Case Study

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Creating Awareness of Deadly Cytokine Storm to Common People and A Self Case Study

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ABSTRACT: This review with case study covers the severity and hidden symptoms of cytokine storm that were missed in other articles. Most of the review studies focus on cytokine storm in a random way but this paper creates awareness to common people so that the intensity of the disease spreading can be minimized and fatality can be prevented. Cytokine storm is an umbrella term encompassing several disorders of immune disregulation. The symptoms, properties, mechanism and treatment methods for cytokine storm have been discussed along with preventive methods. Details about silent hypoxemia and its effects were also highlighted which are a major reason for not detecting this disease at early stages. This paper also describes a case of life-threatening cytokine storm caused by COVID-19 infection that was treated with clonal antibody and suppressed the cytokine release. This paper also highlights the importance of Vitamin D level in a body, which can suppress cytokines production by simultaneously boosting the innate immune system. Lesson learnt from this disease are elderly patients, especially males, with comorbidities, demonstrate increased susceptibility to poor prognosis or increased risk of severe condition or even fatality from COVID-19. Reports indicate that men appear to suffer more severe cases and die of the disease at greater rates than women, with deaths possibly up to 20 percent higher. This issue leads to future research and can work on the methods to increase the immunity of men to reach at least the immunity level of women so that fatality rate can be minimized. It has been concluded that if covid is left untreated, the cytokine starts releasing from the body and progress to extensive tissue damage, organ failure, and death.

Keywords: COVID-19, Cytokine Storm, SARS-CoV-2, Immune Disregulation, Hypoxemia

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I. INTRODUCTION

1.1 BACKGROUND OF STUDY

Cytokine storms are associated with a wide variety of infectious and noninfectious diseases. The term was popularized largely in the context of avian H5N1 influenza virus infection. Observations of some patients revealed that those who died of COVID-19 complications had higher serum levels of C-reactive protein (CRP), interleukin (IL)-6 and ferritin, suggesting an underlying hyperactive inflammatory process[1]. It occurs when large numbers of white blood cells are activated and release inflammatory cytokines, which in turn activate yet more white blood cells. A cytokine storm occurs when there is an excessive and uncontrolled release of pro-inflammatory cytokines. Another study showed that patients experiencing COVID-19-related cardiac injury with the elevated levels of troponin also demonstrated significantly higher CRP and procalcitonin levels and experienced increased morbidity and mortality[2]. It can result in acute respiratory distress syndrome (ARDS), multiple organ failure and death.

1.2 EARLY RESEARCH STUDY

Cytokine storms were seen in severe SARS and MERS patients in the past, and COVID-19 can have a similar cytokine profile. From a historical perspective, cytokine storm was previously referred to as an influenza-like syndrome that occurred after systemic infections such as sepsis and after immunotherapies such as Coley's toxins[3]. It is a condition in which a large amount of chemicals produced by the body's immune system is released into the bloodstream in a short time, creating an overabundance of these chemicals. The early recognition of storm and the prompt treatment can lead to better outcome. IL-1 receptor antagonist, which is used in treatment of rheumatoid arthritis, was proven helpful in a disease associated with severe cytokine storm[4].

1.3 LACK OF RESEARCH AND GAPS

Particular cutoffs of cytokines as biomarkers for disease processes have not been well studied, and this warrants to potentially improving diagnosis for diseases with inflammatory markers. The reason for all the deaths during the pandemic period is suspected to be by "cytokine storm" which has not been reached the people and lack of awareness leads to more number of deaths. Much attention on cytokine storm disease has not been shown because very few people were getting affected till 2019. Awareness and seriousness about this disease are not reached people because less research work is going on. This paper explored the efficacy and safety of potential treatments and their molecular mechanism. There is still lacking sufficient evidence supporting the regulation of cytokine expression may be beneficial to the mortality of COVID-19.

1.4 NEED OF THE STUDY AND NOVELTY

This study is need of an hour because the corona virus is highly contagious and infection results more number of deaths. Due to very uncertain data on the spread of the virus in the population, it is difficult to estimate the mortality rate. Even under maximum intensive care treatment, a very high mortality rate of approximately 80-100% was observed in this patient group. In humans, an infection with the virus can cause respiratory infections and even very severe pneumonia, which often ends fatally, especially in old and previously ill patients. Due to the novelty of the virus, the data basis for therapy is very limited. To correlate β data, there are no clinical data for an effective specific therapy and hence intensive care treatments for severe cases must concentrate only on supportive treatment of lung failure and other complications.

1.5 AIM AND OBJECTIVE

The aim of this paper is to study the cytokine storm response in SARS-CoV-2 and to explore the early treatment options for patients who are critically ill with the coronavirus disease (COVID-19) in the early stages of the disease by reviewing the literature. Our objective is to provide physicians with a conceptual framework, a unifying definition, and essential staging, assessment, and therapeutic tools to manage cytokine storm.

