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Cytokine storm as a predictor of covid-19 infection prognosis

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Abstract

The role of the immune system is to protect the host from exogenous and endogenous pathogens. Usually, pro- and anti-inflammation mechanisms are regulated to counter the infectious event. A pro-inflammatory mechanism controls the initial phase; however, anti-inflammation should be initiated early to maintain equilibrium and to achieve tissue repair processes. Many pathogens, malignant cells, autoimmune diseases as well as genetic changes can disturb this equilibrium and result in an excessive release of cytokines. In its severe form, this is referred to as cytokine storm. This results in positive feedback mechanisms and activation of immune cells resulting in hyper inflammation which can lead to life-threatening conditions. In patients with severe COVID-19, multiple organ dysfunction syndrome (MODS), and mortality can be a result of cytokine storm. High levels of pro-inflammatory cytokines, as interleukin-1 (IL-1), IL-2, IL-6, interferon (IFN) γ and IL-10 and so on, have been found in patients with severe COVID-19. Here, we review the involvements of the inflammatory cytokines in SARS-CoV-2 infection and their roles in triggering cytokine storm, which help to explain the pathogenesis of severe COVID-19. This will help to develop an effective therapeutic intervention, such as neutralizing antibody for certain cytokines or inhibition of some inflammatory pathways.

Keywords: Cytokine storm, Covid-19 infection, Hyper inflammation.

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1. Introduction

Cytokines are a broad category of small proteins which are important in cell signaling. Cytokines are formed of peptides which cannot cross the lipid bilayer of cells, so they cannot enter the cytoplasm. Cytokines are involved in autocrine, paracrine as well as endocrine signaling as immune modulating agents [1]. Coronavirus Disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) rapidly spread in the whole world and was declared to be a pandemic in early 2020. COVID-19 affected people's mental and physical health. In May 18, 2021, 163 million infections were recorded, including 3.38 million deaths. SARS-CoV-2 invades the host by angiotensin converting enzyme 2 (ACE2) receptors which are broadly distributed on various tissues and immune cells [2]. The virus can result in a wide range of clinical manifestations which can be in mild forms such as fever, cough, and myalgia or moderate forms that require hospitalization (pneumonia and localized inflammation) or severe forms with fatal outcomes [3]. Severe or critical infection manifests as pneumonia, disseminated intravascular coagulation (DIC), acute respiratory distress syndrome (ARDS) and multi organ failure [4-8].

Several lines of evidence showed that immune pathological damage may result in the deterioration of COVID-19 patients [9]. Multiple studies have reported that high levels of pro-inflammatory cytokines are produced during COVID-19 infection, which linked the cytokine storm (CS) with the severe complications and poor prognosis in this infection [10-14]. CS is a life-threatening clinical condition in which the overproduction of pro inflammatory cytokines and excessive activation of immune cells results in complicated medical syndromes which ranges from a persistent fever, nonspecific muscle pain, and also hypotension, to DIC, ARDS, multi-organ failure, and death if treatment is not effective [15]. Therefore, the time of diagnosis and treatment of CS is life-saving. The term CS was used for the first time in 1993 in many inflammatory diseases such as autoimmune conditions, organ transplantation and, most recently, in COVID-19. However, the profile and the effect of CS in different situations can greatly vary. Precise diagnosis and treatment for CS in most of the conditions is important. Understanding the exact alterations and pathogenic roles of cytokines involved in the COVID-19 CS (COVID-CS) is thus extremely important for the development of accurate diagnosis and effective treatment [16].

2. A cytokine storm in COVID-19

Cytokine storm can be due to a number of infectious and noninfectious causes, especially respiratory viral infections such as H1N1 influenza, H5N1 influenza, SARS-CoV-1, and SARS-CoV-2and Para influenza virus. The viruses invade

lung epithelial cells as well as alveolar macrophages to produce the viral nucleic acid, which in turn stimulates the infected cells to release cytokines that activate macrophages, dendritic cells, and other cells [17]. Cytokine storm is a diverse set of conditions which can result in life threatening complications [18]. COVID-19 infection can trigger a cytokine storm in pulmonary tissue by hyper activation of the immune system and the inadequate and uncontrolled release of cytokine [19]. Cytokine storm is cause by release of proinflammatory cytokines such as IL (interleukin)-2, IL-6, IL-8 and TNF (tumor necrotic factor-α) causing unwanted hyper immune response. This pathologic immune response leads to acute lung injury as well as acute respiratory distress syndrome (ARDS) [20]. Targeting cytokine storm in treatment plan can help in achieving a better outcome in Covid-19infections.

