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Humor and cognitive disorders in adult patients with mastocytosis

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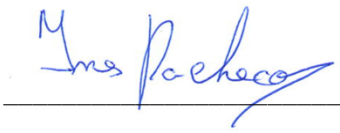

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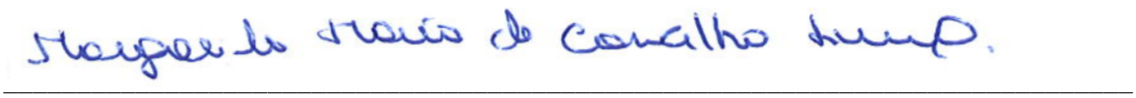

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Resumo

Introdução: As mastocitoses são um grupo heterógeno de doenças raras, que se caraterizam pela proliferação e acumulação anormal de mastócitos em um ou mais órgãos. A última atualização da classificação das mastocitoses, publicada pela Organização Mundial de Saúde em 2016, divide estas doenças em 3 grupos – mastocitoses cutâneas (MC), mastocitoses sistémicas (MS) e sarcoma de mastócitos. As manifestações clínicas das mastocitoses são muito diversas, podem ser cutâneas ou sistémicas, e resultam quer da libertação de mediadores produzidos pelos mastócitos quer da infiltração tecidular por estas células. Perturbações do humor ou cognitivas em doentes com mastocitose já foram descritas, mas a sua prevalência e características não estão bem caracterizadas.

Objetivos: Clarificar a prevalência das perturbações do humor cognitivas e caracterizá-las, numa população de doentes adultos seguidos na Consulta Multidisciplinar de Linfomas Cutâneos e Mastocitoses do CHP.

Métodos: O estudo consistiu em aplicar quatro questionários validados para avaliar as perturbações cognitivas e do humor. Os questionários usados para avaliar as perturbações cognitivas foram o Questionário das Falhas Cognitivas (QFC) e o Mini-Mental State (MMS). Para avaliar as perturbações do humor, usamos a Escala de Ansiedade e Depressão Clínica (EADC) e os Termómetros Emocionais.

Resultados: Da nossa população de base obtivemos uma taxa de resposta de 61% (50 doentes, mediana da idade de 45 anos, dos quais 76% tinham mastocitose sistémica e, 64%, a forma indolente da mastocitose sistémica). Em relação às perturbações cognitivas, no QFC obtivemos 28% de casos anormais, com apenas 10% dos casos sendo considerados anormais com o MMS. Já nas perturbações do humor, na subescala da depressão do EADC encontramos 22% de pacientes em risco de terem depressão e, no Termómetro Emocional da Depressão, 34% dos casos eram anormais. Na subescala da ansiedade do EADC, 56% dos pacientes tinham sintomatologia de ansiedade e, no Termómetro Emocional da Ansiedade, 72% dos casos eram anormais. O soma total dos Termómetros Emocionais permitiu ainda estratificar as perturbações do humor de acordo com a severidade: 24% foram classificadas como severas, 24% como moderadas e 24% como ligeiras.

Conclusões: O nosso estudo confirmou e ampliou conclusões de estudos prévios, ao sugerir uma alta prevalência de perturbações do humor e cognitivas em doentes adultos com mastocitose. Permitiu ainda fazer o rastreio de doentes que possam beneficiar de uma avaliação mais completa, assim como uma melhor compreensão das manifestações clínicas associadas à mastocitose.

Palavras-chave: Mastócitos; mastocitose; perturbações do humor; depressão; ansiedade; perturbação cognitiva.

Abstract

Background: Mastocytosis comprises a heterogeneous group of rare disorders characterized by the expansion and accumulation of clonal mast cells (MC) in one or more organs. The last classification split these diseases into cutaneous mastocytosis (CM), systemic mastocytosis (SM), and localized mast cells tumors. The clinical manifestations of SM are diverse, with both cutaneous and systemic symptoms, being the result of MC mediator release and infiltration into target organs. Humor and cognitive disorders have been reported in patients with mastocytosis, but their prevalence and characteristics are not precisely described.

Aims: To clarify the prevalence of humor and cognitive disorders and to characterize them in a population of adult patients with mastocytosis followed at a specialized multidisciplinary out clinic for mastocytosis.

Methods: The study consisted mainly in applying four validated questionnaires to evaluate both the cognitive and humor disorders. The questionnaires used to evaluate the cognitive disorders were The Cognitive Failures Questionnaire (CFQ) and the Mini-Mental State Examination (MMSE). For accessing the humor disorders, we used the Hospital Anxiety and Depression Scale (HADS) and the Emotion Thermometers (ET).

Results: From our basis population, we obtained a 61% response rate (50 patients, median age of 45 years, from which 76% had systemic mastocytosis and 64% had the indolent form of the disease). Concerning cognitive disorders, using the CFQ, 28% of the cases were abnormal, with only 10% of cases being abnormal when using the MMSE. Regarding humor disorders, in the HADS-Depression we found 22% of the patients in risk for depression, and in the Depression-ET, 34% of cases were abnormal. In the HADS-Anxiety, 56% of the patients had anxiety symptomatology and, in the Anxiety-ET, 72% of cases were abnormal. The total ET-score allowed for stratifying the humor disorders according to the severity: 24% were severe, another 24% were moderate and 24% were mild.

Conclusions: Our study confirm and extend previous observations, suggesting a high prevalence of humor and cognitive disorders in adult patients with mastocytosis, and allow the screening of patients who benefit for a more complete evaluation, and a better understanding of the clinical manifestations associated with mastocytosis.

Keywords: Mast cells; mastocytosis; humor disorders; depression; anxiety; cognitive impairment.

