Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Impact of mental health on disease activity in mastocytosis during COVID-19 pandemic

Nida Öztop a, Semra Demir a, Şengül Beyaz a, Derya Ünal b, Bahauddin Çolakoğlu a, Suna Büyüköztürk a, Aslı Gelincik a, b, *

a Division of Immunology and Allergic Diseases, Department of Internal Medicine, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey
b Division of Immunology and Allergic Diseases, Department of Internal Medicine, Yedikule Education and Training Hospital, Istanbul, Turkey

ARTICLE INFO

Article history:
Received 23 April 2021
Received in revised form 6 July 2021
Accepted 19 July 2021
Available online xxx

Keywords:
COVID-19
DASS-21 scale
Fear of COVID-19
Mastocytosis
Mental health

Abbreviations:
AdvSM, Advanced systemic mastocytosis;
AS, Anxiety subscale; CM, Cutaneous mastocytosis;
COVID-19, Coronavirus Disease-19; CRH, Corticotrophin releasing hormone; CRHR-1, Corticotrophin releasing hormone receptor-1; DS, Depression subscale; FCV-19S, Fear of COVID-19 Scale; ISM, Indolent systemic mastocytosis; IQR, Interquantile range; LP, Lockdown Period; MCs, Mast cells; RTNP, Return to Normal Period; SARS-COV2, Severe Acute Respiratory Syndrome Coronavirus2; SCORMA, Scoring Mastocytosis Index; SS, Stress subscale; tDASS-21, total Depression-Anxiety-Stress Scale; NS, Not significant

ABSTRACT

Background: Mast cell-related symptoms might be influenced by mental health status in mastocytosis. In this study, we aimed to investigate the influence of mental health problems developed during the COVID-19 pandemic on the course of mastocytosis.

Methods: Mental health status in 60 adult patients with mastocytosis was prospectively evaluated with the total Depression-Anxiety-Stress Scale (tDASS-21) and Fear of COVID-19 Scale (FCV-19S) in the lockdown period (LP) and the return to normal period (RTNP) during the pandemic. The disease course was assessed from emergency and outpatient medical reports, including Scoring Mastocytosis (SCORMA) index and serum baseline tryptase levels, by telephone interviews and clinical visits.

Results: The mean FCV-19S and median tDASS-21 scores were significantly higher in LP than RTNP (p < 0.001) and there was a positive correlation between FCV-19S and tDASS-21 in LP (r = 0.820, p < 0.001) and in RTNP (r = 0.572 p < 0.001). Disease-related symptoms including skin lesions, flushing and anaphylaxis attacks increased in 22 patients in LP, and in this group, mean FCV-19S and median tDASS-21 were higher than those without symptom exacerbation (p < 0.001). During the study period, four (6.7%) patients who experienced COVID-19 recovered without any requirement for hospitalization and had not experienced symptom exacerbation.

Conclusions: Fear of COVID-19 can be a reason for mental health changes, including depression, anxiety and stress which may further increase mast cell-related symptoms. Therefore, psychological support is important to control the severity of mast cell-related symptoms in mastocytosis during a pandemic.

Copyright © 2021, Japanese Society of Allergology. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

The coronavirus disease 19 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-COV2), is considered the major global health crisis of our century. After the declaration of the first case on March 11, 2020 by the Turkish Ministry of Health, the first restrictions on transportation were imposed on March 13, 2020, and a national lockdown in Turkey was declared on April 11, 2020 similar to other countries. Turkish Ministry of Health announced that 163,942 people were infected with COVID-19 and 4540 people died due to COVID-19 in Turkey from March 2020 to the end of May 2020. Social restrictions together with the fear of the disease itself, have affected mental health by increasing depression, anxiety, fear, insomnia and stress

* Corresponding author. Division of Immunology and Allergic Diseases, Department of Internal Medicine, Istanbul University Faculty of Medicine, Turgut Ozal Millet Cad, 34093, Fatih, Istanbul, Turkey.
E-mail address: gelincikasi@hotmail.com (A. Gelincik).
Peer review under responsibility of Japanese Society of Allergology.

Please cite this article as: Öztop N et al., Impact of mental health on disease activity in mastocytosis during COVID-19 pandemic, Allergology International, https://doi.org/10.1016/j.alit.2021.08.002
in the general population.6,7 Fear of being infected or dying, unemployment and thoughts of an uncertain future are some consequent results of this pandemic-related social life.6,8 It is a matter of concern that patients with chronic diseases can be more affected by this situation. In recent studies, the impact of COVID-19 on patients with chronic diseases has been reported,6,7 however, there is no data about the psychological effects of the pandemic on symptoms of mastocytosis.

