Short Communication

Cytokine Storm Syndrome – a Bird's Eye View

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Abstract

In COVID19 infection, the most dreaded complication that may cost life is 'Cytokine Storm Syndrome' (CSS) also called as 'Cytokine Release Syndrome". The term is new even for many medical professionals. There seems to be genetic predisposition to develop this complication. Cytokines seem to be double edged weapons depending on the time of infection and quantity of release. Knowledge on and recognition of CSS has become essential due to COVID pandemic affecting about 5% of infected. Being a newly emerged virus, researches are ongoing throughout world to find out its mutation behaviour, sensitivity to drugs and to invent an effective vaccine. Though we have enough knowledge on auto Immunity and hyper sensitivity disorders, significance of cytokines' functions and effects of dysregulation is vast and needs emphasis. Hence this article aims to provide a birds' eye view of CSS and its various aspects

Key words: Chemokines, COVID19 & Cytokine Storm Syndrome

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Introduction

With the Corona Virus (COVID 19) pandemic, the virus has spread all around the world. It is found to have high infectivity& might kill 3% of its host defying medical treatment. People are worried if they will be in the category of asymptomatic & mild symptoms (85%) or moderate to severe illness category recovering without the need for mechanical ventilation support (10%-15%) or requiring mechanical ventilation to survive to recover (2%) or die despite treatment with all possible medical management(3%-7%).The 5% of patients suffering severely seem to be affected by poor antiviral immunity initially resulting in failure to clear virus leading to high viral load with hyper responsiveness of immune system later leading to Cytokine Storm Syndrome(CSS). Though, mortality has been ascertained to be more with risk factors like obesity, uncontrolled hypertension & diabetes, immunodeficiency states due to iatrogenic factors such as immunosuppressive therapy for organ transplantation, autoimmune disorders, hypersensitivity & infective immunodeficiency conditions, chronic respiratory & cardiac problems,

there seems to be a genetically determined propensity to develop CSS. Thus, COVID19 has woven a painful suspense on our survival until it mutates to a less harmful virus or a new vaccine is being discovered.

The term "cytokine storm" by itself calls up vivid images of an immune system gone awry and an inflammatory response flaring out of control. The term has captured the attention of the public and the scientific community alike and is increasingly being used both in popular media and in scientific literature. However, while the general concept of an excessive or uncontrolled release of pro-inflammatory cytokines is well known, we may not have clear idea on the following,

- An actual definition of what constitutes a cytokine storm
- What are the conditions in which we shall expect a patient to develop cytokinestorm?
- Molecular events that precipitate a cytokine storm
- Why do a few only develop cytokinestorm?
- What are the therapeutic strategies that might be used to prevent the storm or quell it once it has started?

Cytokine Storm Syndrome (CSS) or Cytokine Release Syndrome are a group of disorders of massive Systemic Inflammatory Response Syndrome (SIRS), caused by the elaboration of extreme amounts of inflammatory mediators resulting from unchecked feed forward immune activation and amplification. The initiating factors leading to the end state of cytokine storm are heterogeneous and derive from genetic, autoimmune / inflammatory, iatrogenic and infectious causes with the final common result of overwhelming systemic inflammation, hemodynamic instability, multiple organ dysfunction, and potentially death. In some cases, persistent tissue damage without severe microbial infection in the lungs is also associated with a cytokine storm and clinical manifestations that mimic sepsis syndrome. It is the common end point of different initial insults. In COVID19 too it is due to viral sepsis with over activation of immune system.

Conditions that can lead to CSS

Infectious Diseases

- Viral Infections: Cytomegalovirus, Epstein-Barrvirus(hemophagocyticlymphohistiocytosis), H5N1 influenza virus infection, Variola & Ebola viruses, Severe Acute Respiratory Syndrome –CoronaVirus (SARS-CoV)
- Dengue
- Malaria
- Sepsis – Bacterial Group A streptococcus & others
- Fungal infections

Non-Infectious Diseases

- Allergens
- Multiple sclerosis
- Pancreatitis
- Juvenile Rheumatoid arthritis
- Multiple organ dysfunction syndrome

Therapeutic interventions

- Immune Suppressive Therapy - Anti CD28 monoclonal Ab to prevent chronic rejection of Renal Allograft leading to graft-versus-host disease
- Human or Humanized Antibody-based therapies such asrituximab[2],anti-thymocyte globulin (ATG)[1]
- Administration of non-protein-based cancer drugs
- Donor stem cell transplantation.

