A Rare Case of Systemic Mastocytosis in a 72-year-old Female with Gastrointestinal Bleeding

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Abstract

Mastocytosis is a rare disorder that results from the clonal proliferation of abnormal mast cells which accumulates in the skin and extracutaneous organs. Its prevalence is estimated at1 in 10,000 persons. Cutaneous mastocytosis occurs in less than 5% of adults while adult-onset mastocytosis is suggestive of systemic progression. Involvement of the gastrointestinal tract occurs in 14-85% of patients diagnosed with systemic mastocytosis. This case involves a 72-year-old female previously diagnosed with cutaneous mastocytosis who presented with gastrointestinal symptoms fifteen years later. Workups done included CT scan, colonoscopy, and bone marrow aspiration. Colonic and bone marrow tissue samples revealed eosinophilia with CD117 positivity. The patient was started on therapy with imatinib. No recurrence of hematochezia was observed on follow-up.

Keywords: Systemic mastocytosis, GI bleeding, Imatinib

Introduction

Mastocytosis is a rare disorder that results from the clonal proliferation of abnormal mast cells which accumulates in the skin and extracutaneous organs such as the gastrointestinal tract and bone marrow.[1] It is estimated to have a prevalence of in 1 in 10,000 persons and has a slight female predominance.[2,3] Cutaneous mastocytosis occurs in less than 5% of adult cases while late-onset mastocytosis is suggestive of systemic progression.[4] The gastrointestinal system is involved in 14-85% of cases of systemic disease and common symptoms include abdominal pain, vomiting, nausea, diarrhea and bleeding.[5]

These were confirmed in a review of gastrointestinal manifestations by Sokol et. al., with abdominal pain seen in nearly half of patients, followed by diarrhea (40%), nausea and vomiting (30%) and bleeding (10%).[6] Upon a thorough literature search in local publications and databases, we have not found any case of systemic mastocytosis presenting in an adult as hematochezia and thus, we present our case.

Case

The patient is a 72-year-old female, Filipino, with a previous diagnosis of cutaneous mastocytosis, who presented with one month of hematochezia. She was diagnosed with cutaneous mastocytosis fifteen years earlier through a skin biopsy. She underwent photochemotherapy with good response and was treated with hydroxyzine. Close monitoring for systemic progression was done until 2018. No other symptoms were noted, and patient was lost to follow-up with her dermatologist. In the interim, the patient's skin lesions, characterized as multiple. non-pruritic, well-defined, flat erythematous to hyperpigmented coalescing macules progressed and was eventually noted all over the body *(Fig 1A, 1B, 1C)*.

The patient was admitted to our institution due to intermittent hematochezia associated with crampy abdominal pain located at the left hemiabdomen of one month's duration. The patient's stool was formed and blood-streaked, and was associated with generalized body weakness, nausea, and vomiting. Laboratory work-up done showed normal hemoglobin and white blood cell count with moderate thrombocytopenia (platelet count of 58 x 10^9/L) and patient was assessed by hematology prior to undergoing colonoscopy. Hematological assessment at this time was consumptive thrombocytopenia with consideration of bone marrow involvement (*Table I*). Other laboratory work-up were within normal levels (*Table II*). Whole abdomen CT scan

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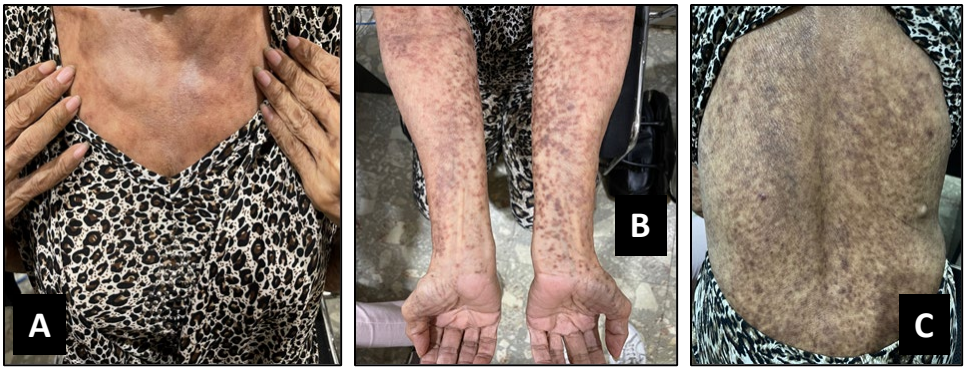

Figure 1. Non-pruritic multiple, flat, well-defined erythematous to hyperpigmented coalescing macules on the patient's chest (A), upper extremities (B) and trunk (C).

