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SYSTEMIC MASTOCYTOSIS: CASE REPORT

Pathology

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ABSTRACT

Systemic mastocytosis (SM) is a heterogeneous disease characterized by clonal proliferation and accumulation of abnormal mast cells in one or more extracutaneous organs. It is a rare disease with a prevalence of approximately 13 in 100,000 cases(1). We reported a case of systemic mastocytosis primarily presented with non-specific gastrointestinal system symptoms. A thorough literature review is included in this paper as well.

KEYWORDS

Systemic, Mastocytosis, Case, Report

Introduction:

Systemic mastocytosis is a rare disease process caused by clonal activation and accumulation of mast cells in one or more extracutaneous organ systems, such as bone marrow, gastrointestinal tract, liver, and spleen. It is driven by a somatic mutation in the KIT gene (D816V) in more than 90% of affected adult patients.

Mast cells (MC), produced from hematopoietic progenitors, are tissue-fixed cells of inflammation and allergy reactions with variable function depending on their terminal differentiation site. The wide range of clinical presentations, from cutaneous, mild to severe disease, and the lack of particular symptoms may be explained in this way. We reported a case of systemic mastocytosis primarily presented with non-specific gastrointestinal system symptoms and a review of the pathophysiology, diagnostic criteria, morphology, and recent (WHO and ICC) updates regarding this entity, was included.

Case report:

A 68-year-old lady presented to a primary health care physician with complaints of intermittent abdominal pain, diarrhea, dizziness and weight loss. The symptoms began 2 years before the presentation and she has been referred to a gastroenterologist for further evaluation. No family history of celiac disease, or inflammatory bowel disease was reported. Her physical examination was unremarkable, and She had no skin lesions, nor lymphadenopathy. No organomegaly.

The laboratory tests were resulted as follows:

Test	Patient result	Reference ranges
White cells	3.920 × 10^ 9/L	4-11× 10^ 9/L
Hemoglobin	109 gm/L	120-140 gm/L
Platelets	260 × 10^ 9/L	150-450× 10^ 9/L
Neutrophils	57.6% (2.3×10^ 9/L)	
Tryptase	586 ug/l	< 11.4 ug/l
ALT	45.50 IU/L	0-45 IU/L
AST	37.40 IU/L	0-35 IU/L
Albumin	34 g/L	35-55 g/L
Alkaline phosphatase	240.00 IU/L	44-147 IU/L
GGT	357.00 IU/L	0-30 IU/L
Abdominal ultrasound	No organomegaly	

Upper gastrointestinal endoscopy and colonoscopy were requested to rule out inflammatory bowel disease. The findings were not suggestive for microscopic colitis, celiac, or inflammatory bowel disease. The biopsy specimens from the small intestine and colon showed increased number of mast cells with positive tryptase immunostain. That was most probably explained by gastrointestinal mastocytosis.

The peripheral blood smear showed no definitive circulating blasts nor mast cells were identified. The red blood cells are normocytic normochromic with rare elliptocytes and tear drops poikilocytes.

A bone marrow biopsy was obtained. The aspirate was particulated with cellular particles and trails. The megakaryocytes were adequate with unremarkable morphology. The myelopoiesis and Erythropoiesis were active. The eosinophils were increased. No significant dysplasia was encountered in the three linages. The blasts were less than 1% while the mast cells represent around 4%. The mast cells was varied in size ranging from small to giant, some of which showing cytoplasmic projection.

The flow cytometry detected 3% mast cells (bright CD117 and high side scattered). It showed positive expression of CD13, bright CD33, dim CD11c, dim CD2, dim CD25, dim HLA-DR. They are negative to CD14, CD64, CD300e, CD11b, CD16, CD15 and CD34. (figure 1)

The pathology examination of the bone marrow biopsy revealed an attached large muscle, trabecular bone, and adequate hematopoietic areas with mild hemorrhagic background. The overall cellularity is 60%, hypercellular for the patient's age. Multiple small-medium foci of abnormal cellular collections composed of medium sized, round and spindle shaped cells are seen (figure2). These cells were proved to be abnormal mast cells by immunohistochemistry (positive for Tryptase, CD2 and CD117). It is admixed with some eosinophils, mature lymphocytes and histocytes in between. The infiltrating mast cells represent around 25% of the total BM cells. CD34 showed <1% blasts. Reticulin stain shows no increased in fibrosis, MF-0 (WHO semi-quantitative grading system, 2017).