Cancers

- T Cell Leukemia& Lymphomas

The clinical presentations of CSS in all the conditions can be strikingly similar, creating diagnostic uncertainty. However, treatment of CSS in different conditions is not the same as their inciting inflammatory insults vary widely. Failure to identify and address this underlying trigger will result in delayed, non-optimal or potentially harmful consequences.

Cytokines &Chemokines

Cytokines & Chemokines are chemicals that act like hormones. There are more than 100 cytokines & over 40 Chemokines[3]. All most all cells of our body can secrete one or more of these. They are a diverse group of small proteins that are secreted by cells for the purpose of intercellular signaling and communication. Specific cytokines have autocrine, paracrine, and/or endocrine activity and, through receptor binding, can elicit a variety of responses, depending upon the cytokine and the target cell. Cytokines &Chemokines play vital role in the control of cell proliferation and differentiation, regulation of angiogenesis, immune and inflammatory responses.

Etiologic Factors

An analysis of the underlying pathophysiology of all CSS supports this simple but essential postulate: cytokine storm results from excessive proinflammatory stimuli, inadequate regulation of inflammation, or elements of both. Proinflammatory stimuli can include antigens, superantigens as in the case of Enterotoxin& Toxic Shock Syndrome Toxin 1 of Staphylococcus Aureus2 (compounds that trigger non-specific but massive activation of T cell receptors), adjuvants (such as toll-like receptor (TLR) ligands, allergens (antigens triggering an allergic response), and proinflammatory cytokines themselves. Anti-inflammatory mechanisms can be humoral or cellular and seek to dampen or terminate a proinflammatory pathway. Defects leading to excessive pro or inadequate anti-inflammatory responses can be host-derived or environmental.

Host Factors

Host Susceptibility to the Cytokine Storm

One of the challenging clinical questions about the cytokine storm is why some individuals seem to be particularly susceptible while others are relatively resistant.

Genome-wide association studies (GWAS) have answer for this question. They have associated TLR4 (the principal receptor for lipopolysaccharide) polymorphisms with increased susceptibility to pathogens and severity of disease. Genetic polymorphisms contribute to the severity of the host response in sepsis and the cytokine storm;

- Hyper and hypo responders to bacterial products are identifiable in the healthy population, which is explainable in part by genetically determined differences in the structure and function of TLR receptors, particularly TLR1. Those with a single nucleotide polymorphism (SNP) marking a hyper functioning variant of TLR1 had increased organ dysfunction and morbidity from Gram-positive bacteremia.
- Multiple polymorphisms in cytokine-inducible Proto-Oncogene Tyrosine-Protein Kinase Sarcoma (SRC) homology 2 (SH2) domain protein that controls IL-2 signaling were associated with increased susceptibility to bacteremia, tuberculosis, and severe malaria

- Variants of IFN-λ3 were associated with spontaneous resolution and successful treatment of hepatitis C virus (HCV) infection.

Apart from above mentioned genetic variations that predispose to CSS, subjects suffering from the following conditions are also prone for developing CSS.

- Conventional Immunodeficiencies
- FamilialHemophagocyticLymphohistiocytosis (fHLH)
- X-linked lymphoproliferative Syndromes (XLP)
- Persons infected with Epstein Barr Virus (encoding an IL-10 homologue), Cytomegalovirus, HIV and herpes viruses' infections triggering TLR9 & producing IFNγ in abundance facilitating hemophagocytosis
- Host of Rheumatic conditions leading to Macrophage Activation Syndrome
- Malignancies
- Subjects on Immunosuppressive therapy

Hypersensitivity - Allergens being potent source of antigenic stimulation without infection is associated with cytokine IL-4 induced hemophagocytosis independent of IFN-γ.

Pathophysiology of CSS

Cytokine storm due to massive T cell stimulation is a proposed mechanism of severe viral infections such as influenza.

CSS can be induced by direct target cell lysis with consecutive release of cytokines like interferon gamma (IFN-γ) or tumour necrosis factor alpha (TNF-α) or by activation of T cells due to therapeutic stimuli with subsequent cytokine release. These cytokines trigger a chain reaction due to the activation of innate immune cells like macrophages and endothelial cells with further cytokine release.

