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Journal Pre-proof

COVID-19 infection in patients with mast cell disorders including mastocytosis does not impact mast cell activation symptoms

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COVID-19 infection in patients with mast cell disorders including mastocytosis does not impact mast cell activation symptoms

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Conflict of Interest Disclosures:

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Methods:

This study was conducted under Mass General Brigham IRB protocols 2012P002481 and 2018P000122. All data was gathered from retrospective electronic medical record review. Data on demographics, level of care, laboratory results, and mast cell activation symptoms were collected. Assessment of mast cell activation symptoms was completed by the treating physician.

Figure 1

COVID-19 infection in patients with mast cell disorders including mastocytosis does not impact mast cell activation symptoms

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Clinical Implications

COVID-19 mortality in patients with mast cell disorders is comparable to the general population.

Bone marrow mast cells lack ACE-2 receptors. These data argue against clinically significant mast cell activation during COVID-19 infection.

Journal Pre-proof

SARS-CoV-2 is a novel coronavirus responsible for the clinical syndrome COVID-19. This virus was initially recognized in December 2019 in Wuhan, China and has since spread leading to a global pandemic. Mast cells (MCs) are tissue resident innate immune cells that play a pathobiologic role in a range of diseases, such as asthma, rhinitis and food allergy and MC activation disorders. MC activation leads to the release of inflammatory mediators, including tryptase and several cytokines such as interleukin (IL)-6. MCs are often active participants in propagation of inflammation during viral infection.(1) Reports of serious COVID-19 infections have identified IL-6, TNF and IL-1 β as hallmarks of cytokine storm leading to severe outcomes.(2) MCs are a source of IL-6 and other proinflammatory mediators, leading to the possibility of MCs directly contributing to the severity of SARS-CoV-2 infection. However, studies involving allergic asthma, a disease associated with increased lung MC numbers and activation, have not shown an increased risk for severe outcomes.(3) Thus, the role of MCs in SARS-CoV-2 infection remains unknown.

Symptoms of SARS-CoV-2 infection include cough, fever, dyspnea, and diarrhea. These overlap with some clinical symptoms of MC activation which also include urticaria, flushing, and hypotension, among other symptoms. Because mast cells have been shown to activate during viral infection, increased severity of SARS-CoV-2 infection in patients with MC disorders is possible.(4) Here we report the impact of SARS-CoV-2 infection in 28 patients with clonal (n=24) MC disorders including mastocytosis and in patients with clinical symptoms of MC activation and elevated baseline serum tryptase with (n=4) . This cohort of patients did not have increased COVID-19 mortality and lacked clinical symptoms of MC activation.

Twenty-eight patients with mast cell disorders and confirmed SARS-CoV-2 infection were identified by EHR review, of which 57% were female and average age was 50 years. The average baseline serum tryptase was 40.5ng/mL (range 5.9-140 ng/mL). Average total serum IgE was 28.9 IU/ml (range: 2.0-159 IU/ml), data not shown. Seventeen patients had indolent systemic mastocytosis (ISM) diagnosed according to WHO criteria.(5) Five patients had cutaneous mastocytosis and two had systemic mastocytosis with an associated hematologic neoplasm (SM-AHN). Four patients had elevated baseline serum tryptase and symptoms of MC activation. Subjects were included on the basis of a positive SARS-CoV-2 PCR test during acute

infection in 23/28 (82%) and/or antibody test after convalescence 5/28 (18%). Baseline characteristics are described in Table 1.

Most patients had a mild course of COVID-19. Inpatient hospitalization was required in 12/28 (43%). One patient required intensive care unit admission for hypoxia; none required full mechanical ventilation. One patient with ISM died from SARS-CoV-2-associated pneumonia. His medical history was notable for multiple comorbidities that placed him at high risk for poor outcomes including coronary artery disease with three stents, aortic valve replacement, atrial flutter, obstructive sleep apnea and chronic obstructive pulmonary disease. Regarding COVID-19 directed therapy, 8/28 (28%) were treated with hydroxychloroquine. Five were treated with antiretroviral therapy (ritonavir/lopinavir). One patient received systemic steroids. None was treated with remdesivir or tocilizumab. One patient was pregnant during the course of infection and delivered a healthy baby without complications. The longest reported symptom duration was greater than 2 months and the shortest was 7 days, with an average symptom duration of 29 days.

