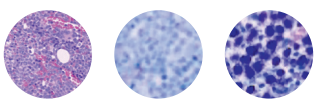
blueprint MEDICINES

Mastocytosis
Pathology Tool Kit



Introduction

Mastocytosis is considered a rare disease. However, recent improvements related to diagnostic methods could have led to an increased incidence and prevalence (>28 in 100.000). Still, a relatively large number of patients remains incompletely diagnosed or misdiagnosed, while time to diagnosis is generally long and delays the start of potential targeted treatment.[1,2]

With the most prevalent types of mastocytosis being mastocytosis in the skin (MIS), indolent systemic mastocytosis (ISM) and cutaneous mastocytosis (CM)[1] it is worthwhile to be noted that adult-onset MIS and CM are highly suggestive of systemic mastocytosis[3], which again highlights the importance of proper diagnostic workup by experienced pathologists.

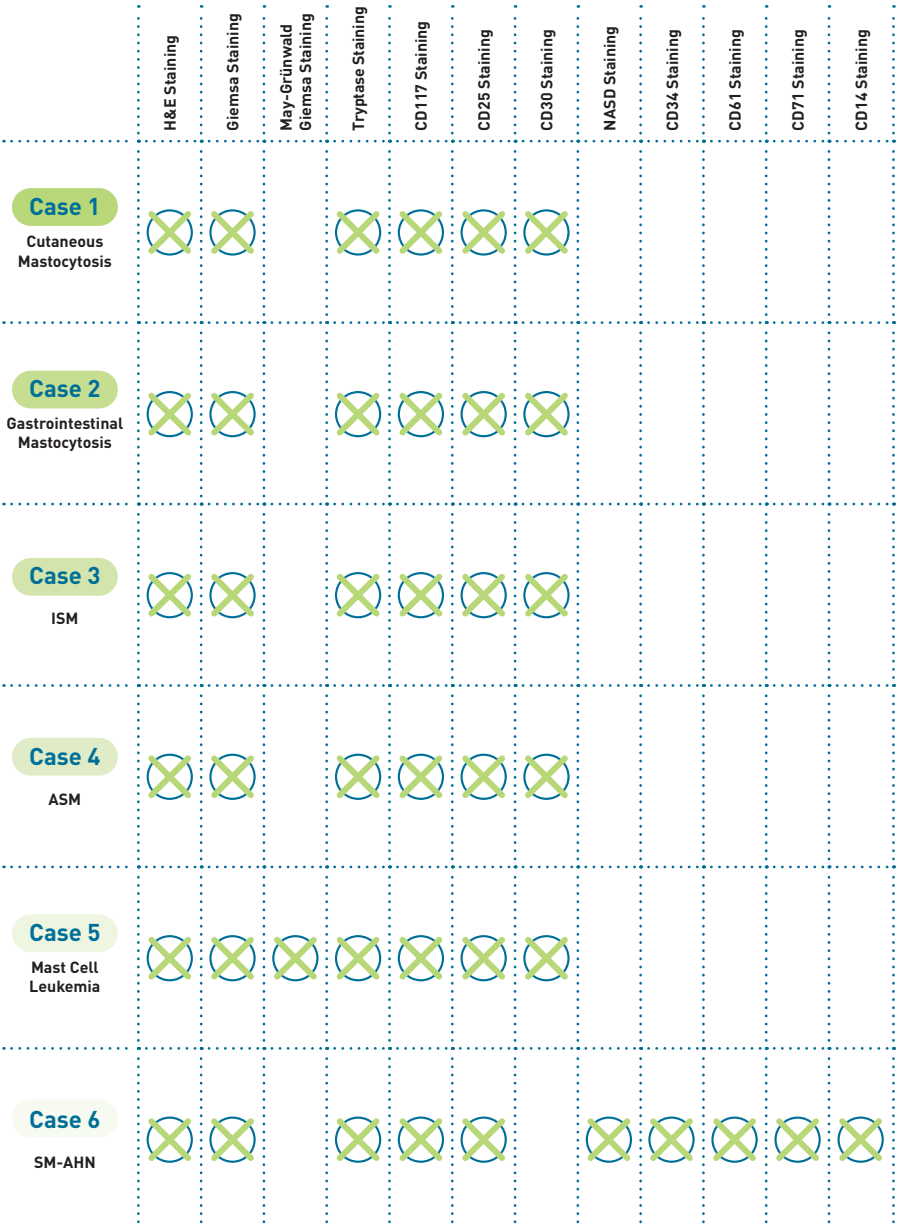
Pathologists are pivotal in diagnosing systemic mastocytosis (SM), distinguishing it from other neoplasms and reactive conditions, and monitoring the disease under therapy. The key morphological feature of SM is the accumulation of spindle-shaped, hypogranulated mast cells (MCs) in the bone marrow (BM) and other extracutaneous tissues. Pathologists can address four of the five World Health Organization-defined diagnostic criteria: compact MC aggregates (major criterion), atypical MC morphology, activating KIT point mutations, and aberrant expression of CD25, CD2, and/or CD30 in MCs (minor criteria).[4]