CSS in cases of administration of T cell-engaging therapies in cancers[3]is usually due to target effects induced by binding of the bispecific antibody or Chimeric Antigen Receptor T cell to its antigen and subsequent activation of bystander immune cells and non-immune cells, such as endothelial cells. Activation of the bystander cells results in the massive release of a range of cytokines. IL-6, IL-10, and interferon (IFN)-Y are among the core cytokines that are consistently found to be elevated in serum of patients with CSS. In the setting of T cell engaging therapies, CSS is triggered by the massive release of IFN-γ by activated T cells or the tumour cells themselves.

IFN-γ causes fever, chills, headache, dizziness and fatigue. Secreted IFN-γ induces activation ofother immune cells, most importantly macrophages. The activated macrophages produce excessive amounts of additional cytokines such as IL-6, TNF-α, and IL-10.TNF-α elicits flu-like symptoms similar to IFN-γ with fever, general malaise, and fatigue but furthermore is responsible for watery diarrhea, vascular leakage, cardiomyopathy, lung injury, and the synthesis of acute phase proteins.

Interleukin 6 (IL-6) seems to hold a key role in CSS pathophysiology since highly elevated IL-6 levels are seen in patients with CSS and in murine models of the disease. It contributes to many of the key symptoms of CSS. Via trans-signaling, IL-6 leads to characteristic symptoms of severe CRS, i.e. vascular leakage, and activation of complement and coagulation cascade inducing disseminated intravascular coagulation (DIC). Inaddition, IL-6 likely contributes to cardiomyopathy by promoting myocardial dysfunction.

A hallmark of severe CSS seems to be the activationof endothelial cells. Typical marker of

endothelial activation such as Angioptin-2 and Von Willebrand Factor are often elevated in the serum of patients with CSS. Endothelial cells seem to be an important source of IL-6 in severe CSS. This indicates that the endothelium plays an important role in pathophysiology of CSS both by amplifying the inflammatory response and as a target organ. The crucial contribution of endothelial dysfunction in the pathogenesis of CSS provides an explanation for some of the hallmarks of severe CSS, i.e. Capillary leakage, hypotension, and coagulopathy. Endothelial activation and the ensuing vascular dysfunction might be the mechanistic factor linking CSS with neurotoxicity too. IL-6 may also promote the development of HLH/ Macrophage Activation Syndrome (MAS) in the setting of CSS by inducing dysfunction of cytotoxic activity in T and NK cells, which is a hallmark of HLH and MAS. In patients with CSS who develop a HLH/MAS-like syndrome additional cytokines such as IL-18, IL8, IP10 – a T cell recruiting chemokine, Macrophage Chemo attractant Protein(MAP)1, MIG – Monokine secreted by neutrophil on stimulation by IFN-γ, and Macrophage Inflammatory Protein 1β are also elevated. These cytokines also are elevated in classical HLH and MAS. Some patients may harbour genetic variants that predispose them to developing HLH/MAS.

Clinical presentation

CSS can present with a variety of symptoms ranging from mild, flu-like symptoms to severe life-threatening manifestations of the overshooting inflammatory response. Mild symptoms of CSS include fever, fatigue, headache, rash, arthralgia, and myalgia. More severe cases are characterized by fever, tachycardia, tachypnea, hypotension, malaise, generalized swelling, altered mental status, diffuse lymphadenopathy, organomegaly (particularly of the liver and spleen), and often erythematous or purpuric rash. Hypotension can progress to an uncontrolled systemic inflammatory response with vasopressor-requiring circulatory shock, vascular leakage, disseminated intravascular coagulation, and multi-organ system failure.

Respiratory symptoms are common in patients with CSS. Mild cases may display cough and tachypnea but can progress to acute respiratory distress syndrome (ARDS) with dyspnea, hypoxemia, and bilateral opacities on chest X-ray. ARDS may sometimes require mechanical ventilation. Patients with severe CSS can also develop renal failure or signs of cardiac dysfunction with reduced ejection fraction on ultrasound. In addition, patients with severe CSS frequently display vascular leakage with peripheral and pulmonary edema. In severe cases, CSS can be accompanied by clinical signs and laboratory abnormalities that resemble hemophagocyticlymphohistiocytosis (HLH) or macrophage activation syndrome (MAS). Neurologic symptoms might span from mild confusion with word-finding difficulty, headaches and hallucinations to aphasia, hemi paresis, cranial nerve palsies, seizures and somnolence.