Abbreviations

BM, Bone Marrow
CFQ, Cognitive Failures Questionnaire
CHUP, Centro Hospitalar Universitário do Porto
CM, Cutaneous Mastocytosis
CMCL, Consulta Multidisciplinar de Mastocitoses e Linfomas Cutâneos
ECNM, European Competence Network on Mastocytosis
ET, Emotion Thermometers
GI, gastrointestinal
HADS, Hospital Anxiety and Depression Scale
IDO-1, Indoleamine 2,3-dioxygenase 1
ISM, Indolent Systemic Mastocytosis
MC, Mast Cells
MMSE, Mini-Mental State Examination
SH-AHN, Systemic Mastocytosis with an Associated Hematological Neoplasm
SM, Systemic Mastocytosis
SSM, Smoldering Systemic Mastocytosis
TRP, Tryptophan

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Introduction

Mast cells (MC) are cells from the immune system, derived from hematopoietic stem cells in the bone marrow, found in peripheral organs and tissues where they produce and release mediators upon activation by several stimuli. Once activated, MC release a variety of vasoactive, neurosensitizing and pro-inflammatory substances, known as MC mediators. These include, amongst others, biogenic amines (i.e. histamine, serotonin), proteolytic enzymes (i.e. tryptase, chymase, and acid hydrolases), lipid metabolites (i.e. prostaglandins and leukotrienes), cytokines (i.e. Tumor necrosis factor alpha), vascular and neural growth factors (e.g. Vascular endothelial growth factor and Neural growth factor) and neuropeptides (such as Substance P) [(1)].

Mastocytosis comprises a heterogeneous group of rare disorders characterized by expansion and accumulation of clonal / neoplastic MC in one or more organ systems. In patients with systemic involvement, neoplastic mast cells form focal and/or diffuse infiltrates in various organs, including the skin, bone marrow, spleen, liver, and the gastrointestinal tract. Mast cells in mastocytosis derive from neoplastic cells that display *KIT* mutations, mainly D816V. Because these mutations lead to the activation of the KIT receptor (CD117) they have been implied in the genesis of mastocytosis [(2)].

The last update on the Mastocytosis classification, published by the World Health Organization in 2016, split these diseases into three groups – cutaneous mastocytosis (CM), systemic mastocytosis (SM), and localized MC tumors – and define the criteria for diagnosis of SM and its classification in subtypes [(3)].

Cutaneous mastocytosis comprises maculopapular CM, also termed urticaria pigmentosa, diffuse cutaneous mastocytosis, and localized mastocytoma of skin. It is usually diagnosed in childhood, has a good prognosis, and in many cases, the skin lesions fade away and disappear during puberty [(3)].

Systemic mastocytosis is divided into indolent SM (ISM), smoldering SM (SSM), SM with an associated hematological (non-MC lineage) neoplasm (SM-AHN), aggressive SM (ASM), and mast cell leukemia (MCL). Systemic Mastocytosis usually develops in adults and prognosis depends on the disease subtype. The major criterion for diagnosis of SM is the presence of dense MC aggregates in internal organs, including the BM. Minor SM criteria comprise an abnormal MC morphology, expression of CD2 and/or CD25 in MCs, an activating mutation at codon 816 of *KIT* (most frequently D816V) in extracutaneous tissues, and basal serum tryptase levels higher than 20 ng/ml. For the diagnosis of SM we need a major and at least one minor SM criterion, or at least three minor criteria [(3)].

The clinical manifestations of SM are diverse, with both cutaneous and systemic symptoms, being the result of MC mediator release and/or infiltration into target organs. Indolent SM, representative of most cases of SM, is a chronic condition and does not shorten the patient's life expectancy. However, some may suffer from symptoms that greatly influence their quality of life such as cutaneous manifestations, cardiovascular (i.e. flushing and hypotension), gastrointestinal (i.e. diarrhea and abdominal pain), and musculoskeletal disorders (i.e. bone pain and fractures), allergic reactions (i.e. anaphylaxis), and constitutional symptoms like fatigue, cognitive and humor disorders, amongst others [(4)].

The existence of extensive lines of communication between the nervous system and immune system represents a fundamental principle underlying neuroinflammation. Understanding neuroinflammation also requires the understanding that non-neuronal cell, both glia and MC are an integral part of the inflammation process. Mast cells are closely related to the blood-brain barrier, playing a role in the regulation of cerebral activity and contributing to the neuroinflammation processes that are in the base of some neuropsychiatric disorders. However, due to mastocytosis being a rare disease, there are to date only a few studies on the neuropsychiatric symptoms associated to the disease, with a scarce number of patients and very shortsighted conclusions [(5)].

Humor and cognitive disorders have been reported in patients with mastocytosis, but their prevalence and characteristics are not precisely described, and, to the best of our knowledge, all the studies performed were from the same group [(6–10)]. In addition, the impact of therapies targeting MC proliferation, differentiation and degranulation on psychic symptoms of depression have been poorly investigated [(6)]. In previous studies, the prevalence of depression in mastocytosis varied between 40% and 75% [(7)]. Data suggest that depression associated to mastocytosis comprises affective-cognitive aspects (depressed mood, guilt, feelings of failure) and poor motivation (loss of interest in the work and activities) as well as anxio-somatic aspects (somatic and psychic anxiety, middle and late insomnia) [(8)].

Cognitive complaints (such as memory and attention disturbances) are also common in mastocytosis patients. A study published in 2012, with a cohort of 57 patients, found that cognitive impairment was highly prevalent (38.6%), and not related to depression [(9)]. This cognitive impairment seems to appear in the form of brain "fog", which is a constellation of symptoms that include reduced cognition, inability to concentrate and multitask, as well as loss of short and long-term memory [(11)]. Considering that, there are, to date, only a few studies, so, understanding cognitive impairment in patients with mastocytosis needs for further studies.