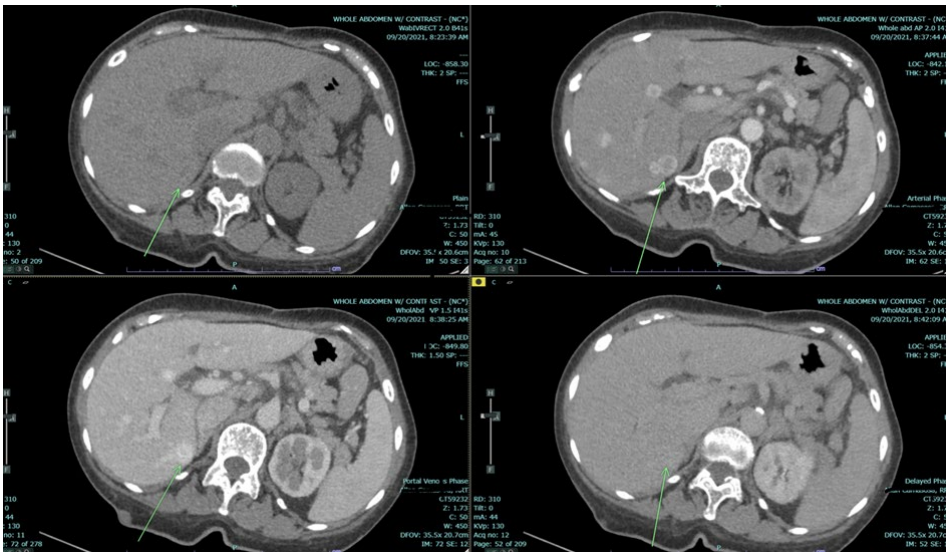

Figure 2. Multiple hepatic nodules with flash-filling hemangiomatas noted on whole abdomen CT scan with IV contrast.

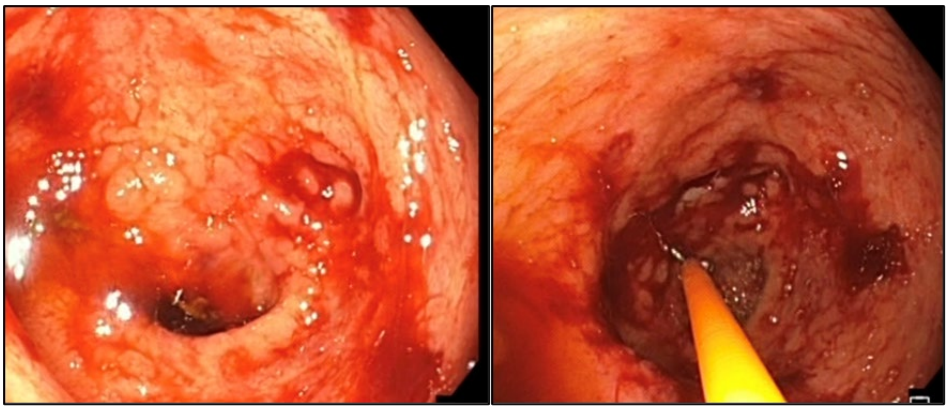

Figure 3. On colonoscopy, the cecum appeared nodular with fresh blood. Multiple biopsies were taken from the area for histopathological analysis.

with IV contrast showed multiple hepatic nodules with enhancement pattern suggestive of flash-filling hemangiomatas (*Figure 2)*.