The final classification of SM variants – whether BM mastocytosis (BMM), ISM, smoldering SM (SSM), aggressive SM (ASM), SM with an associated hematologic neoplasm (SM-AHN), or mast cell leukemia (MCL) – is crucial for prognosis and requires integrating morphological, clinical, radiological, and biochemical data, known as B- and C-findings. Especially diagnosing advanced SM variants, such as ASM, MCL, and SM-AHN, presents significant challenges for both pathologists and clinicians.[4]

To address the challenges in diagnosis of this rare hematologic disorder with common involvement of skin and other organ systems, this folder aims to provide a foundational overview of systemic mastocytosis, equipping pathologists with the knowledge and tools necessary to recognize and classify this condition accurately.

By leveraging the information and tools provided in this folder, pathologists can enhance their diagnostic capabilities, ultimately leading to better identification and management of SM.

Guidelines for Diagnosis of Systemic Mastocytosis:
Standards of Pathology in the Diagnosis of Systemic Mastocytosis: Recommendations of the EU-US Cooperative Group
https://www.jaci-inpractice.org/article/S2213-2198(22)00587-6/abstract



Case 1

Cutaneous Mastocytosis

Case Report

Years

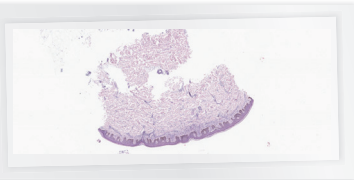
Gender

Baseline disease burden

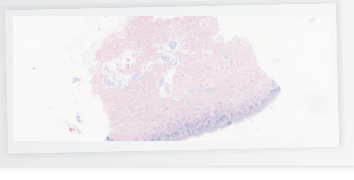
	Baseline disease burden
NGS	KIT
Tryptase (µg/L)	not specified
KIT D816V-VAF	5.6 %

Please scan the code to view original samples

H&E Staining



Giemsa Staining

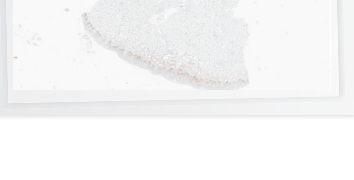


Tryptase Staining

CD117 Staining

CD25 Staining

CD30 Staining



Case 2

Gastrointestinal Mastocytosis

Case Report

Years

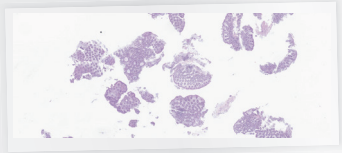
Gender

Baseline disease burden

	Baseline disease burden
NGS	KIT, TET2
Tryptase (µg/L)	339
KIT D816V-VAF	29.0 %

Please scan the code to view original samples

H&E Staining



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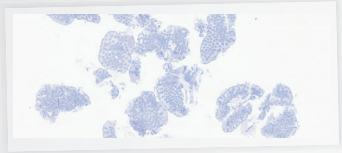
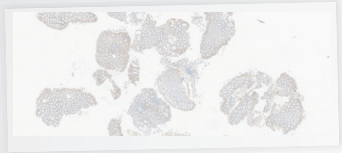


Tryptase Staining



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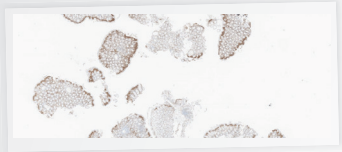