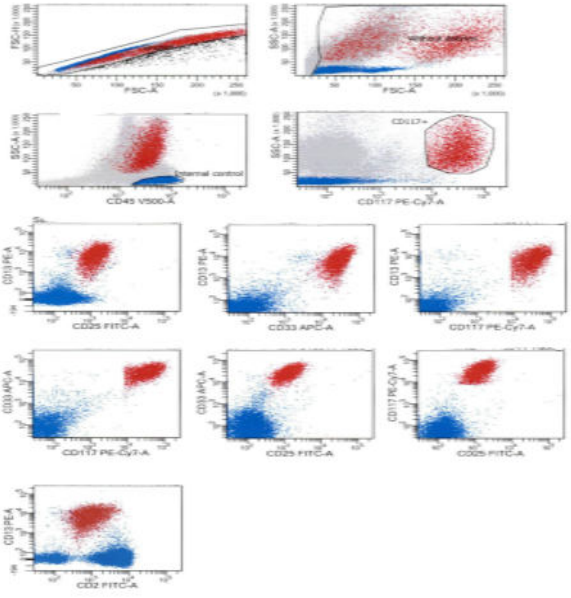

Figure 1: Bone marrow aspirate was processed for 8 colors immunophenotyping, detect 3% mast cells (bright CD117 and high side scattered) with positive CD25 and CD2 expression.

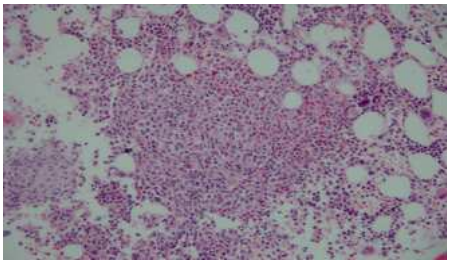

figure 2: BM trephine biopsy section, showing hypercellularity with a loose focal aggregate of mast cells (centre). H&E ×20

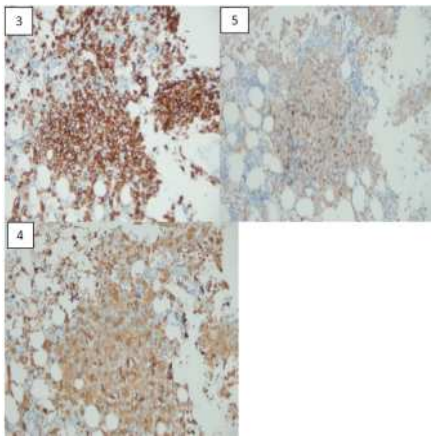

Figure 3,4, and 5: CD117 highlighted multifocal infiltrates of spindle-shaped and atypical mast cells (25%) in aggregates (figure 3; H&E, original magnification ×20) with positive tryptase (figure 4; H&E, original magnification ×20). And CD2 (figure 5; H&E, original magnification ×20).

JAK2 and BCR-ABL1 on PB were negative. Fluorescence in situ hybridization studies were negative for PDGFRA, PDGFRB and FGFR1. The pathogenic mutation was identified in c-KIT at codon 816 on exon 17 by myeloid NGS in the bone marrow sample. No additional myeloid mutations are detected.

The combination of the histologic appearance (major criterion), high serum tryptase level, KIT mutation and antigenic aberrancy (minor criterion) fulfilled the diagnostic criteria of systemic mastocytosis.

