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Recommended Citation

Afrin, Lawrence B; Weinstock, Leonard B; and Molderings, Gerhard J, "Covid-19 hyperinflammation and post-Covid-19 illness may be rooted in mast cell activation syndrome." *International journal of infectious diseases*. 100, 327 - 332. (2020).

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Perspective

Covid-19 hyperinflammation and post-Covid-19 illness may be rooted in mast cell activation syndrome

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ARTICLE INFO

Article history:

Received 9 August 2020

Received in revised form 28 August 2020

Accepted 7 September 2020

Keywords:

Covid-19

SARS-CoV-2

Mast cell activation syndrome

Mast cell activation disease

Medical hypothesis

ABSTRACT

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

Methods: Observations of Covid-19 illness in patients with/without MCAS were compared with extensive clinical experience with MCAS.

Results: The prevalence of MCAS is similar to that 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 preliminarily been observed to be helpful in Covid-19 patients. None of the authors' treated MCAS patients with Covid-19 suffered severe infection, let alone mortality.

Conclusions: Hyperinflammatory cytokine storms in many severely symptomatic Covid-19 patients may be rooted in an atypical response to SARS-CoV-2 by the dysfunctional MCs of MCAS rather than a normal response by normal MCs. If proven, this theory has significant therapeutic and prognostic implications.

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Introduction

Since December 2019, the Covid-19 pandemic, due to the SARS-CoV-2 coronavirus, has been rapidly spreading throughout many parts of the world. It has been calamitous to the personal health and finances of millions and also—largely due to the infection's high mortality rate—to global healthcare systems and societal economic welfare. Approximately 15–20% of Covid-19-infected patients suffer a severe form of the acute infection (Bulut and Kato, 2020; Rabec et al., 2020; Grasselli et al., 2020) hallmarked by hyperinflammatory cytokine storms causing far more morbidity and mortality than from any direct viral cytotoxicity. This has a high mortality risk (Zhou et al., 2020a)—≥50% 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 requires

hospitalisation and, often, mechanical ventilation. The Covid-19 cytokine storm is characterised by rapid proliferation and hyperactivation of T cells, macrophages, and natural killer cells, and the overproduction of >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 recognise viral products, they are activated and synthesise 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

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(Abraham and St John, 2010; Krystel-Whittemore et al., 2016; St John et al., 2011).

The roles of MCs in coronavirus-induced inflammation (Kritas et al., 2020; Kilinc and Kilinc, 2020; Theoharides, 2020; Zhou et al., 2020b) and cytokine storms (Theoharides, 2020) have been recently discussed. Although MCs can recognise 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), they also express angiotensin converting enzyme 2 (ACE2), now known as the principal receptor for SARS-CoV-2, thus defining a route by which MCs could also become hosts for this virus (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 form of Covid-19 infection have been identified (e.g. older age, obesity and/or other chronic pre-existing illness); however, specific mechanisms by which such factors would permit more severe infection remain unclear. After an acute infection with Covid-19, many people soon manifest a variety of chronic and 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 who are infected but is severely symptomatic, often life-threatening, in a sizeable minority. In other words, what causes the immune system to so catastrophically suddenly overreact in certain Covid-19 patients while remaining properly regulated in the majority? Another important question regards the aetiology of chronic post-Covid-19 illnesses. Although solid data on which these questions can be answered are not yet available, this paper summarises the evidence suggesting that mast cell activation disease—the majority of which comprises the prevalent, but only recently recognised, mast cell activation syndrome (MCAS)—fits very well with these puzzling observations.

This study offers a potentially important conjecture spurred by (1) familiarity (across several thousand cases over the last dozen years) with MCAS (mainly presenting 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) the theory that Covid-19 inflammatory illnesses may be due to abnormal hyperactivation by SARS-CoV-2 of the dysfunctional, likely mutated portion of the MC population 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, 2016b). MCAS is known to permanently escalate its baseline level of dysfunction of the affected MCs shortly after a major stressor (likely due to acquisition—due to complex interactions between epigenetic abnormalities 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 is increasingly being 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 is possible that at least some of the patients

previously thought to have suffered repeat bouts of Covid-19 infection might have only suffered 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 developed world) (Molderings et al., 2013) closely correspond with estimates of prevalence of severe Covid-19 infection. MCs—present in all vascularised tissues but dominant 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., 2020b), leading to MC activation and resulting release of various subsets of the MC's >1000 potent multi-action mediators (Ibelgafts, 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, at least some of which are increasingly thought to play key roles in driving the hyperinflammation of severe Covid-19 illness (Kempuraj et al., 2020; Valent et al., 2020).