Mastocytosis is a rare heterogeneous disease characterized by abnormal proliferation and accumulation of mast cells in different organs.9 Depending on the mediators released from mast cells (MCs), clinical symptoms can vary from flushing to severe anaphylaxis.10 Although most MC-related symptoms can occur spontaneously in mastocytosis, insects can be a common etiologic factor of anaphylaxis.11 Furthermore, it has been reported in mice and human studies that psychological and environmental stress can cause an increase in MC-related symptoms.9 Interestingly, in a study, stress by stimulating coronary MCs has been shown to induce or worsen coronary artery diseases.12 However, there is limited data that show the impact of mental health problems on MC mediator-related symptoms in patients with mastocytosis.14,16,17

By the onset of the COVID-19 pandemic, many people with chronic diseases have been declared as risky groups for a more severe COVID-19 course which increased the concerns for other candidate chronic diseases like mastocytosis resulting in fear of getting infected in such patients. In this current study, we aimed to investigate the effects of mental health problems developed in relation to COVID-19 pandemic on symptoms of mastocytosis.

Methods

Patient recruitment and study design

Sixty adult mastocytosis patients, diagnosed and classified according to the recent World Health Organization diagnosis and classification criteria,11 were included in the study. Patients who had psychiatric diseases and/or those who were receiving psychiatric medication were excluded from the study. According to the level of social restrictions applied by the government, the study included two periods. The first period, defined as the lockdown period (LP), was in March—May 2020, when strict restrictions were announced with the detection of the first case in the country, and the second period, called the return to normal period (RTNP), was in June—August 2020, when the previous restrictions were lessened with the permission of the controlled social life.19

Patient assessments, including disease-related symptoms and mental health status, were completed by telephone interviews and face-to-face visits in late May 2020 and late September 2020 at the end of the LP and RTNP, respectively. During the assessment calls, sociodemographic and clinical features including age, education, employment status, smoking habits, alcohol consumption, comorbid diseases, disease-related symptoms, hospital admissions for treatment or follow-up, treatment changes and diagnosis of COVID-19 during the pandemic were evaluated. Disease-related symptoms defined as anaphylaxis, flushing and increased skin lesions which are caused by mast cell activation. For the evaluation of disease-related symptoms, patients were questioned in terms of flushing attacks, skin lesions and anaphylaxis attacks. In LP or RTNP, the patients who described skin lesions were invited to the outpatient clinic and examined for skin lesions by the same physician. The scoring mastocytosis SCORMA index,20 for evaluation of skin lesions in mastocytosis, was used and compared to baseline measures that had been applied before the pandemic. The patients who declared anaphylaxis attacks were also invited to the clinic and questioned in terms of triggers, attack numbers, intervention and emergent medications. Also, medical records of emergency room applications were reviewed. Those only experiencing a sensation of flushing were asked to take photographs when they felt flushing to be evaluated by the physicians in the clinic afterwards. In addition, if patients had COVID-19 during the study period, they were evaluated in terms of suspicious contact history, the course of the infection, treatment of COVID-19, hospital or intensive care unit admissions and possible drug reactions. Serum baseline tryptase levels were measured during the LP and compared with pre-pandemic values found in the patients’ files.

Evaluation of mental health

During the LP and RTNP, mental health status including depression, anxiety and stress were evaluated with the validated Turkish version of Depression-Anxiety-Stress Scale 21 (DASS-21),22,23 a four-point Likert scale, consisting of seven items for three subscales with a rating system (0: never, 1: sometimes, 2: often, 3: almost always) (Table 1).21

The fear of COVID-19 was determined during the LP and RTNPs with the validated Turkish version of the Fear of COVID-19 Scale (FCV-19S),23,24 a self-reported seven-item, five-point Likert scale. A total score ranging from seven to 35 meant that the higher the score, the greater the fear of COVID-19 (Table 1).23,24 DASS-21 and FCV-19S were eligible for self-administration and did not require psychiatrist evaluation.

This study was approved by the local institution’s ethics committee (Approval number: 2020–86348) and received permission from the Turkish Ministry of Health (Approval number: 2020-06-03T12_43_29). Written informed consent was received from all study participants.

Statistical analysis

The data were analysed using the Statistical Package for Social Sciences (SPSS Inc. Armonk, NY, USA) v22.0, and GraphPad Prism Software 8 (San Diego, CA, USA) was used for figures. Demographic and clinical features were assessed by descriptive analysis and shown as percentages and mean ± standard deviation or median with interquartile range percentile 25–75 (IQR 25–75) according to the distribution of the data. The Kolmogorov–Smirnov test was used to assess the distribution pattern of the quantitative data. Continuous variables were compared by Independent t Test or Mann Whitney-U test between the two groups. Wilcoxon rank test and Paired Sample T Test were used to compare dependent means, and correlation analysis was performed by Pearson’s or Spearman’s correlation tests depending on the distribution of the data. Binary regression analysis was used to determine the association between mental health status and increased disease symptoms. In all analyses, p values less than <0.05 were considered as statistically significant.

