

Increased Mast Cell Activation may be Responsible for the Critical Conditions in COVID-19 and Targeting Mast Cells and Their Mediators can Bring New Treatment Prospects

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ABSTRACT

Outbreaks of infection with SARS-CoV-2 e.g., COVID-19, have led to major global health crisis since December 2019 because of having infected more than 4.5 million people with 300 thousand death around the world in 5.5 months. SARS-CoV-2 is a highly pathogenic virus and may cause severe lung diseases such as acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) especially in a risk group. Kawasaki disease, which has increased in children in recent months, seems to be among the severe diseases that this virus is responsible for. Development of these critical clinical conditions have been suggested to be related cytokin storm due to pathogenic/dysregulated host immune response by immune and nonimmune cells. Among these cells, mast cells may play an important role because they are activated and synthesize many cytokines and chemokines not only when they recognize viral products, but also some of the secreted cytokines either by other cells such as T cells, damaged epithelial and endothelial cells or by themselves. Moreover, with the activation, mast cells degranulate preformed mediators and synthesize other mediators such as leukotrienes, prostoglandins and growth factors. Mast cells regulate functions of immune cells and provide recruitment of them to the inflamed tissue by the effect of many of these mediators. Medications, targeting mast cells such as mast cell stabilizers may decrease overproduction of these mediators including cytokines and chemokines and also progression of inflammation. Leukotriene receptor antagonist may also provide additional benefits for controlling this inflammation. Investigating the effects of them either only a mast cell stabilizer or with a leukotriene receptor antagonist may bring new possibilities in preventing the development of critical conditions, related to COVID-19.

Keywords

COVID-19, Mast cells, Mast cell stabilizer, Leukotriene receptor antagonist, Kawasaki disease, Tryptase.

Introduction

Since December 2019, COVID-19, which is a coronavirus disease due to the novel SARS-CoV-2, is spreading rapidly starting from the city of China, Wuhan, all over the world as a pandemic. It is an acute respiratory disease and common clinical features are self limited fever, cough, sore throat, fatigue, headache, myalgia, breathlessness and gastrointestinal symptoms (in a small group) [1-3]. The clinical features of COVID-19 are variable like asymptomatic state, pneumonia, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), coagulation defects, shock

and death. The critical conditions develop usually in the elderly (>65 years old) and in individuals with comorbid conditions such as hypertension, chronic obstructive pulmonary disease, cardiovascular and cerebrovascular diseases, diabetes and renal failure [1-3]. Kawasaki disease, which is increasing in parallel with the COVID-19 outbreak, may be considered among these critical situations.

According to the recent data the mortality rate of COVID-19 is ~6%, in previous coronavirus infections these rates are ~9% and ~36%; death numbers are nearly 800 and 700 for SARS-CoV and MERS-CoV infections, respectively [4]. COVID-19 is a more contagious disease and leads to a critical healthcare crisis. The number of people who died is very high, exceeded 300 thousand

in last 5.5 months. Elderly and those with comorbid disease make up 50-75% of them [2].

Human coronaviruses are low and highly pathogenic viruses. While low pathogenic coronaviruses infect the upper respiratory tract and cause mild disease, highly pathogenic ones infect the lower tract and may be fatal in some of the infected patients [4]. SARS-CoV, MERS-CoV [4] and novel SARS-CoV-2 are highly pathogenic viruses. These viruses also cause mild disease in a large group of those infected but they can lead to severe disease such as ALI and ARDS [4]. The critical conditions develop in 20% of patients with COVID-19 [2].

In highly pathogenic coronavirus infections, viral and host factors affect the course of the disease [4,5]. Increased initial viral titers in the airways and rapid virus replication are among the viral factors that cause severe disease [6,7]. Pathogenic/dysregulated host immune response out of control with elevated pro-inflammatory cytokine/chemokine levels (cytokine storm) have also suggested in the development of severe COVID-19 such as in severe SARS-CoV and MERS-CoV infections [1,4,5,8]. For example, severe SARS-CoV infected patients have elevated serum levels of pro-inflammatory cytokines (IFN γ , IL1, IL6, IL12, IL8 and TGF β) and chemokines (CCL2, CXCL10, CXCL9) compared to individuals with uncomplicated ones [4]. Similar result were obtained also in patients with severe COVID-19. Patients, admitted to the intensive care unit (ICU) were found as with significantly elevated IL2, IL7, IL10, GSCF, IP10, MCP1, MIP1A, and TNF α levels compared with non-ICU patients [9].

