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Short Communication

Cytokine Storm in COVID- 19: A Thing to Worry About or Not?

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SHORT COMMUNICATION

The SARS CoV- 2 or severe acute respiratory syndrome coronavirus- 2 pandemic, originating in China, has still been a matter of deep concern across the globe. Although most of the cases of COVID- 19 or coronavirus disease- 2019 show recovery within few weeks, several other cases become severe depending on the immune system of an individual. Various drugs and vaccines which are under clinical run have created a buzz among health practitioners and scientists [1]. The severe cases of COVID- 19 have Acute Respiratory Distress Syndrome (ARDS) and multiple organ failure, which leads to the death of the patients [2]. The severity associated with COVID- 19 has been attributed to the Cytokine Storm (CS). This word was first coined for the syndrome that accompanied organ transplantation (graft versus host disease) [3]. These patients experience hyper-activated immune system and excessive release of cytokines in the blood. There is no widely accepted definition of this disorder as it is difficult to distinguish CS with other inflammatory disorders. This phenomenon leads to life threatening conditions hence it is of utmost importance to recognize and distinguish CS to carry out an appropriate diagnostic, prognostic and treatment procedure [4].

SARS CoV- 2, when it enters into the epithelial cell by interacting with angiotensin-converting enzyme receptor- 2 (ACE- 2), elicits a strong immune response and releases cytokines and weak interferons. Cytokines hence released, recruit CD14+ CD16+ monocytes, and activates the functioning of Th1 cells. These cells release more cytokine, which further triggers the release of Interleukin- 6 (IL- 6), Granulocyte-macrophage colony-stimulating factor (GM-CSF), and Tumor necrosis factor (TNF). In a positive feedback loop, these mediators further recruit monocytes, macrophages, and neutrophils. This process leads to cytokine storm or cytokine release syndrome (CRS) [5,6]. Severe COVID- 19 cases have been reported with high levels of IL- 6, IL- 1, IL- 2, IL- 7, IL- 10, IL- 17, Interferon-gamma induced protein- 10 (IP- 10), Monocyte chemoattractant protein 1 (MCP-1), Macrophage inflammatory protein-1 alpha(MIP-1α), GM-CSF,and TNF [7]. Of all the cytokines released in the CS/ CRS, IL- 6 plays a critical role and has been mentioned several times in various findings. IL- 6 is a cellular senescence marker [8]. [Figure 1]

There are several ways by which hyperactive immune response is attenuated. Anti- IL- 6, anti- GM- CSF, anti- TNF, Janus Kinase inhibitors, etc., are used for this purpose. Drugs like Tocilizumab and sarilumab target the IL- 6 receptor and inhibit the production of IL- 6; hence there is no further secretion of cytokines [5,7]. Intravenous administration of polyclonal antibody (plasma therapy) and use of polypeptide hormone for maturation of T cells are also in use. Certain drugs that inhibit JAK/ STAT pathway like ruxolitinib are also under study. JAK/ STAT pathway, upon activation, activates several cytokine signaling pathways [9]. Anakinra has been used to inhibit IL- 1 in rheumatoid arthritis and is now being used to suppress CS in COVID- 19 [10]. To reduce the recruitment of mononuclear macrophages, the CC chemokine receptor type- 2 (CCR- 2) is silenced by small interfering RNA or siRNA [11].

Low doses of corticosteroids like dexamethasone, which have shown a low mortality rate, are given for their immunosuppressive properties. NFKB is blocked by thalidomide. Natural killer cells obtained from healthy donors are also under study for CS. Also, the immunomodulatory property of Mesenchymal Stem Cells (MSCs) has been utilized to inhibit the abnormal activation of T lymphocytes and macrophages [11,12]. To restore the T cell functionality which has been lost due to CS, rapamycin, an m- TOR inhibitor, can be used [13]. Also, COVID- 19 specific T cells can be obtained and infused in patients, but in the very first place, characterization and recognition of such specific T cells are necessary. Immune checkpoints can also be targeted for reversing the T cell exhaustion [3].

