HOMEOPATHIC APPROACH IN A CASE OF SYSTEMIC MASTOCYTOSIS

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INTRODUCTION

Mastocytosis represents a clonal, neoplastic proliferation of morphologically and immunophenotypically abnormal mast cells, organized in multifocal clusters, in one or more organ systems.[1] It is considered a rare hematological condition, with a prevalence of 1 in 10.000 persons. [2] However, mastocytosis remains underdiagnosed, due to the heterogeneous clinical presentation.

[3] Based on the site of the clonal proliferation, mastocytosis can be divided into cutaneous mastocytosis and systemic mastocytosis (SM). Cutaneous mastocytosis is generally benign, primarily affects children within the first two years of life, and remits around adolescence. It usually manifests with skin lesions, gastrointestinal cramps, and anaphylaxis. [1,2] SM mainly affects adults. The clonal proliferation involves the bone marrow, the skin, and other organs and it has a chronic evolution, with a poor prognosis.[4] Besides skin rashes and gastrointestinal symptoms, patients with SM may experience cardiovascular problems, like an irregular heartbeat; neuropsychiatric [5,6]complications including anxiety or depression; osteoporosis due to mast cell infiltration into bones; anaphylaxis and hypotension.

The pathophysiology of SM is represented primarily by mutations in the KIT gene, particularly the KITD816V variant, which leads to uncontrolled mast cell proliferation.[1, 3, 7]

The diagnosis of SM usually requires a bone marrow biopsy. A positive diagnosis is based upon the 2016 WHO (World Health Organization) criteria (Table 1): one major and one minor criterion is required, or in the absence of the major criteria, three minor criteria need to be met.[1, 2, 3, 7]

The treatment strategy of SM is highly reliant upon the subtype,[3] mast cell leukemia having the worst prognosis out of all the subtypes, with a median survival of 2 months.[8] In this regard, easier forms, benefit supportive treatment of mast cell mediator-related symptoms and osteoporosis. Mast cell mediator-related symptoms can be treated with antihistamines, H2-inhibitors, or aggressive treatment with epinephrine, corticosteroids, leukotriene receptor antagonists, or omalizumab in case of anaphylaxis. [9] Osteoporosis prevention and treatment can be done with calcium+D3 supplements, bisphosphonates, or alpha interferon. More advanced forms benefit from cytoreductive therapy, often with Midostaurin because it is currently considered the gold-standard treatment with a response rate of 60% and the best results in the aggressive SM subtype.[7] Usually it is well tolerated, and it can also be used as a maintenance therapy after an allogeneic stem cell transplant. There are very few studies that have demonstrated the superiority of allogeneic stem cell transplants over KIT inhibitors. Therefore, this treatment is reserved for cases of SM with severe symptoms

that are refractory to standard therapy.[3]

CASE HISTORY

Case presentation

A 35-year-old Caucasian man, residing in an urban area, with right laterality was admitted to our Neurology department in April 2022.

He was diagnosed with SM in October 2021 according to the latest criteria from the WHO. Bone marrow biopsy showed multifocal, dense infiltrates of mast cells ([?]15 mast cells in aggregates) positive for c-Kit CD 117. Serum basal tryptase measurements were positive. At the time of diagnosis, complete blood count did not show anaemia, thrombocytopenia, leukopenia or leucocytosis and abdominal ultrasound was normal. Treatment with multikinase inhibitor Midostaurin 200mg/day was initiated.

In April 2022 the patient was admitted to the Emergency Department for 3 subnitrate generalized tonic-clonic seizures associated with urine incontinence, after a period of sleep deprivation and consumption of neurostimulator drinks. His vital signs showed tachycardia with a heart rate of 96 beats/minute, blood pressure of 85/60 mmHg, oxygen saturation level of 85%, and temperature of 36 degrees Celsius. The patient was unresponsive to first and second-level antiepileptic drugs, with a tendency to vascular collapse. Considering the worsening of the clinical condition, he was sedated with Thiopental and intubated, receiving mechanical ventilation and high doses of inotropic medication due to persistent hypotension. Laboratory values at admission showed elevated liver enzymes, mild hyponatremia, and hypokalaemia, mild normocytic normochromic anemia, and high serum creatine kinase levels. Head computed tomography angiography showed no signs of cerebral hemorrhage, stroke, or other abnormalities.

