# Covid-19 Hyperinflammation and Post-Covid-19 Illness

# May Be Rooted in Mast Cell Activation Syndrome

Lawrence B. Afrin, M.D.,[1] Leonard B. Weinstock, M.D.[2], and Gerhard J. Molderings, M.D.[3]

[1]Department of Mast Cell Studies, AIM Center for Personalized Medicine, Purchase, New York, United States

[2]Department of Medicine, Washington University, St. Louis, Missouri, United States

[3]Institute of Human Genetics, University Hospital of Bonn, Bonn, Germany

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Corresponding and Guarantor Author:

Lawrence B. Afrin, M.D.
Department of Mast Cell Studies
AIM Center for Personalized Medicine
3010 Westchester Avenue, Suite 404
Purchase, NY 10577
E-mail: drafrin@armonkmed.com
Telephone: 914-730-7390
Fax: 914-730-7391

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Abbreviations Used:

JAK: Janus kinase

MC: mast cell

MCAS: mast cell activation syndrome

Abstract

Objectives: One-fifth of Covid-19 patients suffer a severely symptomatic, hyperinflammatory course, but specific causes remain unclear. Mast cells (MCs) are activated by SARS-CoV-2. Though only recently recognized, MC activation syndrome (MCAS), usually due to acquired MC clonality, is a chronic multisystem disorder with inflammatory and allergic themes and estimated prevalence of 17%. We describe a novel conjecture explaining how MCAS might cause propensity for severe acute Covid-19 infection and chronic post-Covid-19 illnesses.

Methods: Observations of Covid-19 illness in patients with/without MCAS, set against our extensive clinical experience with MCAS.

Results: The prevalence of MCAS is concordant with the prevalence of severe cases within the Covid-19-infected population. Much of Covid-19's hyperinflammation is concordant with manners of inflammation which MC activation can drive. Drugs with activity against MCs or their mediators have been preliminarily observed helpful in Covid-19 patients. None of our treated MCAS patients who have endured Covid-19 infection have suffered severe courses of the infection, let alone mortality.

Conclusions: Hyperinflammatory cytokine storms in many severely symptomatic Covid-19 patients may be rooted in aberrant response to SARS-CoV-2 by the dysfunctional MCs of MCAS rather than normal response by normal MCs. If provable, our conjecture has significant therapeutic and prognostic implications.

Keywords: Covid-19, SARS-CoV-2, mast cell activation syndrome, mast cell activation disease, medical hypothesis

Perspective

Since December 2019, the Covid-19 pandemic, due to the SARS-CoV-2 coronavirus, has been spreading rapidly throughout many parts of the world, calamitous not only to the personal health and finances of millions but also – largely due to the infection's high mortality rate – to health care systems and societal economic welfare around the globe. Approximately 15-20% of Covid-19-infected patients suffer a severe course of the acute infection (Bulut and Kato, 2020; Rabec and Gonzalez-Bermejo, 2020; Grasselli et al., 2020) hallmarked by hyperinflammatory cytokine storms causing far more morbidity and mortality than from any direct viral cytotoxicity, and conferring high mortality risk (Zhou et al., 2020a), even 50% or more in some subpopulations (e.g., patients with cardiac injury or requiring continuous renal replacement therapy) (Fominskiy et al., 2020; Shi et al., 2020; Bhatraju et al., 2020; Chen et al., 2020), and requiring hospitalization and, often, mechanical ventilation. The Covid-19 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 (Sun et al., 2020; Mangalmurti and Hunter, 2020). Among these inflammatory cells, mast cells (MCs) 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 (Mukai et al., 2018), or even by themselves (Hermans et al., 2019), stimulate MC activation. MCs regulate the functions of immune cells such as dendritic cells, monocytes/macrophages, granulocytes, T cells, B cells, and NK cells. They also recruit immune cells to inflamed tissue by secreting chemokines and other mediators which locally increase vascular permeability

