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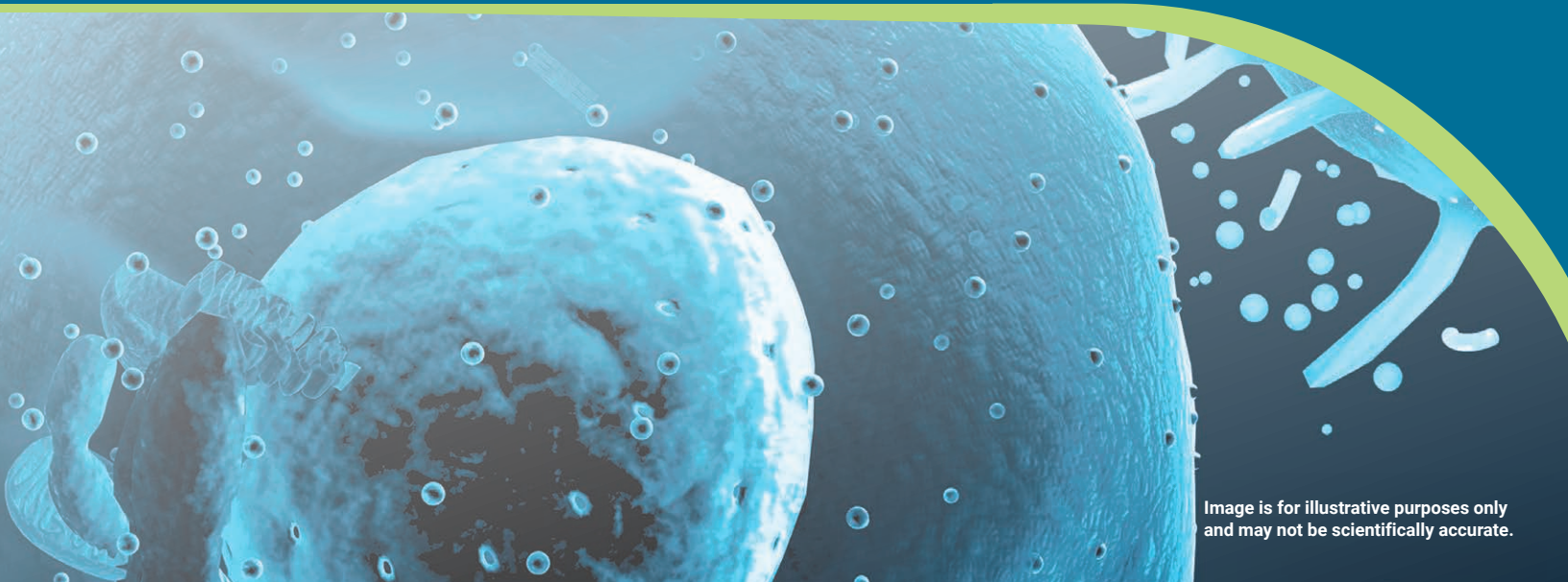
THE INTEGRAL ROLE OF A HEMATOPATHOLOGIST IN THE DIAGNOSIS OF SYSTEMIC MASTOCYTOSIS

The complexity of a systemic mastocytosis (SM) diagnosis calls for a thorough analysis by a hematopathologist[1]



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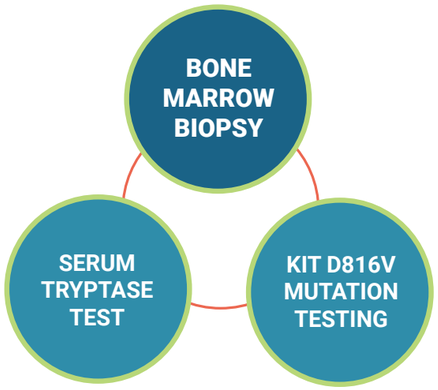
THE HEMATOPATHOLOGIST'S ROLE IN MAKING AN ACCURATE SM **DIAGNOSIS IS CRITICAL**

Systemic mastocytosis is a clonal mast cell neoplasm characterized by abnormal production and accumulation of mast cells in organs and tissues[2,3]



Due to its heterogeneous and nonspecific symptoms, SM is often mistaken for other disorders. Receiving an accurate diagnosis can take an average of **~6 years** from symptom onset.[4,5]

- The delay in diagnosis is particularly notable given the detrimental long-term effects that SM can have on patients, such as decreased overall survival from organ damage in Advanced SM[6,7]

Patients with monoclonal mast cell activation syndrome (MMAS) do not meet the criteria for SM but have 1 or both clonal markers—a KIT D816V mutation and/or CD25 expression.[8]

An SM diagnosis requires a thorough workup that includes a pathological assessment[1]

The criteria for diagnosing SM primarily depend on the histopathological investigation of a bone marrow biopsy specimen[9,10]

A diagnosis of SM can be made using criteria established by the World Health Organization (WHO) and/or the International Consensus Classification (ICC).*

