SARS-CoV-2 Infection In Patients With Mastocytosis: An EPICOVIDEHA Report

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Systemic mastocytosis (SM) is a rare hematological disease characterized by neoplastic proliferation of clonal mast cells (MCs). It involves the gastrointestinal tract, bone, liver, and spleen in addition to bone marrow and skin [1]. The symptoms caused by release of MC mediators and organ infiltration can seriously affect quality of life and survival [2].

Patients with SM are not expected to have a higher risk of infection by SARS-CoV-2 [3]; however, this risk can be augmented by comorbidities and impairment of organ function due to infiltration by MCs. Treatment of SM is based on different classes of drugs, which may have an impact on outcome in SARS-CoV-2 infection. However, no study has reported the determinants of outcomes in patients with SM and SARS-CoV-2 infection, according to concurrent treatment.

The World Health Organization diagnostic criteria for SM and SARS-CoV-2 infection and the characteristics of the Epidemiology of COVID-19 Infection in Patients with Hematological Malignancies: A European Hematology Association Survey (EPICOVIDEHA) [4,5] are reported in Appendix 1. The clinical characteristics of the patients and the timepoints for infection and vaccination are reported in the Supplementary Table. The study population comprised 9 women and 11 men with a median age of 59 years (range, 24-78) who had contracted SARS-CoV-2 infection after a median time from diagnosis of SM of 60 months (range, 2-252 months). Five presented at least 1 relevant comorbidity (25%), and 6 were active smokers (30%). The whole blood count was normal in all patients, and no exacerbations of mediator release symptoms were reported during SARS-CoV-2 infection. After receiving H1 antihistamines as premedication, 5 and 2 patients received 2 doses and 1 dose of Pfizer-BioNTech mRNA vaccine, respectively, while 1 patient received a dose of AstraZeneca vaccine. Six patients (30%) were affected by SM with associated hematological neoplasm, 3 (15%) by aggressive SM, and 11 (55%) by indolent SM. At the time of infection, 8 patients were not receiving any treatment for SM and 3 were treated with antimediator drugs. Of the 6 patients treated with midostaurin, 1 case received an allogeneic stem cell transplant (ASCT) because of a concomitant hematological neoplasm, 1 required cladribine owing to unresponsiveness to midostaurin, and 1 indolent SM patient received midostaurin for extensive vertebral fractures. The last 3 patients received treatments for concomitant hematological neoplasm (radiation therapy, hydroxyurea, and midostaurin plus chemotherapy and ASCT) (Supplementary Table).

Symptoms of infection were absent, mild, and critical in 1 case each after a single dose of vaccine and mild in 3 cases and asymptomatic in 2 cases after administration of 2 doses. Considering the clinical course of infection, patients generally presented few symptoms. Six patients remained asymptomatic, while 10 patients had a mild infection, 3 had a severe infection, and 1 had a critical infection. Among 3 patients with at least 2 comorbidities, 2 patients had a severe and critical infection. A comparison of the severity of SARS-CoV-2 infection between patients with indolent SM and advanced SM did not reveal any statistically significant differences (P=.1296, Fisher exact test). As regards therapy for SARS-CoV-2 infection, 10 patients did not receive any treatment, 3 patients received isolated corticosteroids, 2 patients received monoclonal antibodies, 2 received antiretroviral treatment, and 1 received antiviral therapy. Four patients were admitted to hospital for fever, cough, dyspnea, and worsening of symptoms (cases #1, #12, #13, and #14), with a median hospital stay of 14 days (range, 6-36 days). All patients required oxygen therapy. Cases #1, #12, and #14 required corticosteroids and cases #1 and #13 required antiretroviral therapy.

Two patients who underwent ASCT presented different clinical characteristics. One patient (case #20) required hospitalization owing to acute grade 3 gastrointestinal and cutaneous graft versus host disease (GVHD) and had asymptomatic SARS-CoV-2 infection during her stay. She received prophylactic antiviral treatment and concomitant corticosteroids and immunosuppressive drugs. The other patient (case #12) was receiving topical and oral corticosteroids for chronic GVHD and antifungal prophylaxis for previous *Aspergillus* pneumonia. He was admitted to hospital for fever and respiratory symptoms and died despite corticosteroids, inotropic support, blood component transfusions, invasive ventilation, and dialysis. At the time of this report, the other 19 patients were still alive, with a median overall survival of 139 days (range, 32-681 days).