A significant number of fatal cases of Covid-19 infection are due to cardiovascular complications such as pulmonary embolism, thromboembolism, sepsis and multiorgan failure. It has been shown that MCs play a significant role in promoting thrombotic diseases and complications; it has also been shown that stabilising MCs helps to prevent fatal sepsis (Ramos et al., 2010). As another example, neuropsychiatric disease appears common in both MCAS (Afrin et al., 2015) and Covid-19 illness (Romero-Sánchez et al., 2020), and although the acute and subacute neurological disease in Covid-19 illness is thought to be principally due to inflammation-induced coagulation, the authors 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 to be helpful in modulating the severity of Covid-19 infection (e.g. famotidine (Freedberg et al., 2020) and aspirin) (Viecca et al., 2020), and for which anti-viral actions seem extremely unlikely, have actions which include inhibiting MC activation or antagonising released MC mediators. Other drugs or drug classes with activity against MCs or their released mediators have been proposed for, or are actively involved in, trials against Covid-19 infection, including: 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 Bagca and Biray Avci, 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 et al., 2020), low-dose naltrexone (Sims, 2020), quercetin (Onal, 2020; Colunga Biancatelli et al., 2020), and ascorbic acid (Colunga Biancatelli et al., 2020).

MCAS remains a relatively unrecognised entity, despite its great prevalence, which has likely 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 MCAS in some patients may be purely secondary to another process (e.g. autoimmunity or cancer), it clearly is a primary disease for those in whom it is currently possible to demonstrate MC-relevant clonality in the clinical laboratory. This is performed either by KIT mutation analysis (currently 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 majority of MCAS cases, the disease is currently 'idiopathic', solely because clonality cannot be demonstrated through the available clinical testing. Studies to date have consistently shown, via

sequencing of MC isolates obtained from MCAS patients, that the MCs in almost all MCAS patients bear a wide variety of mutations across KIT (just not in codon 816) and also dozens of other MC regulatory genes (Molderings et al., 2007; Molderings et al., 2010; Afrin et al., 2016c; Altmüller et al., 2017).

Therefore, mainly due to this extreme clinical heterogeneity and recent recognition of the existence of the disease (implying that most physicians remain unaware of it), most MCAS patients remain undiagnosed and 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 tend to minimise their problems, sometimes deceptively declaring themselves as 'healthy'. This perhaps accounts for some of the many severe Covid-19 patients described as 'healthy' prior to infection. In the authors' 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 MCs play a crucial role in the development of fibrotic conditions. Given that up to 17% of the population is generally pre-disposed to developing syndromes and diseases related to MC activation (Molderings et al., 2013), it is conceivable that people with this predisposition might have increased risk of 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 of poor outcomes 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., 2020b).

MCAS-targeted therapy (e.g. inexpensive, safe histamine H₁ and H₂ receptor antagonists) immediately upon recognition or suspicion of onset of Covid-19 illness might mitigate the severity of the illness. The impact on reducing hospitalisations, morbidity and mortality warrants further investigation. Evaluation of MCAS in patients who develop chronic post-Covid-19 illnesses is also recommended.

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 MCs such as tryptase, heparin, histamine and derivatives, prostaglandin D₂ and derivatives) (Afrin et al., 2020; Afrin and Molderings, 2014) during acute Covid-19 infection. However, the potential personal and societal implications of the conjecture described here are huge and rapid formal investigation is recommended. 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 H₁ and H₂ receptor antagonists. Note that most MCAS-targeted therapies are sufficiently safe to make their empiric initiation reasonable.