In this study, we intended to evaluate cognitive and humor disorders in adult patients with mastocytosis followed at a specialized multidisciplinary out clinic for adult patients with

mastocytosis, of a University hospital. Our objectives were to clarify the prevalence of humor and cognitive disorders and characterize them, to evaluate the relation between the humor and cognitive disorders and the type of mastocytosis, and to open a path to a better clinical approach to mastocytosis patients.

Patients and Methods

Host institution and research team

This study was performed at the Centro Hospitalar Universitário do Porto (CHUP), in the environment of an out clinic for patients with cutaneous lymphoma and mastocytosis (Consulta Multisciplinar de Linfomas Cutâneos e Mastocitoses, CMLC). The CMLC is a multidisciplinary weekly consultation, assured simultaneously by hematologists and dermatologists that receives patients from abroad, mainly from the northern region of Portugal. It has partnerships with other foreign mastocytosis specialized centers and it is recognized by the European Competence Network on Mastocytosis (ECNM) and by the EuroBloodNet, the European Reference Network in Rare Hematological Diseases, as a reference center for the diagnosis, treatment and follow-up of adult patients with mastocytosis.

The study was part of the training on clinical research of a medical student, Inês Pacheco, who designed the research proposal in the first half of 2018, and conducted the study, from July 2018 to March 2019, under the supervision of Margarida Lima, MD, PhD, immunohemotherapist, responsible for the curricular unit "Initiation to Clinical Research" and head of the CMLC. The study also had the support of a dermatologist (Iolanda Fernandes) and a hematologist (Renata Cabral), as well as a neuropsychologist (Sara Cavaco), a clinical onco-psychologist (Margarida Branco) and onco-psychiatrist (Sara Moreira), and Isabel Fonseca, a nutritionist with skills on biostatistics applied to clinical studies.

Literature review

The literature review was based on a search, via PubMed, of original and review manuscripts published in Medline indexed medical journals, using relevant keywords such as "cognitive impairment", "depression", "neurological features" and "mastocytosis".

Ethics statement, study approval and access of clinical information

The study proposal, entitled "Cognitive and mood disorders in adult patients with mastocytosis", registered at the CHUP with the number 2018.141 (122-DEFI/121-CES), was approved by the scientific and ethic committees, and authorized by the Direction of Hospital in June 2018. All participants gave written informed consent. Access to and use of clinical records complied with applicable legal requirements (Article 9 of the Portuguese Law 26/2016, of August 22, which approves the regime for access and re-use of administrative documents, transposing the Directives of the European Parliament and of the European Council, 2003/4/EC, of January

18, and 2003/98/EC, of November 17), and having been authorized by the Responsible for Access to Information at the CHUP.

Study population

The study population consists in adult patients with mastocytosis followed at the CMLC. Inclusion criteria were being observed at the CMLC, having 18 years old or more, having mastocytosis, having scheduled appointments during the recruitment period (1st of July of 2018 to 31st of March of 2019), and agreeing in participating in this study. There were no exclusion criteria.

Study procedures

The study consisted mainly in applying four validated questionnaires to evaluate both the cognitive and humor disorders. During the medical consultations, one of the medical assistants informed the patients about the study, and requested their permission to participate, together with the signature of an informed consent. Thereafter, the student applied the questionnaires, which took about 20-30 minutes per patient. The demographic data, disease classification, main clinical manifestations, and the serum tryptase level at the day of the consultation, were recorded from the electronic hospital registries. The use (or not) of antidepressant and/or anxiolytic medications, and the frequency (or not) of psychology and/or psychiatric consultations were also collected.

Questionnaires

The questionnaires used to evaluate the cognitive disorders were The Cognitive Failures Questionnaire (CFQ) (Broadbent, Cooper, FitzGerald & Parkes, 1982, adapted and validated in Portuguese by Ana Allen Gomes, 2016) [(12)(13)] and the Mini-Mental State Examination (MMSE) (Folstein, Folstein & McHugh, 1975, adapted and validated in Portuguese by Guerreiro and collaborators, 1994) [(14)(15)]. For accessing the humor disorders, we used the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983, validated in Portuguese by José Pais-Ribeiro) [(16)(17)], and the Emotion Thermometers (NCCN, Alex Mitchell, validated in Portuguese by Pereira, Teixeira & Figueiredo, Universidade do Minho, 2010) [(18)].

The Cognitive Failures Questionnaire

The CFQ is a 25-item self-report questionnaire assessing failures in perception, memory, and motor function in the completion of everyday tasks in the past 6 months [(12)]. Individuals are asked to rate the frequency experiences and behaviors on a 5-point scale: 0-Never, 1-Very

rarely, 2-Ocasionally, 3-Quite often, 4-Very often. A total score, ranging from “0” to “100”, is obtained by summing up the ratings of the 25 items, each scored from “0” to “4”. A study by Rast et al. (2008) indicates that the CFQ items load on three different factors. Summing scores across the relevant items will yield subscale scores representing three dimensions of cognitive impairment, each of them scoring from “0” to “24”. These dimension are: forgetfulness ("tendency to let go from one's mind something known or planned, for example, names, intentions, appointments, and words", as measured by the items 1, 2, 5, 7, 17, 20, 22, and 23); distractibility ("mainly in social situations or interactions with other people such as being absentminded or easily disturbed in one's focused attention"; evaluated by the items 8, 9, 10, 11, 14, 19, 21, and 25); and false triggering ("interrupted processing of sequences of cognitive and motor actions"; assessed by the items 2, 3, 5, 6, 12, 18, 23, and 24) [19].