In addition to symptoms of viral upper respiratory tract infection (URI), we recorded symptoms of MC activation. Among the 28 patients, no patient endorsed MC activation symptoms during viral illness. Specifically, none reported infection-associated urticaria or anaphylaxis. Several noted an improvement in baseline pruritus, bloating, and diarrhea. These MC activation symptoms recurred after convalescence from COVID-19.

Infection with SARS-CoV-2 can induce MC activation and symptoms such as urticaria, flushing, diarrhea and hypotension(3), especially in patients with MC disorders. The absence of clinical MC activation in all 28 patients with COVID-19 is a striking finding. Lack of MC activation suggests the absence of direct MC infection, lack of secondary MC activation, or active MC suppression. Notably, SARS-CoV-2 has been reported to suppress other innate immune system pathways such as type-I interferon, suggesting the potential for a similar suppressive mechanism with MC activation.(6)

To further understand the lack of MC activation during SARS-CoV-2 infection and explain this unexpected clinical observation, we examined retrospective gene array data from highly purified

bone marrow (BM) MCs from patients with mastocytosis and healthy control subjects.(7)
BMMC gene expression data was obtained in 2013 and did not include any patients reported in
this study. BM-resident MCs did not express detectable levels of *ACE2*, consistent with reports
that oral mucosa MCs also lack *ACE2*, which likely precludes direct infection of the MC.(8)
MCs from mastocytosis patients did express elevated levels of *TLR3* and *IL1RL1*, encoding the
IL33 receptor ST2, relative to healthy controls, suggesting potential modalities for MC activation
in response to viral infections (Figure 1).

Absence of clinical evidence for MC activation during COVID-19 has been observed in other
conditions driven by MC activation, most notably in asthma. Current evidence suggest that
SARS-Cov-2 infection does not cause asthma exacerbations and is not associated with worse
outcomes in asthmatic patients.(9) Further, Th2-high asthma is known to be driven by MC-
mediated inflammation, and this condition may not increase severity of COVID-19 disease.⁵ This
is in stark contrast to other viral URIs, which are common triggers for asthma exacerbation. Our
study suggests that, in patients with mast cell disorders, MC activation does not play a major role
in the inflammatory response to SARS-CoV-2. Mast cell mediators during acute infection was
available in only one patient and was unchanged from baseline, suggesting lack of acute MC
activation in this patient.

The hospitalization rate in our cohort is higher than current United States rates in the general
population; however, this may be due to international variation across sites, particularly in Spain
and Italy during the early months of the pandemic. It is also possible patients seek additional care
and/or are prophylactically hospitalized given the mast cell disorder comorbidity. The incidence
of asymptomatic MC activation patients infected with COVID-19 is unknown, and larger studies
are needed to validate our observations. Our study is also limited by patient recall of symptoms,
which can be subjective. Due to the nature of COVID-19, direct observation of patients and
collection of empiric data such as mast cell mediators was not practical for most patients. It is
also possible that medications (antihistamines, receptor antagonists, etc) may have impacted
mast cell activation symptoms and/or COVID-19 disease severity.

To our knowledge this is the first report detailing the clinical course and outcomes of patients with MC disorders and confirmed SARS-CoV-2 infection. Our international cohort spans pediatric and adult patients with clonal and nonclonal MC disorders. We did not observe clinical evidence of SARS-CoV-2-induced MC activation. Based on these data, we hypothesize that SARS-CoV-2 infection may not cause direct or indirect MC activation. Patients with MC disorders have mortality outcomes similar to the general population when infected with SARS-CoV-2.