2 SYMPTOMS OF CYTOKINE STORM

It is characterized by constitutional symptoms, systemic inflammation, and multiorgan dysfunction that can lead to multiorgan failure if inadequately treated[5]. The major unnoticeable symptom is giddiness and unconsciousness for a long period with constant temperature for a long time. The primary symptoms of a cytokine storm are high fever, swelling and redness, extreme fatigue and nausea. In some cases, the immune reaction may be fatal. In severe cases of cytokine storm, renal failure, acute liver injury or cholestasis, and stress-related diseases can also develop[6]. In addition, patients may have fatigue, anorexia, headache, rash, diarrhea, arthralgia, myalgia and neuropsychiatric findings. If cytokine storm is due to covid -19 virus then symptoms like cough, tiredness and loss of taste or smell. Less common symptoms like sore throat, headache, aches and pains, diarrhea, a rash on skin, or discoloration of fingers or toes and red or irritated eyes. Serious symptoms like difficulty breathing or shortness of breath, loss of speech or mobility, or confusion and chest pain. Silent hypoxia is when a pulse oximetry check on a patient who does not appear to be short of breath, results in an oximetry finding lower than a physician would expect.

3 PROPERTIES AND MERITS OF CYTOKINES

Cytokines affect several processes in parallel and others can compensate the effects achieved by blocking one specific cytokine activity. The cytokine network is a balanced system and its alteration may lead to impaired immune response. Inhibition of regulatory cytokines can result in autoimmunity or tissue damage. The recombinant cytokines and antibodies have limited shelf half-life, require controlled storage conditions[7]. Cytokines are small proteins that are crucial in controlling the growth and activity of other immune system cells and blood cells. Cytokines enhance or suppress the production of other cytokines. Treatment that uses substances made by immune cells to help the body to fight against cancer, infection, or other diseases. Cytokines play an important role in the body's immune response. They can also be made in the laboratory to use as treatment for different diseases. This may be "good" when stimulating the immune system to fight a foreign pathogen or attack tumors. Other "good" cytokine effects include reduction of an immune response, for example interferon β reduction of neuron inflammation in patients with multiple sclerosis. Auto inflammatory diseases like hereditary inflammatory, improved beta cells function in type 2 diabetes,

remodeling following myocardial infarction, smoldering myeloma and a variety of other disorders[8.]

4   MECHANISM OF CYTOKINES

Cytokines are a broad and loose category of small proteins (~5–20 kDa) important in cell signaling. Cytokines are peptides and cannot cross the lipid bilayer of cells to enter the cytoplasm. Cytokines have been shown to be involved in autocrine, paracrine and endocrine signaling as immunomodulation agents. During infection, bacterial and viral such as bacterial lipopolysaccharide (LPS), cause the release of cytokines from immune cells. Many cell populations make Cytokines, but the predominant producers are helper T cells (Th) and macrophages. These cytokines can reach the brain by several routes.

5   INFLUENCE OF FOOD

Maintaining a correct nutrition status is crucial, especially in a period when the immune system might need to fight back[9].It may be hard to resist desserts, pastries, chocolate bars, sodas, even fruit juices. However, the processed sugars, sugar and high-fructose corn syrup, artificial Trans fats, vegetable and seed oils, refined carbohydrates, excessive alcohol and processed meat favors cytokines release. Natural immunosuppressant compounds, derived from plant sources are known to inhibit the production and release of pro-inflammatory cytokines and chemokines. Flax seeds and other rich sources of omega-3 fatty acids reduces cytokines. The enormous effects of garlic on the management of diseases have led to another misapprehension that garlic impedes the growth of the virus, similar to its action on bacteria[10].

6   TREATMENT METHODS

6.1   BLOOD PURIFICATION TREATMENT

The blood purification treatments currently used in clinic practice can remove inflammatory factors to a certain extent. Blood purification system including plasma exchange, adsorption, perfusion, blood/plasma filtration, etc., can remove inflammatory factors, and block the "cytokine storm", to reduce the damage of inflammatory response to the body[11]. Artificial liver transplantation method can eliminate inflammatory factors on a large scale. This technology has also been used to resist the cytokine storm of H7N9, and its application on COVID-19 has achieved certain efficacy[12].

6.2   MEDICINAL TREATMENT

In cancer, cytokine therapy may help the immune system kill cancer cells or keep them from growing[13]. The two main types of cytokines used to treat cancer are interleukins and interferons[14]. Anakinra, an antagonist of IL-1β, can be used to treat the cytokine storm caused by infection. It significantly improved the 28-day survival rate of patients with severe sepsis. Anakinra is also used in combination with other medications to treat rheumatoid arthritis. Tocilizumab, originally designed for rheumatoid arthritis, has already been used to calm such storms in patients receiving advanced immunotherapy treatment for cancer[15]. Glucocorticoids have a powerful anti-inflammatory effect; they were used non-empirically to treat lung inflammation during the SARS and MERS epidemics[16]. Natural immunosuppressant compounds, derived from plant sources like curcumin, luteolin, piperine and resveratrol are known to inhibit the production and release of pro-inflammatory cytokines. Vitamin D also had a beneficial effect on symptoms such as pain, depression, tension/anxiety, and sleeplessness and an overall improvement in vitality/energy levels [17]. Vitamin D (25-OH) test measures the level of Vitamin D (25-OH) in the blood, which is a useful indicator of osteoporosis, rickets and osteomalacia[18].