Mini Mental State Examination

The MMSE questionnaire [14] has being used extensively in clinical and research settings to measure cognitive impairment [20]. The test consists of 30 questions individually scored as “0” (when the individual does not respond or gives an incorrect answer) or “1” (when he provides a correct answer), and allows to assess various cognitive functions, such as spatial-temporal orientation, short and long-term memory, attention, calculus, motor coordination, mental calculation and language. The maximum test score is of 30 points, with higher scores indicating better performances. The most frequently noted disadvantages of the MMSE relates to its lack of sensitivity to detect mild cognitive impairment, and the impact of schooling in overall performance. In Portugal, the first studies of adaptation, standardization and validation were performed by Guerreiro et al., in the 1990´s. Based on the validated Portuguese version, cutoff values according to literacy, were of 15 points for illiterate persons, 22 for individuals with 1 to 11 years of schooling, and 27 for those with more than 11 years of schooling.

Hospital Anxiety and Depression Scale

The HADS is a 14-item self-rated scale consisting of two sub-scales, which score independently: anxiety (7 items, maximum 21 points) and depression (7 items, maximum 21 points), and together yield a total HADS score (14 items, maximum 42 points) [16]. This questionnaire is been considered a “gold standard” for evaluation of anxiety and depression and psychosocial morbidity in cancer settings [21–23]. According to the original studies, a cutoff of “8” on each scale has been proposed for “likely or borderline cases” of both anxiety and depression, respectively, while the cutoff of “11” has been reported to identify more severe cases [21]. The HADS manual indicates that a score between 0 and 7 is “normal,” and equal of higher than “8” is “abnormal” (between 8 and 10 “mild,” between 11 and 14 “moderate,” and between “15”

and “21” “severe”). On the HADS total score, a cutoff of “14” has been shown to be the best predictor of general psychosocial morbidity while the cutoff of “19” has been shown to be the best identify more severe cases (e.g., major depression) [24,25]. A relatively recent systematic review with meta-analysis, on the accuracy of the HADS as a screening tool in cancer patients showed that the best thresholds were of “15” for the HADS total, “7” for the HADS depression subscale, and “10” or “11” for the HADS anxiety subscale [23]. In this study, we considered a score of ≥11 for each subscale as indicating the probable presence (“caseness”) of a mood disorder (“abnormal”), and a score of “8” to “10” being just suggestive of the presence of the respective state (“borderline”); as for the total HADS scale, a total score of ≥ 11 was considered to indicate a possible psychosocial morbidity.

Emotion Thermometers

The ET tool is a simple modular screening tool with a visual-analogue design for detection and monitoring of emotional disorders in clinical practice. The original 2007 version comprise four ET6/7/19 2:17:00 PM: distress-ET, anxiety-ET, depression-ET, and anger-ET – and a help thermometer. When looking for a specific emotion, it has been suggested to use a fixed cutoff of “4” in each thermometer. Patients with a score ≥4 should be considered to further enquiry / assessment, especially when requesting "help". When looking for overall emotional problems, a sum of the scores from the four mood thermometers should be performed, to obtain a total ET score, for which the following cutoffs have been proposed: >9 = mild, >14 = moderate, and >20 = severe.

Statistical analysis

Statistical analysis was performed using SOFA Statistics, version 1.0.4. Descriptive statistics comprise absolute numbers and relative frequencies (expressed as percentages), as well as median, minimum and maximum, and percentiles 25 and 75 values. The Spearman rank correlation test was used to assess a possible two-way linear association between two continuous variables, correlation being measured by the Spearman's rank correlation coefficient. The Mann-Whitney U test was used to compare groups. when the dependent variable was ordinal or continuous. Frequencies of categorical variables between two groups were compared using the Chi-square (χ^2) test. P values lower than 0.05 were considered statistically significant.

Results

Socio-demographic characterization, disease classification and clinical features

From a total number of 82 patients with mastocytosis observed at the CMLC from July 2018 to March 2019, fifty patients enrolled this study, accounting for a 61% response rate. The socio-demographic, clinical and laboratory data of these patients are summarized in Table 1, and did not differed significantly from the studied population (data not shown).

From the patients who participated in the study, 33 (66%) were women, and the median age was of 45 years, ranging from 21 to 84 years.

Most patients (n=38, 76%) suffered from SM, and six patients (12%) were diagnosed with CM. The differential diagnosis between SM and CM was uncertain in the remaining six patients (12%), mostly due to patients rejecting the BM study. Concerning the subgroup of SM, most patients (n=32, 64%), had the indolent form of the disease, followed by 6% (n=3) with SM-AHN, then 4% (n=2) of patients with SSM and last 2% (n=1) of patients with ASM.

Regarding the clinical manifestations commonly associated with mastocytosis and according to the medical records, 96% (n=48) of the patients had cutaneous lesions (Table 1). Sixty-four percent of the patients (n=32) presented neuropsychiatric manifestations, followed by 56% (n=28) having osteoarticular and/or musculoskeletal affection. Headaches were present in 52% (n=26) of the patients and half of the patients (n=25, 50%) presented upper gastrointestinal tract manifestations such as dyspepsia, pyrosis and postprandial fullness. A lower number of patients (11; 22%) reported cardiovascular symptoms (e.g. episodes of flushing, tachycardia, and hypotension). In addition, genitourinary symptoms (e.g. recurrent cystitis episodes, pelvic pain), allergic symptomatology or lower tract GI manifestations (diarrhea, abdominal pain, etc.), were found in 10 (20%) patients each. Lastly, 12% (n=6) of patients presented otolaryngologic manifestations, such as vertigo and tinnitus, and 6% (n=3) had respiratory problems (bronchospasm, dyspnea, etc.).

Regarding the neuropsychiatric aspects, 32 patients (64%) were considered by the physician as suffering from anxiety and/or depression, and, at the date of the consultation, 15 (30%) were medicated with antidepressants and/or anxiolytics. In addition, cognitive disturbances were mentioned in clinical registries in 26 cases (52%). These include, among others, short-term memory problems, lack of concentration or mental clarity, and/or or the inability to focus on a task, and other issues usually recognized as “brain fog”. However, only five patients (10%) had been previously observed in psychology and/or psychiatry consultations.

