Title: A Case of Mast Cell Leukemia: A Review of the Pathophysiology of Systemic Mastocytosis and Associated Psychiatric Symptoms

Authors and Affiliations: Nathan K. Jamison[a] and Emily G. Holmes[a,b]

a. Department of Psychiatry, Indiana University, 355 W. 16th Street, Suite 2800 Indianapolis, IN 46202
b. Indiana University Health University Hospital, 550 University Blvd, Indianapolis, IN 46202

Corresponding author:
Emily Holmes
Email: egholmes@iu.edu
355 W. 16th Street, Suite 2800
Indianapolis, IN 46202
Ph 317-944-1720
Fx 317-963-7325

Introduction

Mast cells, a type of white blood cell, are activated by allergens and stimulate the immune system. Once activated, these cells release immune mediators in a process called degranulation. These immune mediators include tryptase, histamine, serotonin, and cytokines and are responsible for producing inflammation. Mast cells are found throughout the body, including in the brain, especially around blood vessels and nerve endings. Mast cell degranulation is responsible for common allergic responses including eczema and anaphylaxis. However, mastocytosis is characterized by the over-proliferation and degranulation of mast cells, resulting in a variety of physical symptoms.

Mastocytosis is rare, affecting approximately one in 60,000 people in the United States.(1) The disease is divided into two forms: cutaneous mastocytosis (CM) and systemic mastocytosis (SM). CM, in which the mast cells accumulate in the skin, is more benign and more commonly affects children. In SM mast cells accumulate in the bone marrow and organs, resulting in a variety of chronic symptoms including diarrhea, lymphadenopathy, headaches, and pain from infiltration of the bone. Degranulation can cause acute flairs of symptoms including anxiety, flushing, diarrhea, and pruritus. SM is more common in adults and can be indolent and benign or aggressive, even rarely progressing to mast cell leukemia, which has a poor prognosis.(2) Though indolent SM does not shorten a patient's lifespan, it is associated with increased disability.(3)

In 2016 the World Health Organization (WHO) updated the diagnostic criteria for SM. These criteria include evidence of mast cell infiltration in the bone marrow and other organs. A minor diagnostic criterion is a serum tryptase level of 20ng/mL or higher. Some patients with

This is the author's manuscript of the article published in final edited form as:

Jamison, N. K., & Holmes, E. G. (2018). A Case of Mast Cell Leukemia: A Review of the Pathophysiology of Systemic Mastocytosis and Associated Psychiatric Symptoms. Psychosomatics. https://doi.org/10.1016/j.psym.2018.02.002

SM have tryptase levels less than 20ng/mL, but increasing tryptase is the most specific serum marker of disease, and higher tryptase levels are associated with more aggressive disease.(4,5)

SM is associated with neuropsychiatric symptoms including fatigue, headaches, depression, anxiety, and cognitive impairment. For this reason, it is helpful for the consult-liaison psychiatrist to be familiar with this disease and how its unique pathophysiology can influence treatment. This case report presents the common features of mastocytosis and the challenges of treating the associated psychiatric symptoms.

Case

Approximately two years prior to hospitalization at our hospital, Ms. S, a 27 year-old previously healthy woman, developed cervical adenopathy and was diagnosed with Hodgkin lymphoma. Over the subsequent months, she was evaluated by multiple hematologists who proposed a number of diagnoses including Hodgkin lymphoma, SM, and mast cell sarcoma. She was treated with cladribine, then imatinib, and then brentuximab; some of these treatments resulted in decreased lymphadenopathy but none resulted in response of her bone marrow aspirates. Approximately five months prior to hospital admission, she developed rapidly-expanding cervical lymphadenopathy that was treated with methylprednisolone 30mg by mouth daily. She was continued on this dose for the two months. At this time her tryptase level was 127 ng/mL.

Three months before hospitalization she was evaluated in an outside emergency department after she became highly anxious, tearful, and agitated on the way home from infusion. She was also disorganized, making bizarre statements. She was evaluated by a psychiatrist, who diagnosed acute stress reaction, prescribed lorazepam, and discharged the patient home. Ms. S described this event as a “brief psychotic moment” which involved intense feelings of depersonalization; however, there was no clear report of actual psychotic symptoms or of the presence or absence of cognitive complaints. She was still taking steroids at this time, and her tryptase level had risen to 252 ng/mL,

Six weeks prior to admission, her hematologist noted ongoing anxiety and prescribed fluoxetine 20mg daily. Additionally, he began decreasing her steroid dose, ultimately down to methylprednisolone 4mg daily, resulting in some improvement in her anxiety and irritability. In the workup just days before admission, a computed tomography (CT) scan was notable for innumerable lytic metastatic spinal lesions, and a biopsy confirmed aggressive mast cell proliferation, consistent with mast cell leukemia. Her tryptase level was >400 ng/mL.

