Indolent systemic mastocytosis and aleukemic mast cell leukemia: Subtle diagnostic differences with distinct management approaches

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INTRODUCTION

Mastocystosis is characterized by accumulation of mast cells in tissues, with systemic disease presenting on a spectrum of severity. Indolent systemic mastocytosis (ISM) is marked by absence of hepatosplenomegaly, bone marrow, skeletal, or gastrointestinal (GI) dysfunction. Smoldering systemic mastocytosis (SSM) presents with involvement of the bone marrow, liver, spleen, and lymph nodes.[1] Both indolent and smoldering subtypes have a better prognoses than advanced systemic mastocytosis, including mast cell leukemia (MCL). Here, we report a case of ISM, to highlight management options for this spectrum of disease.

Abbreviations used:

GI:	gastrointestinal
ISM:	indolent systemic mastocytosis
LFT:	liver function tests
MCL:	mast cell leukemia
SSM:	smoldering systemic mastocytosis

CASE REPORT

A 52-year-old woman with a history of hyperlipidemia, psoriasis, and GI polyps presented with longstanding but asymptomatic skin lesions. Biopsy 13 years prior was nonspecific, revealing spongiotic dermatitis with perivascular inflammation composed of lymphocytes, histiocytes, eosinophils, and scattered mast cells. She reported years of nonspecific skin findings, including a history of hives as a teenager during stressful periods. She had noted multiple longstanding, asymptomatic skin lesions scattered across her body, initially on her trunk and spreading distally to the lower portion of her legs. She also reported greater difficulty in breathing through the nostrils. Additional history revealed bloating and intermittent loose stools a few times in the year prior, but none at presentation. She denied dyspnea, bone pain, or history of fractures. Prior bee stings elicited no significant swelling or redness.

Physical examination revealed discreet, 3- to 5-mm, light pink-to-tan macules scattered across the abdomen and proximal extremities (Fig 1). There was no hepatosplenomegaly on examination. The darier sign was negative.

Punch biopsy demonstrated increased superficial perivascular and interstitial mast cells consistent with mastocytosis. Serum tryptase level was elevated to 98.9 mcg/L (normal <11.0 mcg/L). Complete blood cell count and liver function tests (LFTs) were unremarkable. Mast cells were absent in peripheral blood; bone marrow biopsy demonstrated $CD117^{+}$ and $CD25^{+}$, with partial expression of CD2 mast cells with a hypercellular marrow (80%) with a large mast cell aggregates comprising >20% cellularity. Because of the absence of mast cells in peripheral blood, aleukemic MCL was initially favored. The second opinion of the case favored <20% mast cell cellularity. On next-generation sequencing assay, aspirate KIT D816V testing was negative, and cytogenetics showed a normal female karyotype. There

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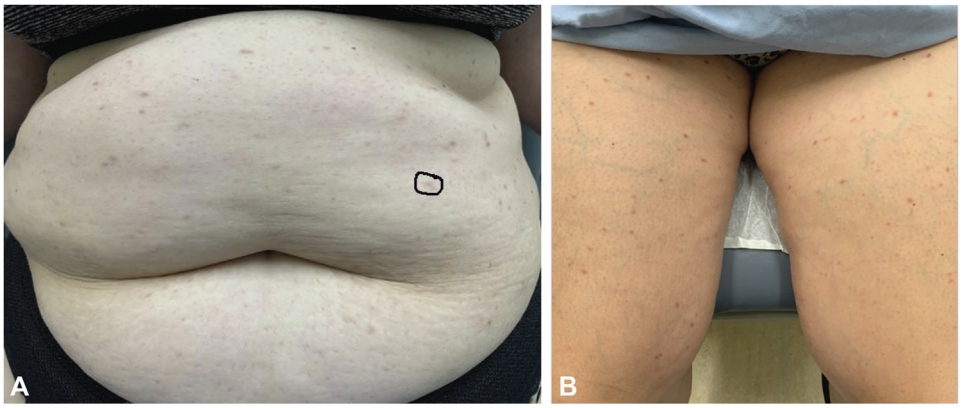

Fig 1. Overall 3- to 5-mm, light pink-to-tan macules scattered across the (**A**) abdomen, (**B**) lower extremities, biopsy site shown.

Table I. Systemic mastocytosis diagnostic criteria (requires 1 major and 1 minor criteria OR 3 minor criteria)

Major SM criteria
Multifocal dense infiltrates of MCs ($\geq$15 MCs in aggregates) in BM biopsies and/or in sections of other extracutaneous organ(s)
Minor SM criteria
1. >25% of all MCs are atypical cells (type I or type II) on BM smears or are spindle-shaped in MC infiltrates detected on sections of visceral organs
2. *KIT* point mutation at codon 816 in the BM or another extracutaneous organ
3. MCs in BM or blood or another extracutaneous organ exhibit CD2 and/or CD25
4. Baseline serum tryptase level of >20 ng/mL (in case of an unrelated myeloid neoplasm, item d is not valid as an SM criterion)
"B" findings
1. Bone marrow biopsy showing >30% infiltration by mast cells (focal, dense aggregates) and/or serum total tryptase level of >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
"C" findings
1. Bone marrow dysfunction manifested by $\geq$1 cytopenia (ANC <1 $\times$ 109/L, Hb <10 g/dL, or platelets <100 $\times$ 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 because of gastrointestinal mast cell infiltrates
Mast cell leukemia criteria
1. Bone marrow biopsy shows diffuse infiltration, usually compact, by atypical, immature mast cells.
2. Bone marrow aspirate smears show $\geq$20% mast cells.