Results

Results of demographic and clinical characteristics of the patients

The demographic and clinical features of the patients are demonstrated in detail in Table 2. The mean age of the patients was 43.60 ± 9.90 years and 56.7% of the patients (n = 34) were female.
Table 1
The psychological scales used in the evaluation of the patients.

| DASS-21 Scale | 0 Did not apply to me at all | 1 Applied to me to some degree, or some of the time | 2 Applied to me a considerable degree, or a good part of the time | 3 Applied to me very much or most of the time |
|---------------|-----------------------------|-----------------------------------------------|-------------------------------------------------|-----------------------------------------------|
| I found it hard to wind down | 0 | 1 | 2 | 3 |
| I was aware of dryness of my mouth | 0 | 1 | 2 | 3 |
| I couldn’t seem to experience any positive feeling at all | 0 | 1 | 2 | 3 |
| I experienced breathing difficulty (e.g., excessively rapid breathing, breathlessness in the absence of physical exertion) | 0 | 1 | 2 | 3 |
| I found it difficult to work up the initiative to do things | 0 | 1 | 2 | 3 |
| I tended to over-react to situations | 0 | 1 | 2 | 3 |
| I experienced trembling (e.g., in the hands) | 0 | 1 | 2 | 3 |
| I feel that I was using a lot of nervous energy | 0 | 1 | 2 | 3 |
| I was worried about situations in which I might panic and make a fool of myself | 0 | 1 | 2 | 3 |
| I felt that I had nothing to look forward to | 0 | 1 | 2 | 3 |
| I found myself getting agitated | 0 | 1 | 2 | 3 |
| I found it difficult to relax | 0 | 1 | 2 | 3 |
| I felt down-hearted | 0 | 1 | 2 | 3 |
| I was intolerant of anything that kept me from getting on with what I was doing | 0 | 1 | 2 | 3 |
| I felt I was close to panic | 0 | 1 | 2 | 3 |
| I was unable to become enthusiastic about anything | 0 | 1 | 2 | 3 |
| I felt I wasn’t worth much as a person | 0 | 1 | 2 | 3 |
| I felt that I was rather touchy | 0 | 1 | 2 | 3 |
| I was aware of the action of my heart in the absence of physical exertion (e.g., sense of heart rate increase, heart missing a beat) | 0 | 1 | 2 | 3 |
| I felt scared without any good reason | 0 | 1 | 2 | 3 |
| I felt that life was meaningless | 0 | 1 | 2 | 3 |

FCV-19 Scale

| 1 strongly disagree | 2 disagree | 3 neither agree or disagree | 4 agree | 5 strongly agree |
|---------------------|------------|---------------------------|-------|-----------------|
| My hands become clammy when I think about coronavirus-19 | 1 | 2 | 3 | 4 | 5 |
| I am afraid of losing my life because of coronavirus-19 | 1 | 2 | 3 | 4 | 5 |
| When watching news and stories about coronavirus-19 on social media, I become nervous or anxious | 1 | 2 | 3 | 4 | 5 |
| I can not sleep because I’m worrying about getting coronavirus-19 | 1 | 2 | 3 | 4 | 5 |
| My heart races or palpitates when I think about getting coronavirus-19 | 1 | 2 | 3 | 4 | 5 |

While 35 patients (58.3%) were living in Istanbul, the others were living in neighbouring cities. Fifty-four (90%) and 26 (43.3%) patients could not come to the hospital for follow-up visits in LP and RTNP, respectively. Eight patients (13.3%) with mastocytosis continued receiving venom immunotherapy either every four or eight weeks. Five (8.33%) with uncontrolled recurrent anaphylaxis attacks and two patients (3.33%) with increased skin lesions were on omalizumab treatment and continued their treatment without any interruption during the pandemic. All patients had c-KIT D816V gene mutation.

Comparison of mental health status measures in LP and RTNP

The median (IQR 25–75) values of tDASS-21 were 8.5 (0–20) and 0 (0–3), and the mean values of FCV-19S were 21.07 ± 7.52 and 15.63 ± 5.56 in LP and RTNP, respectively. The median tDASS-21 and the mean FCV-19S significantly decreased in RTNP compared to LP (p < 0.001). In addition, the median (IQR 25–75) values of depression (DS), anxiety (AS) and stress (SS) subscale scores were lower in RTNP than those in LP (p < 0.001, for each comparison). In Figure 1, comparison of FCV-19S, tDASS-21, DS, AS, SS and median, mean and p values in LP and RTNP were shown.

The distribution of the patients according to the severity of their mental health findings is shown in Table 3. While more patients had normal mental health status or mild mental health findings in the RTNP, the number of patients with moderate to severe mental health findings was higher in the LP (Table 3).

