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Impact of cytokine storm in covid-19 patients & treatment methods

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ABSTRACT

The new coronavirus can harm the heart, kidneys, liver, and other organs, and 14 to 30 percent of COVID-19 patients in Wuhan have lost renal function, necessitating dialysis or kidney transplants. The new coronavirus infects people by targeting the ACE2 receptor on lung cells, which causes cytokine storms that harm human lungs, causing hyper inflammation and driving immune cells to kill healthy cells. This is why certain COVID-19 patients require specialized treatment. The liver produces proteins that protect the body from infections as a result of the inflammatory chemicals generated by COVID-19 infection. These proteins, on the other hand, can cause blood clotting, which can clog blood arteries in the heart and other organs, depriving the organs of oxygen and nutrition, leading to multiorgan failure and, eventually, acute lung damage, acute respiratory distress syndrome, and death. The effects of cytokine storm on bodily organs and management of cytokine storm in COVID-19 patients will be discussed in this review.

Keywords: Cytokine storm, Coronavirus, ACE2 receptor, hyper inflammation

INTRODUCTION

The phrase "cytokine storm," also known as hypercytokinemia, was originally used in a 1993 study about graft-versus-host disease. However, since the year 2000, cytokine storms have been linked to a variety of infectious illnesses, therefore this word is now most usually used to characterize an immune system's unrestrained inflammatory response. Acute inflammation is characterized by five distinct symptoms: rubor, or redness, tumour, or swelling, calor, or heat, dolor, or pain, and functio laesa, which means "loss of function" in Latin.

Increased blood flow will often accompany these symptoms, allowing plasma proteins and leukocytes to reach the sites of injury, regardless of where the inflammation is happening. While this cellular response is beneficial for the host's defence against bacterial infections, it frequently comes at the price of local organ function. A cytokine storm can develop in addition to the typical reaction to inflammation. Various inflammatory cytokines are generated at a considerably faster rate than normal during a cytokine storm. Positive feedback on other immune cells occurs as a result of the overproduction of cytokines, allowing additional immune cells to be drawn to the site of injury, potentially leading to organ damage. Acute respiratory distress syndrome (ARDS), which has caused a considerable number of deaths from SARS-CoV-2, is one of the most well-known clinical disorders linked to cytokine storms.[1-5]

Cytokine Storm in Covid-19

SARS-CoV-2 causes Covid-19, which causes a wide range of symptoms from moderate tiredness to life-

threatening pneumonia, cytokine storm, and multiorgan failure. Cytokine storm has also been documented in SARS patients, and it has been linked to poor outcomes. [6]While the mechanisms of lung injury and multiorgan failure in Covid-19 are still being investigated, reports of hemophagocytosis and elevated cytokine levels — as well as the beneficial effects of immunosuppressive agents — in affected patients, particularly the most severely ill, suggest that cytokine storm may play a role in Covid-19 pathogenesis. [7, 8] Serum cytokine levels that are elevated in patients with Covid-19–associated cytokine storm include interleukin-1β, interleukin-6, IP-10, TNF, interferon-γ, macrophage inflammatory protein (MIP) 1α and 1β, and VEGF. [9, 10] Higher interleukin-6 levels are strongly associated with shorter survival.[11]In Covid-19, the relative frequencies of circulating activated CD4+ and CD8+ T lymphocytes, as well as plasmablasts, are higher.[12]In addition to heightened systemic cytokine levels and activated immune cells, Covid-19 exhibits a number of clinical and laboratory problems, including high CRP and d-dimer levels, hypoalbuminemia, renal failure, and effusions, as seen in cytokine storm diseases. In Covid-19, data from laboratory tests indicating hyper inflammation and tissue damage were observed to predict deteriorating outcomes. [13]

Although immunologic dysregulation has been found in severe Covid-19 cases, it is unclear if this is due to immunological hyperactivity, a failure to resolve the inflammatory response due to continued viral replication, or immunological dysregulation. The relationship between nasopharyngeal viral load and cytokine levels (e.g., interferon-, interferon-, and TNF), as well as a decline in viral load in moderate but not severe cases, shows that the immune response is favourably related to viral burden. In contrast, the discovery of type I interferon immunity inborn defects and autoantibodies against type I interferons in the most severe instances of Covid-19 suggests that an insufficient antiviral response may be a contributing factor in certain Covid-19 patients. [14, 15] Between asymptomatic patients (who have effective control of SARS-CoV-2) and patients with severe Covid-19 (who are unable to control the virus), host immune responses and immune-related symptoms are extremely variable; suggesting that host immune dysregulation may play a role in pathogenesis in some cases. Another theory is that autoimmunity is caused by molecular mimicry between SARS-CoV-2 and a self-antigen, resulting in autoimmune. These mechanisms may be implicated in certain patient subgroups, such as children with post infection multisystem inflammatory syndrome, a condition that appears to be improved by immunomodulatory treatments like intravenous immune globulin, glucocorticoids, and anti–interleukin-1 and anti–interleukin-6 therapies. Because SARS-CoV-2 is no longer present, patients with multisystem inflammatory syndrome certainly satisfy the description of cytokine storm; however, it is uncertain whether the cytokine storm is a primary or secondary cause of Covid-19. Patients with SARS-CoV-2 infection can also be asymptomatic or have acute Covid-19 with varying degrees of severity, a chronic course of Covid-19, or multisystem inflammatory syndrome. The mechanisms that lead to the severe cytokine storm–like phenotype seen in a small percentage of individuals are a key topic. More severe cases of Covid-19 are connected with coexisting illnesses like as hypertension, diabetes, and obesity, potentially because to a preexisting chronic inflammatory state or a lower threshold for the development of organ dysfunction from the immunological response.