She started on FMS-like tyrosine kinase inhibitor, midostaurin 25mg orally twice a day. Two months later, she has improved clinically but she still has colicky pain and serum tryptase has increased again to a level of (474). Therefore, the dose of the treatment regimen was increased to 50mg twice daily. Follow up will be after 2 months.

Discussion:

The mast cells usually constitute < 1% of marrow components.(2) On the other hand, autoimmune and allergic reactions are associated with elevated mast cell counts. Its development and proliferation from bone marrow progenitors are maintained by cytokines including GM-CSF, TNFα, IL-3, IL-4, IL-5, IL-6, IL-10, and IL-13.(3)

The mast cells possess several receptors on their cellular membranes that govern their growth, movement, and activation. Nevertheless, the primary receptors that regulate mast cell function are c-kit and the high-affinity receptor for IgE (FcRI).

Activation of mast cells occurs when the FcRI surface receptor is stimulated by IgE, leading to the activation of these immune cells. The contents of the secretory granules are then released. These granules contain a variety of substances, such as histamine, serotonin, and tumor necrosis factor (TNF), along with a high concentration of proteases, representing up to 50% of the total protein content of the granule.

It has a unique immunophenotype, expressing a bright CD117, positive CD9, CD33, and CD71, weak CD11b and CD38 expression, and negative for CD34 and human leukocyte antigen-DR isotype (HLA-DR).

Systemic mastocytosis (SM) is a heterogenous condition marked by the abnormal growth and proliferation of mast cells in one or more extra-cutaneous organs. It is a rare disease with a prevalence of approximately 13 in 100,000 cases.(1)

It is usually diagnosed after the second decade of life. Both male and female can be affected, with a male to female ratio range from 1:1 to 1:1.5. Among adults, systemic mastocytosis (SM) accounts for 95% of all mastocytosis types.

Maculopapular rash and gastrointestinal symptoms are the most common initial manifestations, with reported prevalence rates of 70-80% and being caused by mast cell degranulation.(4)

The classification of systemic mastocytosis (SM) according to The World Health Organization (WHO) 2022 classification of myeloid neoplasms includes the following types: There are several types of systemic mastocytosis (SM), including indolent SM (ISM), smoldering SM (SSM), SM with an associated hematological neoplasm (SM-AHN), aggressive SM (ASM), mast cell leukemia (MCL), and bone marrow mastocytosis (BMM).(5, 6) The subtype that is most frequently observed among patients with systemic disease is ISM, accounting for 90-95% of cases. BMM, ISM, and SMM are regarded as nonadvanced while ASM, MCL, and SM¬-AHN are regarded as advanced SM. High MC disease burden is shown in features of organ involvement without organ failure (also known as B-findings), and organ damage brought on by MC infiltration (C-findings). These features are utilized to differentiate between ASM, SMM, and ISM.(7) Minor modifications have been made to the ICC, namely regarding the inclusion of cytopenias that fail to meet the criteria for C-findings.(6) KIT D816V mutations with variant allele frequencies (VAF) >10% are now classified as B-findings by the WHO.(1)

In Systemic mastocytosis, the bone marrow is almost always involved. To confirm or rule out a diagnosis, carful Morphological and molecular analysis of BM specimen is strongly recommended. Also, It is imperative in clinical practice to looking for an occult associated myeloid neoplasm, If somatic mutations other than KIT D816V are found. In contrast, if a KIT D816V mutation is found in patients with CMML, the most often associated myeloid neoplasm, the physician should search for clonal mast cells.(8)

Bone marrow mastocytosis (BMM) is newly classified as a distinct subtype of SM in the WHO 5th edition, with definite criteria of serum tryptase <125 ng/ml, BM involvement, no skin lesions, and no B-findings. While in the ICC (international consensus classification) it is a Clinicopathologic variant of SM with similar criteria. Well-differentiated systemic mastocytosis (WDSM) “not a distinct category” is a rare (5%) morphological subtype occurring in any SM subtype. In which the mast cells are mature and well-granulated without atypia. The vast majority of these instances lack KIT D816V while also being CD25 negative, CD2 negative, and frequently CD30 positive. Mature mast cell SM in ICC resembles to WHO's Well Differentiated Systemic Mastocytosis.