In highly pathogenic coronavirus infections, critical conditions develop due to excessive inflammation caused by dysregulated immune responses. These patients have reduced lung capacity as a result of massive inflammatory cell infiltration, pulmonary tissue damage due to increased epithelial and endothelial apoptosis and accumulation of fluid due to increased vascular leakage [4,5]. On the other hand in patients having the protective/regulated inflammation, lung changes are minimal epithelial and endothelial apoptosis and vascular leakage [4].

The development of a cytokine storm is characterized by rapid proliferation and hyperactivation of T cells, macrophages, natural killer cells and the overproduction of more than 150 inflammatory cytokines and chemical mediators released by immune or nonimmune cells [8]. Among these cells, mast cell may play an important role because when they recognize viral products they are activated and synthesize many chemokines and cytokines. In addition, some cytokines secreted by other cells such as T cells, damaged epithelial and endothelial cells [10] or even by themselves [11] stimulate mast cells. Mast cells regulate the functions of immune cells such as dendritic cells, monocytes/macrophages, granulocytes, T cells, B cells and NK cells. They also provide the recruitment of immune cells to the inflamed tissue by secreting chemokines and some other mediators which locally increase vascular permeability [12-14]. The role of mast cells in coronavirus induced inflammation [15-17] and cytokin

storm [17] have recently been published.

The cytokine storm hypothesis have also been considered for other severe highly pathogenic respiratory viral infections such as related H1N1 and H5N1 influenza viruses [18]. In animal studies with H1N1 and H5N1 influenza viruses, an association with mast cells and severe histopathological findings were shown [19,20]. Moreover, the relationship between mast cells or mast cell specific mediators and the severity of diseases caused by Dengue virus (DENV) and Japanese encephalitis virus (JEV) [21-25] were demonstrated.

Other important findings obtained from animal studies were achieving successful results with treatments, targeting mast cells or their mediators in viral infections that can cause severe disease [20,22,24,25]. While these findings support the relationship between mast cells and severe viral diseases and also raise the possibility of new treatment regimens in highly pathogen virus infections. In COVID-19 patients, preventing or suppressing severe pulmonary disease may be possible to control cytokine production and hence inflammatory response with mast cells or their mediators targeting medications.

In this article, it has been emphasized that detrimental effects of mast cells in some viral infections may be valid in COVID-19 and medications, targeting mast cells (e.g., mast cell stabilizers) with or without their mediators (e.g., leukotriene receptor antagonists) may provide benefits in preventing severe disease conditions.

Mast cells against pathogens

Until recently, mast cells were thought to be involved only in IgE-mediated allergic reactions. Nowadays, they have been understood to be multifunctional cells which are effective in several physiological and pathological conditions [10,13]. One of their physiological functions is to protect the body from pathogens [12,13,26]. Their protective effect has been reported previously for only parasitic infections. In fact, there have been strong evidence to show the importance of mast cells in innate and adaptive immune responses for bacterial, fungal and viral infections [10,12,26,27].

Mast cells are tissue resident cells and widely distributed throughout the body. They are particularly abundant at the host-environment interfaces such as skin and mucosal tissues of respiratory and gastrointestinal tracts [12,26]. Mast cells populate in the connective tissue below the epithelium in the mucosa, too close to the blood and lymphatic vessels [12,13,26,28]. It has been hypothesized that this localization makes them the first immune cells to encounter pathogens which are enter the body [12,27,29]. Mast cells are present within the alveolar wall with the average concentration of 350 cell/mm² and they occupy approximately 1.2-2% of the area of the alveolar wall [30].