Ms. S was admitted to the hematology service for progressive hypercalcemia and severe pain in her lower back, ankle, and calf. Other symptoms included chronic constipation, abdominal bloating, dry mouth, rashes, fever, chills, night sweats, and nausea and vomiting. Heart rate on admission was 117, otherwise vital signs were within normal limits. Initial physical

exam demonstrated an anxious and tearful very thin woman in moderate distress. Initial labs were significant for corrected calcium of 11.4, hemoglobin of 5.3, and platelets of 8,000. The goals for hospitalization were to stabilize her anemia and start midostaurin in hopes of preventing disease progression and achieving some level of symptomatic improvement.

Neurosurgery was consulted on hospital day (HD) two and ordered a magnetic resonance image with and without contrast as well as CT of lumbar and thoracic spine. Imaging revealed a diffuse marrow-replacing process throughout the spine and multiple lesions in the lumbar and thoracic vertebrae, T12 and L5 pathologic compression fractures, diffuse tumor involvement of the sacrum and iliac bones, and a small amount of extra-osseous spread. Due the patient's clinical status and thrombocytopenia, she was not a surgical candidate.

For the mast cell leukemia, midostaurin 100mg daily was started. In addition, she received methylprednisolone 20mg IV every eight hours, which was transitioned to dexamethasone 4mg IV twice daily on HD ten. She also received loratidine 10mg daily, famotidine 20mg twice daily, and hydroxyzine 100mg twice daily.

Pain and nausea were difficult to control throughout admission. She required increasing doses of oxycodone and then morphine until she was stabilized on morphine extended release 60mg in the morning, 60mg at midday, and 100mg every evening with morphine immediate release 30 mg every three hours as needed for breakthrough pain. For nausea, she was taking ondansetron 8mg three times per day and promethazine 20mg three times daily.

For depression and anxiety, she was continued on her home doses of fluoxetine and lorazepam, 20mg daily and 0.5mg twice daily, respectively, and trazodone 50mg at night for insomnia. However, psychiatry was consulted on HD eight due to Ms. S's persistent anxiety. Psychiatric history was obtained from both the patient and her mother. Ms. S had no psychiatric history or significant symptoms of depression or anxiety prior to the initial diagnosis of Hodgkin lymphoma. She attributed at least some of her anxiety to the uncertainty of her diagnosis and prognosis over the prior two years.

She also endorsed depressed mood for the past three months, which she described as "seeing the world without color." She reported anhedonia, fatigue, poor appetite, and significant difficulty concentrating but otherwise denied problems with memory. However, since starting fluoxetine six weeks prior to admission, and she was able to enjoy some activities with modest improvement in mood. Her anxiety, however, had persisted and worsened as her physical health continued to decline, despite the decrease in her steroid regimen.

Mental status exam revealed an anxious, cachectic woman. She was able to participate in conversation for approximately ten minutes before she could no longer focus, frequently deferring to her mother. She did not demonstrate evidence of psychosis or cognitive impairment, other than difficulty with attention.

Our psychiatry consult team diagnosed her with depression and anxiety due to a general medical condition (mast cell leukemia) and recommended increasing fluoxetine to 40mg daily. The primary team was adjusting her lorazepam to help with nausea, so further titration was deferred to them. Ultimately, her dose was titrated up to lorazepam 1mg every 12 hours with 0.5mg twice daily as needed.

Ms. S was discharged home after 18 days but was readmitted to an outside hospital four days later due to continued anemia and thrombocytopenia. She developed disseminated intravascular coagulation and after three days was discharged to a hospice facility, where she died three days later.

Discussion

This case highlights a number of features associated with SM that are relevant to the psychiatrist. The patient had mast cell infiltration of the vertebrae, resulting in lower back pain, and several other distressing symptoms including severe fatigue, persistent nausea and vomiting, and fevers. She also endorsed significant anxiety and depression, likely due to a combination of her underlying disease, the corticosteroid treatment, and existential distress due to her very poor prognosis. However, it is important to note that due to her diagnosis of mast cell leukemia, her case was far more aggressive and her prognosis poorer than most cases of SM encountered by psychiatrists.

A few mechanisms have been proposed to explain the neuropsychiatric symptoms associated with SM. The release of inflammatory cytokines, such as histamine and TNF-alpha may mediate some of the symptoms. Altered tryptophan metabolism, resulting in oxidative stress, has also been proposed as a potential etiology.(6) One neuroimaging study has shown white matter abnormalities and increased perfusion of the putamen in patients with indolent SM and psychiatric and cognitive symptoms.(7) In this particular case, treatment with corticosteroids likely exacerbated some of her anxiety and insomnia, though she reported depressed mood that started when she was initially misdiagnosed with Hodgkin lymphoma.