The patient developed a high temperature, 24 hours before admission, for which a lumbar puncture was performed, an emergency MRI (Magnetic Resonance Imaging) with gadolinium and empiric antimicrobial therapy with Ceftriaxone 4 grams/day and Clindamycin 2,7 grams/day was initiated. The results of the lumbar puncture were within normal limits (negative results for multiplex panel) and the brain MRI revealed pansinusitis and bilateral mastoiditis. Considering the MRI images, the otorhinolaryngologist performed an otoscopy and established the diagnosis of right suppurating otitis media, for which he drained the secretions with a favourable result at the 48-hour reassessment. After 5 days of admission, it is decided to safely extubate the patient with a slowly favourable evolution, the patient being later transferred to the Neurology department.

The neurological examination showed the following: normal level of alertness, pyramidal tract signs characterized by tetraparesis with a score of 4/5 at lower limbs and 3/5 at upper limbs (on the MRC—Modified Research Council scale). The psychological examination revealed mild cognitive dysfunction (MMSE- Mini-Mental State Examination 24/30), executive dysfunction, and behavioural disinhibition. Immediately after the patient was admitted to the Neurology department, he became unstable and presented with decreased oxygen saturation and hypotension. He was transferred to the Intensive Care Unit (ICU) and after 3 days, he was transferred back to the Neurology department.

One hour after the patient was admitted to the Neurology department, he presented with a sudden change in general condition, dyspnoea, severe diffuse headache without loss of consciousness, decreased oxygen saturation (up to 55% in ambient air), hypotension (70/40mmHg) and tachycardia. During the episode of decompensation, the patient insisted that we do not say anything to his mother about the worsening of his clinical condition and wanted to draw up the will, but still he was not afraid of death. Therefore, in association with the medical treatment comprising of inotropic medication, oxygen therapy with increased flow on a simple mask, corticotherapy and antihistamines, he also received a homeopathic remedy: Carbo Vegetabilis 30 CH 5 granules every 5 minutes (for 20 minutes). The patient's general condition improved.

During hospitalization, the patient repeatedly expressed his wish to sue the hematologist who prescribed Midostaurin. Upon talking to his father, we found out that the patient has a highly reactive and compulsive personality and a low tolerance for injustice. Taking this into account, the patient was prescribed Causticum

30 CH seven granules administered sublingually daily, for one month. During and after hospitalization, the patient was treated with conventional therapy and a series of individualized homeopathic remedies, as it is presented in Table 2.

Considering the low tolerance of the patient to the treatment with Midostaurin (nausea, vomiting, abdominal pain, hepatocytolysis), upon the recommendation of the hematologist, the therapy was stopped. He was discharged with a diagnosis of severe SM with repetitive vasomotor collapses and generalized tonic-clonic seizures.

Outcome

The recommended treatment when the patient was discharged from the hospital was with H1 type antihistamines, corticotherapy, proton pump inhibitor, antiepileptic drugs, and Luteolin because of his anti-inflammatory and mast cell inhibitory activity. Regarding the homeopathic treatment, upon discharge the patient continued the administration of Causticum 30CH 7 granules/day, initiated during hospitalization. After four weeks of treatment with Causticum 30 CH, a homeopathic re-evaluation was done and the remedy was changed to Nux Vomica 30CH, seven granules administered sublingually, for 30 days. In only 1 month the clinical, mental, and emotional state of the patient improved significantly. The bone marrow biopsy also showed lower levels of mast cells. Considering these results, it is decided to reduce the dose of corticotherapy and antiepileptic treatment.

After 2 months, the patient continued to improve on all levels of health, so corticosteroid and antihistaminic therapy were completely stopped, and the antiepileptic drug was reduced to a minimum dose (300mg Carbamazepine/day).

We mention that the patient is still monitored and periodically re-evaluated from a neurological and homeopathic point of view.

DISCUSSIONS

A diagnosis of SM was proposed for our patient based on the clinical features and bone marrow biopsy.