Colonoscopy showed nodularities at the cecum *(Figure 3)* up to the descending colon with multiple non-inflamed diverticular openings in the sigmoid. Biopsy of the cecal mucosa was sent for histopathological analysis and revealed mucosal erosion and eosinophilia *(Figure 4)*.

Specimen was submitted for immunohistochemical staining with CD117, which showed presence of foci with

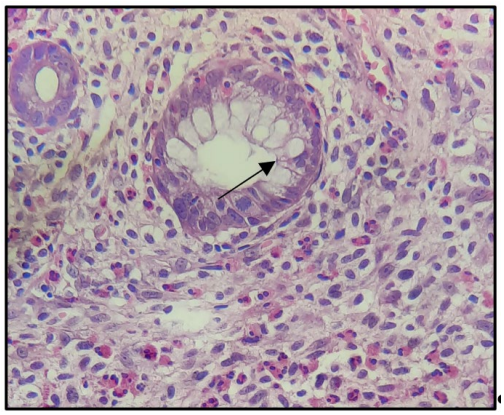

Figure 4. Microscopic examination shows residual mucosal glands with an intense inflammatory infiltrate and mucosal erosions with no evidence of dysplasia.

more than 20 mast cells per high-power field confirming the diagnosis of systemic mastocytosis (*Figure 5*).

Table I. Patient's complete blood count upon admission.

Complete Blood Count	Reference Range	Patient
Hemoglobin (g/L)	120-150	122
Hematocrit (%)	0.37-0.45	0.39
RBC (10^{12}/L)	4-5	4.39
MCV (fL)	80-96	88.8
MCH (pg/RBC)	27-33	27.8
MCHC g/dL	33-36 /dL	31.3
RDW (%)	11.6-14.6	13.2
WBC (10^9/L)	5-10	6.8
Neutrophils	0.55-0.65	0.88
Stabs	0.01-0.05	0
Lymphocytes	0.25-0.40	0.08
Monocytes	0.02-0.06	0.03
Platelet Count (10^9/L)	150-400	58

The patient underwent bone marrow aspiration and core biopsy with results showing hypercellular marrow for age with mast cell infiltration (*Figure 6A)* with mast cell infiltration positive for CD117 *(Figure 6B)*. Fluorescence *in situ* hybridization (FISH) analysis were negative for

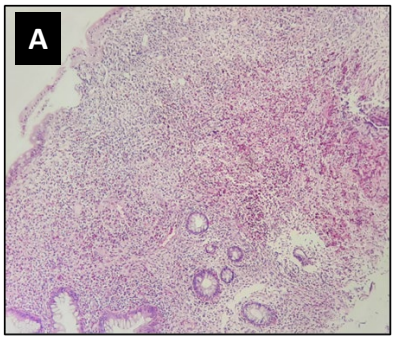

Figure 5. Microscopic evaluation of the biopsy at low power view (100x) (A) shows that the normal architecture has been disrupted by round to spindle cells in clusters and sheets, surrounding the residual colonic mucosa. The mucosa shows slight distortion changes without any prominent dysplastic features. High power view (400x) (B) shows scattered round to spindle cells with numerous admixed eosinophils. These cells have pale nuclei with inconspicuous nucleoli and granular cytoplasm.

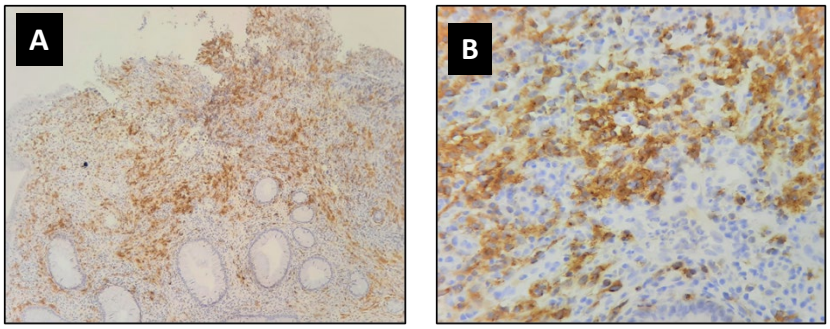

Figure 6. Immunostaining for anti-CD117 (KIT) shows mast cells with strong membrane staining in micronodular pattern or in small clusters (arrow) as seen in low power view (A), and on high power view (B), these cells form clusters (arrow) of more than 15 cells

