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The Ideological Submersion-Systemic Mastocytosis

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Systemic mastocytosis is a heterogeneous disorder characteristically demonstrating mast cells with aberrant cytology and immuno-phenotype accumulated within diverse organs. The condition exhibits an anomalous pattern of neoplastic evolution.

World Health Organization (WHO) classification 2008 denominates distinct categories of mastocytosis as

- Cutaneous mastocytosis.
- Indolent systemic mastocytosis with minimal burden of mast cells and absence of cutaneous lesions.
- Systemic mastocytosis associated with clonal hematologic non mast cell lineage disease as myelodysplastic syndrome (MDS), myeloproliferative neoplasm(MPN), acute myeloid leukaemia(AML) or lymphoma.
- Aggressive systemic mastocytosis exemplifying diagnostic criteria of systemic mastocytosis, absence of mast cell leukaemia or incrimination of cutaneous surfaces.
- Mast cell leukaemia with mast cells configuring > 20% of nucleated marrow cells or an aleukemic variant with < 10% of circulating white blood cells as mast cells.
- Extra-cutaneous mastocytoma constituted of unifocal mast cell tumour demonstrating a non destructive neoplastic configuration.
- Mast cell sarcoma is articulated of unifocal neoplasm exhibiting a destructive tumour configuration and constituent mast cells delineating aggressive cytological features [1, 2].

The uncommon systemic mastocytosis depicts a male predominance. A bimodal age of disease emergence is encountered with incrimination of paediatric subjects and adults.

Incrimination of bone and bone marrow is encountered in a majority (~90%) of instances, followed in frequency by disease occurrence within diverse organs.

Mast cells configuring systemic mastocytosis are derived from hematopoietic cell precursors which are immune reactive to CD34+, CD13+ and c-KIT+ [1, 2].

c-KIT is encoded as a proto-oncogene upon chromosome 4 and manifests as a type III tyrosine kinase receptor situated upon mast cell surface. General hematopoietic growth factor (SCF) and associated diverse factors contribute to terminal differentiation of mast cells. KIT appears to be dimerized by SCF with consequent initiation of signal transduction mechanisms and cellular proliferation.

Mastocytosis is associated with KIT genomic mutation with subsequent, SCF independent activation of KIT. c-KIT implicates cellular proliferation, maturation, adhesion, chemotaxis and cell survival.

Commonly discerned KIT mutation emerges as KITD816V whereas genetic mutations as KITV1815, KITD816F or KITD820G are infrequently discerned [1, 2].

Mastocytosis incriminates bone directly with neoplastic growth and indirectly with secretion of mediators as histamine which promote osteoblasts, heparin and prostaglandin D2 with consequent induction of bone resorption and activation of osteoclasts.

Systemic mastocytosis exhibits a variable clinical course and may emerge as benign, self limited disease or an aggressive condition. Spectrum of clinical symptoms is contingent to disease subtype and diarrhoea, weight loss, weakness, fractures, osteoporosis, arthralgia, flushing or bronchospasm may be variably discerned [1, 2].

Cutaneous surfaces are frequently incriminated with emergence of urticaria pigmentosa. Implication of bone marrow can be appropriately predicted with evaluation of serum tryptase levels. Systemic mastocytosis may concur with clonal association of myeloid neoplasm as primary myelofibrosis [1, 2].

Besides, clinical symptoms concordant with mast cell degranulation as episodic blisters, flushing, diarrhoea, abdominal pain, musculoskeletal pain, hypotension or peptic ulcer may be discerned.

Musculoskeletal symptoms are comprised of arthralgia, myalgia, bone pain, osteoporosis and bone fracture.

Clinical symptoms contingent to non mast cell clonal disorders as encountered with systemic mastocytosis associated with clonal haematological non mast cell lineage disease may appear.

Clinical symptoms concordant with monoclonal involvement of diverse organ systems with mast cells arise due to cytopenias, lymphadenopathy or hepatosplenomegaly [1, 2].

C-findings are comprised of features such as cytopenia, pathological fracture, malabsorption, hypoalbuminemia, weight loss, hepatomegaly, ascites, splenomegaly and hypersplenism.

B findings are constituted of bone marrow mast cells >30% and / or serum tryptase levels > 200 nanogram/millilitre.

Bone marrow appears hyper-cellular with dysmyelopoiesis and absence of cytopenia [1, 2]. Organomegaly may ensue in the absence of functional impairment.

