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# Mastocytosis

## Definition

- Mastocytosis is a proliferation of mast cells and their subsequent accumulation in one or more organ systems.
- Mast cells are derived from hematopoietic progenitors, thus mastocytosis is a hematopoietic disorder.
- The manifestations of mastocytosis are heterogeneous, ranging from skin lesions that may spontaneously regress to highly aggressive neoplasms associated with multisystem involvement and short survival times.

# Definition

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- In cutaneous mastocytosis (CM), the mast cell proliferation is confined to the skin.
- Systemic mastocytosis (SM) is characterized by involvement of at least one extracutaneous organ, with or without evidence of skin infiltration.

# Synonyms

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- Mast cell disease
- Mast cell proliferative disease

# Epidemiology

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- Mastocytosis may occur at any age.
- Cutaneous mast cell disease is most common in children.
- It may be present at birth, and 80% of afflicted children demonstrate lesions by 6 months of age.

# Epidemiology

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- In adults, CM usually appears in the third and fourth decade of life.
- There is no sex predilection reported for CM.
- Systemic mastocytosis is generally diagnosed after the third decade of life; the male to female ratio has been reported to vary from 1 to 1:3.

# Sites of Involvement

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- **Skin:** in approximately 80% of patients, only the skin is clinically involved. Skin lesions occur in 50% or more of the patients with SM, and when present they usually imply an indolent course.
- **BM:** in patients who have SM, BM involvement is almost always morphologically apparent, and a BM biopsy is the usual specimen from which the diagnosis of SM is established.

# Sites of Involvement

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- **PB:** PB rarely shows circulating mast cells.
- **Other organs:** spleen, lymph nodes, liver or GI tract, but any tissue may show deposits of abnormal mast cells.



## **Clinical findings:** *Cutaneous Mastocytosis*

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- Includes several distinct clinicohistopathological entities.
- The lesions of all forms of CM may urticate when stroked (Darier's sign) and most may show pigment which is epidermal in location.

## Clinical findings: *Cutaneous Mastocytosis*

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- The term "urticaria pigmentosa" describes these two clinical features (urticaria and hyperpigmentation) and has been used as a general term for all forms of cutaneous mastocytosis.
- Blistering or bullous mastocytosis represents an exaggerated Darier's sign, usually in very young patients, and can occur in any form of pediatric mastocytosis.



**Cutaneous matocytosis, macular lesions**



**Darier's sign (urticaria)**







## Clinical findings: *Systemic Mastocytosis*

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- Organ dysfunction may be due to infiltration by mast cells or to the release of various biochemical mediators, such as histamine, eicosanoids, proteases or heparin.
- GI complaints, such as peptic ulcer disease and diarrhea, are more commonly due to release of biologically active mediators than to infiltration of the GI tract by abnormal mast cells.



## **Clinical findings: *Systemic Mastocytosis***

- Signs and symptoms at presentation that can generally be grouped into the following categories:
- 1) constitutional symptoms: fatigue, weight loss, fever, sweats
- 2) skin manifestations: pruritus, urticaria, dermatographism
- 3) mediator-related events: abdominal pain, GI distress, flushing, syncope, hypertension, headache, hypotension, tachycardia, respiratory symptoms
- 4) bone-related complaints: bone pain, fractures, arthralgia

## Clinical findings: *Systemic Mastocytosis*

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- Physical findings at the time of diagnosis may include splenomegaly.
- Lymphadenopathy and hepatomegaly are found less frequently.
- Symptoms are mild in many patients, but in others the mediator-related events or organ impairment may be life threatening.

## **Clinical findings: *Systemic Mastocytosis***

- Hematological abnormalities occur in a significant number of patients with SM.
- Anemia, leukocytosis or leukopenia, and thrombocytopenia or thrombocytosis may occur; bone marrow failure can be seen in patients with marked marrow infiltration.
- Eosinophilia may be observed, and is sometimes so marked that it mimics the hypereosinophilic syndrome.
- Circulating mast cells are infrequently observed, except in rare cases of mast cell leukemia.