Laboratory Findings

Apart from host of non-specific acute phase reactants, CSS also have a number of common laboratory abnormalities. Hematologic parameters like leukocytosis or thrombocytosis, raised ESR, CRP can indicate the acute phase response.

Alternatively, elevated cell counts can drop precipitously as a feature of nearly all CSS, suggesting consumption.

Akin to acute cytopenias, an acute drop in ESR and fibrinogen are most associated with Macrophage Activation Syndrome (MAS), but can be seen in any cytokine storm syndrome and often suggest active disseminated intravascular coagulopathy (DIC).

Screens for coagulopathy such as fibrin split products and d-dimer are often elevated in CSS even in the absence of overt DIC, suggesting subclinical endothelial activation. Likewise, hypoalbuminemia is frequently observed and likely represents systemic capillary leak.

Routine testing often reflects various organs in distress including the liver, pancreas, and kidneys. Such tests are rarely capable of distinguishing direct inflammatory damage from that induced by insufficient oxygen delivery.

Laboratory abnormalities that are common in patients with CSS include cytopenia, elevated creatinine and liver enzymes, deranged coagulation parameters, and a high CRP. Patients with CRS associated with HLH display the typical laboratory findings of HLH/MAS such as highly elevated ferritin levels, and hyper triglyceridemia.

Markers of macrophage activation: Ferritin levels in MAS and HLH are often above10,000 ng/mL; while such values are in the range of a few hundred ng/mL in sepsis. Other markers of macrophage activation, such as neopterin, soluble CD163, and soluble CD25 (aka soluble IL-2 receptor - α, or sIL2Rα), may show more clinical utility as they become available outside of reference laboratories.

The Pro Inflammatory Cytokines in COVID19: Following SARS-CoV infection, high virus titers and dysregulation of cytokine/chemokine response cause an inflammatory cytokine storm. A cytokine profile resembling sHLH is associated with COVID-19 disease severity characterized by increased IL-2, IL-7, G-CSF, IF-γ Inducible Protein 10, Monocyte Chemo attractant Protein 1, Macrophage Inflammatory Protein 1-α, and TNFα.

Predictors of fatality included elevated ferritin (mean 1297·6 ng/ml in non-survivors *vs* 614·0 ng/ml in survivors; p<0·001) and IL-6 (p<0·0001)[6].

Treatment strategy in inflammatory cytokine storm

The experience from treating SARS and MERS shows that reducing viral load by anti-viral agents in the early stages of the disease and controlling inflammatory responses through immune modulators are effective measures to improve the prognosis of HCOV infection.

Glucocorticoid in the short term (3–5 days) is appropriate and the recommended dose is no more than equivalent to methyl prednisolone1–2 mg/kg/day.

Chloroquine inhibits the production and release of TNF and IL-6, which indicates that chloroquine may suppress the cytokine storm in patients infected with COVID-19.

Intra venous Immuno Globulin therapy from convalescent human plasma has dual effects of immune substitution and immune modulation. Its practical application value in treatment of COVID-19 needs confirmation in future studies.

IL-6 antagonist Tocilizumab is very costly & not available like plasma exchange, adsorption, perfusion, blood/plasma filtration; IFN- αß receptor blockers or antagonists; Ulinastatin is a natural anti-inflammatory substance that inhibits mononuclear macrophage recruitment and function; Eritoran is a TLR4 antagonist & Mesenchymal stem cells (MSC) have strong anti inflammatory and immune regulatory functions.

Conclusion

Inflammation is an essential part of an effective immune response. It is difficult to eliminate infections successfully without inflammation. The inflammatory response begins with an initial recognition of pathogens. The pathogens then mediate the recruitment of immune cells, which eliminates the pathogens and ultimately leads to

tissue repair and restoration of homeostasis.
However in some infected individuals host &agent's interaction lead to excessive and prolonged cytokine/chemokine responses, known as the cytokine storm. Cytokine storm causes ARDS and multiple organs dysfunction, which leads to physiological deterioration and death. Timely control of the cytokine storm in its early stage through such means as removal of inciting agent, use of immune modulators and cytokine antagonists are keys to improve the treatment success rate and reduce the mortality rate of patients with CSS.

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