EDITORIAL

COVID-19 and multisystem inflammatory syndrome, or is it mast cell activation syndrome?

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Received October 1, 2020 - Accepted October 7, 2020

COVID-19 derives from infection with Coronavirus [severe acute respiratory syndrome (SARS)-CoV-2] and is associated with high morbidity and mortality due to release of a storm of pro-inflammatory cytokines and thrombogenic agents resulting in destruction of the lungs. Many reports indicate that a considerable number of patients who are positive for SARS-CoV-2 are asymptomatic or have mild symptoms. However, increasing evidence suggests that many such patients who either recovered from or had mild symptoms after COVID-19 exhibit diffuse, multiorgan, symptoms months after the infection. These symptoms include malaise, myalgias, chest tightness, brain fog and other neuropsychiatric symptoms that were originally reported in children and named Multisystem Inflammatory Syndrome (MIS-C). Now the US Center for Disease Control (CDC) has announced the recognition of a similar condition in adults, named Multisystem Inflammatory Syndrome (MIS-A). The symptoms characterizing these conditions are very similar to those associated with Mast Cell Activation Syndrome (MCAS, US ICD-110 code D89.42-idiopathic mast cell activation syndrome). Hence, the possibility of MCAS should be evaluated in any patient with MIS and/or multisystem inflammatory symptoms. In either case, these syndromes should be addressed with liposomal formulation (in olive pomace oil) of the flavone luteolin (e.g. PureLut® or FibroProtek®) together with the antihistamine rupatadine, which also has anti-platelet activating factor (PAF) activity and inhibits mast cells that have been implicated in the pathogenesis of cytokine storms in COVID-19.

The recent Coronavirus [severe acute respiratory syndrome (SARS)-CoV-2] is associated with a high morbidity and mortality in adults, known as COVID-19 (1). Infected patients who recover have increased levels of specific antibodies and activated T cells (2, 3), but dysfunctional immune system (4). In particular, the pulmonary pathology results from release of multiple pro-inflammatory cytokines, especially IL-6 (2, 5), but also microthromboses that may involve platelet activating factor (PAF) (6).

Children and adolescents do get sick with COVID-19 (7), but generally present with milder symptoms than adults (8, 9). Nevertheless, a number of papers have reported the presence in children of Multisystem Inflammatory Syndrome (MIS-C) with symptoms resembling toxic shock or Kawasaki syndrome (10, 11). Symptoms in children were mostly nonspecific and included rash (52%), diarrhea (52%), vomiting (45%) and conjunctival injection (45%) with all children having increased indexes of inflammation (12).

Key words: multisystem inflammatory syndrome; MIS-C; MIS-A; COVID-19; SARS-CoV-2; inflammation; mast-cell; immunity; cytokine storm

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0393-974X (2020)

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There has been increased realization that COVID-19 is associated with many extrapulmonary manifestations, including thrombotic complications, arrhythmias, gastrointestinal symptoms, as well as dermatologic and neurologic complications (12). In fact, the Centers for Disease Control (CDC) recently recognized the existence of a similar syndrome in adults, (https://www.cdc.gov/mis-c/) named Multisystem Inflammatory Syndrome (MIS-A). The symptoms characterizing this syndrome are numerous and affect almost all organs, including cardiovascular, gastrointestinal, dermatologic and neurologic symptoms, especially brain fog (Table I) (13, 14). Prominent among the neurologic manifestations is brain fog associated with confusion, inability to focus, loss of memory, and inability to find the right words that has been termed "COVID Brain Fog" (https://www.nytimes.com/2020/10/11/health/covid-survivors.html). MIS-A symptoms typically appear weeks to months after infection, giving the term "longhaulers" to such patients, and are worsened by psychological stress (15, 16). MIS-A symptoms and their worsening by stress are very similar to those (Table II) experienced by patients with mastocytosis (17) or mast cell activation syndrome (MCAS) (18). A unique aspect of MCAS is that the mast cells in these patients are stimulated by numerous non-allergic triggers, including stress-related peptides (19) without the release of histamine or tryptase (20).

A key source of pro-inflammatory cytokines in COVID-19 (21) is the mast cells (17, 22), which can be triggered by viruses (23), including SARS-CoV-2 (24), and secrete multiple pro-inflammatory mediators (25, 26), including IL-6 (27) and IL-1β (28), thus potentially contributing to COVID-19 pathology (24). Mast cells are ubiquitous in the body, located perivascularly, especially in the lungs where they mature under the influence of local micro-environmental factors resulting in different phenotypes. Mast cells are typically stimulated by allergens crosslinking allergen-specific immunoglobulin E (IgE) bound to high affinity Fc epsilon receptor 1 (FcεRI) (17), but also by non-IgE stimuli (29) such as cationic compounds via activation of the low affinity G-coupled receptor MRGPRX2 (30), as well as neuropeptides, including corticotropin-releasing hormone (CRH), neurotensin (NT), and substance P (SP) via high affinity receptors (31).

Following stimulation, mast cells rapidly secrete the preformed, granule-stored, heparin, histamine, tryptase and TNF, as well as newly synthesized leukotrienes, PAF, prostaglandin D_2 (PGD_2), cytokines (IL-5, IL-6, IL-31, IL-33 and TNF) and chemokines (CCL2, CCL5 and CXCL8) released 6-24 hours later (25). Some of these "late phase" mediators can be released without degranulation (19), as we showed for IL-6 (27) and IL-1β (28). Mast cell-derived vasoactive mediators, especially cytokines (32), can also increase the permeability of the blood-brain barrier (BBB) (33). Hence, SARS-CoV-2 could lead to "COVID Brain Fog" either directly via activation of mast cells or by permitting cytokines to enter through a disrupted BBB.

Inhibition of mast cell-associated inflammation is necessary (34) and could be accomplished with some naturally occurring flavonoids, especially luteolin (23), which inhibits release of pro-inflammatory molecules

Table I. *Working criteria for MIS-A*

1. Severe illness requiring hospitalization in a person >21 years old
2. Positive test result for SARS-CoV-2 infection (current or within past 12 weeks)
3. Severe dysfunction of one or more extrapulmonary organ systems
4. Laboratory evidence of severe inflammation
5. Absence of severe respiratory illness

https://www.cdc.gov/mis-c/

Table II. *Common symptoms present in MIS-A and MCAS*

- Angioedema
- Arrythmias
- Brain fog
- Confusion
- Diarrhea
- Dizziness
- Dysautonomia
- Fatigue
- Gastrointestinal complaints
- Headache
- Hives
- Hypotension
- Lightheadedness (syncope)
- Inability to find the right word
- Memory loss
- Myalgias
- Palpitations
- Shortness of breath
- Skin rashes
- Weakness

from mast cells and also has anti-viral properties (24). Due to the poor solubility and oral absorption of luteolin, preferable formulations would be those using liposomal luteolin (e.g. FibroProtek®, BrainGain®) (35).

The presence of diffuse, multisystem inflammatory symptoms, especially "COVID Brain Fog" may be indicative of MCAS (24). Hence, in addition to the inflammatory markers discussed, it would be important to investigate mast cell-associated mediators and attempt to inhibit their release and/or their biological actions.

ACKNOWLEDGEMENTS

This work was supported by anonymous donations.

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