Only a small number of studies have investigated neuropsychiatric symptoms in patients with SM. The first of these was in 1986, when Rogers et al., using diagnostic interview, found that eight of ten patients reported changes in mood, especially increased irritability, and that four of ten patients were diagnosed with depression of sufficient severity to warrant medication management or psychiatric hospitalization.(8)

In 2008, Hermine et al. conducted a case control study to assess perceived disability due to a diagnosis of either CM or SM. Of these patients, 57% (205/362) identified as having a disability due to their depression, and 6% (22/362) believed that they had a severe or intolerable disability due to their depression. Of 88 patients who completed a Hamilton Rating Scale for Depression (HAM-D), 66 (75%) scored 10 points or higher, an objective cutoff the authors used

to measure disability. Interestingly, disability due to depression was not affected by whether the patient was diagnosed with CM or SM. Likewise, the authors did not see a difference in disability due to depression when comparing study participants with tryptase levels of 20ng/mL or lower and above 20.(3)

A third study of depressive symptoms in CM and SM was published in 2011. Moura et al. distributed the HAM-D to 288 patients. A total of 56% (raw numbers not provided) scored between 8 and 22, falling into the category of moderate depression, and 23 (8%) scored 23 or higher, indicative of severe depression. The authors further examined the specific symptoms reported by the study participants and found those with moderate depression were more likely to report symptoms of hypochondriasis, while those with severe depression were more likely to report impairment in work and activities, depressed mood, somatic anxiety, and guilt. Somatic symptoms of depression, such as weight loss, gastrointestinal symptoms, general somatic symptoms, and psychomotor retardation were less frequently reported. Therefore, the authors surmised that the symptoms of depression seen in SM occurred independently of the somatic symptoms experienced by the patients.(9)

Taken together, these three studies estimate the prevalence of depression in SM to be 40-75%. These prevalence differences may be accounted for by different sample sizes and different means of diagnosing depression (diagnostic interview versus HAM-D as a structured interview versus HAM-D given as a self-report measure). Additionally, the two studies that used the HAM-D used different cutoffs to diagnose depression. In the earlier study by Rogers et al, irritability and anger were main features of the depression, while the Moura et al. study identified depressed mood, guilt, anhedonia, and somatic anxiety as predominant symptoms.(3,8,9)

Though rates of specific anxiety disorders have not been published for this population, researchers and clinicians note high anxiety in patients with SM. Moura et al. examined subscales of the HAM-D that assessed anxiety. Of the patients with severe depression, 83% had high rates of somatic anxiety, and patients with moderate depression had high rates of psychic anxiety (44%) and hypochondriasis (34%).(9) Additionally, patients with mastocytosis have demonstrated high levels of perceived stress and disability.(3,10)

Cognitive impairment, especially impairment in attention and concentration, is another common symptom associated with SM. In the 1986 Rogers et al. study, 7 of 10 patients reported diminished attention and memory impairment.(8) In one study of 57 patients, 74% endorsed subjective cognitive complaints and 39% had evidence of memory impairment on the Wechsler clinical memory scale. There was no correlation between cognitive impairment and degree of mastocytosis. Interestingly, the authors note that the prevalence of cognitive impairment associated with mastocytosis is similar to the prevalence of cognitive impairment in multiple sclerosis, another disorder that may be associated with abnormal mast cell degranulation.(11)

In the Hermine et al. study, 66% of patients (240/362) identified as disabled due to memory impairment and 9% (34/362) perceived that their disability was severe or intolerable. As with the depression findings, perceived disability was not associated with tryptase levels of 20 or greater, suggesting that cognitive impairment is associated with both milder and more severe forms of mastocytosis.(3)

Currently, treatment of mastocytosis is symptomatic and not curative. Common treatments include antihistamines and corticosteroids. A relatively new development is the use of tyrosine kinase inhibitors, such as masitinib (only available in Europe) and midostaurin, which prevent proliferation of the mast cells. Interestingly, masitinib has been associated with improvement in depression symptoms, including subscales of anxious depression and sleep disturbances, even after controlling for improvements in quality of life.(9)

Antidepressants should be started for patients with mastocytosis suffering from depression and anxiety. One study has suggested that antihistamines may help improve cognitive function; therefore, antidepressants with antihistaminic properties, such as mirtazapine and doxepin may be particularly useful in this patient population.(8) However, a separate study did not observe a positive or negative relationship between use of antihistamines and cognitive impairment, suggesting that this relationship is still unclear.(11) As in the case presented, benzodiazepines may also be needed in cases of severe anxiety, though the escalating use of benzodiazepines may become problematic in more indolent, chronic forms of the disease. In terms of cognitive symptoms, there are no studies that have examined the use of cognitive enhancers such as acetylcholinesterase inhibitors or memantine in this patient population.

Though mastocytosis is quite rare, it is a disease with significant psychiatric comorbidity that consultation-liaison psychiatrists may encounter. The pathophysiology of the disease is relevant to treatment of the disease process itself as well as a potential guide in better understanding physiological models of depression, anxiety, and cognitive impairment, especially in autoimmune diseases.

Declarations of interest: none.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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