RMMG
Revista Médica de Minas Gerais

CASE REPORT

Advanced systemic mastocytosis with isolated gastrointestinal presentation: case report

Mastocitose sistêmica avançada com apresentação gastrointestinal exclusiva: relato de caso

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ABSTRACT

Introduction: Systemic Mastocytosis is a rare hematologic disorder characterized by clonal proliferation of mast cells, typically involving the skin, bone marrow, and visceral organs. **Case Report:** We report a case of a 78-year-old woman presenting with anemia and chronic diarrhea, without cutaneous signs. Extensive gastrointestinal investigation revealed no etiology. Laboratory evaluation showed elevated serum tryptase (>200 µg/L), bone marrow biopsy demonstrated dense mast cell infiltration with immunohistochemical positivity for CD25, c-KIT, and tryptase. The presence of the KIT D816V mutation confirmed the diagnosis of Systemic Mastocytosis. The patient exhibited organ dysfunction with gastrointestinal malabsorption and weight loss, classifying the case as Advanced Systemic Mastocytosis. This report highlights an uncommon Systemic Mastocytosis presentation limited to gastrointestinal symptoms and anemia, without skin involvement, which delayed diagnosis. **Conclusion:** These findings emphasize the importance of considering rare systemic hematologic conditions in unexplained gastrointestinal presentations and support the need for heightened clinical suspicion and appropriate diagnostic approaches in atypical cases.

Keywords: Mastocytosis; Gastrointestinal diseases; Hematologic disease; Immunohistochemistry; Case report.

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Supporting sources:

The research was conducted with the authors´ own resources.

Conflicts of interest:

None.

RESUMO

Introdução: Mastocitose Sistêmica é uma doença hematológica rara, caracterizada pela proliferação clonal de mastócitos, envolvendo tipicamente a pele, a medula óssea e órgãos viscerais. **Relado de Caso:** Relatamos o caso de uma paciente de 78 anos, com quadro de anemia e diarreia crônica, sem sinais cutâneos. Investigação gastrointestinal extensa não revelou etiologia. A avaliação laboratorial mostrou triptase sérica elevada (>200 µg/L) e a biópsia de medula óssea demonstrou infiltração densa por mastócitos com positividade imunohistoquímica para CD25, c-KIT e triptase. A presença da mutação KIT D816V confirmou o diagnóstico de Mastocitose Sistêmica. A paciente apresentava disfunção orgânica com má absorção gastrointestinal e perda de peso, classificando o caso como Mastocitose Sistêmica Avançada. Este caso destaca uma apresentação incomum de Mastocitose Sistêmica, limitada a sintomas gastrointestinais e anemia, sem envolvimento cutâneo, o que retardou o diagnóstico. **Conclusão:** Este relato enfatiza a importância de considerar doenças hematológicas sistêmicas raras em apresentações gastrointestinais inexplicadas e reforça a necessidade de alta suspeição clínica e abordagens diagnósticas adequadas em casos atípicos.

Palavras-chave: Mastocitose; Gastroenteropatias; Doenças hematológicas; Imuno-Histoquímica; Relato de caso.

Ethic Committee:
This study was approved by the Research Ethics Committee and registered under number 6.826.704 (CAAE: 77990724.9.0000.5156).

Received on: September 23, 2025.
Approved on: May 9, 2026.
Publication Date: July 27, 2026.

DOI: 10.5935/2238-3182.2025e36411-en

Introduction

Systemic mastocytosis (SM) is a rare hematologic disorder with an undefined epidemiology[1, 2]. Its incidence ranges from 0.77 to 1.1 cases per year per 100,000 individuals, with a prevalence between 9.59 and 13 per 100,000[1]. SM can manifest at any age but is more frequently diagnosed after the age of 50; without sex predominance[1, 2].

SM is characterized by the clonal expansion of mast cells (MC), which can accumulate in cutaneous tissue, bone marrow (BM), liver, spleen, and gastrointestinal tract[2-4]. MC proliferation leads to the release of chemical mediators, most notably histamine, resulting in variable symptomatology[2-5]. The most common symptoms are cutaneous, including flushing, pruritus, urticaria, and skin eruptions[2-5]. Occasionally, tachycardia, chest pain, arterial hypotension, osteodynia, myalgia, headache, mental confusion, anxiety, depression, nausea, vomiting, epigastralgia, abdominal pain, constipation alternating with diarrhea, dysphagia, and oral ulcers may be observed. Most cases of SM present mutations in the *KIT* gene at codon 816 and are frequently associated with IgE-dependent allergies, vitamin D deficiency, and mental health disorders[2-6].