In the correlation analysis, FCV-19S was positively correlated with tDASS-21 (LP; r = 0.621, p < 0.001; RTNP; r = 0.399, p = 0.002) and with DASS-21 three subscales in both LP and RTNP [(with DASS-21 DS scores: in LP; r = 0.746, p < 0.001; in RTNP; r = 0.372, p = 0.003) (with DASS-21 AS scores: in LP; r = 0.893, p < 0.001; in RTNP; r = 0.399, p = 0.002) (with DASS-21 SS scores: in LP; r = 0.702, p < 0.001, in RTNP; r = 0.621, p < 0.001)]. In Figure 2, correlations of FCV-19S, tDASS-21, DS, AS, SS and median, mean and p values and r correlation coefficients in LP and RTNP were shown.

Frequency of disease-related symptoms and their correlation with mental health status in the LP and RTNP

The patients were further allocated into two groups: those with and without an increased number of disease-related symptoms.
Disease-related symptoms were more common among younger patients (p = 0.036, Table 4). During the LP, anaphylaxis, flushing attacks and skin rash increased in number in three, 12 and seven patients, corresponding to 36.7% (n = 22) of the patients when compared to the frequency of symptoms during the pre-pandemic period, respectively (p < 0.001). Anaphylaxis was seen in two patients with indolent systemic mastocytosis (ISM) and in one patient with advanced systemic mastocytosis (AdvSm) in LP. No triggers for anaphylaxis were detected in these patients. The mean SCORMA index in seven patients significantly increased in the LP when compared to their baseline mean SCORMA index (34.95 ± 5.98 vs 26.15 ± 5.09, p < 0.001). Skin lesions increased in two patients with cutaneous mastocytosis (CM) and in five patients with ISM, however, in AdvSm, no skin lesion increases were seen. Flushing attacks were seen in 11 patients with ISM and one patient with AdvSm in LP. During the RTNP, 13.3% (n = 8) of the patients had only an increased number of flushing attacks in the RTNP when compared to the number of attacks during the pre-pandemic period, there were not detected any increases in anaphylaxis attack or skin lesions in RTNP.

The mean value of FCV-19S and the median values of tDASS-21, DS, AS and SS scores were significantly higher in patients with increased disease-related symptoms than in others in both the LP and RTNP (please refer to Table 4 for p values).

Median (IQR 25–75) serum baseline tryptase levels before the pandemic and during LP were 26 (13.3–60) kU/L and 26 (12.1–61) kU/L, respectively (p = 0.161). When comparing the serum baseline tryptase levels measured before the pandemic and during the LP among the patients with increased symptoms in LP, the median (IQR 25–75) serum baseline tryptase levels were significantly higher during LP than before the pandemic [30.71 (13.5–38) kU/L vs 42.25 (17.17–52.2) kU/L, p < 0.001].

In correlation analysis between mental health scales in the group with increased disease-related symptoms, FCV-19S was positively correlated with tDASS-21 (r = 0.764, p < 0.001), DASS-21 DS (r = 0.544, p = 0.009), DASS-21 AS (r = 0.786, p < 0.001) and DASS-21 SS (r = 0.412, p < 0.001) in LP. When correlation analysis was done in the RTNP, FCV-19S was positively correlated with tDASS-21 (r = 0.522, p = 0.013) and DASS-21 SS (r = 0.588, p = 0.004), but there was no correlation with DASS-21 AS (r = 0.379, p = 0.08) and DASS-21 DS scores (r = 0.350, p = 0.111).

According to the binary regression analysis, there were no relationships between FCV-19S, tDASS-21 and DASS-21 AS scores and increased number of disease-related symptoms, while DASS-21 DS and DASS-21 SS were related to the presence of an increased number of disease-related symptoms (Table 5). There were no association between FCV-19S, tDASS-21, DASS-21 DS, DASS-21 AS, DASS-21 SS and working or education status.

**Demographic and clinical features of the patients who were diagnosed with COVID-19**

Four patients (6.7%), mean age 38.75 ± 21.48 years, had COVID-19 in the LP. All patients had positive polymerase chain reaction for COVID-19, and two patients’ thoracic computerized tomography findings were compatible with COVID-19. None of them needed to stay at the hospital, and all of them well tolerated the medications for COVID-19. During COVID-19 infection, increased MC-related symptoms weren’t seen in any of the patients. The demographic and clinical characteristics of these patients are summarized in Table 6.

**Discussion**

The current study evaluates the effects of psychological factors related to the COVID-19 pandemic on the course of mastocytosis for the first time and reports a mastocytosis patient series having COVID-19. It reveals that mental health deterioration due to the pandemic can negatively influence mastocytosis symptoms even though the patients are not infected, especially during the strict social restriction measures applied during the pandemic.