When more than 20% of mast cells are identified in bone marrow or more than 10% of immature mast cells are found in peripheral blood, a diagnosis of the leukemic variant of Systemic mastocytosis (SM) is made.

Even though diagnostic criteria are based on recognizable genetic and phenotypic markers, the underlying cause of this abnormal condition remains unknown. Mastocytosis is related to a gain-of-function mutation in c-KIT which is detected in Greater than 90% of patients and more than 80% will be found to have the KIT D816V mutation.(9, 10) This oncogene encodes a transmembrane tyrosine kinase receptor and located on chromosome 4q12. Exon 17 carries the key mutation in codon 816 (KIT D816V). KIT D816V is of greatest significance because it is an oncogenic, driver mutation of the disease, one of the minor diagnostic SM criterion according to the WHO classifications; also its association with aberrant expression of CD25 and/or CD2 and because of targeted drug therapy (tyrosine kinase inhibitors, TKIs).

The abnormal mast cell infiltration into organs affected by SM varies greatly, and therefore does depend on the degree to which the KIT D816V mutation is present. Also one study found that, KIT mutation prevalence differed across skin, bone marrow (BM), and blood.

furthermore, may be detected at a frequency as low as 0•03% mutated cells. The mutational sensitivity reaching up to 95% in BM, and 81% in peripheral blood.(11) Prescence of KIT activating mutations other than D816V is now a new minor diagnostic criteria for SM according to 2022 WHO classification and ICC.

Next generation sequencing to identify the presence of highrisk mutations SRSF2, ASXL1, and RUNX1 enables prognostic risk stratification. Also, presence of myeloid mutations, eg, TET2, JAK2, DNMT3A, NRAS, CBL, and EZHZ, which may be detected in patients with an SM-AHN.(12, 13) Serum tryptase levels that are measured to be abnormally high are characteristic of SM. The study conducted by Sperr et al, found a strong correlation between serum tryptase levels and the extent of neoplastic mast cell invasion in the bone marrow of 43 patients with systemic mastocytosis (SM).(14) However, Three patients in that group had serum tryptase levels below 20 ng/ml and were diagnosed as isolated BM mastocytosis. Elevated serum tryptase >200 ng/ml in SM patient is one of the B findings which indicate organ involvement.

Approximately 50% of instances of SM are associated with eosinophilia. If there are no clusters of abnormal mast cells identified, no KIT mutation or its variants detected, and only an abnormal mast cell population expressing CD25, CD2, and/or CD30 is found, it is highly recommended to perform fluorescence in situ hybridization (FISH) testing for PDGFRA, PDGFRB, and FGFR1 gene rearrangements. This is to exclude the possibility of myeloid/lymphoid neoplasms with eosinophilia, as it is not uncommon to observe a few abnormal mast cell populations in these neoplasms using flow cytometry. Furthermore, according to the ICC it is must be excluded before diagnosing SM.

On the other hand, For those without evidence of a clonal cause of mast cell activity should be evaluated for mast cell activation syndrome (MCAS), a benign condition characterized by Episodic symptoms of mast cell degranulation, Increase in serum total tryptase by at least 20% above baseline, meeting only 1 or 2 of the minor diagnostic criteria, Lack the characteristic BM mast cell aggregates and response of clinical symptoms to mast cell stabilizers.