Finally, for the serum tryptase levels at the time of the study, we obtained a median value of 16.0, with a minimum of 2.5 and a maximum of 216 (percentiles 25 and 75 obtained were of 9.2 and 40.3, respectively). Patients with SM had serum tryptase levels significantly higher as compared to patients with CM (median values of 21.8, ranging from 3.8 to 216, and of 5.2, ranging from 2.5 to 7.2, respectively; $p < 0.001$; Mann Whitney U test). In addition, the serum tryptase level appears to have a positive correlation with age (both at the date of the consultation) ($p<0.001$, $R = 0.462$; Spearman´s test).

Data concerning psychological measures

Cognitive disorders

In the CFQ, scoring from "0" to "100", we obtained a median score of "26", ranging from "7" and to "71" (Table 2). Regarding these values, 28% of the cases were considered abnormal. For the three different dimensions evaluated with this questionnaire, we obtained a median value of "11", ranging from "0" to "27", for "forgetfulness"; a median value of "9", ranging from "1" to "24" for "distractibility", and a median value of "6", ranging from "0" to "24" for "false triggering". In addition, for "forgetfulness" 62% of the results were considered abnormal, whereas for "distractibility" 48% were considered abnormal, and for "false triggering" 32% of the results were considered abnormal (Table 2).

In the MMSE questionnaire, scoring from "0" to "30", we obtained a median score of "29", with a minimum of "21" and maximum of "30" (Table 2). Having in account the distinct cut-off values for different education levels, in this questionnaire only 10% of the cases were considered abnormal (Table 2).

Humor disorders

In the HADS questionnaire, with each subscale (anxiety and depression) ranging from "0" to "21", we obtained distinctive results (Table 3).

In the HADS-Anxiety scale, we obtained a median score of "8", with a minimum of "1" and a maximum of "19". Moreover, 24% of the cases were considered abnormal, 32% were considered borderline, and the remaining 44% were considered normal (Table 3).

In the HADS-Depression scale, we obtained a median score of "5", with a minimum of "1" and a maximum of "14". In addition, 8% of cases were considered abnormal, 14% were considered borderline, and 78% were considered normal (Table 3).

In the ET tool, we obtained the following results in each thermometer (Table 3).

In the Distress-ET, we found a median score of "4", with a minimum of "0" and a maximum of "10". Therefore, 52% of the cases were considered abnormal.

In the Anxiety-ET, we obtained a median score of “6”, with a minimum of “0” and a maximum of “10”, with 72% of the cases being considered abnormal.

In the Depression-ET, we obtained a median score of “2”, with a minimum of “0” and a maximum of “10”, with 34% of the cases being considered abnormal.

The median score obtained in the Anger-ET was “5”, ranging from “0” to “10”, and in this case, 46% of the cases were considered abnormal.

Considering the total score of the previous four ET, we obtained a median score of 14, with a minimum of “0” and a maximum of “40”. According to the previously exposed cut-offs, 24% of the cases were considered severe, 24% of the cases were considered moderate, 24% of the cases were considered mild, and the remaining 28% were considered normal (Table 3).

In the Help-ET, the median score was of “3”, with a minimum of “0” and a maximum of “10”, and 46% of the cases were considered abnormal.

Since we used two different tools to evaluate both depression and anxiety, with one being the HADS questionnaire and the other the ET, we wanted to see if we had correlation between these two questionnaires. We found statistically significant correlation between the HADS anxiety and the Anxiety-ET scores, as well as a statistically significant correlation between the HADS for depression and the Depression-ET scores ($p<0.001$ in both cases; Spearman´s test) (Figure 1). We did not find other statistically significant correlations between the parameters under study. In particular, there were not statistically significant correlations between the scores obtained for anxiety and depression and the serum tryptase levels (data not shown).

Discussion

In line with previous studies and using different instruments, our work has led us to conclude that there is a high prevalence of cognitive and humor disorders amongst mastocytosis patients. The evidence from this study also suggests that, in adult patients with mastocytosis, humor disorders are probably more prevalent than cognitive impairment, and there is a higher prevalence of anxiety disorders in comparison to depression.

For a rare group of diseases like mastocytosis, it is especially hard to gather as many as 82 patients, especially in a small country as Portugal. With a response rate of 61% (n=50), and with the socio-demographic and disease classification clinical features being similar in both groups (data not shown), we consider our results representative of the adult patients with mastocytosis followed at the CMLC.

Concerning the evaluation of cognitive impairment using the CFQ, we obtained 28% of abnormal cases, which is in line with a previous study, where cognitive impairment showed a prevalence of 39% in a cohort of 57 of patients (9). Differences between studies, although small, can be due to differences on the characteristics of the study populations (e.g. age, prevalence of the different mastocytosis subtypes, and medications), but also to the different instruments used to evaluate cognitive impairment. On the other hand, having different diagnostic tools obtaining results suggestive of cognitive impairment in mastocytosis supports the idea that there is, in fact, a higher prevalence of cognitive impairment due to this disease. The CFQ questionnaire also assesses three different dimensions of cognitive impairment: “forgetfulness”, which appears as the most relevant cognitive dysfunction in our patients; “distractibility”, the second most reported dimension in this series, being associated with easily disturbed attention and being absentminded especially in social interactions. A lower fraction of our patients had “false triggering” symptomatology, related to “interrupted processing of sequences of cognitive and motor actions".

In the second tool we used to evaluate cognitive impairment, the MMSE, which has been recognized as sensitive and specific to identify severe cognitive impairment as seen in pathologies like dementia (26), only five cases (10%) were abnormal. This might be due to a low sensitivity of this instrument to detect mild cognitive impairment in various clinical conditions (26), such as it could happen in mastocytosis. Therefore, in the end, this questionnaire ended up not being an adequate tool to evaluate the cognitive impairment in this group of patients, in which the type of cognitive impairment described by the patients is more suggestive of the subjective complaint of “brain fog”, or inability to concentrate and do multiple tasks at the same time.