Mast cells can recognize pathogens by directly or pathogen specific antibody binding with Fc receptors if patients become sensitized to their antigens previously [12,27]. Direct recognition occurs when pattern recognition receptors (PPRs) are activated by pathogen-

associated molecular patterns (PAMPs). PPRs are diverse, some of them are Toll-like receptors (TLRs) and different TLRs can induce different responses [12,27]. Mast cells can also be activated by IFN γ released from T cells and IL33 released from damaged endothelial and epithelial cells [10]. Releasing from T cells, IL4 and IL9 are the other cytokines which stimulate mast cells [10]. These two cytokines are also synthesized by mast cells. Mast cells can activate themselves in an autocrine manner, such as through IL-5 and tryptase [11].

Mast cells are activated when they recognize pathogens and alter the inflammatory environment by degranulation of preformed (e.g., histamine, heparin, proteases such as tryptase and chymase, TNF) and releasing newly synthesized (e.g., cytokines, chemokines, prostaglandins, leukotrienes, growth factors) mediators [11,12,26,29,31]. Some of these mediators (e.g., histamine, IL1 β , TNF, VEGF, tryptase, chymase, prostoglandins, leukotrienes, heparin) regulate vascular integrity, tone and function [21,28]. In the inflammatory response these mediators released from the activated mast cells near the vessels and contribute to local increase vascular permeability acting on vascular endothelium [12,13,22,28,29]. Hence the immune cells can move from the blood stream to the affected tissue [13,28]. Chemokines and also TNF, heparine, proteases, lipid mediators are effective in the recruitment of immune cells to the inflamed tissue [12,13,29].

Depending on the type of stimulus/stimuli, mast cells can secrete different preformed and/or newly synthesized mediators [10]. Various cell wall products of bacteria activate mast cells by different TLRs and release different mediators such as lipopolysaccharide stimulation through TLR4 causes cytokine production without degranulation, peptidoglycan stimulation through TLR2 causes both degranulation and cytokine production [12]. Many viral products stimulate mast cells through TLR3 and cause degranulation [14,20-22,29,32] and release newly synthesized mediators such as cytokines; IFNs, TNF, IL6, IL8, IL10, IL18, GMCSF, VEGF [14,29] several chemokines [14] and leukotrienes [4,33].

Mast cells promote the development of adaptive immunity to pathogens and even they can present antigen to T cells [12,34]. Mast cells induce the migration of antigen-presenting dendritic cells and T cells from infected tissues to draining lymph nodes [12,27].

Detrimental effects of mast cells in viral infections

While mast cells provide effective immunity against pathogens, they can contribute to dysregulated immune responses that can increase host morbidity and mortality [31-34]. In acute viral infections mast cells may also show beneficial or detrimental effects [27,29].

An example of these two different effects is seen in DENV infection. This is an arthropod-borne disease and transmits by bite of infected mosquitoes. DENV infection can be asymptomatic or self-limited disease with fever, headache, muscle and joint pain

and skin rashes [22,27]. Mast cells in the skin are among the first immune cells to encounter this virus. It was demonstrated that mast cells can inhibit viral spread via the recruitment of NK cells and T cells bearing NK cell markers [14]. In contrast, increased viral burden within draining lymph nodes was shown in mast cell-deficient mice [14].

On the other hand, a small percentage of patients with DENV infection develop life-threatening critical conditions such as Dengue shock syndrome (DSS), Dengue hemorrhagic fever (DHF) [22,27] and hepatic or neurological organ dysfunctions [27]. These patients have vascular complications such as increasing vascular permeability, leaking plasma including water and salt into tissues and coagulation/bleeding abnormalities [27]. Mast cell-derived vasoactive mediators (e.g., leukotrienes, chymase, tryptase, TNF, VEGF) have been thought to be responsible for these vascular pathologies in severe DENV infections [21,22,27].