Contingent to World Health Classification (WHO) classification 2008, mastocytosis is categorized as

- Cutaneous mastocytosis demonstrates urticaria pigmentosa-like lesions which commence as reddish brown macules or papules. Generally, lesions are discerned within 6 months of infancy and may ameliorate. Incriminated subjects are devoid of systemic symptoms, absent bone marrow infiltration, concurrent haematological abnormalities or infiltration of diverse organs and display normal serum tryptase levels.
- Systemic mastocytosis may be classified pertaining to concurrence of singular major criterion along with minimally ≥ singular minor criterion [1, 2].
  Major criterion are denominated as
  ~Multifocal, dense compact aggregates of neoplastic mast cells (≥ 15) configured within bone marrow or diverse organs. Minor criterion are designated as
  ~< 25% of neoplastic mast cells confined within bone marrow [1, 2]. Upon examination of bone marrow tissue sections, neoplastic mast cells appear spindle shaped or exhibit atypical morphology. Alternatively, > 25% of mast cells within bone marrow smears appear atypical or immature.
  ~KIT activating point mutation emerging at codon D816 is discernible within bone marrow or diverse extra-cutaneous organs.

~CD25 or CD2 expression is encountered along with immune reactivity to diverse mast cell antigens.
~persistently elevated serum tryptase levels.

- Indolent systemic mastocytosis delineates pertinent diagnostic criterion of systemic mastocytosis with decimated mast cell burden, associated cutaneous involvement and presence of B features in the absence of C features.
- Systemic mastocytosis with an associated clonal hematopoietic non mast cell lineage disease demonstrates precise diagnostic criteria of systemic mastocytosis accompanied by diverse clonal hematopoietic non mast cell neoplasms.
- Aggressive systemic mastocytosis exemplifies precise diagnostic criterion of systemic mastocytosis with occurrence of characteristic C features. However, criterion determining mast cell leukaemia are inadequately expressed.
- Mast cell leukaemia configures > 20% mast cells within bone marrow smears or > 10% mast cells within peripheral blood.
- Mast cell sarcoma lacks pertinent diagnostic criterion of systemic mastocytosis although focal, destructive lesions comprised of infiltrating neoplastic monoclonal mast cells with aggressive cytological features are encountered.
- Extra-cutaneous mastocytoma is devoid of cogent diagnostic criterion of systemic mastocytosis although focal, non-destructive lesions with infiltration of neoplastic, monoclonal mast cells with indolent cytological features are observed [2, 3].

Cytological examination of smears obtained from bone marrow or peripheral blood exhibit enhanced quantifiable mast cells, a feature which is concurrent with prognostic outcomes [2, 3].

Mast cell leukaemia is categorized with > 20% mast cells within bone marrow smears or > 10% mast cells circulating within peripheral blood. Generally, mast cells represent as spherical to polygonal cells permeated with abundant cytoplasm, basophilic cytoplasmic granules and spherical to elliptical nuclei. Neoplastic mast cells depict variable atypia, hypo-granulation, configuration of spindle shaped cells and elliptical, eccentric or multi-lobulated nuclei [2, 3].

Upon microscopy, bone marrow and diverse organs appear infiltrated with neoplastic mast cells, contingent to subtype of mastocytosis. Systemic mastocytosis delineates a dense, compact infiltrate of neoplastic mast cells confined to hepatic parenchyma, spleen, lymph nodes or gastrointestinal tract.

Bone marrow demonstrates

~compact, miniature foci of ≥ 15 spherical to elliptical mast cells intermingled within a fibro-histiocytic matrix.
~multifocal or disseminated neoplastic mast cell aggregates.
~a perivascular or peri-trabecular pattern of tumour configuration.
~granulomatoid appearance with a mixed cellular infiltrate.
~commingling of reactive inflammatory cells as eosinophils, plasma cells, lymphocytes, histiocytes.
~significant angiogenesis.
~foci of haematopoiesis.
~mature adipose tissue cells appear variably incriminated, contingent to subtype of mastocytosis.