In respect to humor disorders, our study also corroborates the results from other studies indicating the existence of an elevated risk of humor disorders amongst patients with mastocytosis, despite using different tools. Although, it is important to note that, at the time of the survey, 30% of the patients were medicated with either antidepressant or anxiolytic medications, which might considerably underestimate the real number of patients affected by these conditions.

When applying the HADS questionnaire, we obtained a prevalence of 8% for depression and 14% for borderline results (requiring further studies), accounting for 22% of patients in risk for depression. The prevalence we found for depression was even higher when using the Depression-ET (34%). Our results, even though underestimated by the circumstances, support previous studies regarding the existence of a high prevalence of depression in patients with mastocytosis. It is important to denote the existence of a positive correlation between the score obtained in the HADS-Depression subscale and the self-reported score depression (depression-ET), since these two tools are completely different ways for evaluating the same conditions.

When evaluating anxiety, we obtained much higher values than the ones for depression. In the HADS for anxiety, 24% of the cases abnormal, and another 32% were borderline, accounting to as much as 56% of patients with anxiety complaints. In line with this, the ET showed a percentage of 72% of patients denoting anxiety. Again, it is important to denote the existence of a positive correlation between the scores obtained in HADS-Anxiety subscale and in the Anxiety-ET. This suggests that Depression-ET and Anxiety-ET, which are much more simply to apply in the routine clinical practice and less time-consuming, can be used for the screening of humor disorders in patients with mastocytosis.

Our study shows that there are both an anxiety and depressive facets in humor disorders associated with mastocytosis, together with a great amount of these patients reporting other symptomatology such as distress (52%) and anger (46%).

The total score for the ET allows to stratification of the humor disorders according to the severity: 24% of the cases were severe, 24% of the cases were moderate and 24% were mild. In a previous study the severity of depression was severe in 8% of the cases and moderate in 56% (6).

The mechanisms by which mastocytosis associates with humor disorders and cognitive dysfunction is poor understood. Previous studies point to a role for inflammation in the development of humor disorders and cognitive dysfunction in patients with mastocytosis. In accordance, Georgin-Lavialle *et al*. have shown that, when compared to healthy individuals, patients with mastocytosis had significantly lower levels of tryptophan (TRP) and serotonin, higher indoleamine 2,3-dioxygenase 1 (IDO-1) activity, and higher levels of kynurenic and

quinolinic acids, with an imbalance towards the latter (10). In addition, they found an association of high depression scores with low TRP and high IDO-1 activity (10). Thus, an abnormal TRP catabolism seems to play a major role in inflammation-induced depression in patients with mastocytosis.

The main limitation of this study, in line with the limitations of previous ones, is that, as we are dealing with a rare disease, it is hard to gather many patients to be inquired. In addition, since the majority of our patients have ISM, there is also a limitation when it comes to assess differences in the prevalence of neurocognitive disorders in the different subtypes of mastocytosis, since we have just a few patients with other forms of the disease (i.e. CM, SSM, ASM, and LSM). Moreover, our study provided only cross-sectional data: a follow-up research would be important to investigate the evolution of these impairments. Finally, the fact that nearly one third of the patients were already medicated with antidepressants and/or anxiolytics at the time of the study may have influenced the results obtained on the prevalence of depression and anxiety in mastocytosis.

In conclusion, by evaluating mood disorders and cognitive dysfunctions in mastocytosis, we hope to improve the health care provided to these patients, to open a path for a better comprehension of the role of MC in brain functions, and to highlight the importance of research in neurological therapies targeting MC and MC mediators.