Mastocytosis is classified into three types: cutaneous mastocytosis, systemic mastocytosis, and mast cell sarcoma[6,7]. The systemic form is further subdivided into six variants: BM mastocytosis, indolent systemic mastocytosis, smoldering systemic mastocytosis, aggressive systemic mastocytosis (ASM), systemic mastocytosis associated with a hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL)[6]. The term "Advanced Systemic Mastocytosis" (AdvSM) refers to the group comprising ASM, SM-AHN, and MCL, which present signs of organ dysfunction[8].

According to the diagnostic criteria of the World Health Organization in its 5th edition[6], the diagnosis of SM is confirmed in the presence of one major criterion and one minor criterion, or three minor criteria. The major criterion considers dense and multifocal MC infiltrates (≥15 in aggregates) in BM biopsies and/or other extracutaneous organs. Minor criteria include: (a) ≥25% of MC exhibit immature (blast-like) or spindle-shaped (atypical) morphology in BM smears or in other extracutaneous organs; (b) Presence of mutations (single or multiple) in codon 816 or other critical regions of the *KIT* gene in BM or another extracutaneous organ; (c) MC in BM, blood, or other extracutaneous organs express CD2, CD25, and/or CD30; (d) Baseline serum tryptase concentration >20 ng/mL (in cases of an unrelated myeloid neoplasm, elevated tryptase does not count as an SM criterion. In cases of known HαT, the tryptase level must be adjusted)[6,9].

For the classification of SM and AdvSM, B and C findings are evaluated[6,10]. B findings include: (a) High MC burden (MC infiltration in BM ≥30%, and/or serum tryptase ≥200 ng/mL without another evident cause, and/or *KIT* D816V mutation with variant allele frequency ≥10% in leukocytes from BM or peripheral blood); (b) Mild signs of myelodysplasia and/or

myeloproliferation (hypercellular BM with loss of adipose cells and elevated myelopoiesis ± leukocytosis and eosinophilia, and/or mild signs of myelodysplasia, such as <10% neutrophils, erythrocytes, and megakaryocytes); (c) Organomegaly (palpable hepatomegaly without ascites or other signs of organ damage, and/or palpable splenomegaly without hypersplenism or weight loss, and/or lymphadenopathy with palpable or visceral lymphonode enlargement >2 cm detected on ultrasound or CT). C findings are related to organ dysfunction and include: (a) One or more cytopenias (neutrophils <1 × 10^9/L; Hb <10 g/dL; platelets <100 × 10^9/L); (b) Liver involvement (ascites and elevated liver enzymes ± hepatomegaly or cirrhotic liver ± portal hypertension); (c) Spleen involvement (palpable splenomegaly with hypersplenism ± weight loss ± hypoalbuminemia); (d) Gastrointestinal involvement (malabsorption with hypoalbuminemia ± weight loss); (e) Bone involvement (osteolysis ≥2 cm with pathological fracture ± bone pain)[6,10].

Individuals with a high MC burden (B findings) indicate SM and possible involvement of multiple myeloid lineages, without organ dysfunction[6,10]. In contrast, the presence of SM-related organ damage confirmed by biopsy characterizes the "C findings," which are observed in advanced forms[6,10].

The objective of this case report was to describe a rare case of AdvSMpresenting exclusively with anemia and gastrointestinal symptoms, without cutaneous involvement.

This study was approved by the Research Ethics Committee involving human Subjects and registered under number 6.826.704 (CAAE: 77990724.9.0000.5156), issued on May 15, 2024, in accordance with Resolution No. 466/2012[11] of the Brazilian National Health Council.

Case Report

A 78-year-old female was referred to a specialized hematology clinic in May 2023 due to refractory anemia for two years, accompanied by a sensation of gastric fullness and changes in bowel habits, predominantly diarrhea. History of weight loss of 6 kilograms in the last 12 months. She had undergone extensive prior investigation by Gastroenterology, including gastric endoscopic studies and multiple colonoscopies, which identified only a small hiatal hernia and diverticular disease without evidence of bleeding. She was a non-drinker and non-smoker and had a positive family history of colorectal neoplasia.