- Aggressive systemic mastocytosis is comprised of significantly elevated quantifiable and atypical mast cells with decimated hematopoietic precursors.
- Cutaneous mastocytosis is associated with a normal bone marrow. Cutaneous mastocytosis enunciates dermal, perivascular and peri-adnexal infiltration of neoplastic mast cells. Epidermotropism is absent.
- Indolent systemic mastocytosis exhibits normal haematopoiesis.
- Mast cell leukaemia demonstrates an extremely hyper-cellular bone marrow with compact neoplastic cellular infiltrate, preponderantly depleted hematopoietic cell precursors and mature adipose tissue cells.
- Systemic mastocytosis with associated clonal haematopoietic non mast cell lineage disease configures as an associated haematological, non mast cell neoplasm delineating concurrent diagnostic criterion of mastocytosis [2, 3].

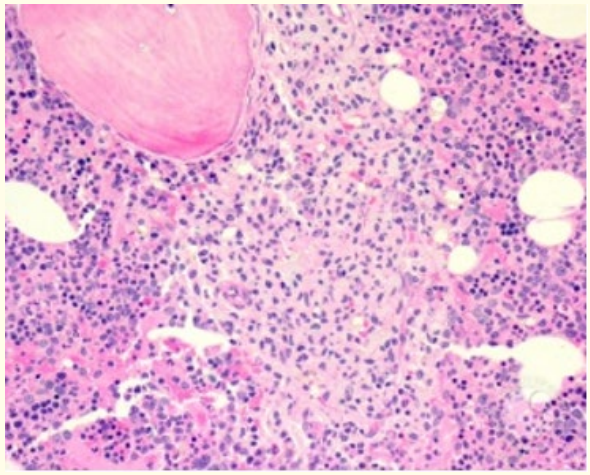

Figure 1: Systemic mastocytosis demonstrating inter-trabecular aggregates of atypical mast cells with abundant cytoplasm, basophilic granules, hypo-granulation, elliptical or multi-lobed nuclei admixed with reactive histiocytes, lymphocytes and eosinophils [6].

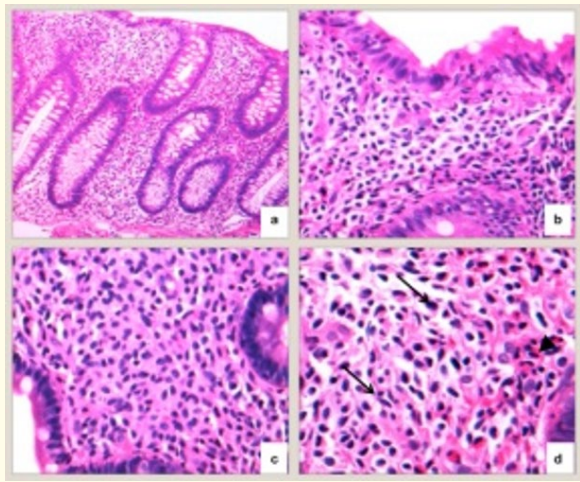

Figure 2: Systemic mastocytosis enunciating aggregates of atypical mast cells with abundant cytoplasm, minimal basophilic granules and oval, multi-lobed nuclei confined to lamina propria [7].

B Findings	*C Findings (organ damage)*
High MC burden	
BM infiltration≥30% on histology or immunohistochemistry	
Serum tryptase≥200ng/ml	
KIT D816V VAF≥10% in BM or PB leucocytes	
Myeloproliferation or myelodysplasia	Cytopenias (one or more): absolute neutrophil count<1x 10^9/L
Hyper-cellular BM, loss of fat cells, prominent myelopoiesis ± left shift, leucocytosis, eosinophilia, discrete signs of myelodysplasia (<10% neutrophils, erythrocytes, megakaryocytes)	Haemoglobin<10gm/dl, platelets<100x10^9/L
Organomegaly: palpable hepatomegaly with absent ascites or organ damage	Hepatopathy: ascites, elevated liver enzymes± hepatomegaly or cirrhotic liver± portal hypertension
Palpable splenomegaly, absent hypersplenism, weight loss,	Palpable splenomegaly with hypersplenism ±weight loss ± hypoalbuminemia
Palpable lymphadenopathy, visceral LN enlargement on US or CT(>2cm)	GIT: malabsorption with hypoalbuminemia±-weight loss
	Bone: large osteolysis(≥2cm) with pathologic fracture± bone pain

BM: Bone marrow, PB: Peripheral blood, MC: Mast cells, VAF: Variant allele frequency, US: Ultrasound, CT: Computerized tomography, GIT: Gastrointestinal tract, LN: lymph node

Table 1: Proposed B and C Findings in Systemic Mastocytosis [2, 3].