In the current study, we determined that depression, anxiety and stress levels are higher in patients with mastocytosis in the LP and can decrease when the restriction measures are lessened. In the past, during similar pandemics, serious concerns such as the fear of death arose; furthermore, during lockdown, anxiety and anger developed in people due to loneliness and uncertainty about the future.23 Additionally, during the COVID-19 pandemic, the study scale, DASS-21, revealed rises in depression, anxiety and stress levels in the general population in India,26 Mexico25 and Philippines.27 Karabacak et al. have recently reported the pandemic effect on hereditary angioedema attacks by using the same psychiatric scales and have found that the restriction measures during COVID-19 outbreak can cause an increase in the number of HAE attacks in relation to anxiety, depression, stress and fear of COVID-19.28 Up to now, no studies evaluating the influence of mental health problems developed during the COVID-19 pandemic on the course of mastocytosis have been published, and our findings are important in this sense. Due to the rapid spread and pandemic announcement of COVID-19, worldwide fear of infection has increased.3,24 Interestingly, it was assumed that fear-induced stigma in a pandemic can hide clinically relevant early symptoms and increase the transmission of the virus in a community.29 Reducing fear and stigma between individuals during pandemics can be important in controlling transmission and mental health.29 Consequently, a validated tool assessing the level of fear

| Table 2 | Demographic and clinical features of the patients with mastocytosis. |
|---------|-----------------------------|
| Age (years, mean ± SD) | 43.60 ± 9.90 |
| Gender | |
| Female (n,%) | 34 (56.7%) |
| Male (n,%) | 26 (43.3%) |
| Smokers (n,%) | 38 (63.3%) |
| Alcohol consumption (n,%) | 10 (16.7%) |
|Education | |
| Not going to school (n,%) | 4 (6.7%) |
| Primary school (n,%) | 14 (23.3%) |
| High school (n,%) | 21 (35%) |
| University (n,%) | 21 (35%) |
| Working status (n,%) | |
| Active work (n,%) | 7 (11.7%) |
| Flexible work (n,%) | 23 (38.3%) |
| Housewife (n,%) | 19 (31.7%) |
| Salary without work (n,%) | 6 (10%) |
| Retired (n,%) | 3 (5%) |
| Fired (n,%) | 2 (3%) |
| Comorbid diseases | |
| Diabetes mellitus (n,%) | 9 (15%) |
| Hypertension (n,%) | 13 (21.7%) |
| Hyperlipidemia (n,%) | 4 (6.7%) |
| Hypothyroidism (n,%) | 3 (5%) |
| Malignancy (n,%) | 2 (3.3%) |
| Type of mastocytosis | |
| CM (n,%) | 5 (8.3%) |
| ISM (n,%) | 50 (83.3%) |
| AdvSm (n,%) | 5 (8.3%) |
| Duration of disease (years, mean ± SD) | 6.27 ± 4.91 |
| Serum baseline tryptase level (kU/L), (median, IQR 25–75) | 25.7 (12.65–38.55) |
| Regular visit to hospital for follow-up in LP (n,%) | 6 (10%) |
| Regular visit to hospital for follow-up in RTNP (n,%) | 34 (56.7%) |

AdvSm, Advanced systemic mastocytosis; CM, Cutaneous mastocytosis; FCV-19S, Fear of COVID-19 scale; ISM, Indolent systemic mastocytosis; LP, Lockdown period; RTNP, Return to Normal period; SD, Standart deviation.

Please cite this article as: Oztap N et al., Impact of mental health on disease activity in mastocytosis during COVID-19 pandemic, Allergology International, https://doi.org/10.1016/j.alit.2021.08.002
associated with COVID-19, FCV-19S, to reduce the mental health problems that may develop during the pandemic has been developed and used in many countries. In our study, the mean FCV-19S was significantly higher in the LP than in the RTNP in strong correlation with tDASS-21 and DASS-21 subscale scores. It has been reported that factors about pandemic could have negative effects on mental health in healthy population in general also anxiety, depression, fear and stress were seen not only in patients with COVID-19, it has also seen in healthy individuals. In Turkey, it has been reported that increased depression and anxiety frequencies were detected in healthy population during the pandemic. Although we have no data about the mental health status of our mastocytosis patients before the pandemic, according to these findings, we can speculate that anxiety, depression and stress developed during the pandemic are related to the fear of COVID-19 in mastocytosis. However, since we did not have a healthy control group, we could not know how much the effect of COVID-19 on mental health in mastocytosis compared to the normal population.

There are several clinical clues showing the role of psychological stress in inducing MC-related diseases, including mastocytosis. Psychological stress, by stimulating the release of corticotrophin releasing hormone (CRH) into the serum, can induce MC degranulation. In case of acute stress, increased serum CRH can lead to a rise in skin vascular permeability by stimulating MCs. Additionally, MCs can synthesize CRH and express CRH receptor-1 (CRHR-1). Both environmental and psychological stress can worsen symptoms of anxiety, flushing and angioedema in patients with MC-associated diseases like anaphylaxis, asthma, CM and angioedema. An increase in skin lesions after an acute anxiety attack in a female patient with urticaria pigmentosa was found to be associated with high serum CRH levels and skin CRH-R1 expression. In another case report, anaphylaxis induced by psychological stress was detected in a 33-year-old female patient. In line with these reports, in our study, an increase in disease related symptoms in correlation with mental health status findings was observed in 22 patients during the LP and in eight patients during the RTNP. In patients with increased symptoms in LP, serum baseline tryptase