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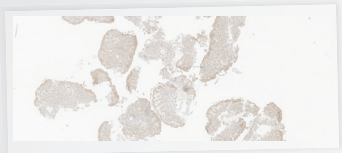
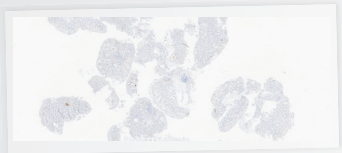


CD30 Staining



Case 3

Indolent Systemic Mastocytosis

Case Report

Years

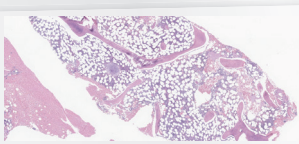
Gender

Baseline disease burden

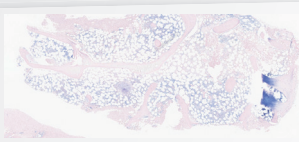
	Baseline disease burden
NGS	negative
Tryptase (µg/L)	27
KIT D816V-VAF	1.3 %

Please scan the code to view original samples

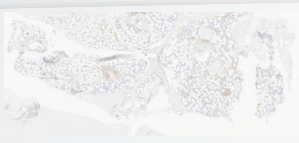
H&E Staining



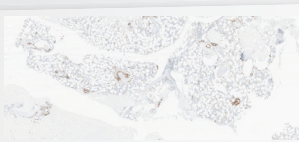
Giemsa Staining



Tryptase Staining



CD117 Staining



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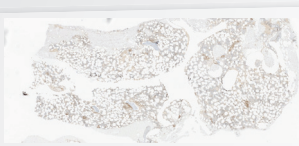
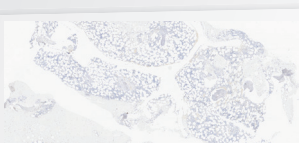


CD30 Staining



Case 4

Aggressive Systemic Mastocytosis

Case Report

Years

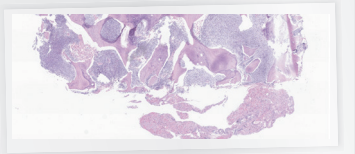
Gender

Baseline disease burden

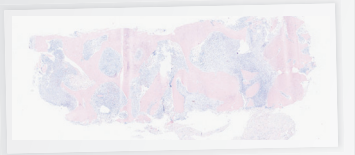
	Baseline disease burden
NGS	KIT, TET2
Tryptase (µg/L)	339
KIT D816V-VAF	29.0 %

Please scan the code to view original samples

H&E Staining

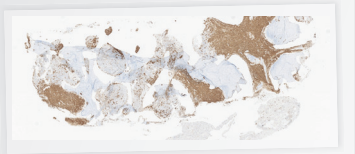


Giemsa Staining



Tryptase Staining

CD117 Staining



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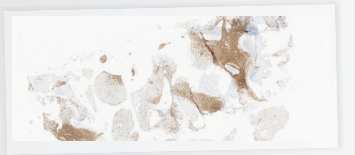

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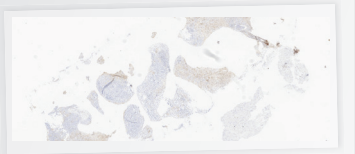


Case 5

Mast Cell Leukemia

Case Report

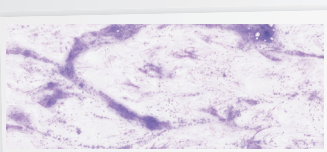
Years 56

Gender

Baseline disease burden

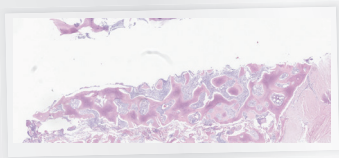
	Baseline disease burden
NGS	KIT
Tryptase (µg/L)	> 500
KIT D816V-VAF	17.0 %

May-Grünwald-Giemsa Staining



Please scan the code to view original samples

H&E Staining



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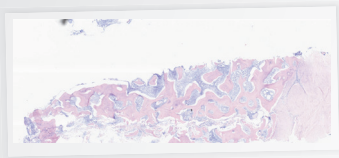
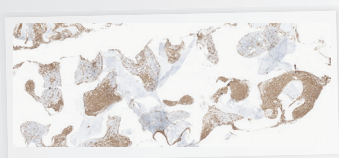