Only 1 international study to date has reported on the outcome of patients with clonal MC disorders infected by SARS-CoV-2 (24 patients) [5]. The authors stated that infection was mild in most cases and did not cause exacerbation of symptoms caused by mediator release. Few patients received hydroxychloroquine, antiretroviral therapy, or corticosteroids for SARS-CoV-2 infection, and 1 patient died from pneumonia.

In this paper, none of the patients reported a significant increase in mediator release symptoms during SARS-CoV-2 infection or its treatment. No risk factors associated with severity of infection, need for hospital admission, or overall survival were identified, particularly according to previous or concomitant therapy for SM per se.

Although anaphylaxis has been reported following vaccination with the Pfizer-BioNTech mRNA vaccine, vaccination was successful with appropriate premedication [6,7]. In our population, 8 patients were vaccinated without reactions but contracted SARS-CoV-2 infection: symptoms were mild, and hospital care was not required in 6 of them. As in the general population, vaccination is not expected to eliminate the risk of infection, although it plays a key role in reducing severity of symptoms and mortality.

Case #12 received 1 dose of vaccine only 11 days before SARS-CoV-2 infection; however, he died from an infection resulting from his ASCT 17 months previously. Compared with the SM population overall, both immunosuppressive therapy and chronic GVHD may have played a major role in worsening outcomes. The other transplant recipient (case #20) was also infected during immunosuppressive treatment for acute GVHD, although she had been vaccinated 300 days before the infection and 173 days before the ASCT. It is probable that the different timing of vaccination may have affected the immune response to the vaccine, the level of protection of the humoral response, and, ultimately, outcome.

Neither SM itself nor concomitant therapy seems to have a strong impact on the clinical course of SARS-CoV-2 infection. Vaccination was safe, as no adverse events were reported after

appropriate premedication. ASCT might be a risk factor for mortality, owing to possible long-term immunosuppressive therapy and reduced response to vaccination.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Metcalfe DD. Mast cells and mastocytosis. Blood. 2008;112:946-56.
2. Muñoz-González JI, Álvarez-Twose I, Jara-Acevedo M, Zanotti R, Perkins C, Jawhar M, et al. Proposed global prognostic score for systemic mastocytosis: a retrospective prognostic modelling study. Lancet Haematol. 2021;8(3):e194-e204.
3. Valent P, Akin C, Bonadonna P, Brockow K, Niedoszytko M, Nedoszytko B, et al. Risk and management of patients with mastocytosis and MCAS in the SARS-CoV-2 (COVID-19) pandemic: Expert opinions. J Allergy Clin Immunol. 2020;146(2):300-6.
4. Salmanton-García J, Brusca A, Cornely O, Corradini P, Hoenigl M, Klimko N, et al. EPICOVIDEHA: A Ready to Use Platform for Epidemiological Studies in Hematological Patients With COVID-19. Hemasphere. 2021;5(7): e612.
5. Pagano L, Salmanton-García J, Marchesi F, Brusca A, Corradini P, Hoenigl M, et al. COVID-19 infection in adult patients with hematological malignancies: European Hematology Association Survey (EPICOVIDEHA). J Hematol Oncol. 2021;14:168.
6. Giannetti MP, Weller E, Alvarez-Twose I, Torrado I, Bonadonna P, Zanotti R, et al. COVID-19 infection in patients with mast cell disorders including mastocytosis does not impact mast cell activation symptoms. J Allergy Clin Immunol Pract. 2021;9(5):2083-6.
7. Rama TA, Moreira A, Castells M. mRNA COVID-19 vaccine is well tolerated in patients with cutaneous and systemic mastocytosis with mast cell activation symptoms and anaphylaxis. J Allergy Clin Immunol. 2021;147(3):877-8.
8. Rama TA, Alvarez-Twose I. Delving Into COVID-19 Vaccination–Induced Anaphylaxis: Are mRNA Vaccines Safe in Mast Cell Disorders? J Investig Allergol Clin Immunol. 2021;31(2):193-5.

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