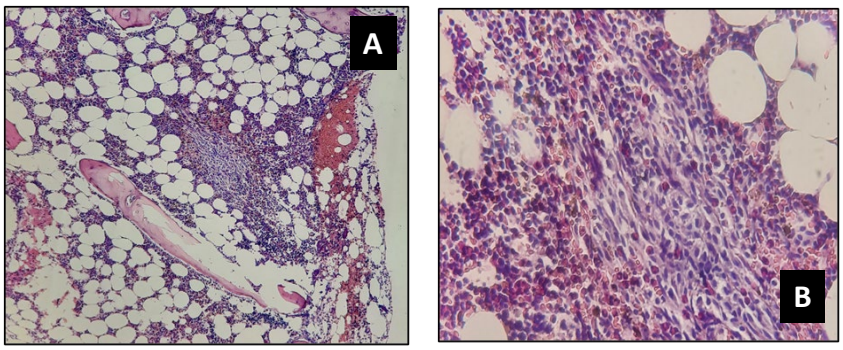

Figure 7. Microscopic examination of the core tissue reveals a slightly hypercellular marrow for age (30-40%). A portion of the marrow cellularity is attributed to the presence of a cluster of spindled to polygonal mast cells in a fibrohistocytic matrix with surrounding eosinophils, infiltrating bone marrow tissue as seen on low power view (A) On higher magnification (B), the mast cells are seen to have round to oval nuclei with faint cytoplasmic basophilic granules, which contribute to less than 30% of the marrow cellularity. There is presence of erythrogranulopoiesis with full maturation and megakaryocytes.

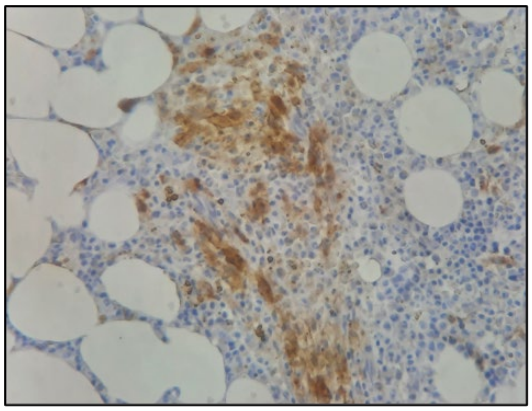

Figure 8. Immunohistochemistry staining shows the focal cluster of spindled to polygonal mast cells with strong cytoplasmic membrane positivity for CD117. No definite signs of significant dysplasia or myeloproliferation in non-mast cell lineage identified.

Table II. Patient's Laboratory Test Results Upon Admission

Test	Reference Range	Patient
Creatinine (μmol/L)	53-106	80.40
BUN (mmol/L)	3.50-7.20	8.07
Potassium (mmol/L)	3.6-5.3	3.37
Sodium (mmol/L)	136-146	138
SGPT (U/L)	10-41	16.99
SGOT (U/L)	0-55	29.97

Table III. Patient's Bleeding Parameters Upon Admission.

Parameter	Reference Range	Patient
Activated Partial Thromboplastin Time (secs)	27-40.0	28.6
Control		27.8
Prothrombin Time (secs)	11-14.0	12.5
Control		12
INR	0.90-1.19	1.04

eosinophilia panel, and was also negative for F1P1L1, PDGFRa and PDGFRb (*Table IV*)

Diagnosis was established to be systemic mastocytosis, and patient was started on imatinib 400 mg daily. At present, there has been no recurrence of hematochezia and patient was advised follow-up for close monitoring of response to treatment.