3. Cytokine storm

The term cytokine storm was described for the first time in the published medical literature by James Ferrara in 1993 during a discussion about graft versus host disease, a condition in which the role of excessive cytokine release was under discussion for many years [21]. It was believed that cytokine storms were responsible for the large number of healthy young adult deaths that occurred during the 1918 influenza pandemic, which killed about 50 million people worldwide. In this condition, a healthy immune system could have been a liability rather than being an asset [22]. Human deaths due to the bird flu H5N1 involve cytokine storms as well [23].

4.Pathophysiology of cytokine storm in Covid-19 patients

Inflammation is the way that organisms can defeat invasive pathogens and initiate repairing injured tissue. A balanced inflammatory response is achieved by diverse mechanisms and needs action of both pro- as well as anti-inflammatory pathways in the innate and the acquired immune systems. The immune system is able to recognize and counteract unknown pathogens by initiating different protective pathways. After successful defense and healing, the immune system can return to a state of homeostasis and apply a wait-and-see role. This is achieved by complex mechanisms which are controlled and balanced by different activating and inhibitory feedback loops. Cytokines play a major role in these control mechanisms through regulating the immune response, which they can not only amplify, but also dissolve. Also, their comparatively short biological half-lives are important to prevent remote effects away from the inflammatory foci. In case of disseminated infections, increased levels of the circulating cytokines may also occur and this is generally considered pathological. However, this systemic effect can lead to collateral damage to many vital organ systems. Many pro and anti-inflammatory factors are involved in the dysregulated inflammatory response, as in CS. In addition to cytokines, the complement and coagulation systems, cellular responses which are mediated by, e.g., monocytes, macrophages, neutrophils and NK cells also play a role [24].

5. Clinical symptoms of cytokine storm in Covid-19 patients include

The cytokine storm symptoms are variable and might include:

- Fevers with chills.
- Fatigue.
- Swelling of both extremities.
- Nausea and vomiting.
- Muscle and joint pain.
- Headache.
- Rash.
- Cough.
- Dyspnea.
- Seizures.
- Difficulty in coordinating movements.
- Confusion and hallucination.
- Lethargy with poor responsiveness [25].

Cytokine storm diagnosis in Covid-19 patients is achieved by the underlying medical condition when diagnosing cytokine storm, a person might need to be diagnosed with:

- A genetic disorder.
- An autoimmune disease.
- An infectious disease, as Covid-19.

Depending on the underlying condition, this might require different kinds of medical tests, accurate medical history and physical examination to provide diagnostic points. This is important because cytokine storm can affect many different systems of the body. Also, Laboratory abnormalities are also seen in basic blood tests and can provide clues. People with cytokine storm might show abnormalities as:

- Decreased number of immune cells.
- Elevation in biomarkers of kidney or liver enzymes like (ALT &AST).
- Elevation in inflammatory markers like c-reactive protein (CRP).
- Abnormalities in the markers of blood clotting [26].
- Elevated ferritin level (involved in infection response) [27].

6. Cytokine storm treatment in Covid-19 patients

Supportive care has a critical role in the treatment of cytokine storm. If an individual is experiencing severe symptoms as difficulty in breathing, they may need admission to an intensive care unit. This includes support as follows:

- Intensive monitoring of the vital signs.
- Mechanical Ventilation support.
- Fluid intravenously.
- Management of electrolyte imbalance.
- Hemodialysis.

In some situations, it might be possible to treat the underlying cause of the cytokine storm. Example if the cytokine storm is due to bacterial infections, the antibiotics may be helpful [28].

4. Conclusions

The cytokine storm in Covid -19 infection can lead to deleterious clinical manifestations or even mortality in critically ill patients. It also may cause damage of organs, impaired acquired immune responses and inadequate inflammatory innate responses. Early control and management of the cytokine storm through therapies, such as immune modulators and cytokine antagonists, is important to improve the survival rate of the patients.

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