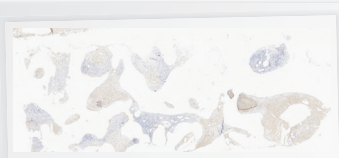
Tryptase Staining

CD117 Staining



CD25 Staining

CD30 Staining



Case 6

SM-AHN

Case Report

Years

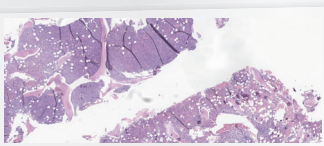
Gender

Baseline disease burden

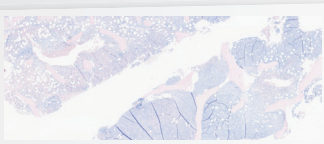
	Baseline disease burden
NGS	ASXL1, SRSF2, TET2, KIT
Tryptase (µg/L)	not specified
KIT D816V-VAF	3.6 %

Please scan the code to view original samples

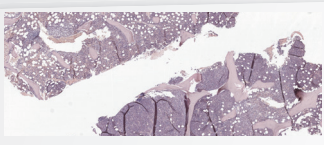
H&E Staining



Giemsa Staining

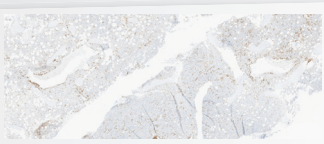


Tryptase Staining

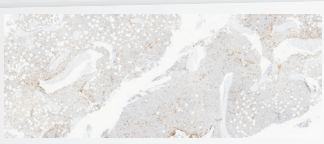


CD117 Staining

CD25 Staining



CD30 Staining

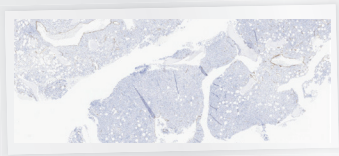


Case 6

SM-AHN (continued)

Please scan the code to view original samples

CD34 Staining



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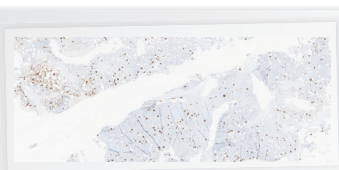
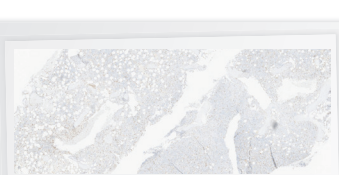


CD71 Staining

CD14 Staining



Conclusion

We hope that the detailed examples and annotated slides provided in this folder will significantly contribute to a better understanding of the morphology of SM and the steps necessary for its proper diagnosis and classification. While this resource does not claim to be exhaustive, our goal is to raise awareness and support pathologists in making accurate diagnoses, ultimately leading to better management of patients.

Given the rarity of SM, building expertise in every center can be challenging. Therefore, in cases that are difficult or questionable, it may be prudent to seek a second opinion and send samples to a center of excellence. These specialized centers have the experience and resources to provide more definitive diagnoses, ensuring that patients receive the most appropriate care.

Special thanks for providing the cases and the annotations goes to Prim. Univ.-Prof. Dr. Karl Sotlar (Uniklinikum Salzburg, Austria).

Notes

Your Partner in Systemic Mastocytosis

1. Joergensen et al. Incidence and Prevalence of Mastocytosis in Adults: A Danish Nationwide Register Study. *Blood* (2023) 142 (Supplement 1): 6339. https://doi.org/10.1182/blood-2023-188451.
2. Bergström et al. Epidemiology of mastocytosis: a population-based study (Sweden). *ACTA ONCOLOGICA* 2024, VOL. 63, 44–50 https://doi.org/10.2340/1651-226X.2024.31406.
3. Berezowska et al. Adult-onset mastocytosis in the skin is highly suggestive of systemic mastocytosis. *Modern Pathology* (2014) 27, 19–29.
4. Sotlar et al. Standards of Pathology in the Diagnosis of Systemic Mastocytosis: Recommendations of the EU-US Cooperative Group. *J Allergy Clin Immunol Pract* 2022;10:1986–98).

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