Bibliography

1. Skaper SD, Facci L, Zusso M, Giusti P. An Inflammation-Centric View of Neurological Disease: Beyond the Neuron. Front Cell Neurosci. 2018;12:72.
2. Valent P, Akin C, Hartmann K, Nilsson G, Reiter A, Hermine O, et al. Advances in the Classification and Treatment of Mastocytosis: Current Status and Outlook toward the Future. Cancer Res. 2017 15;77(6):1261–70.
3. Valent P, Akin C, Metcalfe DD. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. Blood. 2017 16;129(11):1420–7.
4. Carter MC, Metcalfe DD, Komarow HD. Mastocytosis. Immunol Allergy Clin North Am. 2014 Feb;34(1):181–96.
5. Theoharides TC, Weinkauf C, Conti P. Brain cytokines and neuropsychiatric disorders. J Clin Psychopharmacol. 2004 Dec;24(6):577–81.
6. Moura DS, Sultan S, Georgin-Lavialle S, Pillet N, Montestruc F, Gineste P, et al. Depression in patients with mastocytosis: prevalence, features and effects of masitinib therapy. PloS One. 2011;6(10):e26375.
7. Moura DS, Georgin-Lavialle S, Gaillard R, Hermine O. Neuropsychological features of adult mastocytosis. Immunol Allergy Clin North Am. 2014 May;34(2):407–22.
8. Georgin-Lavialle S, Gaillard R, Moura D, Hermine O. Mastocytosis in adulthood and neuropsychiatric disorders. Transl Res J Lab Clin Med. 2016;174:77-85.e1.
9. Moura DS, Sultan S, Georgin-Lavialle S, Barete S, Lortholary O, Gaillard R, et al. Evidence for cognitive impairment in mastocytosis: prevalence, features and correlations to depression. PloS One. 2012;7(6):e39468.
10. Georgin-Lavialle S, Moura DS, Salvador A, Chauvet-Gelinier J-C, Launay J-M, Damaj G, et al. Mast cells' involvement in inflammation pathways linked to depression: evidence in mastocytosis. Mol Psychiatry. 2016;21(11):1511–6.
11. Theoharides TC. Brain "fog," inflammation and obesity: key aspects of neuropsychiatric disorders improved by luteolin. Front Neurosci [Internet]. 2015 [cited 2019 May 31];9. Available from: http://journal.frontiersin.org/Article/10.3389/fnins.2015.00225/abstract
12. Broadbent DE, Cooper PF, FitzGerald P, Parkes KR. The Cognitive Failures Questionnaire (CFQ) and its correlates. Br J Clin Psychol. 1982 Feb;21 (Pt 1):1–16.
13. Allen Gomes A. Questionário de Falhas Cognitivas – versão portuguesa autorizada do CFQ de Broadbent et al., 1982. Fac Psicol E Ciênc Educ Universidade Coimbra. 2016;
14. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975 Nov;12(3):189–98.
15. Guerreiro, M., Silva, A., Botelho, M. A., Leitão, O., & Garcia, C. (1994). Adaptação à população portuguesa na tradução da "Mini Mental State Examination" (MMSE). Rev Port Neurol. 1(9):9–10.
16. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand. 1983 Jun;67(6):361–70.
17. Pais-Ribeiro J, Silva I, Ferreira T, Martins A, Meneses R, Baltar M. Validation study of a Portuguese version of the Hospital Anxiety and Depression Scale. Psychol Health Med. 2007 Mar;12(2):225–35; quiz 235–7.
18. Mitchell AJ, Baker-Glenn EA, Granger L, Symonds P. Can the Distress Thermometer be improved by additional mood domains? Part I. Initial validation of the Emotion Thermometers tool. Psychooncology. 2010 Feb;19(2):125–33.
19. Rast P, Zimprich D, Van Boxtel M, Jolles J. Factor Structure and Measurement Invariance of the Cognitive Failures Questionnaire Across the Adult Life Span. Assessment. 2009 Jun;16(2):145–58.
20. Finney GR, Minagar A, Heilman KM. Assessment of Mental Status. Neurol Clin. 2016 Feb;34(1):1–16.
21. Carroll BT, Kathol RG, Noyes R, Wald TG, Clamon GH. Screening for

depression and anxiety in cancer patients using the Hospital Anxiety and Depression Scale. Gen Hosp Psychiatry. 1993 Mar;15(2):69–74.

22. Smith AB, Selby PJ, Velikova G, Stark D, Wright EP, Gould A, et al. Factor analysis of the Hospital Anxiety and Depression Scale from a large cancer population. Psychol Psychother. 2002 Jun;75(Pt 2):165–76.

23. Vodermaier A, Millman RD. Accuracy of the Hospital Anxiety and Depression Scale as a screening tool in cancer patients: a systematic review and meta-analysis. Support Care Cancer Off J Multinatl Assoc Support Care Cancer. 2011 Dec;19(12):1899–908.

24. Razavi D, Delvaux N, Farvacques C, Robaye E. Screening for adjustment disorders and major depressive disorders in cancer in-patients. Br J Psychiatry J Ment Sci. 1990 Jan;156:79–83.

25. Ibbotson T, Maguire P, Selby P, Priestman T, Wallace L. Screening for anxiety and depression in cancer patients: the effects of disease and treatment. Eur J Cancer Oxf Engl 1990. 1994;30A(1):37–40.

26. Santana I, Duro D, Lemos R, Costa V, Pereira M, Simões MR, et al. Mini-Mental State Examination: Avaliação dos Novos Dados Normativos no Rastreio e Diagnóstico do Défice Cognitivo. Acta Médica Port. 2016 Apr 29;29(4):240.

Table 1. Sociodemographic and clinical characterization of the mastocytosis patients enrolled in this study, accordingly to the medical records (n = 50)

Age, years	45 (21-84)
Gender	
Males	17 (34%)
Females	33 (66%)
Male/female ratio	0.52
Mastocytosis classification	
Cutaneous Mastocytosis	6 (12%)
Systemic Mastocytosis	38 (76%)
ISM	32 (64%)
SSM	2 (4%)
ASM	1 (2%)
MS-AHN	3 (6%)
Non-classified	6 (12%)
Tryptase	
Basal serum level (ng/ml)	16.0 (2.5-216.0)
Abnormal (>11.4) ng/mL	34 (68%)
Criterium minor for SM (>20 ng/mL)	33 (66%)
Clinical manifestations	
Cutaneous	48 (98%)
Gastrointestinal	27 (54%)
Upper	25 (50%)
Lower	10 (20%)
Cardiovascular	11 (22%)
Osteoarticular and musculoskeletal	28 (56%)
Respiratory	3 (6%)
Otorhinolaryngological	6 (12%)
Urological	10 (20%)
Allergic	10 (20%)
Neuropsychiatric*	
Emotion disorders	32 (64%)
Cognitive disturbances	26 (52%)

The results are presented as absolute and relative frequencies (percentages), and as median (minimum-maximum) values.

* Five patients (10%) had previously been consulted by Psychologists and/or Psychiatrists. Concerning medication, at the time of the study, 11 patients (22%) were receiving treatment with anxiolytics, 10 patients (20%) were receiving antidepressants, and six patients (12%) were receiving treatment with both.

Table 2. Cognitive evaluation of patients with mastocytosis under study

COGNITIVE FAILURE QUESTIONNAIRE (CFQ, Broadbent)	
Scores	
Total (0-100)	26 (7-71); 21-42
Forgetfulness (0-24)	11 (0-27); 8-15
Distractibility (0-24)	9 (1-24); 5-13
False Triggering (0-24)	6 (0-24); 3-13
Potentially abnormal cases	
Total (≥ 40)	14 (28%)
Forgetfulness (≥ 10)	31 (62%)
Distractibility (≥ 10)	24 (48%)
False Triggering (≥ 10)	16 (32%)
MINIMENTAL STATE questionnaire (MMSE)	
Score	
Total score (0-30)	29 (21-30); 28-30
Potentially abnormal cases	
Cognitive impairment*	5 (10%)

The results are presented as absolute and relative frequencies (percentages), and as median (minimum-maximum), and P25-P75 values.