The released cytokines by mast cell degranulation can cause acute symptoms of mastocytosis like anaphylactic shock and syncope, or chronic symptoms, such as skin lesions and abdominal discomfort.[11,12] About one-third of patients have neuropsychological symptoms, which suggests the cerebral impact of mast cells. Stress is a major factor in symptom outbreaks and is frequently disregarded while treating mastocytosis.[14] Emotional stress anticipated vasomotor collapse events in our patient, especially during ICU admissions. Moreover, research indicates that stress-induced mast cell activation has a role in neuroinflammatory diseases such as multiple sclerosis, asthma, and atopic dermatitis. [15]Through corticotropin-releasing hormone (CRH), stress activates the hypothalamic-pituitary-adrenal axis, inducing neuroinflammation and disruption of the blood-brain barrier, which may lead to seizures. Histamine neurons in the hypothalamus, which control oxytocin, vasopressin, and ACTH,[17] may have a role in mastocytosis by influencing the central nervous system. Specifically, H3 histamine receptors are essential for the blood-brain barrier to function, and their activation can affect neuroinflammatory responses by lowering the release of dopamine, serotonin, and norepinephrine.[18] This suggests that stress-related mast cell degranulation might cause vascular instability and seizures because of the irritative effects of histamine on the brain. Thus, we recommend the patient avoid stressful triggers, alcohol, non-steroidal anti-inflammatory drugs, beta-blockers, and cholinergic antagonists.[19]

Considering the strong relationship between emotions and physical symptoms in mastocytosis, a holistic approach was proposed based on homeopathy. Based on the "Law of Similars," homeopathy stimulates the body's natural healing processes by using extremely diluted compounds from plants, minerals, or animals. [20] Homeopathy is a safe and effective alternative treatment that helps enhance the body's ability to restore balance, speeds healing and is also inexpensive.[21, 22] In contrast to focusing just on symptoms, which may only provide temporary relief, this holistic approach treats the individual as a whole, considering both mental and physical symptoms.[23] Moreover, according to homeopathy, each person's health is ranked on a scale, with

greater health and resistance to illness being associated with an effective defense system. Using suppressive techniques to treat acute symptoms might impair one's health, putting the patient down on the scale and raising the chance of developing more serious conditions. [24]

CONCLUSIONS

This case underlines the relevance of considering the early diagnosis of mastocytosis in the presence of suggestive symptoms while stressing the need for a large spectrum of therapeutic options, including a complementary approach like homeopathy. In this case, the homeopathic treatment associated with the classical treatment was decisive in stabilizing and curing the patient. This is the only case of mastocytosis treated with homeopathy presented in the literature.

ABBREVIATIONS

SM- systemic mastocytosis

WHO- World Health Organization

MRI- magnetic resonance imaging

ICU- Intensive Care Unit

CRH- corticotropin-releasing hormone

ACTH- adrenocorticotrophic hormone

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

VV: served as the principal author, collected, analyzed the data, and wrote the article. CV, IR, AS, CM, MT: collected the data and contributed to the writing process. GV: provided guidance and supervised the manuscript.

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ETHICAL APPROVAL

The ethical principles in this case were applied. This case report was performed in accordance with the Declaration of Helsinki and approved by the ethics committee.

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TABLES

Table 1. WHO diagnostic criteria for SM (adapted from[1, 3])

Major criterion
Multifocal, dense infiltrates of mast cells ([?]15 mast cells in aggregates) detected on bone marrow biopsy and/or on extracu

Table 3. Homeopathic interventions based on the clinical outcome.

Date	**Symptoms**
19.04.2022	A short time after admission to the Neurological Department the patient presented: dyspnoea, severe diffuse h
20.04.2022	During hospitalization, the patient often showed signs of compulsiveness, anger, and a very low tolerance for ir
05.05.2022	At the homeopathic re-evaluation after discharge, the patient presented with extreme irritability that caused m
02.06.2022	The patient reported improvement of the clinical features both physically and mentally, without any new symp
22.06.2022	Remission of the motor deficit in the left hemibody, and significant improvement of irritability, which led to a
21.07.2022	The patient had a good general condition both mentally and physically. He reported significant improvement i