(Abraham et al., 2010; Krystel-Whittemore et al., 2016; St John et al., 2011). The roles of MCs in coronavirus-induced inflammation (Kritas et al., 2020; Kılınc and Kılınc, 2020; Theoharides, 2020; Zhou et al., 2020) and cytokine storms (Theoharides, 2020) have been discussed recently. Although MCs can recognize viruses by diverse mechanisms (e.g., Toll-like receptor 3 detection of viral double-stranded ribonucleic acid (RNA), viral sphingosine-1-phosphate (S1P) binding to S1P receptors, and retinoic acid-induced gene I (RIG-I) recognition of uncapped viral RNA) (Criado et al., 2020), MCs also express angiotensin converting enzyme 2 (ACE2), now appreciated as the principal receptor for SARS-CoV-2, thus defining a route by which MCs could become hosts for this virus, too. (Theoharides, 2020) MCs also express many serine proteases (including tryptase), which are necessary for SARS-CoV-2 infection. (Theoharides, 2020) Some risk factors for a severe course of Covid-19 infection have been identified (e.g., greater age, obesity and/or other chronic pre-existing illness), but specific mechanisms by which such factors would permit more severe infection remain unclear. After the acute infection with Covid-19, many then soon manifest a variety of chronic, often inflammatory multisystem illnesses (Wang et al., 2020; Bulut and Kato, 2020; Scala and Pacelli, 2020; Troyer et al., 2020; Hays, 2020).

Another mystery about the Covid-19 pandemic is why the infection is mildly symptomatic or even asymptomatic in the majority of those infected but is severely symptomatic, even often life-threatening, in a sizable minority. In other words, what causes the immune system to suddenly overreact so catastrophically in certain Covid-19 patients while remaining properly regulated in the majority? Another important question regards the etiology of chronic post-Covid-19 illnesses. Although solid data on which a proof can be based are not yet available, we

summarize the evidence suggesting that mast cell activation disease, the majority of which is constituted by the prevalent, but only recently recognized, mast cell activation syndrome (MCAS), fits very well with these enigmatic findings.

We offer a potentially important conjecture, spurred by (1) our familiarity (across several thousand cases over the last dozen years) with MCAS (presenting principally as a chronic multisystem polymorbidity of general MC-mediator-driven themes of inflammation ± allergic-type issues (Afrin et al., 2016a; Afrin et al., 2020)) and (2) our theory that Covid-19 inflammatory illnesses may be due to abnormal hyperactivation by SARS-CoV-2 of the dysfunctional portion of the population of the mutated MCs underlying primary MCAS as opposed to normal activation of normal MCs by the virus.

Primary MCAS has been thought by some to underlie, to at least some extent, many of the risk factors identified thus far for severe Covid-19 infection (Afrin et al., 2016b). Also, it is the natural history of MCAS to permanently escalate its baseline level of dysfunction of the affected MCs shortly following a major stressor (likely due to acquisition, due to complex interactions between epigenetic aberrancies and the stressor's induced cytokine storm, of additional mutations by the mutated stem cells from which the mutated/dysfunctional MCs are derived) (Molderings, 2015; Haenisch et al., 2014; Molderings, 2016; Altmüller et al., 2017; Haenisch et al., 2012; Molderings et al., 2010; Molderings et al., 2007). As such, the assortment of (generally inflammatory) post-Covid-19 illnesses seen in many Covid-19 patients would be a natural course for MCAS. In fact, Covid-19 would be far from the first infection for which post-infectious chronic multisystem inflammatory illness increasingly is coming to be suspected to be

rooted in (initiation of, or more likely escalation of pre-existing) MCAS (e.g., Epstein-Barr virus infection, tick-borne infections) rather than chronic active infection (Afrin, 2016b, Kempuraj et al., 2020). Again, since MCAS is a chronic multisystem inflammatory disease (with intermittent acute flares) if it is nothing else, it even is possible that at least some of the patients previously thought to have suffered repeat bouts of Covid-19 infection might in truth have suffered only an initial bout of infection followed some time later by symptomatic flaring of escalated MCAS (e.g., fatigue, myalgias).

Of further interest, estimates of MCAS prevalence (17%, at least in the first world (Molderings et al., 2013)) are closely concordant with estimates of prevalence of severe Covid-19 infection. MCs, present in all vascularized tissues but dominantly at the environmental interfaces and in vessel walls (Akin and Metcalfe, 2004), are activated by the SARS-Cov-2 coronavirus which causes Covid-19 infection (Kritas et al., 2020; Theoharides, 2020; Zhou et al., 2020), leading to MC activation and resulting release of various subsets of the MC's >1000 potent multi-action mediators (Ibelgaufts, 2020) (including biogenic amines (e.g., histamine), proteases (e.g., tryptase and chymase), cytokines (e.g., interleukins and TNF-α), eicosanoids (e.g., prostaglandins and leukotrienes), heparin, and growth factors) increasingly thought to play a key role in driving the hyperinflammation of severe Covid-19 illness (Kempuraj et al., 2020; Valent et al., 2020).