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191 **Table I:** Baseline characteristics of patients and SARS-CoV-2 infection data and outcome.¹

Patient	Age	Sex	Mast Cell Disorder	Baseline Tryptase (ng/mL)	KIT D816V	SARS-CoV-2 Diagnosis	Viral Symptoms	Level of Care	Oxygen Requirement	MCAS Symptoms/ Anaphylaxis	Outcome
1	52	M	ISM	140.0	-	PCR	R, C, F, M, GI	Hosp	LF	N	recovery
2	50	M	ISM	28.8	+	PCR, IgG	R, C, F, GI, T, N	Hosp	N	N	recovery
3	77	F	ISM	94.2	+	PCR	R, C, F, M	Hosp	LF	N	recovery
4	65	F	ISM	62.9	+	PCR	R, C, M	Hosp	LF	N	recovery
5	65	F	ISM	6.9	-	PCR	R, C, F	ICU	HF	N	recovery
6	38	F	ISM	66.3	+	PCR	F	Home	N	N	recovery
7	53	M	ISM	23.8	+	PCR	none	Home	N	N	recovery
8	40	F	ISM+	18.3	-	PCR	A, H, C, M	Home	N	N	*on going
9	54	F	ISM+	9.61	-	PCR	R, C, F, M, A, GI, H	Hosp	N	N	recovery
10	55	F	ISM +	97.6	+	PCR	A	Home	N	N	recovery
11	54	F	ISM +	101.0	+	PCR	C, T, N, D	Home	N	N	recovery
12	52	F	ISM +	45.0	+	IgM / IgG	A, D	Home	N	N	recovery
13	56	F	ISM +	5.9	+	IgG	R, M, H, GI	Hosp	N	N	recovery
14	61	M	ISM +	93.9	+	PCR, IgG	C, M, F, GI	Home	N	N	recovery
15	49	M	ISM +	25.8	+	IgG	C, F, R, H	Hosp	LF	N	recovery
16	72	M	ISM +	55.1	+	PCR	R, C, F, M, T	Hosp	LF	N	Death
17	45	F	ISM+	7.2	+	PCR	F, CH, M	Home	N	N	recovery
18	76	M	SM AHN	82.1	+	PCR, IgG/ IgM	F, R	Hosp	LF	N	recovery
19	60	M	SM AHN	30.6	+	PCR	C, F, M, GI	Hosp	LF	N	recovery
20	61	F	CM	16.8	+	PCR	H, M, A	Home	N	N	recovery
21	11	M	CM	18.3	-	PCR	C, GI, T, M	Home	N	N	recovery
22	16	M	CM	10.4	+	IgM	T, H, M, A	Home	N	N	recovery
23	39	F	CM	13.5	-	PCR	F, M	Home	N	N	recovery
24	6	M	CM	6.8	+	PCR	none	Home	N	N	recovery

¹ISM: Indolent systemic Mastocytosis; ISM+: Indolent systemic mastocytosis with maculopapular cutaneous mastocytosis; CM: Cutaneous mastocytosis; H α T: Hereditary alpha tryptasemia; MCAS: Mast cell activation syndrome.

Viral symptoms. R: dyspnea, C: cough, F: fever, M: malaise/fatigue, H: headache, A: anosmia, GI: nausea/diarrhea, CH: chills, T: sore throat, N: rhinorrhea, D: dysgeusia

Oxygen requirement: LF: low flow nasal cannula, HF: high flow CPAP

*Denotes MCAS with elevated baseline serum tryptase

25	51	F	H α T α 2 β 3	18.6	-	PCR	R, C, F, M	Hosp	LF	N	recovery
26	41	F	MCAS ^a	11.4	-	PCR	C, F, T, N	Home	N	N	recovery
27	51	M	MCAS ^a	15.5	-	IgG	C, F, M, A, GI, D	Home	N	N	recovery
28	58	F	MCAS ^a	26.4	-	PCR	C, F, M, H, GI, N	Home	N	N	recovery

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199 **Figure 1:** Gene expression of *ACE2*, *TLR3*, and *IL1RL1* on highly purified bone marrow mast cells from
200 normal/reactive (n=7) and systemic mastocytosis patients (n=26) from a 2013 study prior to the COVID-
201 19 pandemic.

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