The role of mast cells for the development of vascular leakage in DENV infection was shown with less alterations in mast cell-deficient mice than in wild-type mice [22]. Additionally, an association between increased serum chymase [21-23] and tryptase [21] levels which are important mast cell derived prestored proteases and Dengue disease severity were found in some studies. It has been also concluded that chymase, might serve as good predictive marker of Dengue disease severity [20-22]. Tryptase is considered as specific for mast cells and even preferred for the diagnosis of mast cell activation syndrome [35]. In a recent study, chymase and tryptase levels were compared and tryptase was found most effective for vascular leakage than chymase [24]. In one of these studies, it was also shown that while mast cell stabilizing drugs such as ketotifen and cromolyn or leukotriene receptor antagonist such as montelukast restored vascular integrity; anti-TNF did not [22]. In the last study, nafamostat mesylate, highly specific inhibitor of tryptase and also an approved for clinical use for intravascular coagulation, showed therapeutic effect on DENV-vascular leakage [24].

Mast cell-derived chymase was also found to be responsible for vascular endothelial damage in encephalitis due to JEV [25]. Mast cells are also located close to blood-brain barrier (BBB). Activation and degranulation of brain mast cells and chymase were shown the key modulators of BBB leakage. Moreover, it was found that mast cells promote increased JEV penetration, enhanced neurological deficits, and reduced survival. When JEV-infected mice treated with TY-51469 which inhibits chymase activity showed significantly improved survival from lethal JEV infection [25].

Mast cell activation with typical degranulation, releasing histamine, tryptase and IFN- γ as the first-line immunological responses was shown in animal models with H5N1 influenza virus infections [20]. Additionally, dramatically increased numbers of mast cells in the nasal mucosa, trachea, hilar lymph nodes and lung on the 1st, 3rd, 5th post infection days and dramatically reduced lung lesions treatment with ketotifen were also demonstrated [20].

In severe lung diseases of COVID-19, increased mast cell-derived mediators due to increased mast cell activation may play some roles for massive inflammatory cell infiltration, epithelial and endothelial damage and increased vascular leakage.

May mast cells play a role in the development of Kawasaki disease in COVID-19?

Recently, many clinicians have suggested a strong association between the SARS-CoV-2 and Kawasaki disease. Kawasaki disease is an acute systemic vasculitis of small and medium-sized arteries including coronary artery and usually affects children under the age of 5 years [36,37]. The development of this vasculitis has been thought to be related a series of aberrant immune responses triggered by a pathogen [37]. One of these pathogens may be SARS-CoV-2 because children with the disease have increased simultaneously with the outbreak of COVID-19 disease in recent months.

Increased systemic mast cell activation may play some role for the development of Kawasaki disease in children with COVID-19. Mast cells are found close to small blood vessels in connective tissue. Systemic activation of them may cause small-sized vasculitis after perivascular connective tissue inflammation. They may explain the erythema, edema and desquamation of extremity of these children. Systemic activation of mast cells may be due SARS-CoV-2 viremia. Animal studies have demonstrated that innate immune pathogen-associated molecular patterns (PAMPs) can cause vasculitis in Kawasaki disease [36]. On the other hand systemic mast cell activation may be due to increased blood cytokines related host defence. Because significantly elevated levels of IFN γ , IL4 and IL17A were demonstrated in children with Kawasaki disease [37] IFN γ and IL4 are the cytokines that can activate mast cells [10].

May the treatment, targeting mast cells and their mediators be beneficial?

Although, several antivirals (remdesivir, favipiravir) and antimalarials (chloroquine, hydroxychloroquine) have emerged as potential therapies, there are no effective drugs against SARS-CoV-2. Treatment of COVID-19 is essentially supportive and symptomatic [1,38].

For many years, chloroquine and its derivative hydroxychloroquine have been used for the treatment of malaria and some autoimmune disorders [38,39]. These two drugs also have been considered to have possible antiviral activity against SARS-CoV and SARS-CoV-2 [38]. Chloroquine has some important side effects such as cardiomyopathy, fatal arrhythmia, complete heart block and toxic retinopathy [39]. Although hydroxychloroquine which is less toxic than chloroquine was found to be more potent than chloroquine for inhibiting SARS-CoV-2 in vitro [40]. It has been also suggested that the immunomodulatory effect of hydroxychloroquine may be useful in controlling the cytokine storm that occurs late-phase in critically ill SARS-CoV-2 infected patients [40]. This may be due to inhibiting effect of hydroxychloroquine on mast cells.