A significant number of fatal courses of Covid-19 infection are due to cardiovascular complications such as pulmonary embolism, thromboembolism, sepsis, and multi-organ failure. It has been shown that MCs play a significant role in promoting thrombotic diseases and

complications; it also has been shown that stabilizing MCs helps prevent fatal sepsis (Ramos et al., 2010). As another example, neuropsychiatric disease appears common in both MCAS (Afrin et al., 2015) and in Covid-19 illness (Romero-Sánchez et al., 2020), and though the acute and subacute neurological disease is thought to be due principally to inflammation-induced coagulation, we conjecture that chronic neuropsychiatric symptoms may be due more to escalated (and likely pre-existing) MCAS. Additionally, some of the drugs or drug classes at least preliminarily shown helpful in modulating the severity of Covid-19 infection (e.g., famotidine (Freedberg et al., 2020), aspirin (Viecca et al., 2020)), and for which anti-viral actions seem extremely unlikely, have actions which include inhibiting MC activation or antagonizing released MC mediators. Other drugs or drug classes, too, with activity against MCs or their released mediators have been proposed for, or are actively in, trials against Covid-19 infection, too [e.g., cromolyn (Sestili and Stocchi, 2020; Sepay et al., 2020; Gigante et al., 2020), flavonoids (Theoharides, 2020), leukotriene inhibitors (Almerie and Kerrigan, 2020), Janus kinase (JAK) inhibitors (Goker and Biray, 2020; Seif et al., 2020; Luo et al., 2020; Spinelli et al., 2020; Meyer et al., 2020), dexamethasone (Meyer et al., 2020; RECOVERY Collaborative Group, 2020), low-dose naltrexone (Sims, 2020), quercetin (Onal, 2020; Colunga Biancatelli, 2020), and ascorbic acid (Colunga Biancatelli, 2020)].

MCAS remains a relatively unrecognized entity in spite of its great prevalence, which likely has been “camouflaged” by its extreme heterogeneity of clinical presentation (Afrin et al., 2016a; Afrin et al., 2017), as driven by its underlying extreme mutational heterogeneity. Although the MCAS in some patients may be purely secondary to another process (e.g., autoimmunity or cancer), MCAS clearly is a primary disease in the few in whom it is presently possible to

demonstrate MC-relevant clonality in the clinical laboratory (either by KIT mutation analysis (presently largely limited to probing by polymerase chain reaction for codon 816 mutations, almost always present in mastocytosis but rarely found in MCAS) or by flow cytometry for cell surface co-expression of CD117 together with either CD25 and/or CD2); in the great majority of MCAS cases, the disease presently is "idiopathic" solely because clonality cannot be demonstrated through clinically available testing, though studies to date have consistently shown, via sequencing in research laboratories of MC isolates obtained from MCAS patients, that the MCs in almost all MCAS patients bear a wide variety of mutations across not only KIT (just not in codon 816) but also dozens of other MC regulatory genes. (Molderings et al., 2007; Molderings et al., 2010; Afrin et al., 2016c; Altmüller et al., 2017) Therefore, due principally to the aforementioned extreme clinical heterogeneity and the only recent recognition of the existence of the disease (implying that most physicians remain unaware of it), most MCAS patients remain undiagnosed and thus untreated, and therefore their dysfunctional MCs, whether causing mild or severe illness, are uncontrolled and may react inappropriately to SARS-CoV-2 (Table 1). Another confounding issue is that many MCAS patients who have been undiagnosed for decades ultimately minimize their problems, sometimes deceivingly declaring themselves as "healthy," thus perhaps accounting for at least some of the many severe Covid-19 patients described as "healthy" prior to infection. Provocatively, in our own MCAS patients (i.e., patients already diagnosed and treated, and thus already with at least partial control over their MCAS; note many of these patients had long suffered severe courses of MCAS prior to diagnosis and having it brought under at least partial control with treatment) who have come to suffer Covid-19 infection, none of them have suffered a severe course of the infection (i.e., none have required mechanical ventilation, let alone died), and we conjecture it is precisely because