6.3   ONGOING TRIALS

Lopinavir and Ritonavir reduces body temperature and had viral detection negative faster. Some of the Side effects are nausea, diarrhea and hepatotoxicity. Remdesivir inhibits RNA-dependent RNA polymerase (RdRp), leading to an incomplete RNA transcription, with potential against many families of viruses. Favipiravir is also a blocker of RdRp, with in vitro benefit over oseltamivir-resistant influenza. *Umifenovir* impairs the viral fusion with the host cells by inhibition of clathrin-mediated endocytosis. It is used for treatment and prophylaxis of influenza[19]

7   SELF CASE STUDY- SUMMARY

R. Baskaran 50 years aged and have a background history of blood pressure with a body mass index of 30 Kg/m2. I had first dose of covid vaccination and do not even get any common effects like fever or body pain. After the prescribed duration, I had second dose of vaccine. During this gap between first and second vaccine, myself has got affected with covid virus, which I could not found out because no symptoms has been experienced. After I had second vaccine, I was suffering with high fever and severe body pain as all people facing after vaccine. I was thinking that these effects were due to vaccine and hence I was given paracetamol (dolo 650) for every 6 hrs. I was admitted 5 days after symptom onset of sore throat, 5 days of fever and cough, and 6 hours of half conscious. On admission, I was tachycardia (heart rate 114 bpm), feverish at 39.4°C and oxygen saturation was 88% on room air. My health slowly starts deteriorating and CRP, D –Dimer and ferritin values were erratic and cytokine started releasing. Blood tests showed a white cell count of 14.38×10^9/L, lymphocytes 1.72×10^9/L and C reactive protein (CRP) 128 mg/L and the average levels of markers shown were ferritin 1,395, D-dimer 5.11 and CT Chest has given the value of 23/25. Multiple logistic regression analysis determined that average CRP during the stay was the only predictor of survival. Major portion of my lungs of about 90 % got involved due to cytokine release from my body, which affects O_2 supply to major organs and leads to multiple organ failure. On day three of my admission, deteriorated with increasing oxygen requirements and my inflammatory markers continued to rise despite antibiotics. In mean time, group of doctors gave medications, which includes clonal antibody with constant supply of 40 liters of oxygen. By God's grace and wish along with doctor's efforts, my body had started responding to medications and cytokines has been stopped in several hours. Following commencement of antibody there was a noticeable reduction in oxygen requirements and, within 48 hours I had for the first time become afebrile and ferritin had significantly reduced and CRP to 88 mg/L. After 1-week course of medications, oxygen requirements were minimal with oxygen saturations of 80%. My blood parameters had also improved. On day 21 of my admission, having significantly improved including my chest X-ray. After 60 days, my health become normal after taking fibroids tablets and steroids with breathing exercises.

8   DISCUSSION

As of May 18, 2021, 163 million infections, including 3.38 million deaths, have been recorded (source: World Health Organization). Many patients of COVID-19 remain asymptomatic, some patients get pneumonia and 10% of cases require mechanical ventilation and ICU admission. Patients usually present with fever, dry cough, and shortness of breath, headache, malaise, muscle, and bony aches. Less common symptoms include sore throat, confusion, productive cough, hemoptysis, diarrhea, nausea, and chest pain[20]. Lymphopenia or lymphocyte count can be used as an indicator of severity of this cytokine storm. Vitamin D can suppress cytokine production by simultaneously boosting the innate immune system[21]. Persons who are likely to have deficient vitamin D levels at the time of COVID-19 testing were at substantially higher risk of testing positive for COVID-19 than were persons who were likely to have sufficient levels[22]. Adults with pre-existing cardiovascular diseases, respiratory diseases, endocrine diseases, diabetics, or immunocompromised adults remain the most exposed to serious complications of COVID-19[23]. Studies have indicated that the rapid clinical deterioration and high mortality risk in severe COVID-19 could be related to cytokine storm[24]

9   CONCLUSION

When covid left untreated, the cytokine starts releasing from
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the body and produces immunopathogenic damage that not only leads to ARDS in many cases but also can also further progress to extensive tissue damage, organ failure, and death. Treatment is required in either hospital or ordering medicines online[21] and quarantine at home based on the severity of the disease. Patients will reach an unconscious state, which is a primary symptom of this cytokine storm. Lymphopenia or lymphocyte count can be used as an indicator of severity of this cytokine storm. Inflammatory markers like CRP, Ferritin and D – Dimer values are elevated in COVID-19 infections and hence this has to be done before taking vaccination or if any symptoms of covid.

10   AUTHOR CONTRIBUTION STATEMENT

Dr.R.Baskaran manuscript preparation and wrote the main part and self-case study part of the manuscript. Ajay Rajasekaran has helped in evidence collection and wrote the parts of the manuscript with many professional suggestions. Dr.A.M. Nithiya has helped by giving constructive medical related discussions. Ms.A.M. Aparna has helped to revise the manuscript and done manuscript editing. All authors approved the final version of the manuscript.

11   CONFLICT OF INTEREST

Conflict of interest declared none

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