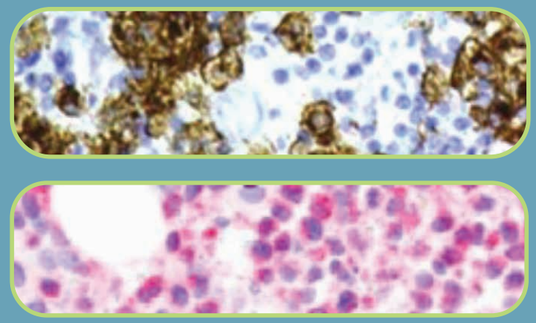
- **Major criterion:** Multifocal dense infiltrates of **tryptase** and/or **CD117** positive mast cells†‡
- **Minor criteria:**
  - >25% of mast cells are **spindle shaped** or have an **atypical or immature** morphology‡
  - **KIT D816V** mutation or other activating KIT mutation‡
  - Elevated **serum tryptase** level, >20 ng/mL§
  - Mast cells‡ express **CD25**, **CD2**, and/or **CD30**

*This highlights the combined key criteria based on the ICC and proposed changes to the WHO 5th edition guidelines and is not intended as diagnostic advice. Full guidelines are available from the WHO and ICC.[9,10]
† ≥15 mast cells in aggregates.[9,10]
‡ In bone marrow biopsies and/or in sections of other extracutaneous organ(s).[9,10]
§ This parameter is not valid in the presence of a myeloid AHN[9,10] and may need to be adjusted in the case of known HαT.[10]

Elevated serum tryptase should increase suspicion of SM.[2]

Once a diagnosis of SM is confirmed, subtyping is a practical next step. ISM represents the largest subtype of the disease[2,11-13]

It is important to explore the minor diagnostic criteria, as ~43% of SM cases do not fulfill the major criterion[9,11]

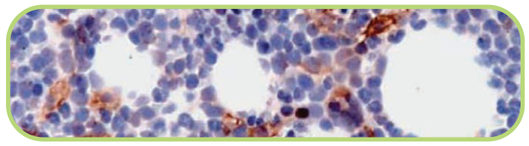


CD117 in mast cells (top), tryptase in mast cells (bottom).[14,15]

All reactive and neoplastic mast cells express tryptase and KIT/CD117.[9]

- Determining mast cell burden is important in suspected cases of SM. CD117 and tryptase are mast cell markers for IHC[9]

Reprinted from *Journal of Clinical and Diagnostic Research*, 2013, Vol 7/ Issue 10, 2276-2277, Mallya KP et al., Systemic mastocytosis: predominantly involving the bone, a case report, with permission from JCDR (top); and *Leukemia Research Reports*, Vol 3/Issue 1, Valent P et al., FLAG-induced remission in a patient with acute mast cell leukemia (MCL) exhibiting t(7;10)(q22;q26) and KIT D816, 8-13, ©2014, with permission from Elsevier (bottom).



CD25 in mast cells.[17]

CD25 expression is found in more than **90% of SM cases**, including cases with a loosely scattered, interstitial pattern of mast cell involvement.[2,16]

- CD30 in combination with CD25 has been shown to increase the diagnostic accuracy of SM[18]

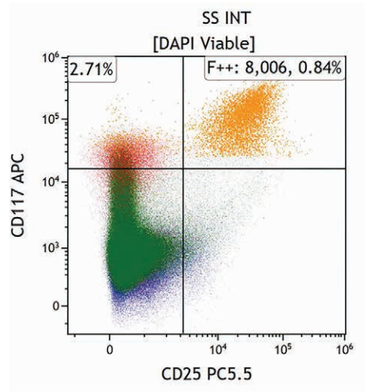


Image courtesy of David P. Ng, MD.

Abnormal mast cells (upper right quadrant) can be characterized by expression of CD25 and CD117 in multiparameter flow cytometry.

If IHC is indeterminate for CD25 expression, rare mast cell populations with an abnormal phenotype can be identified by flow cytometry, first using a mast cell gate that includes CD117[19-21]

Presence of the KIT D816V mutation is a main driver of disease in ~95% of SM cases[22-24]

AHN=associated hematological neoplasm; HαT=hereditary alpha-tryptasemia; ISM=indolent systemic mastocytosis; KIT=KIT proto-oncogene, receptor tyrosine kinase.

IHC=immunohistochemistry.

GUIDELINES RECOMMEND HIGH-SENSITIVITY KIT D816V ASSAYS **WHEN SM IS SUSPECTED**[25]

- The International Consensus Classification (ICC) recommends the use of a high-sensitivity PCR assay for detection of the KIT D816V mutation[10]*
- In 20% of patients, the KIT D816V mutation served as the critical third criterion that confirmed an SM diagnosis[26]
- The KIT D816V variant allele frequency (VAF) is a reliable prognostic marker of SM[25]

Low-sensitivity tests to detect KIT D816V can lead to false-negative results.[27]

Using next-generation sequencing (NGS)?

An incidental KIT D816V mutation found on a myeloid NGS panel should trigger a full diagnostic workup for SM.[25]

NGS in combination with high-sensitivity KIT testing can provide important prognostic information when diagnosing SM; for example, additional mutations in SRSF2, ASXL1, or RUNX1 can be a predictor of poor outcomes.[25]

Evaluation of both the major and minor diagnostic criteria is instrumental in the diagnosis of SM[2]

*If negative, exclusion of KIT mutation variants is strongly recommended in suspected SM.[10]

PCR=polymerase chain reaction.

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03/2024 USBP-DASM-22-011.2