Many studies have claimed that CS or CRS leads to T- cell apoptosis which causes reduced T lymphocyte count. Elderly and immunocompromised patients have fewer functional CD4+ T cells and a high number of senescent cytotoxic T cells (CD 8+ T cells) [13]. T cell depletion is marked by the expression of pre- apoptotic molecules like FAS and TRAIL. It is thus important to mitigate CS to reduce self-damage. Targeting the cytokines that are elevated in CS can help in reducing the effect of CS. Programmed cell death inhibitors can be used to delay T cell exhaustion. However, contradicting views of some studies mention the immunosuppressive role of drugs that interfere with the immune system fighting with the virus, but patients with severe symptoms who are the third stage of this disease need drugs that can pacify the cytokine storm and prevent the senescence of T cells. The role of T cells in fighting off the virus is well known; hence we need to protect them. Additionally, overwhelming infiltration of cytokines and immune cells causes lung tissue injury, and cy-

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tokines induce apoptosis of the lung epithelial cells [2]. Therefore, rather than relying on self-healing and merely taking Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), medications mentioned above should be deployed to make use of T cell's cytotoxic capability. By tackling CS, viral clearance can be achieved naturally.

In conclusion, the levels of cytokines are elevated in severe cases of COVID- 19 causing cytokine storm or cytokine release syndrome. T cell senescence and exhaustion in these patients is attributed to cytokine storm; relying on non-specific treatment strategies is a waste of time, and focus should be shifted to immunomodulatory therapies. By reducing the effects of cytokine storm, precious T cells can be rescued, and viral clearance can be achieved. Various strategies to handle the exaggerated secretion of cytokines in the blood have been mentioned in this as well as several other studies.

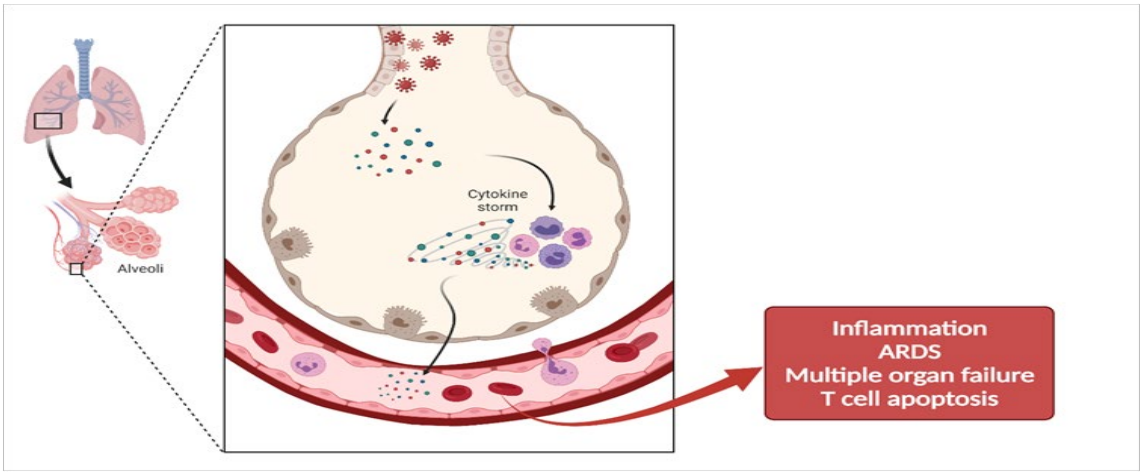

Figure 1: Mechanism of cytokine storm in coronavirus infection. SARS- CoV- 2 infects epithelial cells by its spike proteins and targeting the ACE- 2 receptors. This infection leads to activation and secretion of immune cells and cytokines, respectively. In a feedback loop, secretion of cytokine is elevated, and cytokine storm takes place, affecting the normal physiology and normal immune system of the body.

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