On physical examination, she presented with pale skin, was anicteric, showed no signs of skin excoriations, and had no palpable lymphadenopathy or organomegaly. Laboratory test results are presented in Table 1.

Additional laboratory tests showed thyroid function, autoimmunity tests (including rheumatoid factor and antinuclear antibodies), immunoglobulin levels (IgA 394 mg/dL, IgM 55 mg/dL, IgG 1,029 mg/dL), and renal function without abnormalities. Magnetic resonance imaging of the long bones did not reveal any expansive or lytic lesions.

Abdominal ultrasound examination revealed right renal cysts measuring 1.2 x 1.1 cm, with no other abnormalities. Chest and abdominal CT scan showed no abnormalities. Upon admission to the hematology department, no hepatosplenomegaly, lymphadenomegaly, or ascites were observed.

Other potential causes of diarrhea were excluded, including inflammatory bowel disease, intestinal neoplasia, carcinoid syndrome, Zollinger-Ellison syndrome, and neuroendocrine tumors (see Table 1). Multiple myeloma and other monoclonal gammopathies were ruled out through protein electrophoresis, immunofixation of serum and urinary proteins, absence of CD138 antibodies, no visualization of lytic lesions on imaging studies, and no identification of plasmacytosis in the bone marrow.

Considering the presence of the KIT D816V variant, elevated serum tryptase, mast cell invasion in the bone marrow (Figure 1A-B), and immunohistochemistry positivity for c-KIT and tryptase (Figure 1C-D), the diagnosis of Systemic Mastocytosis was confirmed. The presence of anemia and gastrointestinal malabsorption accompanied by quantified weight loss characterized the “C findings,” leading to the reclassification as Advanced Systemic Mastocytosis.

Table 1. Laboratory and Histopathological results.

Laboratory results		Reference value
Hemoglobin	8.5 g/dL	12 g/dL
Hematocrit	25.70%	36%
Mean corpuscular volume	95 fl	80 - 100 fl
Red Cell Distribution Width	16%	11 - 15%
Total leukocytes	5290	4,000 – 10,000/mm³
Relative eosinophils	0	1 – 6%
Absolute eosinophils	317.4	40 – 600 /mm³
Relative band neutrophils (bands)	2%	2 – 4%
Absolute band neutrophils (bands)	105.8	80 – 400 /mm³
Relative segmented neutrophils	68%	50 – 70%

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Absolute segmented neutrophils	3,597.3	2,000 – 7,000 /mm³
Relative lymphocytes	18%	20 – 40%
Absolute lymphocytes	952.2	800 – 4.000 /mm³
Relative monocytes	6%	4 – 10%
Absolute monocytes	317.4	160 – 1,000 /mm³
Platelets	355,000	140,000 – 450,000 /mm³
Reticulocytes	1,20%	0,9 - 2,4%
Serum Iron	74 mcg/dL	50 - 150 mcg/dL
Ferritine	48,6 ng/mL	30 - 250 ng/mL
Transferrin saturation	21%	20 - 50%
Aspartate aminotransferase (AST)	12	≤ 40 U/L
Alanine aminotransferase (ALT)	7	≤ 40 U/L
Alkaline phosphatase	43	40 - 130 U/L
Gamma-glutamyl transferase (GGT)	33	9 - 36 U/L
Albumin	3.9	3.5 - 6 g/dL
Total bilirubin	1.2	≤ 1.2 mg/dL
Direct bilirubin	0,6	≤ 0.6 mg/dL
Prothrombin time (PT)	30 seconds	30 seconds
Prothrombin activity	100%	100%
Vitamin B12	916 ng/L	200 - 900 ng/L
Zinc	70.5 mcg/dL	60 - 120 mcg/dL
Carcinoembryonic antigen	0.5 ng/mL	≤ 2.5 ng/mL
CA – 19.9	5.9 U/mL	≤ 37 U/mL
Serum tryptase	>200 mcl/L	<11 mcl/L
Lactate dehydrogenase (kinetic)	119 U/L	120 - 246 U/L
Serum protein electrophoresis	Gama = 0.93 g/dL, 14.1% without monoclonal component	0.71 - 1.59 g/dL, 11.1 - 18.8%
Beta-2-Microglobulin	4,260 ng/mL	609 – 2,164 ng/mL
Gastrin	34 pg/mL	< 100 pg/mL
Serum chromogranin A	92 mcg/L	< 100 mcg/L
Urinary 5-Hydroxyindoleacetic acid	8.7 mg/24h	2 - 9 mg/24h
Fecal calprotectin	30 mcg/g	< 50 mcg/g
Histopathological results and Immunohistochemistry		**Reference value**
Bone marrow aspirate/biopsy	Dense aggregates of mononuclear oval cells, with eosinophilic cytoplasm, suggesting mast cell infiltration	-
Bone marrow immunohistochemistry:		
CD2	Negative	Negative
CD30	Not performed	
CD138 – plasma cell antigen (MI15)	Negative	Negative
Kappa light chain (Policlonal)	Negative	Negative
Lambda light chain (Policlonal)	Negative	Negative
Cytokeratin 40, 48, 50 e 50,6 kDa (AE1/AE3)	Negative	Negative