AHN, Associated Hematological Neoplasm; *ANC*, absolute neutrophil count; *BM*, bone marrow; *Hb*, hemoglobin; *MC*, mast cell; *SM*, systemic mastocytosis.

was no evidence of myeloid dysplasia or excess blasts in the bone marrow.

Work up for systemic involvement, including echocardiogram, pulmonary function tests, and computed tomography of the chest, abdomen, and pelvis, were unremarkable. The indolent course of disease, skin biopsy demonstrating mastocytosis, and bone marrow biopsy with atypical spindle-shaped mast cells expressing CD25, combined with elevated serum tryptase levels were consistent with the diagnosis of ISM.

Daily cetirizine was recommended, an epi-pen prescribed, and she was to follow with yearly complete blood cell count, LFTs, and serum tryptase levels. Further treatment options with midostaurin and avapritinib[2] should symptoms progress, were discussed, and the patient has remained stable after 3 years of follow-up.

Table II. Subclassifications for systemic mastocytosis

Indolent SM:	SM diagnostic criteria; no "C" findings
Smoldering SM:	SM diagnostic criteria plus ≥2 "B" findings; no "C" findings
Aggressive SM:	SM diagnostic criteria plus "C" findings; no features of MCL
MCL:	SM diagnostic criteria plus features of MCL

Adapted from Arber et al,[1] Akin et al,[3] and Horny et al.[4]
MCL, Mast cell leukemia; *SM*, systemic mastocytosis.

DISCUSSION

Cutaneous mastocytosis in the adult population is a harbinger of systemic disease, which includes ISM, SSM, and MCL (Tables I and II).[1,3,4] ISM is a systemic disease without major organ dysfunction, whereas SSM has significant organ dysfunction. MCL presents with immature/atypical mast cells comprising at least 20% of the bone marrow and 10% of peripheral blood.[1] Peripheral blood containing <10% atypical cells makes it aleukemic MCL.[5] Findings from skin and bone marrow biopsies, genetic and cytogenetic studies, as well as clinical judgment are needed to discern where the patient lies on this spectrum and to tailor management.

Our case illustrates the spectrum of severity and importance of prognostication, with careful consideration of underlying malignancy, particularly in a patient with a history of hives, persistent macules, GI symptoms, and biopsy-proven cutaneous mastocytosis. No mast cells were found in the peripheral blood, helping to rule out classic MCL. However, bone marrow biopsy interpretation was equivocal around the percentage of mast cells in the bone marrow; >20% would favor aleukemic MCL, whereas <20% would favor systemic mastocytosis. Further interpretation was sought, given the vastly different management, with chemotherapy for the first and antihistamines with yearly monitoring for the latter.

Molecular and cytogenetic analyses help guide the diagnosis and management. KIT mutations have been implicated in the pathogenesis of both cutaneous and systemic mastocytosis, although a negative result alone, cannot rule out systemic mastocytosis. Although >95% of patients with systemic mastocytosis have a C-KIT D816V mutation,[6] a negative result may reflect insufficient sampling of neoplastic cells because atypical mast cells are patchy in distribution and reside in paratrabecular spaces not easily sampled with bone marrow aspirate.

The prognosis may also vary with abnormal karyotypes, such as monosomy 7 or complex karyotype. In a review of 348 cases of systemic mastocytosis, the karyotype was abnormal 15% of the time and was associated with inferior survival.[7,8] Male sex was also associated with poorer prognosis and with an abnormal karyotype.[7,9] Our patient had a normal karyotype, favoring a better prognosis.

GI symptoms are present in 70% of patients with systemic mastocytosis,[10] and often manifest vaguely through bloating and abdominal pain.[11] Diarrhea is more often episodic than chronic, as seen in this patient, linked to the release of mast cell antihistamine and prostaglandins. Hepatomegaly is detected only in 10% to 40% of cases, with abnormal LFTs even less common. Mast cells may also play a role in tumorigenesis of colorectal cancer; overall, however, because of the lack of endoscopic biopsies, the true extent of GI involvement in systemic mastocytosis is poorly defined.[12] Management involves the avoidance of triggers as the most important step in preventing GI symptoms.

We present the case of a 52-year-old woman with ISM. This case highlights the importance of workup and the pivotal role of thorough bone marrow investigation in adult patients with mastocytosis for appropriate diagnosis, prognostication, and management.

Conflicts of interest

None disclosed.

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