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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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Clinical Implications

- COVID-19 mortality in patients with mast cell disorders is comparable with that in the general population. Bone marrow mast cells lack angiotensin-converting enzyme 2 receptors. These data argue against clinically significant mast cell activation during COVID-19 infection.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus responsible for the clinical syndrome coronavirus disease 2019 (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 pathobiological role in a range of diseases, such as asthma, rhinitis, and food allergy and MC activation disorders. Mast cell activation leads to the release of inflammatory mediators, including tryptase and several cytokines such as interleukin (IL)-6. Mast cells are often active participants in propagation of inflammation during viral infection. Reports of serious COVID-19 infections have identified IL-6, tumor necrosis factor, and IL-1β as hallmarks of cytokine storm leading to severe outcomes. Mast cells 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. 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 that also include urticaria, flushing, and hypotension, among other symptoms. Because MCs have been shown to be activators during viral infection, increased severity of SARS-CoV-2 infection in patients with MC disorders is possible. 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 hereditary alpha tryptasemia (n = 4).

This cohort of patients did not have increased COVID-19 mortality and lacked clinical symptoms of MC activation.

Twenty-eight patients with MC disorders and confirmed SARS-CoV-2 infection were identified by electronic health review, of which 57% were female and the average age was 50 years. The average baseline serum tryptase was 40.5 ng/mL (range 5.9-140 ng/mL). Average total serum immunoglobulin E was 28.9 IU/mL (range 2.0-159 IU/mL), data not shown. Seventeen patients had indolent systemic mastocytosis diagnosed according to World Health Organization criteria. Five patients had cutaneous mastocytosis and two had systemic mastocytosis with an associated hematological neoplasm. Four patients had elevated baseline serum tryptase and symptoms of MC activation. Subjects were included on the basis of a positive SARS-CoV-2 polymerase chain reaction test during acute infection in 23 of 28 patients (82%) and/or antibody test after convalescence in 5 of 28 patients (18%). Baseline characteristics are described in Table I.

Most patients had a mild course of COVID-19. Inpatient hospitalization was required in 12 of 28 patients (43%). One patient required intensive care unit admission for hypoxia; none required full mechanical ventilation. One patient with indolent systemic mastocytosis 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 of 28 patients (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 two months and the shortest was seven days, with an average symptom duration of 29 days.

In addition to symptoms of viral upper respiratory tract infection, 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, 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.

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
| Patient | Age (y) | Sex | Mast cell disorder | Baseline tryptase (ng/mL) | KIT D816V mutation | 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, GL, 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                        | Recovery |
| 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   | Home        | 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, IgM/IgG         | R, F          | Hosp        | LF                | N                        | Recovery |
| 19      | 60      | M   | SM AHN            | 30.6                     | +                 | PCR                  | C, F, M, GI   | Home        | 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, GL, 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 |
| 25      | 51      | F   | HαTαβ3            | 18.6                     | -                 | PCR                  | R, C, F, M    | Hosp        | LF                | N                        | Recovery |
| 26      | 41      | F   | MCAS*             | 11.4                     | -                 | PCR                  | C, F, T, N    | Home        | N                 | N                        | Recovery |
| 27      | 51      | M   | MCAS*             | 15.5                     | -                 | IgG                  | C, F, M, A, GL, D | Home | N                 | N                        | Recovery |
| 28      | 58      | F   | MCAS*             | 26.4                     | -                 | PCR                  | C, F, M, H, GL, N | Home | N                 | N                        | Recovery |

A, Anosmia; AHN, associated hematological neoplasm; C, cough; CH, chills; CM, cutaneous mastocytosis; D, dysgeusia; F, fever; H, headache; HF, high-flow continuous positive airway pressure; GI, nausea/diarrhea; HαTαβ3, hereditary alpha tryptasemia; Hosp, hospital; IgG, immunoglobulin G; IgM, immunoglobulin M; ISM, indolent systemic mastocytosis; ISM+, indolent systemic mastocytosis with maculopapular cutaneous mastocytosis; KIT, tyrosine kinase oncogene; LF, low-flow nasal cannula; M, malaise/fatigue; MCAS, mast cell activation syndrome; N, rhinorrhea; PCR, polymerase chain reaction; R, dyspnea; SM, systemic mastocytosis; T, sore throat.

*Denotes MCAS with elevated baseline serum tryptase.
mastocytosis and healthy control subjects. The BM MC gene expression data were obtained in 2013 and did not include any patients reported in this study. The BM-resident MCs did not express detectable levels of angiotensin-converting enzyme 2, consistent with reports that oral mucosa MCs also lack angiotensin-converting enzyme 2, which likely precludes direct infection of the MC. The MCs from mastocytosis patients did express elevated levels of toll-like receptor 3 and interleukin1 receptor like 1, encoding the IL-33 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. Further, helper T2 cells—high asthma is known to be driven by MC-mediated inflammation, and this condition may not increase severity of COVID-19 disease. This is in stark contrast to other viral upper respiratory tract infections, which are common triggers for asthma exacerbation. Our study suggests that, in patients with MC disorders, MC activation does not play a major role in the inflammatory response to SARS-CoV-2. The MC mediators during acute infection were 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 U.S. 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 MC 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. Owing to the nature of COVID-19, direct observation of patients and collection of empirical data such as MC mediators was not practical for most patients. It is also possible that medications (eg, antihistamines, receptor antagonists) may have impacted MC 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.

Acknowledgments

We thank Liqin Wang, PhD, for assistance with data collection.

FIGURE 1. Gene expression of (A) angiotensin-converting enzyme 2 (ACE2), (B) toll-like receptor 3 (TLR3), and (C) interleukin1 receptor like 1 (IL1RL1) on highly purified bone marrow mast cells from normal/reactive (N/RBM; n = 7) and systemic mastocytosis (SM; n = 26) patients from a 2013 study prior to the COVID-19 pandemic.
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