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CD20 – B cell antigen (L26)	Negative	Negative
CD3 – T-cell receptor ε-chain (RBT-CD3)	Negative	Negative
Annexin A1 – lipocortin I; inflammatory mediator (BSB-95)	Negative	Negative
CD117 – KIT gene product (Policlonal)	Positive	Negative
CD34 – hematopoiesis and pericyte antigen (QBEnd 10)	Negative	Negative
Myeloperoxidase – myeloid lineage cells (MPO-7)	Negative	Negative
Tryptase (G3)	Positive	Negative
CD25, alpha chain IL-2 receptor, clone 4C9 (4C9)	Positive	Negative
c-KIT	Positive	Negative
Molecular Array for Mastocytosis		**Reference value**
D816V c-KIT gene mutation	Present	Absent

CD = cluster of differentiation
Source: Prepared by the authors.

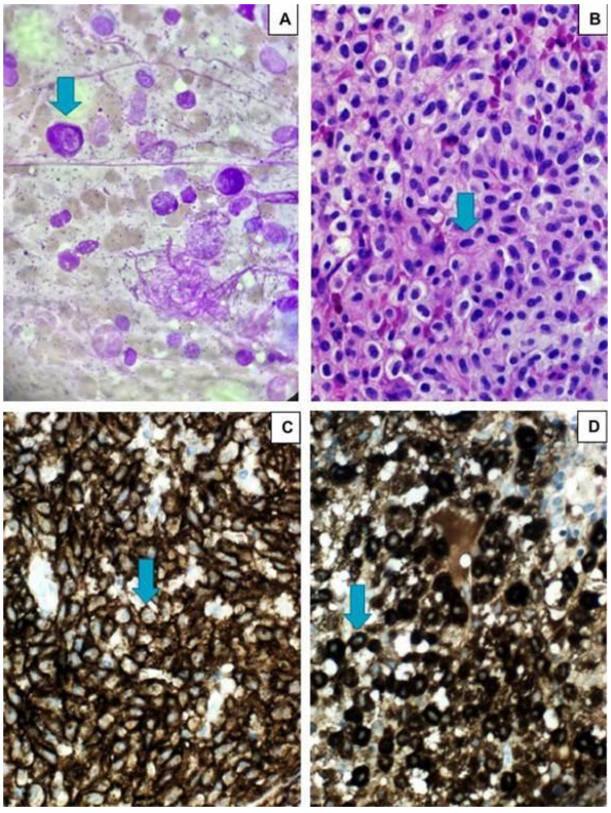

Figure 1. A: Bone marrow (BM) aspirate – oval cells with centralized nucleus and cytoplasmic granules; **B.** BM biopsy – dense aggregates of mononuclear oval cells, with eosinophilic cytoplasm, suggesting mast cell infiltration; **C and D.** Immunohistochemistry on BM biopsy evidencing c-KIT and tryptase positivity, respectively.

Source: Provided by Laboratory Bacchi.

Onco-hematologic treatment with midostaurin was initiated at a dose of 100 mg orally twice a day with an interval of approximately 12 hours between doses, along with occasional transfusional support. The patient remains under follow-up at the hematology department.

Last check-up, in October 2025 (diagnosis in January 2024), maintained the need for monthly transfusions with leukoreduced and phenotyped red blood cell concentrates, with a partial response to medication and maintenance of

tryptase levels above 100 mcl/L. The patient developed ascites and persistent diarrhea.