ICC and WHO 22 diagnostic criteria for the diagnosis of SM

WHO Requires at least 1 major criterion and 1 minor or 3 minor criteria.
Major criterion Multifocal dense infiltrates of MCs (≥15 MCs in aggregates) in BM biopsies and/or in sections of other extracutaneous organ(s)
Minor criteria a. >25% of all MCs are atypical cells (type I or type II) on BM smears or are spindleshaped in MC infiltrates detected on sections of visceral organs b. KIT point mutation at codon 816 in the BM or another extracutaneous organ c. MCs in BM, blood, or another extracutaneous organ exhibit CD2 and/or CD25 d. Baseline serum tryptase level >20 ng/mL In case of an unrelated myeloid neoplasm, item d is not valid as an SM criterion.
ICC Presence of the major criterion is sufficient for diagnosis. In the absence of the major criterion, at least 3 of the 4 minor criteria must be present.
Major criterion Multifocal dense infiltrates of tryptase and/or CD117positive MCs (≥15 MCs in aggregates) detected in sections of BM and/or other extracutaneous organ(s)
Minor criteria a. In BM biopsy or in section of other extracutaneous organs >25% of MCs are spindleshaped or have an atypical immature morphology b. MCs in BM, PB, or other extracutaneous organs express CD25, CD2, and/or CD30, in addition to MC markers c. KIT D816V mutation or other activating KIT mutation detected in BM, PB, or other extracutaneous organs d. Elevated serum tryptase level, persistently >20 ng/mL In cases of SM-AMN, an elevated tryptase does not count as an SM minor criterion.

REFERENCES

1. Brockow K. Epidemiology, prognosis, and risk factors in mastocytosis. Immunol Allergy Clin North Am. 2014;34(2):283-95.
2. Gilfillan AM, Austin SJ, Metcalfe DD. Mast cell biology: introduction and overview. Adv Exp Med Biol. 2011;716:2-12.
3. Moldenhauer A, Genter G, Lun A, Bal G, Kiesewetter H, Salama A. Hematopoietic progenitor cells and interleukin-stimulated endothelium: expansion and differentiation of myeloid precursors. BMC Immunol. 2008;9:56.
4. El Hussein S, Chifotides HT, Khoury JD, Verstovsek S, Thakral B. Systemic Mastocytosis and Other Entities Involving Mast Cells: A Practical Review and Update. Cancers (Basel). 2022;14(14).
5. Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia. 2022;36(7):1703-19.
6. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391-405.
7. Magliacane D, Parente R, Triggiani M. Current concepts on diagnosis and treatment of mastocytosis. Transl Med UniSa. 2014;8:65-74.
8. Scherber RM, Borate U. How we diagnose and treat systemic mastocytosis in adults. Br J Haematol. 2018;180(1):11-23.
9. Wang SA, Hutchinson L, Tang G, Chen SS, Miron PM, Huh YO, et al. Systemic mastocytosis with associated clonal hematological non-mast cell lineage disease: clinical significance and comparison of chomosomal abnormalities in SM and AHNMD components. Am J Hematol. 2013;88(3):219-24.
10. Chatterjee A, Ghosh J, Kapur R. Mastocytosis: a mutated KIT receptor induced myeloproliferative disorder. Oncotarget. 2015;6(21):18250-64.
11. Cruse G, Metcalfe DD, Olivera A. Functional deregulation of KIT: link to mast cell proliferative diseases and other neoplasms. Immunol Allergy Clin North Am. 2014;34(2):219-37.
12. Sperr WR, Kundi M, Alvarez-Twose I, van Anrooij B, Oude Elberink JNG, Gorska A, et al. International prognostic scoring system for mastocytosis (IPSM): a retrospective cohort study. Lancet Haematol. 2019;6(12):e638-e49.
13. Jawhar M, Schwaab J, Schnittger S, Meggendorfer M, Pfirrmann M, Sotlar K, et al. Additional mutations in SRSF2, ASXL1 and/or RUNX1 identify a high-risk group of patients with KIT D816V(+) advanced systemic mastocytosis. Leukemia. 2016;30(1):136-43.
14. Wimazal F, Jordan JH, Sperr WR, Chott A, Dabbass S, Lechner K, et al. Increased angiogenesis in the bone marrow of patients with systemic mastocytosis. Am J Pathol. 2002;160(5):1639-45.