The signalling networks in all inflammatory diseases are extremely complex, and other inflammatory cells besides MCs are inescapably involved in generating the hyperinflammation of Covid-19 infection (e.g. the extreme hyperferritinaemia seen in some cases might easily be a macrophage activation syndrome or secondary haemophagocytic lymphohistiocytosis sparked by a Covid-19-driven escalation of MCAS more so than direct virus-driven macrophage activation, given that hyperferritinaemia 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, it is felt that the clinical patterns seen thus far in the Covid-19 population suggest that MCAS (likely pre-existing) is 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 would be expected if the conjecture described here is correct. Hyperactive MCs can get into a continuous activation loop, leading to cytokine storms which 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 it is felt that MCAS (likely pre-existing) 'fits' well with most of the behaviours of severe Covid-19 infection observed thus far. Blocking MC mediators in Covid-19 patients may

Table 1

Organ and system involvement in mast cell activation syndrome. Conditions highlighted in bold are also seen in Covid-19 acute infection and/or post-infectious syndrome.

Organ/system	Symptom/finding
Constitutional	Fatigue, fevers, chills, weight loss , weight gain
Ears, nose and 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, dyspnoea, wheezing
Urogenital	Frequency, urgency, dysuria, pelvic pain
Oesophageal	Heartburn, dysphagia, globus, chest pain
Stomach	Dyspepsia, nausea, vomiting
Small intestine/colon	Bloating, food intolerance, abdominal pain, diarrhoea , constipation
Hepatic	Elevated transaminases , hepatomegaly
Salivary Glands	Swelling
Lymphatics	Lymphadenopathy
Dermatologic	Flushing, pruritis, urticaria , haemangiomas, nodules, rashes, alopecia
Musculoskeletal	Myalgias , arthralgias, oedema

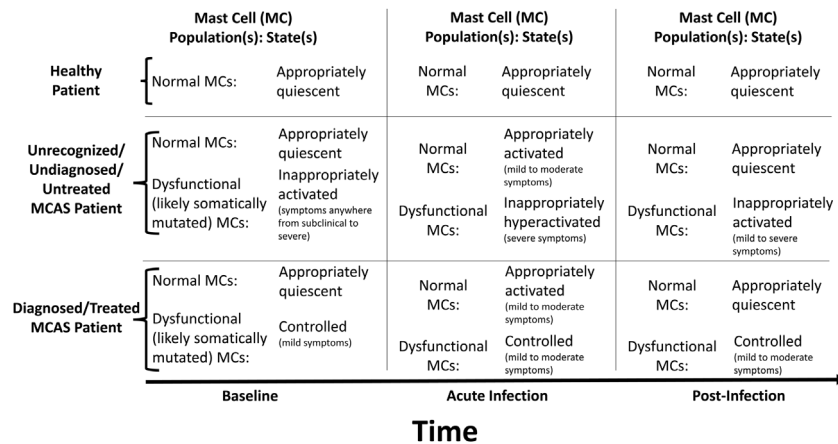


Figure 1. Illustration of proposed model. Normal mast cells (MCs) react normally to SARS-CoV-2, participating in driving mild to moderate symptoms through the network of inflammatory cells, and returning to a quiescent state once the virus has been eradicated. Some of the MCs will be abnormal/dysfunctional 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 and excessively to SARS-CoV-2, driving a hyperinflammatory state via excessive release of their mediators and 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.

help calm MCs and cytokine storms, which may result in better outcomes, including lower mortality rates. Furthermore, using MC stabilisers such as antihistamines and cromolyn may help to 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. These MC-targeted treatment suggestions may be relevant for all Covid-19 patients, not just those with pre-existing MC diseases.

Conflict of interest

Drs. Afrin and Weinstock are uncompensated volunteer medical advisors to the start-up company MC Sciences, Ltd. Dr. Molderings is the chief medical officer of the start-up company MC Sciences, Ltd. All authors disclaim any financial conflicts of interest. All authors report that they had full access to all of the text in this submission and take responsibility for the integrity of any factual statements and analysis. This work has not been previously presented in any other form or venue.

Sources of support

No funding or other support was received for this work from any source.

Author contributions

Dr. Afrin initiated the project and was the principal writer. All other authors contributed equally to the editing of the paper.

Ethical approval

No human subjects were involved in this work and, as such, ethical approval was not required for the development of this article.

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