

# Can Visual Hallucinations be Among the Neuropsychological Manifestations of Systemic Mastocytosis?: A Geriatric Case

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## Abstract

Mast cells are considered sensors of environmental and emotional stress, exist in all body parts and are related to the pathway from stress to inflammation. Mastocytosis defines a rare disease characterized by the accumulation of abnormal mast cells in multiple organs. Here, we present a 77-year-old woman with a background of aggressive systemic mastocytosis who developed impaired cognition, depression, anxiety, visual hallucinations, delusions, and insomnia. Symptoms alleviated only after initiating midostaurin, a tyrosine kinase inhibitor. Systemic mastocytosis should be kept in mind when visual hallucinations are concomitant with chronic or recurrent multi-system disturbances and do not benefit from treatment as usual.

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## INTRODUCTION

Mast cells (MC) are considered sensors of environmental and emotional stress [1], existing in all body parts, and are related to inflammation. Mastocytosis defines a group of rare disorders characterized by neoplastic proliferation

and accumulation of abnormal MCs in organ systems. Pathogenesis includes chronic, episodic MC-mediator release and excessive MC infiltration. Diagnostic criteria of systemic mastocytosis (SM) can be found in Table 1.

**Table 1.** The diagnostic criteria for systemic mastocytosis

Diagnostic criteria for systemic mastocytosis	"C" findings
Major criterion plus one minor criterion or three minor criteria.	1. Bone marrow dysfunction manifested by one or more cytopenia (ANC $<1 \times 10^9/L$ , Hb $<10$ g/dL, or platelets $<100 \times 10^9/L$ ) but no obvious non-MC hematopoietic malignancy.
Major criterion:	2. Palpable hepatomegaly with impairment of liver function, ascites, and/or portal hypertension.
1-Multifocal, dense infiltrates of MCs ( $\geq 15$ MCs in aggregates) detected in sections of bone marrow and/or other extracutaneous organ(s).	3. Palpable splenomegaly with hypersplenism.
Minor criterion:	4. Malabsorption with weight loss due to gastrointestinal MC infiltrates.
1. In biopsy sections of bone marrow or other extracutaneous organs, $>25\%$ of the MCs in the infiltrate are spindle-shaped or have atypical morphology, or of all MCs in bone marrow aspirate smears, $>25\%$ are immature or atypical.	5. Skeletal involvement with large osteolytic lesions and/or pathologic fractures.
2. Detection of an activating point mutation at codon 816 of KIT in bone marrow, blood, or another extracutaneous organ.	6. Life-threatening organ damage in other organ systems that is caused by local MC infiltration in tissues
3. MCs in bone marrow, blood, or other extracutaneous organs express CD2 and/or CD25 in addition to normal MC markers.	
4. Serum total tryptase persistently exceeds 20 ng/mL	

ANC: Absolute neutrophil count

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Depression, anxiety, irritability, emotional instability, deficits in attention, concentration, and memory are common in SM [2, 3] and affect patients' quality of life [4] enormously. This case report presents a sporadic disease with multiple neuropsychological manifestations (NM) and discusses its relevance to psychiatry. Patient informed consent and assent were obtained.

### Case Presentation

A 77-year-old woman presented to our internal medicine outpatient clinic with shortness of breath, palpitations, and watery diarrhea. Medical history revealed abdominal pain, diarrhea, and weight loss five years ago that failed a diagnosis. Stool investigations, upper/lower gastrointestinal endoscopies were unremarkable. She was admitted for abdominal distention and a petechial rash. A computerized abdominal tomography scan revealed free fluid, hepatomegaly, splenomegaly, lymph nodes near the hepatic hilum. Paracentesis revealed serum-ascites albumin gradient of 1,5 g/dL, consistent with portal hypertension. Cytopenia, elevated alkaline-phosphatase (1130 U/L) and serum tryptase increased INR (1.41), hypoalbuminemia (3.1 g/dL), negative viral/autoimmune hepatitis markers, absence of drug allergies and substance use were noted. A positron emission tomography-computed tomography (PET-CT) revealed "possible bone marrow activation/infiltration." Liver biopsy, bone marrow aspiration revealed CD117-positive MC infiltration. Target cell population stained with MC tryptase, consistent with aggressive systemic mastocytosis (ASM). Imatinib, a tyrosine kinase inhibitor (TKI) 400mg q.d. was trialed without relief. She was discharged on partial remission.