**Table 3**

Distribution of patients according to the severity of depression, anxiety and stress in LP and RTNP.

|                | LP             | RTNP            |
|----------------|----------------|-----------------|
| **Depression** |                |                 |
| Normal (n,%)   | 49 (81.7%)     | 59 (98.3%)      |
| Mild (n,%)     | 4 (6.7%)       | 0 (0%)          |
| Moderate (n,%) | 5 (8.3%)       | 1 (1.7%)        |
| Severe (n,%)   | 1 (1.7%)       | 0 (0%)          |
| Extremely severe (n,%) | 1 (1.7%) | 0 (0%) |
| **Anxiety**    |                |                 |
| Normal (n,%)   | 30 (50%)       | 59 (98.3%)      |
| Mild (n,%)     | 7 (11.7%)      | 1 (1.7%)        |
| Moderate (n,%) | 6 (10%)        | 0 (0%)          |
| Severe (n,%)   | 4 (6.7%)       | 0 (0%)          |
| Extremely severe (n,%) | 13 (21.7%) | 0 (0%) |
| **Stress**     |                |                 |
| Normal (n,%)   | 41 (68.3%)     | 60 (100%)       |
| Mild (n,%)     | 10 (16.7%)     | 0 (0%)          |
| Moderate (n,%) | 4 (6.7%)       | 0 (0%)          |
| Severe (n,%)   | 5 (8.3%)       | 0 (0%)          |
| Extremely severe (n,%) | 0 (0%) | 0 (0%) |

LP, Lockdown period; RTNP, Return to normal period.
levels were significantly higher during LP than before the pandemic period. Since serum tryptase level is a marker of mast cell degranulation, this finding can show us that psychological stress and other mental health problems induced during the pandemic are strongly associated with disease activity of mastocytosis and are higher when strict social restriction measures are applied. Although we have no previous data about the mental health status of our patients prior to the pandemic, our findings indicated that fear of COVID-19 during the LP can lead to an increase in MC-related symptoms by causing an increase in the level of stress and depression in patients with mastocytosis.

Due to the rapid spread of COVID-19, many physicians were concerned about the course of COVID-19 in mastocytosis and, however, assumed it to be the same as seen in general population. In our study, all of whom were receiving famotidine and fexofenadine for mastocytosis, were reported as having experienced COVID-19. All these patients well tolerated medications for COVID-19 and did not possess severe COVID-19 symptoms. Also same as

---

**Table 4**

| Features                          | Patients with increased symptoms (n = 22) | Patients without increased symptoms (n = 38) | p     |
|-----------------------------------|----------------------------------------|---------------------------------------------|-------|
| Age (years) (mean ± SD)           | 40.09 ± 7.99                           | 45.63 ± 10.42                               | 0.036 |
| Gender                            |                                         |                                             |       |
| Female (n,%)                      | 15 (68.2%)                             | 19 (50%)                                    | 0.171 |
| Male (n,%)                        | 7 (31.8%)                              | 19 (50%)                                    |       |
| Body mass index (kg/m²) (mean ± SD) | 27.72 ± 4.90                         | 26.46 ± 4.82                               | 0.336 |
| Smoking habits (n,%)              | 13 (59.1%)                             | 25 (65.8%)                                  | 0.604 |
| Type of mastocytosis              |                                         |                                             |       |
| CM (n,%)                          | 2 (9.1%)                               | 3 (7.9%)                                    | 0.872 |
| ESM (n,%)                         | 18 (81.8%)                             | 32 (84.2%)                                  | 0.811 |
| Advanced Systemic Mastocytosis    | 2 (9.1%)                               | 3 (7.9%)                                    | 0.872 |
| Comorbid diseases                 |                                         |                                             |       |
| Diabetes mellitus (n,%)           | 2 (9.1%)                               | 7 (18.4%)                                   | 0.329 |
| Hypertension (n,%)                | 3 (13.6%)                              | 10 (26.3%)                                  | 0.251 |
| Hyperlipidemia (n,%)              | 2 (9.1%)                               | 2 (5.3%)                                    | 0.567 |
| Hypothyroidism (n,%)              | 1 (4.5%)                               | 2 (5.3%)                                    | 0.902 |
| Malignancy (n,%)                  | 1 (4.5%)                               | 1 (2.6%)                                    | 0.691 |
| Duration of diseases (years) (median, IQR 25–75) | 6 (3–9.5)                              | 4.5 (3–6.25)                                | 0.479 |
| Serum baseline tryptase level (kU/L) (median, IQR 25–75) | 26 (142–38)                            | 22.7 (11.7–60)                              | 0.948 |
| FCV-19S (mean ± SD)               |                                         |                                             |       |
| LP                                | 26.36 ± 4.59                           | 18.00 ± 7.20                                | <0.001|
the literature, none of the mastocytosis patients had increased disease related symptoms during COVID-19 infection.\textsuperscript{35} It is hard to make definite conclusions regarding the small number of patients infected during our study; however, we may speculate that being at a younger age, having no comorbidities and taking no immunosuppressive agents during the COVID-19 pandemic might have reduced the mortality and hospitalization rates due to COVID-19 in patients with mastocytosis. In the literature, it has been reported that using high dose famotidine could be effective on improvement COVID-19 symptoms.\textsuperscript{36,37} Since the evidence is very low, we can only speculate that using famotidine could have a positive effect on the improvement of COVID-19 symptoms in our study population. However, further studies with a higher number of patients are needed to confirm these findings.