Discussion

The gastrointestinal system is frequently involved in cases of systemic mastocytosis, but its subtle manifestations make the establishment of the diagnosis challenging as exemplified in this case. Gastrointestinal bleeding in systemic mastocytosis is seen only in 10% of cases, hence, a high index of suspicion is needed and other common gastrointestinal diseases should be first ruled out.[6] In this case, inflammatory bowel disease was initially considered due to the similarity in clinical presentation and colonoscopy findings.

In a clinicopathologic and molecular study of five cases of systemic mastocytosis involving the gastrointestinal tract, the colon was the most involved site followed by the terminal ileum and duodenum respectively.[10] In addition, colonic nodularities were the most frequent endoscopic finding, other non-specific findings include "erosions, loss of mucosal folds and friability."[10] In this case, mucosal erosions were identified in the cecum. The presence of eosinophilic infiltrates is found to obscure the presence of mast cell aggregates as evidenced in the study by Kirsch et. al., therefore immunohistochemical staining is vital in cases where eosinophilia is the initial finding.[10]

Biopsy and immunohistochemical findings definitively revealed mastocytosis with foci of more than 20 mast cells per high-power field on tissue samples obtained from the colon. Furthermore, diagnosis of systemic mastocytosis was confirmed through bone marrow aspiration and core biopsy with results showing mast cells positive for CD117.

The classification and diagnosis of mastocytosis is based on the criteria as outlined by the World Health Organization (WHO) in 2016 and is divided into seven subcategories including cutaneous mastocytosis, indolent systemic mastocytosis (SM), smoldering systemic mastocytosis, systemic mastocytosis with an associated hematological neoplasm (SM-AHN), aggressive systemic mastocytosis (ASM), mast cell leukemia (MCL) and mast cell sarcoma (MCS)[7]. This case is identified as the aggressive subtype by WHO criteria (See *Table V*). Diagnosis is confirmed when one major and one minor criterion or at least three minor criteria are fulfilled. The major criteria include the presence of *"multifocal, dense infiltrates of mast cells (>15 mast cells in aggregates) detected in sections of bone marrow and/or other extracutaneous organs."*[7] Minor criteria include the following *(adapted from Horny et al.):*[7]

Table IV. Fluorescence in situ hybridization (FISH) Analysis Results

Chromosome	Loci	Gene	Result	Aberration identified	Cut-off (%)
4	4q12	F1P1L1	Negative (1.29%)	CHIC2 gene deletion	2.00%
		CHIC2	Negative (0.97%)	CHIC gene rearrangement	3.00%
		PDGFRa	Negative (0.64%)	PDGFRa gene arrangement	1.80%
5	5q32-33	PDGFRb	Negative (1.18%)	PDGFRb gene rearrangement	5.00%
			Negative (0.39%)	Monosomy 5q33	4.00%

Table V. WHO Diagnostic Criteria for Subtypes (Variant Forms) of Systemic Mastocytosis (SM).