their dysfunctional MCs were already under at least partial control throughout the acute infection that they have not suffered severe courses, though their MCAS still places them at increased risk for developing post-infectious illness (Figure 1). Based on current knowledge, Covid-19 infection causes mild to moderate symptoms in the majority of patients. However, these early data also suggest that even if symptoms are just "mild to moderate" during the acute infection, fibrotic lung damage develops in some, potentially leading to long-term complications for a subset of patients (Spagnolo et al., 2020; Leask, 2020; Lechowicz et al., 2020; George et al., 2020). It is well known that over-activated mast cells play a crucial role in the development of fibrotic conditions. Given that up to 17% of the population is generally pre-disposed to develop syndromes and diseases related to MC activation (Molderings et al., 2013), it is conceivable that people with this predisposition might have increased risk for developing the chronic respiratory, neurologic, or other illnesses increasingly being seen following acute Covid-19 illness. Furthermore, the MC activation induced by Covid-19 infection could increase the risk for poor outcome in undiagnosed or uncontrolled MCAS patients. Lung biopsies from Covid-19 patients clearly show a significantly increased number of activated MCs compared to healthy controls, demonstrating an important role of MCs during Covid-19 infections (Zhou et al., 2020).

We theorize that initiation of MCAS-targeted therapy (e.g., inexpensive, safe histamine $H_1$ and $H_2$ receptor antagonists) immediately upon recognition or suspicion of onset of Covid-19 illness might mitigate the severity of the illness. The impact on reducing hospitalizations, morbidity, and mortality warrants investigation. We also recommend evaluation for MCAS in patients who develop chronic post-Covid-19 illnesses.

The fact that MCs normally activate in response to infection precludes diagnostic testing for MCAS (i.e., testing for elevated levels in blood and urine of mediators relatively specific to the MC, such as tryptase, heparin, histamine and derivatives, prostaglandin $D_2$ and derivatives (Afrin et al., 2020; Afrin and Molderings, 2014)) during acute Covid-19 infection. However, the potential personal and societal implications of our conjecture are of sufficient magnitude that we nevertheless recommend rapid formal investigation. Such investigation should include, at a bare minimum, a pilot clinical trial empirically initiating MCAS-targeted therapy in patients newly presenting with suspected Covid-19 illness and in whom careful history-taking (regardless of the initially asserted state of prior health) reveals chronic inflammatory and/or allergic issues suspicious for MCAS. Initial empiric MCAS-targeted therapy could include at least histamine $H_1$ and $H_2$ receptor antagonists. Note most MCAS-targeted therapies are sufficiently safe to make their empiric initiation reasonable.