Systemic mastocytosis is immune reactive to tryptase, CD117, CD2, CD5, CD9, CD33, CD68, CD30, CD45, VEGF and chymase. Mast cells may be highlighted with Giemsa, toluidine blue, polychrome methylene blue or chloroacetate esterase (Leder) stain.

Systemic mastocytosis is immune non reactive to myeloperoxidase, CD15, CD20, CD14 or CD16.

Upon flow cytometry, neoplastic mast cells appear immune reactive to CD2 and CD25 whereas normal mast cells appear non reactive [3, 4].

Neoplastic mast cells configuring systemic mastocytosis demonstrate KIT D816V and associated genetic mutations. Besides, point mutations incriminating exon 17 as D816Y, D816H, D816F may be encountered. Systemic mastocytosis requires segregation from conditions such as mast cell hyperplasia, myeloid neoplasms with mast cell differentiation, carcinoid syndrome, VIPoma, Zollinger-Ellison syndrome, acute urticaria, inflammatory bowel disease, irritable bowel syndrome, malabsorption, myeloproliferative disease or acute myeloid leukaemia (AML) immune reactive to tryptase [4, 5].

Systemic mastocytosis can be appropriately discerned with bone marrow smears subjected to tryptase stain which confirms the occurrence of anomalous, spindle shaped mast cells.

Flow cytometry of bone marrow can discern CD25+ mast cells with aberrant phenotype.

Genomic mutation analysis can be employed to ascertain KIT D816V genetic mutations with the exclusion of associated abnormalities [4, 5].

Mastocytosis can be appropriately discerned and is associated with

~bone marrow aggregates of morphologically anomalous mast cells
~equivocal histological features accompanied by KIT D816V genetic mutation or CD25+ mast cells with aberrant phenotype.
~additional features as absence of BCR–ABL gene, dyserythropoiesis, granulocyte dysplasia, monocytosis and genetic rearrangements of PDGFRA, PDGFRB or FGFR1 gene.
~cogent clinical manifestations.
~elevated serum tryptase levels.
~cogent radiographic features of incriminated site.
~histopathological examination of surgical tissue samples.
~bone marrow biopsy accompanied with pertinent immunohistochemistry ~flow cytometric evaluation of CD2 and CD25 reactive mast cells.
~genetic or molecular assessment of c-KIT.

Serum tryptase levels appear > 200 nanogram/millilitres, denominated as a minor diagnostic criterion. Histamine metabolites can be discerned within 24 hour urine samples although the evaluation lacks sensitivity or specificity [4, 5].

Upon plain radiography, systemic mastocytosis exceptionally represents as a skeletal disorder.

Bone radiography may delineate bone marrow infiltration and diffuse, inadequately demarcated, sclerotic or lucent zones incriminating the axial skeleton. Besides, lytic lesions, osteopenia, osteonecrosis and bone destruction with accompanying circumferential sclerosis may be discerned [4, 5].

Osteosclerosis, elevated volume of bony trabeculae, enhanced cortical thickness and narrowing of bone marrow spaces may occur.

Aforesaid modifications may incriminate axial or appendicular skeleton. Diverse neoplastic patterns appear admixed whereas bone alterations may be diffuse or focal. Pathological fractures may ensue.

Systemic mastocytosis may warrant meticulous counselling and circumvention of factors which trigger or exacerbate the disease. Indolent systemic mastocytosis may not warrant therapeutic intervention. Symptomatic treatment may be optimally adopted [4, 5].

Systemic mastocytosis may be appropriately treated with interferon alpha (IFN α) and cladribine. Generally, the disorder is resistant to imatinib on account of genetic mutation D816V which engenders ligand independent activation of KIT tyrosine kinase [4, 5].

Incriminated pubertal paediatric subjects may demonstrate disease retrogression whereas disease regression is absent within adults. Cutaneous mastocytosis and indolent mastocytosis are accompanied by superior prognostic outcomes whereas aggressive systemic mastocytosis and mast cell leukaemia delineate inferior prognostic outcomes [4, 5].

Factors contributing to inferior prognostic outcomes appear as

~delayed age upon disease onset.
~loss of weight.
~elevated serum lactate dehydrogenase (LDH).
~elevated alkaline phosphatase.
~hypoalbuminemia.
~cytopenias.
~hyper-cellular bone marrow.
~diverse organomegalies.
~organ dysfunction.
~atypical morphology of mast cells [4, 5].

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6. Image 1 Courtesy: ASH.com.
7. Image 2 Courtesy: Science direct.