Indolent systemic mastocytosis (ISM) SM diagnostic crtieria; no "C" findings			
Smoldering systemic mastocytosis (SSM) SM diagnostic criteria plus two or more "B" findings; no C" findings			
Advanced Systemic Mastocytosis: Aggressive systemic mastocytosis (ASM) SM diagnostic criteria plus "C" findings; no features of mast cell leukemia Mast Cell Leukemia (MCL) SM diagnostic criteria plus features of MCL Systemic mastocytosis with an associated hematologic neoplasm (SM-AHN) SM diagnostic criteria plus clonal hematologic nonmast cell lineage disorder (eg, MDS, MPN, AML, lymphoma, other)			
SM Diagnostic Criteria:	"B" Findings	"C" Findings	Features of MCL
Major criterion plus one minor criterion OR three minor criteria. Major criterion: 1. Multifocal, dense infiltrates of mast cells (≥15 mast cells in aggregates) detected in sections of bone marrow and/or other extracutaneous organ(s). Minor criterion: 1. In biopsy sections of bone marrow or other extracutaneous organs, >25% of the mast cells in the infiltrate are spindle-shaped or have atypical morphology, or of all mast cells in bone marrow aspirate smears, >25% are immature or atypical. 2. Detection of an activating point mutation at codon 816 of KIT in bone marrow, blood, or another extracutaneous organ. 3. Mast cells in bone marrow, blood, or other extracutaneous organs express CD25, with or without CD2, in addition to normal mast cell markers. 4. Serum total tryptase persistently exceeds 20 ng/mL (unless there is an associated clonal myeloid disorder, in which case this parameter is not valid).	1. Bone marrow biopsy showing >30% infiltration by mast cells (focal, dense aggregates) and/or serum total tryptase level >200 mg/mL. 2. Signs of dysplasia or myeloproliferation in nonmast cell lineage(s) but insufficient criteria for definitive diagnosis of a hematopoietic neoplasm (SM-AHN) with normal or only slightly abnormal blood counts. 3. Hepatomegaly without impairment of liver function, and/or palpable splenomegaly without hypersplenism, and/or lymphadenopathy on palpation or imaging.	1. Bone marrow dysfunction manifested by one or more cytopenia (ANC <1 × 109/L, Hb <10 g/dL, or platelets <100 × 109/L) but no obvious nonmast cell hematopoietic malignancy. 2. Palpable hepatomegaly with impairment of liver function, ascites, and/or portal hypertension. 3. Skeletal involvement with large osteolytic lesions and/or pathologic fractures. 4. Palpable splenomegaly with hypersplenism. 5. Malabsorption with weight loss due to gastrointestinal mast cell infiltrates.	Bone marrow biopsy shows a diffuse infiltration, usually compact, by atypical, immature mast cells. Bone marrow aspirate smears show ≥20% mast cells.

Adapted from: Horny HP, Metcalfe DD, Bennet JM, et al. Mastocytosis. In: WHO classification of tumours of haematopoietic and lymphoid tissues, 4th ed, Swerdlow SH, Campo E, Harris NL, et al (Eds), IARC: Lyon, 2008. Arber DA, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016; 127:2391.

a. In biopsy sections of bone marrow or other extracutaneous organs, >25% of the mast cells in the infiltrate are spindle-shaped or have atypical morphology or, of all mast cells in bone marrow aspirate smears, >25% are immature or atypical
b. Detection of an activating point mutation at codon 816 of KIT in bone marrow, blood or another extracutaneous organ
c. Mast cells in bone marrow, blood or other extracutaneous organ express CD25 with/without CD2 in addition to normal mast cell markers
d. Serum total tryptase persistently exceeds 20 ng/mL (unless there is an associated myeloid neoplasm, in which case this parameter is not valid)[7]

In this case, the major criterion and one minor criterion (a) have been fulfilled confirming the diagnosis of systemic mastocytosis. Mastocytosis is further classified by WHO based on findings on bone marrow biopsy, serum tryptase levels and involvement of other organs. However, serum tryptase levels were not obtained for this case, and diagnosis was established through involvement of the bone marrow as seen in the results of the biopsy.

Management of systemic mastocytosis focuses on symptomatic relief and response to medical therapy depends on the presence of certain genetic mutations including the c-KIT (D816V) receptor. The pathogenesis of mastocytosis is driven by the mutation in the c-KIT gene involving an extracellular domain that binds to the mast cell growth factor responsible for the proliferation and growth of mast cells. Detection of the c-KIT mutation is done on bone marrow or skin biopsy and is seen in approximately 80% of cases of systemic mastocytosis.[8] Unfortunately, testing for c-KIT is not available locally. Patient was started on imatinib therapy and is for close monitoring of molecular response and progression of symptoms.

Conclusion

After intensive literature search, this is likely the first local case report of systemic mastocytosis in an adult presenting with gastrointestinal manifestations. The diagnosis of mastocytosis involving the gastrointestinal

tract can be challenging due to the subtlety of presenting symptoms, therefore a high index of suspicion and a multidisciplinary approach is needed for prompt diagnosis and treatment.

Recommendations

Patients with dermatologic diseases such as cutaneous mastocytosis suddenly presenting with gastrointestinal bleeding should be thoroughly investigated as this could be an indication of systemic involvement and progression of the disease. A local registry of patients with mastocytosis is imperative and will be helpful for future clinicians and research purposes.

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