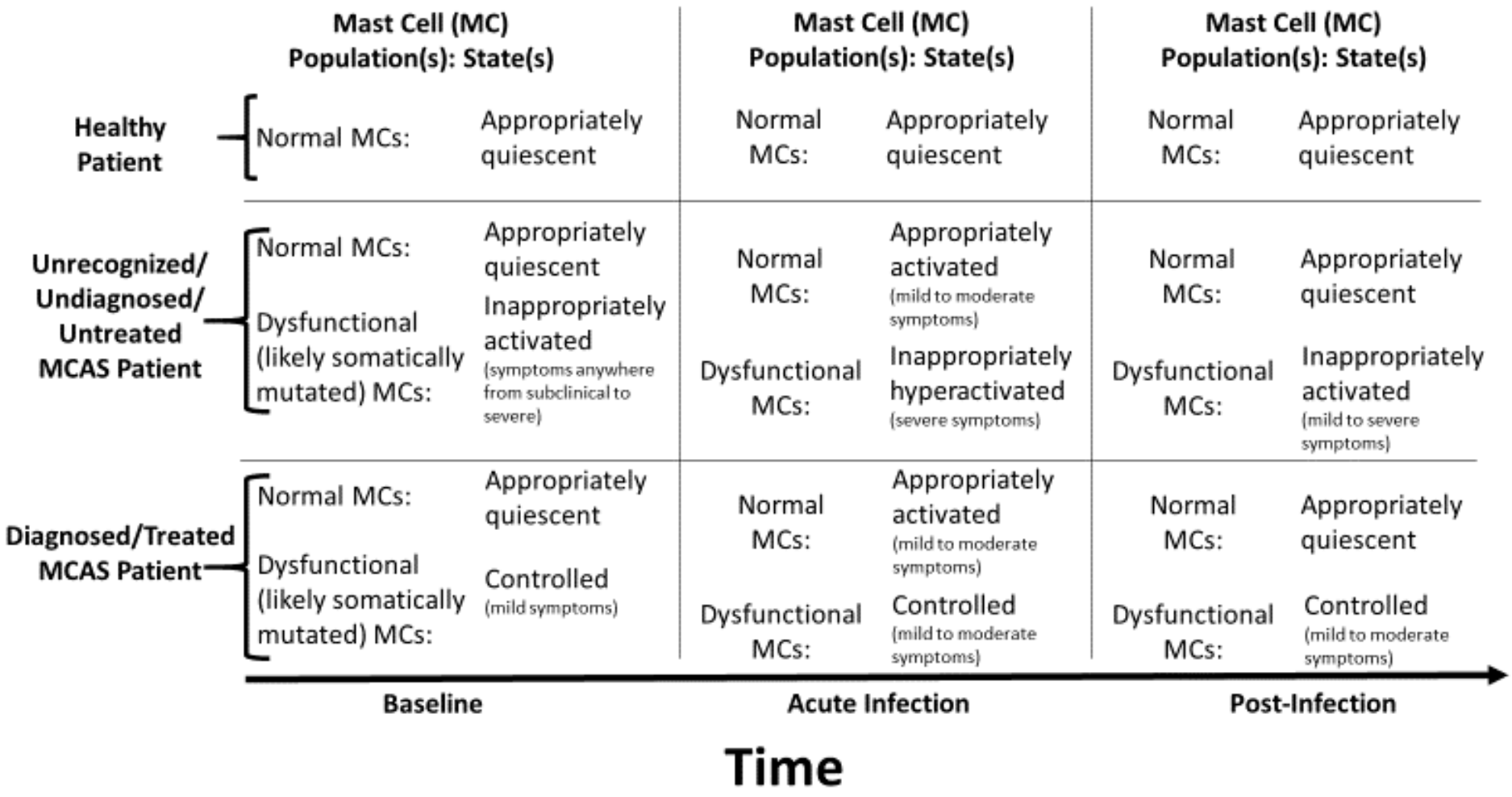
The signaling networks in all inflammatory diseases are extremely complex, and other inflammatory cells besides MCs inescapably are involved in generating the hyperinflammation of Covid-19 infection (e.g., the extreme hyperferritinemia seen in some cases might easily be a macrophage activation syndrome or secondary hemophagocytic lymphohistiocytosis sparked by a Covid-19-driven escalation of MCAS more so than direct virus-driven macrophage activation given that hyperferritinemia is certainly not seen in all patients with severe Covid-19 infection (Gómez-Pastora et al., 2020; Ruscitti et al., 2020; Ruan et al., 2020; Mehta et al., 2020)). However, we feel the clinical patterns seen thus far in the Covid-19 population suggest MCAS (likely pre-existing, at that) to be the root issue in many, perhaps even most, of those suffering "severe" infection. The role that cytokine storms play in severe cases of COVID-19 is what we

would expect to see if our hypothesis is correct. Hyperactive MCs can get into a continuous activation loop, leading to cytokine storms, which then can result in the fluid build-up and pulmonary and other damage often seen in severe Covid-19 patients. In sum, although most MCAS patients do not present with Covid-19-like hyperinflammation, MCAS is an extraordinarily heterogeneous disease and we feel MCAS (likely pre-existing) "fits" well with all the behaviors of severe Covid-19 infection observed thus far. Blocking MC mediators in Covid-19 patients can help calm MCs and cytokine storms, which may result in better outcomes, including lower mortality rates. Furthermore, use of MC stabilizers such as antihistamines and cromolyn may help prevent a significant increase in post-Covid-19 chronic illnesses, which in a significant proportion of such patients may be driven by chronic persistent MC activation. Thus, in the end, our MC-targeted treatment suggestions may be relevant for all Covid-19 patients, not just those with pre-existing MC diseases.

