

## SARS-CoV-2 Infection among Patients with Mastocytosis: An EPICOVIDEHA Report

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**Palabras clave:** Mastocitosis sistémica. SARS-CoV-2.

Systemic mastocytosis (SM) is a rare hematological disease characterized by a neoplastic proliferation of clonal mast cells (MCs) involving gastro-intestinal tract, bone, liver and spleen in addition to bone marrow (BM) and skin [1]. Symptoms from MCs mediators release and organ infiltration can seriously affect quality of life and survival [2].

Patients with SM were 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 MCs infiltration. Treatment of SM is based on different class of drugs, which may have an impact on outcome of patients with SARS-CoV-2 infection. However, no study has reported determinants of outcomes in patients with SM and SARS-CoV-2 infection, according to concurrent treatment.

#### *Clinical characteristics of patients*

WHO diagnostic criteria for SM and SARS-CoV-2 infection and EPICOVIDEHA [4,5] characteristics are reported in appendix 1. The clinical characteristics of the patients, timing of infection and vaccination are reported in Supplementary table. They were 9 female and 11 male patients with a median age of 59 years (range 24-78), and contracted SARS-CoV-2 infection after a median time from SM diagnosis of 60 months (range 2-252 months). Five presented at least a relevant comorbidity (25%) and 6 were active smokers (30%). Whole blood count was normal in all patients, and no exacerbation of mediator release symptoms was reported during SARS-CoV-2 infection. After H1 antihistamines as premedication, 5 and 2 patients received two and one doses of Pfizer-BioNTech mRNA vaccine respectively, while 1 patient received a dose of AstraZeneca vaccine. Six (30%) patients were affected by SM with associated hematological neoplasm (SM-AHN), 3 (15%) by aggressive SM (ASM) and 11 (55%) by indolent SM (ISM). At the time of infection, 8 patients were not receiving any treatment for SM and 3 were treated with anti-mediator drugs. Among 6 patients treated with midostaurin, one case was followed by allogeneic stem cell transplantation (ASCT) for concomitant hematological neoplasm, one required cladribine due to unresponsiveness to midostaurin, and other ISM 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 SARS-CoV-2 infection*

Symptoms of infection were absent, mild and critical in one case each after a single dose of vaccine, while it was mild in 3 cases and asymptomatic in 2 cases after administration of 2 doses. Considering the clinical course of infection, patients mostly presented few symptoms. Six patients remained asymptomatic, while 10 patients presented a mild infection, 3 had a severe and 1 a critical infection. Among 3 patients with at least two comorbidities, 2 patients presented with severe and critical infection. Comparison between patients with ISM and advanced SM, in terms of severity of SARS-CoV-2 infection, did not show any statistical significant difference ( $p = 0.1296$ , Fisher's exact test). As regards therapies for SARS-CoV-2 infection, 10 patients did not receive any treatment, 3 patients received isolated steroids, 2 cases underwent monoclonal antibodies, other 2 antiretroviral treatment and other one antiviral therapy. Four patients were admitted to hospital for fever, cough, dyspnea and worsening clinical conditions (cases #1, #12, #13 and #14), with a median length of in hospital stay of 14 days (range 6-36 days). All patients required oxygen therapy, cases #1, #12 and #14 required steroids and case #1 and #13 required antiretroviral therapy.

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

### *Discussion*

Since now, a single international study reported on outcome of 24 patients with clonal MC disorders infected by SARS-CoV-2 [5]. The authors stated that infection was mild in most cases and did not cause exacerbation of mediator release symptoms. Few patients received hydroxychloroquine, antiretroviral therapy or steroids for SARS-CoV-2 infection, and one patient died from pneumonia.

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

Although anaphylaxis have been documented following vaccination with Pfizer-BioNTech mRNA vaccine, successful vaccination was reported 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 for 6 of them. As in the general population,

vaccination is not expected to eliminate the risk of infection but it is of paramount importance in reducing severity of symptoms and mortality.

Although case #12 received one dose of vaccine just 11 days before SARS-CoV-2 infection, he died due to infection after ASCT 17 months before. Compared to SM population overall, both immunosuppressive therapy and chronic GVHD may have played a major role in worsening outcome. The other transplanted patient (case #20) was infected during immunosuppressive treatment for acute GVHD as well, but she received vaccination 300 days before infection and 173 days before ASCT, respectively. It is probable that the different timing of vaccination may have affected the immune response to vaccine, the level of protection of humoral response and ultimately the outcome.

Neither SM itself nor concomitant therapy seem to have a strong impact on clinical course of SARS-CoV-2 infection. Vaccination was safe, as nobody reported adverse events after appropriate premedication. ASCT might be a risk factor for mortality, due to possible long-term immunosuppressive therapy and reduced response to vaccination.

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### **Conflict of interest**

All the authors have no disclosures to declare for this submitted paper.

## 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 Jul; 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.