Discussion

Cutaneous involvement is present in more than 80% of all cases of Systemic Mastocytosis (SM), regardless of age group[3-10]. Gastrointestinal involvement is also common, most frequently manifesting as nausea, vomiting, abdominal pain, and diarrhea. Malabsorption is considered a C finding and is associated with disease severity[3,8,10].

Chronic diarrhea can have various etiologies, including malabsorption syndrome, inflammatory bowel disease, irritable bowel syndrome, and chronic infections. However, even after extensive and meticulous investigation, many cases remain undiagnosed[5]. In SM, the degranulation of inflammatory mediators released by mast cells (MC) in the intestinal lamina propria can alter intestinal motility, visceral sensitivity, and epithelial barrier function. These changes promote hypersecretion and increase intestinal propulsion, leading to diarrhea and abdominal pain[12].

The absence of cutaneous involvement is associated with more advanced forms of SM and contributes to delayed diagnosis[10]. Seo et al. (2016)[12] reported findings similar to those described by the authors, presenting a clinical case of SM without pigmentary urticaria, skin excoriations, or Darier's sign, with exclusively gastrointestinal symptoms such as dyspepsia and refractory diarrhea, ultimately delaying diagnosis and treatment[11].

According to Dranitsaris et al. (2025)[2] and Veitch and Radia (2023)[8], the most common symptoms were skin-related, in contrast to the findings of Seo et al. (2016)[12] and the case reported by the authors[2,8,11]. However, all patients exhibited elevated serum tryptase levels, atypical MC infiltration in the bone marrow (BM), CD25 positivity, and a mutation in codon 816 of the KIT gene[2,8,11].

The indolent form is characterized by slower progression, while the advanced form progresses with poor therapeutic response and progressive worsening of the patient's status[3]. The mutation in codon D816V, which is the most common mutation in systemic mastocytosis[3,] is a contraindication to imatinib, and the use of midostaurin has been indicated[3].

Midostaurin is a multikinase inhibitor with activity against the KIT D816V and D816Y mutations, approved by the Food and Drug Administration (FDA) in 2017 for the treatment of advanced systemic mastocytosis[3]. Studies have demonstrated an overall response in approximately 60% of patients, with no record of complete responses, and with partial reversal of organ damage in subgroups of responders[2-4]. The safety profile is mainly marked by gastrointestinal adverse events and myelosuppression, which frequently require dose reduction but are generally manageable[3,4,8].

Among patients with prolonged and unexplained bowel dysfunction, a SM diagnosis should be considered. In this case, gastrointestinal biopsies did not identify the presence of MC, which could have led to an earlier diagnosis. A BM biopsy was indicated due to the persistent anemia not explained by other etiologies. The panel of antibodies used in BM immunohistochemistry (*c-KIT*, *CD117*, tryptase, and *CD25*) was essential for diagnostic confirmation. Correlation with serum tryptase levels and molecular studies for the *KIT* D816V variant are valuable and essential diagnostic tools. Furthermore, it is crucial to rule out lymphoproliferative and myeloproliferative diseases.

Conclusion

SM is a rare condition, the absence of cutaneous involvement and systemic symptoms exclusive to the gastrointestinal tract, associated with anemia, is even more infrequent. In this report, the diagnosis was complex and challenging, requiring the use of specialized, intricate, and hard-to-access tests and diagnostic approaches. This report aims to alert to the importance of considering gastrointestinal tract manifestations as part of the spectrum of rare systemic hematologic disorders, suggesting a careful approach for these patients.

Acknowledgements

We are grateful to Elvira Bertges, MD, from Serviço de Anatomia Patológica Ltda (SAP), and Livia Bacchi, MD, from Laboratório Bacchi, who provided the histopathologic images, and we are grateful to the patient for agreeing to participate in this case report.

Authors' contributions

We describe contributions to the papers using the taxanomy (CRediT) provide above:

Conceptualization, Investigation, Methodology, Visualization & Writing–analysis and editing: IL Santos; LF Suassuna; DEM Sana; JLM Machado; DOW Rodrigues. *Project Administration, Supervision & Writing–original draft*: IL Santos; DOW Rodrigues. *Validation*: DOW Rodrigues. *Data Curation & Formal Analysis*: IL Santos; DOW Rodrigues.

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