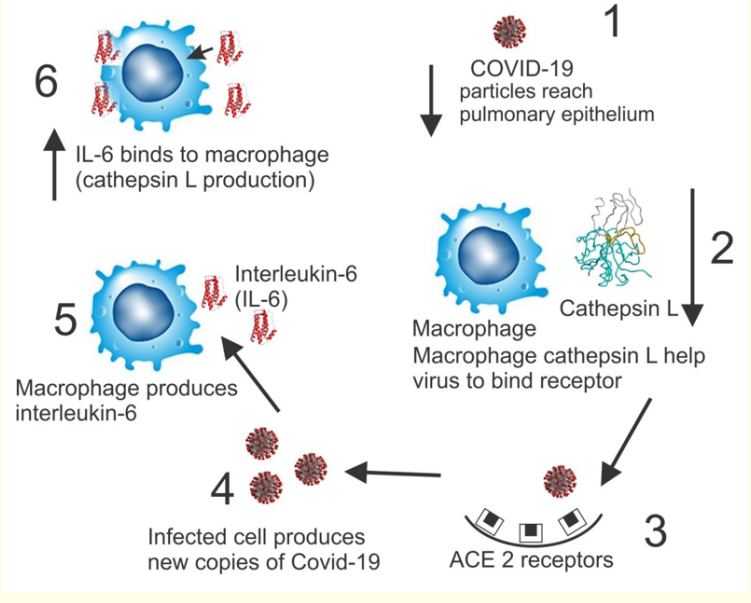

Figure 1: *Cycle induced by interleukin-6 interaction with macrophages and pulmonary epithelium induction of macrophage cathepsin L [step 5].*

Ugurov., *et al*. (2020) describe their clinical experience of extracorporeal blood purification applied on 35 COVID-19 patients using the AN69ST (oXiris®) Hemofilter which has three-fold bigger affinity for both endotoxins and cytokines. They monitored the level of COVID-19 associated biomarkers: interleukins (IL-6, IL-8), TNFs, D-dimers, C-reactive protein (CRP), ferritin and fibrinogen. After ultrafiltration they confirmed of clinical improvement and normalization of thrombocytes and leukocytes, IL-6 (< 50 ng/mL) and decrease of CRP and fibrinogen. They found that extracorporeal blood ultrafiltration by hemofilter which absorb cytokine and that continuous systemic heparin reduced hyperinflammation. These procedures reduce coagulopathy and accelerate clinical recovery [27].

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