Five months later, she suffered from hallucinations, confusion, severe agitation, insomnia, weight loss, difficulty walking, and was admitted to our internal medicine ward. Psychiatry was consulted for severe insomnia without sleep for days. In the two months prior, she was forgetful, depressed, and anxious, impairing functionality. She was brought to another psychiatry clinic and was prescribed clozapine 25mg and quetiapine 50mg q.d. without relief. Psychiatric history revealed two depressive episodes, one occurred 35 years ago and the latter ten years ago that remitted on escitalopram 10mg and bromazepam 6mg q.d. Since; and another short depressive episode 35 years ago. No suicidal thoughts were reported. Mental state examination revealed impaired orientation, concentration, and memory; depressive mood, emotional lability; delusions about 'people stealing her money, planning her murder, her caretaker having an affair with her spouse,' visual hallucinations, difficulties articulating and recalling common words. She denied mental disorders before 42 years of age, prior cognitive decline, neurological disorders, and family history of mental disorders. Neurological examination and cranial MRI were normal. Due to her confusion and psychomotor agitation, neuropsychological testing was not possible. Medications included H1, H2 histamine antagonists, cromolyn sodium (100 mg), imatinib, and melatonin 6mg daily. She was prescribed

quetiapine up to 75mg q.d. moderately alleviating insomnia, while hallucinations, delusions, psychomotor agitation persisted. Ten drops of haloperidol t.i.d and risperidone 1mg q.d. were trialed without therapeutic relief. Imatinib was switched to midostaurin 50mg (FDA-approved TKI for ASM) [5] when obtained, which improved consciousness, sleep and psychomotor agitation in four days. She was discharged on midostaurin 100mg b.i.d., escitalopram 10mg, bromazepam 6mg, and risperidone 1 mg q.d. In the first week follow-up, no hallucinations, paranoid ideation, or insomnia were observed. Risperidone was stopped, escitalopram 10mg and bromazepam 6mg q.d. was continued. She described complete amnesia for the seven-week hospitalization.

### DISCUSSION

This patient presented with impaired cognition, depressive, anxiety, psychotic disorder, and insomnia interfering with daily functions; without a referral investigating an underlying disease. The combination of impairment in attention, concentration, short and long-term memory - called 'brain fog' - presents in two-fifths of SM cases [6] as a primary complaint besides depression [7]. The pathway from 'stress' to brain fog [8, 9] could include MCs located along blood vessels at the level of the blood-brain-barrier [10] releasing inflammatory molecules (adipocytokines, histamine), microglial stimulation, and focal brain inflammation [7]. Secondly, MCs in the blood-brain-barrier can alter permeability, allowing lymphocyte attraction through chemotactic substances [11]. Reduced attention and concentration were reported independent of depression [6, 12].

We do not relate the depressive episodes 35 and 10 years ago to SM as the former completely remitted for 20 years, and the latter differentiated in phenomenology from this episode through the absence of recurrent multi-system disturbances and acutely impaired cognition. Depression and anxiety appear in 40-60 % of SM cases [13]. Depression is suggested as linked to tryptophan metabolism [13] and independent of somatic symptoms [14]. To screen depression and anxiety in SM, hospital anxiety and depression scale; for treatment of depression and anxiety in SM, [15] masitinib (a TKI) is suggested to be beneficial [14].

Our patient presented with extraordinary betrayal delusions and visual hallucinations. Two earlier case studies report persecutory delusions in mast cell leukemia, the rarest, and the most aggressive category of SM [16, 17]. Although reported as observations, visual hallucination was not discussed to this extent regarding the differential diagnosis of a geriatric patient. To our knowledge, betrayal delusions were not previously reported. The patient has no pre-existing cognitive impairment, neurological or psychotic symptoms. The acute onset excluded Alzheimer's, frontotemporal, and Lewy body neurocognitive disorder. Acute cerebrovascular disease and brain injury were

eliminated with an unremarkable brain MRI. Although delusions occur, visual hallucinations are rare in primary depressive, bipolar or psychotic disorders. No evidence from the history, examination, or laboratory findings could be linked to another medical conditions, and symptoms alleviated only after initiating midostaurin, thus excluding delirium. Evaluations yielded a diagnosis of neurocognitive disorder with behavioral disturbance, depressive, anxiety, and psychotic disorders due to ASM. This report adds to the knowledge of visual hallucination and betrayal delusions in the NM of SM.

## CONCLUSION

SM could present with neurocognitive, depressive, anxiety, and psychotic symptoms, which should be considered in diagnosing neurocognitive and psychiatric disorders with chronic or recurrent multisystem disturbances and mediator-induced symptoms of unclear unifying origin. Specialists in neurology and psychiatry should perform specific examinations, including a cerebral scan or MRI [3]; a systematic investigation of depression, anxiety, and cognitive impairment [13]. The treatment of NM in SM is primarily based on the treatment of mastocytosis.

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