| **Table 1.** | **Organ and system involvement in mast cell activation syndrome. Conditions underlined in bold are also seen in Covid infection and post-infectious syndrome.** |
|---|---|
| Organ / System | Symptom / Finding |
| Constitutional | **Fatigue**, **Fevers**, **Chills**, **Weight loss**, Weight gain |
| Ears, Nose, Throat | **Conjunctivitis**, **Rhinitis**, Sinusitis, **Dysosmia/Anosmia**, **Tinnitus**, **Hearing loss**, **Dysgeusia/Ageusia**, **Sore throat** |
| Neurologic | **Headaches**, Migraines, **Brain Fog**, **Anxiety**, Depression, Insomnia, **Seizures** |
| Cardiovascular | **Chest pain**, **Palpitations**, **Hypotension** |
| Pulmonary | **Cough**, **Dyspnea**, **Wheezing** |
| Urogenital | Frequency, Urgency, Dysuria, Pelvic pain |
| Esophageal | **Heartburn**, **Dysphagia**, Globus, **Chest pain** |
| Stomach | **Dyspepsia**, **Nausea**, **Vomiting** |
| Small intestine / colon | Bloating, Food intolerance, **Abdominal pain**, **Diarrhea**, Constipation |
| Hepatic | **Elevated transaminases**, Hepatomegaly |
| Salivary Glands | **Swelling** |

| | |
|---|---|
| Lymphatics | **Lymphadenopathy** |
| Dermatologic | Flushing, Pruritis, **Urticaria**, Hemangiomas, Nodules, **Rashes**, **Alopecia** |
| Musculoskeletal | **Myalgias**, Arthralgias, Edema |

Figure 1. Illustration of Conjectured Model. Normal mast cells (MCs) react normally to SARS-CoV-2, participating in driving mild to moderate symptoms through the network of inflammatory cells, and return to a quiescent state once the virus has been eradicated. Some portion of the MCs will be abnormal/dysfunctional and prone to constitutive and reactive hyperactivation if mast cell activation syndrome (MCAS) is present. If MCAS is undiagnosed and thus untreated, the abnormal MCs may react inappropriately excessively to SARS-CoV-2, driving a hyperinflammatory state via excessive release of their mediators as well as excessive recruitment (also via their released mediators) of other inflammatory cells. If MCAS is diagnosed and treated, the abnormal MCs will be relatively controlled, diminishing their aberrant hyperreactivity to SARS-CoV-2. As major stressors (such as infections and hyperinflammation) can induce major escalations in baseline MC dysfunction in MCAS (likely via induction of additional mutations in the stem cells and multipotent progenitors at the root of the patient's population of dysfunctional MCs), the abnormal MCs in MCAS will have potential to drive post-Covid inflammatory syndrome (with clinical specifics dependent on the mutational profiles in the individual patient's MCs), but the severity of that syndrome may be mitigated by recognition/diagnosis of the patient's MCAS and pharmacologic control of the patient's dysfunctional MCs.


Mast Cell (MC) Population(s): State(s)
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Mast Cell (MC) Population(s): State(s)
Healthy Patient
Normal MCs:
Appropriately quiescent
Normal MCs:
Appropriately quiescent
Normal MCs:
Appropriately quiescent
Unrecognized/ Undiagnosed/ Untreated MCAS Patient
Normal MCs:
Appropriately quiescent
Dysfunctional (likely somatically mutated) MCs:
Inappropriately activated (symptoms anywhere from subclinical to severe)
Normal MCs:
Appropriately activated (mild to moderate symptoms)
Dysfunctional MCs:
Inappropriately hyperactivated (severe symptoms)
Normal MCs:
Appropriately quiescent
Dysfunctional MCs:
Inappropriately activated (mild to severe symptoms)
Diagnosed/Treated MCAS Patient
Normal MCs:
Appropriately quiescent
Dysfunctional (likely somatically mutated) MCs:
Controlled (mild symptoms)
Normal MCs:
Appropriately activated (mild to moderate symptoms)
Dysfunctional MCs:
Controlled (mild to moderate symptoms)
Normal MCs:
Appropriately quiescent
Dysfunctional MCs:
Controlled (mild to moderate symptoms)
Baseline
Acute Infection
Post-Infection
Time

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