*Cutoff values were established according to literacy, were of 15 points for illiterate persons, 22 for individuals with 1 to 11 years of schooling, and 27 for those with more than 11 years of schooling.

Table 3. Evaluation of humor disorders in patients with mastocytosis under study

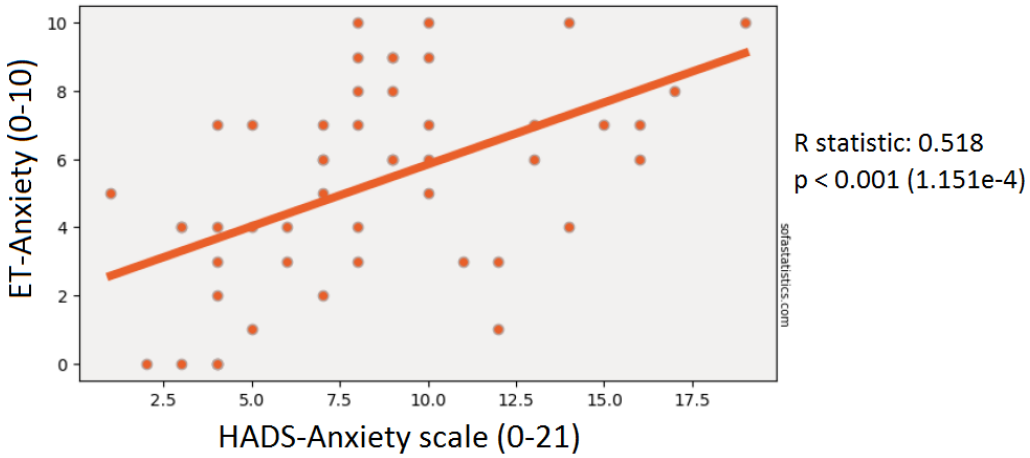
HOSPITAL ANXIETY AND DEPRESSION SCALE questionnaire (HADS)	
HADS-Anxiety	
Scores	
Total score (0-21)	8 (1-19); 5-10
Potentially abnormal cases	
Borderline (8-10)	16 (32%)
Abnormal (≥ 11)	12 (24%)
HADS-Depression	
Scores	
Total score (0-21)	5 (1-14); 2-7
Potentially abnormal cases	
Borderline (8-10)	7 (14%)
Abnormal (≥ 11)	4 (8%)
EMOTION THERMOMETERS (ET)	
Scores	
Total (0-50)	14 (0-40); 9-20
Distress (0-10)	4 (0-10); 1-5
Anxiety (0-10)	6 (0-10); 3-7
Depression (0-10)	2 (0-10); 0-5
Anger (0-10)	3 (0-10); 1-6
Need help (0-10)	3 (0-10); 1-5
Potentially abnormal cases	
Total (> 9)	36 (72%)
Mild]9 - 14]	12 (24%)
Moderate]14 - 20]	12 (24%)
Severe (>20)	12 (24%)
Distress (≥ 4)	26 (52%)
Anxiety (≥ 4)	36 (72%)
Depression (≥ 4)	17 (34%)
Anger (≥ 4)	23 (46%)
Need help (≥ 4)	23 (46%)

The results are presented as absolute and relative frequencies (percentages), and as median (minimum-maximum), and P25-P75 values.

Figure legends:

Figure 1: Correlations between the scores obtained in the Hospital Anxiety and Depression Scale (HADS) questionnaire and in the Emotion Thermometers (ET), for evaluation of anxiety (panel a) and depression (panel b), using the Spearman´s test.

a)


ET-Anxiety (0-10)
HADS-Anxiety scale (0-21)
R statistic: 0.518
p < 0.001 (1.151e-4)
sofastatistics.com

b)

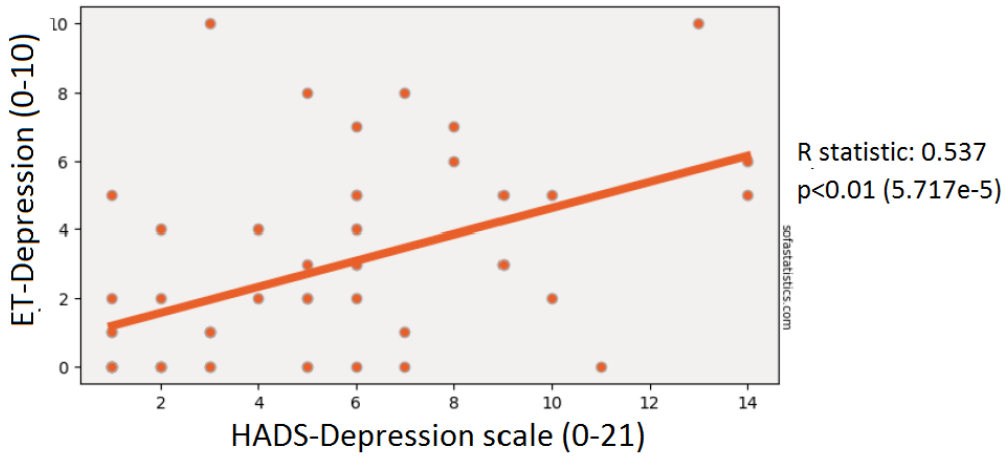

ET-Depression (0-10)
HADS-Depression scale (0-21)
R statistic: 0.537
p<0.01 (5.717e-5)
sofastatistics.com

Figure 1