Our study has several limitations. First, we could not evaluate the mental health status of our patients with the same scales in the pre-pandemic period, which restricted us from reaching more accurate conclusions. However, by excluding those taking psychiatric medications and those having psychiatric diagnoses, we believe that we have increased the strength of our findings. Furthermore, all the patients recovered during the RTNP without applying to a psychiatrist or consuming psychiatric medications during strict social restrictions so that we can assume that the deterioration in mental health status was possibly related to the pandemic rather than the disease itself. A second limitation is that we could not have confirmed the presence of anaphylaxis by measuring serum trypase levels during anaphylaxis episodes since such tests are not available in most emergency rooms. However, the presence of medical records taken during the attacks and the fact that none of the patients’ attacks were their first attacks have supported the anaphylaxis diagnosis of our patients. As a third limitation of our study, we could not compare our findings with a healthy control group since pandemic related social restrictions did not lead healthy subjects’ admissions to a hospital for a clinical study. However, by comparing the data of mastocytosis patients without having any psychiatric comorbidities in two different social restriction periods, our findings can suggest that patients can experience an increase in neuropsychiatric findings influenced by the pandemic that may further cause an increase in mast-related symptoms. Furthermore, the SCORMA index may be argued as not being a precise objective scale in mastocytosis. However, in our clinic, patients with mastocytosis are regularly followed up by the same physicians from their initial visits and are evaluated with this index since it is a determinant for skin lesions.

In conclusion, the fear of COVID-19 occurred as a result of the COVID-9 pandemic, and social restriction measures can deteriorate mental health status and thereby the course of mastocytosis.

### Table 5
Factors in association with increased symptoms in LP according to the binary regression analysis.

| Increased symptoms | OR      | 95% CI for OR (Lower-Upper) | p      |
|--------------------|---------|-----------------------------|--------|
| LP                 |         |                             |        |
| FCV-19S            | 1.131   | 0.751—1.703                 | 0.556  |
| DASS-21 DS         | 0.805   | 1.183—3.357                 | 0.010  |
| DASS-21 AS         | 0.646   | 0.346—1.208                 | 0.171  |
| DASS-21 SS         | 0.372   | 0.207—0.667                 | 0.001  |

AS, Anxiety subscale; CI, Confidence Interval; DASS-21, depression, anxiety, stress scale with 21 questions; DS, Depression subscale; FCV-19S, Fear of COVID-19 scale; LP, Lockdown Period; SS, Stress subscale. P values <0.05 in bold is considered significant.

### Table 6
Demographic and clinical characteristic of patients infected by SARS-COV-2.

| Case No | Age (year) | Gender | Smoker | Job | Comorbidity | Type of treatmnt for | Drug reaction | Drug reaction in history | AS, Anxiety subscale; CI, Confidence Interval; DASS-21, depression, anxiety, stress scale with 21 questions; DS, Depression subscale; FCV-19S, Fear of COVID-19 scale; LP, Lockdown Period; SS, Stress subscale. P values <0.05 in bold is considered significant. | p |
|---------|------------|--------|--------|-----|-------------|----------------------|--------------|--------------------------|-----------------------------|
| 1       | 37         | F      | No     | Nurse | Absent ISM | Positive             | Positive      | HCQ + AZ + FF + Enoxaparin | Negative                    | <0.001 |
| 2       | 69         | F      | No     | Retired | Absent | Positive             | Positive      | HCQ + AZ + FF + Enoxaparin | Negative                    | <0.001 |
| 3       | 30         | F      | Yes    | Student | Absent | Positive             | Positive      | HCQ + AZ + FF + Enoxaparin | Negative                    | <0.001 |
| 4       | 19         | F      | Yes    | Student | Absent | Positive             | Positive      | HCQ + AZ + FF + Enoxaparin | Negative                    | <0.001 |

AZ, Azithromycin; EP, Enoxaparin; F, Female; FP, Favipravir; HCQ, Hydroxychloroquine; HI, Hypertension; I, Indolent systemic mastocytosis; M, Male; No, Negative; O, Omalizumab; No, No; P, Fexofenadine; PP, Placebo; Positive, Positive; Retired, Retired; Student, Student; S, Fexofenadine; SS, Stress subscale.
Therefore, psychological support seems to be important to control the symptoms of mastocytosis in conditions like a pandemic that can affect the patient’s mental health status.