There are some major treatment distinctions between Covid-19–associated cytokine storm and many other cytokine storm illnesses. First, cytokine storm caused by SARS-CoV-2 infection may require different treatments than cytokine storm caused by other causes. Cytokines may be an important component of the cytokine storm as well as an important component of the antimicrobial response. As with influenza virus, inhibiting cytokine signaling may actually hinder SARS-CoV-2 clearance, raise the likelihood of subsequent infections, and result in poor outcomes.[16]Because interleukin-6 and other cytokines are possibly relevant for both a beneficial response to SARS-CoV-2 and a harmful cytokine storm, it's vital that the proper subgroups of Covid-19 patients are treated at the correct time. Despite good anecdotal reports, anti–interleukin-6 receptor antibody therapy did not demonstrate a survival advantage in hospitalized patients with Covid-19 in two large, randomized, controlled studies. [17, 18]

Second, changes in immune responses and processes behind the cytokine storm are most likely influenced by the primary location of infection and illness, which has consequences for therapy. In patients with HHV-8–associated multicentric Castleman's disease, for example, targeted eradication of the major viral reservoir is advantageous, but it is not achievable in individuals with Covid-19. Third, though lymphopenia is uncommon in cytokine storm illnesses, it is a defining feature of severe Covid-19. It is presently unknown whether the lymphopenia seen in Covid-19 is caused by tissue infiltration or lymphocyte destruction.

Fourth, whereas clotting problems can arise in any cytokine storm disease, thromboembolic events appear to be more common in Covid-19-associated cytokine storm. [19]Finally, while cytokine panels have not been measured across Covid-19–associated cytokine storm and other cytokine storm disorders on the same platform, preliminary results suggest that circulating levels of several cytokines, such as interleukin-6, as well as other inflammatory markers, such as ferritin, are less severely elevated in Covid-19 than in some of the other cytokine storm disorders. Inflammatory mediator levels in lung tissue after SARS-CoV-2 infection are unclear.

Despite the many unknowns, a recent randomised, controlled trial showing that dexamethasone reduces mortality in the most severe cases of Covid-19, defined by elevated CRP levels and the need for supplemental oxygen, while potentially worsening outcomes in milder cases, suggests that excessive, late-stage inflammation contributes to mortality. [18]A meta-analysis of seven randomized studies found that those treated with glucocorticoids had reduced 28-day all-cause mortality than those treated with standard care or placebo in critically sick patients with Covid-19. [20] Patients with Covid-19 had a strong response to glucocorticoids when their CRP level is high, but a poor reaction when their CRP level is low, according to an observational research. [21]Positive anecdotal findings of specific antagonists against interleukin-1, granulocyte–macrophage colony-stimulating factor, and JAK1 and JAK2 in patients with Covid-19 add to the growing body of evidence. [22 -25]Similarly, the finding that proinflammatory

agents like inhaled interferon have a positive effect if given early in the disease course fits with a model in which immunostimulation that boosts antiviral activity is beneficial early (but probably harmful later), whereas immunosuppression is beneficial late but harmful early. The timing of medication and the selection of subgroups of patients included in studies, as with dexamethasone, will almost certainly have an impact on results.

Hundreds of immunomodulatory medications are now being studied, despite the fact that the function of immunological dysregulation and cytokine storm in Covid-19 is uncertain. (22nd) Many of these therapies have also been used to treat other types of cytokine storms. Both canakinumab and anakinra, an anti–interleukin-1 monoclonal antibody, are being tested for Covid-19–induced ARDS. Acalabrutinib, a selective inhibitor of Bruton tyrosine kinase, which affects B-cell and macrophage communication and activation, might help Covid-19 reduce its hyper inflammatory response. [26]JAK1 and JAK2 inhibitors have the ability to decrease signaling downstream of type I interferon, interleukin-6 (and other gp130 family receptors), interferon-, and interleukin-2, among other cytokines, and are authorized for the treatment of a number of autoimmune and neoplastic disorders. [27]Inhibition of Bruton tyrosine kinase and JAK, like anti–interleukin-6 antibody treatment, might be harmful or ineffective if administered too soon, when the immune response to SARS-CoV-2 is crucial in limiting viral multiplication and clearance.

Treatment of cytokine storm in COVID-19

A key interval of 5-7 days exists between the time of COVID-19 diagnosis and the onset of multiple organ failure syndrome, according to recent studies (MODS). While roughly 80% of patients improve during this time period, roughly 20% of patients may develop severe pneumonia, and roughly 2% will perish to the infection. The cytokine storm in COVID-19 is being treated with a wide spectrum of anti-inflammatory treatments. Researchers have proposed that immunotherapy be taken at the time of cytokine storm diagnosis to directly lessen the negative effects that the cytokine storm can have on those who test positive for COVID-19. Neutralizing antibodies, which can be obtained from the plasma of patients who have previously survived COVID-19 infection, IFN inhibitors, oxidised phospholipid (OxPL) inhibitors, and sphingosine-1-phosphate receptors 1 (S1P1) antagonists are some of the immunotherapeutic strategies that have been proposed for this purpose. More clinical trials are needed to thoroughly assess these therapy alternatives' capacity to adequately block the cytokine storm generated by COVID-19. (5)

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