In fact, hydroxychloroquine is a preferred drug for the treatment of lupus and some other autoimmune diseases because it is effective with few side effects [41]. In recent years, it has been understood that mast cells play a role in the development of autoimmune diseases [42] and now these disorders have been included among mast cell-driven ones [43]. It was shown that the elevated pro-inflammatory factors and mast cell proteases significantly inhibited by hydroxychloroquine in rosacea-like mice [44]. One of the diseases associated with mast cells is mast cell activation syndrome (MCAS). Interestingly, hydroxychloroquine is also found to be beneficial in patients with MCAS, albeit in a small group [45].

In MCAS, released elevated mast cell mediators cause chronic multisystem polymorbidity [35,46]. The first recommended drugs in MCAS are mast cell stabilizers such as ketotifen and cromolyn sodium and leukotriene receptor antagonists [35,46]. There are many mast cell stabilizers: synthetic, semi-synthetic and natural ones [47]. Quercetin which is one of natural mast cell stabilizers, has been recommended also for the treatment of COVID-19 [17]. Ketotifen (synthetic) and cromolyn (natural) have been used in allergic diseases for many years [47]. In animal studies, they have been shown to have some beneficial effects in acute viral infections [20,22]. Therefore, it may be rational to apply one of these two mast cell stabilizers for preventing cytokine storm. Recently mast cell stabilizers have also been recommended for COVID-19 as a supportive therapy [16]. Taking slow-release forms of ketotifen once a day is sufficient for 24-hour activity. It is not available in oral form in the United States. Cromolyn sodium requires administration four times daily. It was shown that mast cells in lung tissue are inhibited by ketotifen and to a lesser extent by sodium cromoglycate when challenged with an IgE-dependent histamine release mechanism [48].

In animal studies, some beneficial effects were obtained with medications targeting mast cell mediators such as leukotriene [22], tryptase [24] and chymase [25] in acute viral infections. Although they have some psychiatric side effects, leukotriene receptor antagonists are generally recommended for the treatment of mast cell related disorders such as allergic disorders [49] and MCAS [35,46].

In the meantime, it seems appropriate to start 2mg/day ketotifen for the patients with mild disease; in the risk group or all patients have moderated one as soon as COVID-19 is diagnosed. Patients with mild disease are defined as hospitalized or not hospitalized, have SpO₂>94% and normal chest radiographs [38]. The moderate ones, hospitalized have SpO₂<94% and radiographic evidence of pneumonia [38]. Progressing to severe disease may usually develop at end of the first week [2], it may be considered to add a leukotriene antagonist (e.g., montelukast 10mg / day) in moderate cases in the risk group or in cases that did not improve at the end of week one. In severe cases the higher dose of ketotifen (4mg/day) may be considered. Cromolyn sodium can be used as an alternative to ketotifen to be given in the required doses. A low dose mast cell stabilizer can be administered to children who have fever more

than 5 days, to prevent development of Kawasaki disease without even waiting for the development of other findings.

Mast cells play a critical role in the development of pulmonary fibrosis [50]. Therefore, the use of mast cell stabilizers after the patient has improved may be effective in development of less fibrous sequelae [16].

Conclusion

We have no any evidence whether mast cells increase in the lungs of severe COVID-19 patients. Detection of mast cell hyperplasia in autopsy samples staining with toluidin blue will help confirming this issue in the near future.

Nowadays, tryptase may be helpful to show the relationship with mast cells and severe COVID-19 disease and determining the severity of the disease.

The effects of different mast cell stabilizers with or without an leukotriene receptor antagonists for preventing severe COVID-19 disease may be investigated, hence the most effective regime may be found.

Their effects in preventing severe disease of COVID-19 may also be compared with hydroquinoline.

It will be better to investigate the interactions with the medications, targeting mast cells and their mediators and antiviral drugs.

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