Acknowledgements

This study has no funding source. This study was approved by the local institution’s ethics committee (Approval number: 2020–86348) and received permission from the Turkish Ministry of Health (Approval number: 2020-06-03T12_43_29).

Conflict of interest

The authors have no conflict of interest to declare.

Authors’ contributions

NO, SD, Bİ, DO and AG designed the study, contributed to data collection, performed the statistical analysis and wrote the manuscript. SBÜ and BC performed interpretation of the results. All authors read and approved the final manuscript.

References

1. Maggi E, Canonica GW, Moretta L. COVID-19: unanswered questions on immune response and pathogenesis. J Allergy Clin Immunol 2020;146:18–22.
2. Hosoki K, Chakraborty A, Sur S. Molecular mechanisms and epidemiology of COVID-19 from an allergist’s perspective. J Allergy Clin Immunol 2020;146:285–99.
3. Valent P, Akin C, Bonadonna P, Brockow K, Niedozryt M, Niedozryt 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;146:300–6.
4. World Health Organization. WHO characterizes COVID-19 as a pandemic. http://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen. [Accessed 8 September 2020].
5. Turkish Ministry of Health. COVID-19 Information Platform, General Coronavirus Virus, Table 2021. https://covid19.saglik.gov.tr/TR-66935/genel-koronavirüs-tablosu.html.
6. Arafa A, Mohamed A, Saleh L, Sesoys S. Psychological impacts of the COVID-19 pandemic on the public in Egypt. Community Ment Health J 2021;57:64–9.
7. Tórales J, O’Higgins M, Castaldelli-Maia JM, Ventriglia A. The outbreak of COVID-19 coronavirus and its impact on global mental health. Int J Soc Psychiatry 2020;66:317–20.
8. Pfefferbaum B, North CS. Mental health and the Covid-19 pandemic. N Engl J Med 2020;383:510–2.
9. Choi EPH, Hui BPH, Wan EYF. Depression and anxiety in Hong Kong during COVID-19. Int J Environ Res Public Health 2020;17:3740.
10. Orhan F, Civelek E, Şahiner ÜM, Arga M, Can D, Çağançar AZ, et al. Anaphylaxis: Turkish National Guideline 2018. Asthma Allergy Immunol 2018;16:1–62.
11. Arock M, Sotlar K, Gotlib J, Sperr WR, Hartmann K, Schwartz LB, et al. New developments in the field of mastocytosis and mast cell activation syndromes: a summary of the Annual Meeting of the European Competence Network on Mastocytosis (ECNM) 2019. Leuk Lymphoma 2020;61:1075–83.
12. Carter MC, Akin C, Castells MC, Scott EP, Lieberman P. Idiopathic anaphylaxis yardstick: practical recommendations for clinical practice. Ann Allergy Asthma Immunol 2020;124:16–27.
13. Giannetti MP, Akin C, Castells M. Idiopathic anaphylaxis: a form of mast cell activation syndrome. J Allergy Clin Immunol Pract 2020;8:1196–201.
14. Kemperar D, Selvakumar GP, Ahmed ME, Raiwar SP, Thangavel R, Khan A, et al. COVID-19, mast cells, cytokine storm, psychological stress, and neuro-inflammation. Neuroscientist 2020;26:402–14.
15. Alevizos M, Karagkouni A, Panagiotidou S, Vasiadi M, Theoharides TC. Stress triggers coronary mast cells leading to cardiac events. Ann Allergy Asthma Immunol 2014;112:209–16.
16. Georgin-Lavialle S, Moura DS, Salvador A, Chauvet-Geliner JC, Launay JM, Danai G, et al. Mast cells’ involvement in inflammation pathways linked to depression: evidence in mastocytosis. Mol Psychiatry 2016;21:1511–6.
17. Theoharides TC. The impact of psychological stress on mast cells. Allergy Asthma Immunol 2020;125:388–92.
18. Wu Z, McGowan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese center for disease control and prevention. JAMA 2020;323:1239–42.
19. Theoharides TC. Stress, in Theoharides TC. Stress, inflammation, and autoimmunity: the 3 modern pathologies linked to mastocytosis does not impact mast cell activation symptoms. J Allergy Clin Immunol Pract 2021;9:2083–6.
20. Jadwitz T, Gabelen E, Patterson D, Wang TC, Consiglajo J, Tracey K, et al. Famotidine use and quantitative symptom tracking for COVID-19 in non-hospitalised patients: a case series. Gut 2020;69:1592–7.
21. Mather JF, Seip RL, McKay RG. Impact of famotidine use on clinical outcomes of hospitalized patients with COVID-19. Am J Gastroenterol 2020;115:1617–23.