## Clinical findings: *Systemic Mastocytosis*

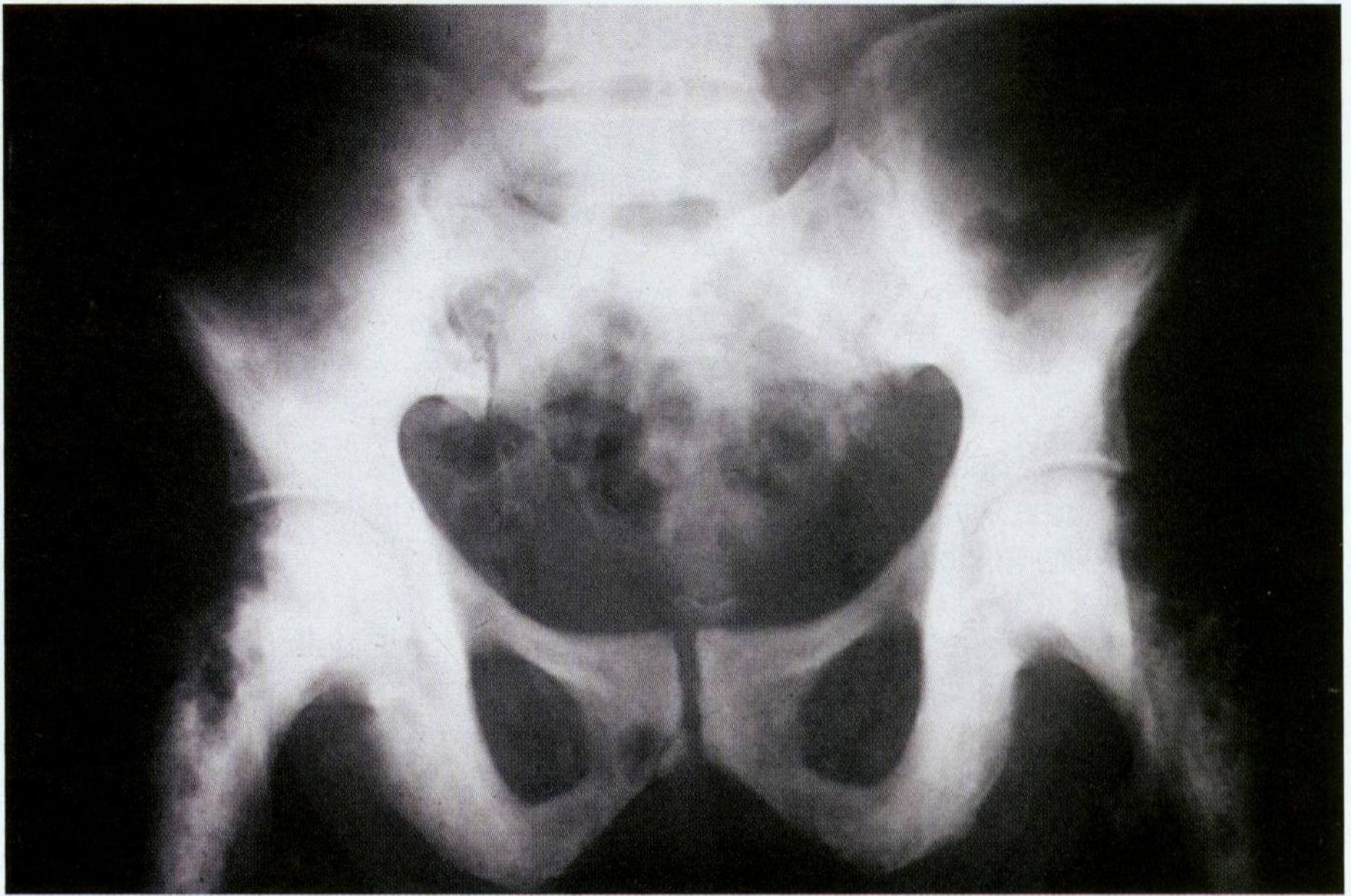
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- In up to 20-30% of cases of SM, an associated, clonal hematopoietic, non-mast cell lineage disorder (AHNMD) may be discovered simultaneously or after the diagnosis of mastocytosis.
- In such cases, symptoms may be related to the associated hematological disorder as well as to the SM.

## Clinical findings: *Systemic Mastocytosis*

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- Serum total tryptase is a useful test in the evaluation of patients with mastocytosis.
- In the absence of other myeloid disorders, the finding of serum total tryptase levels  $>20$  ng/mL is indicative of SM.
- In contrast, serum total tryptase levels are normal ( $<1$  to  $15$  ng/mL) or only slightly elevated in patients with pure CM.

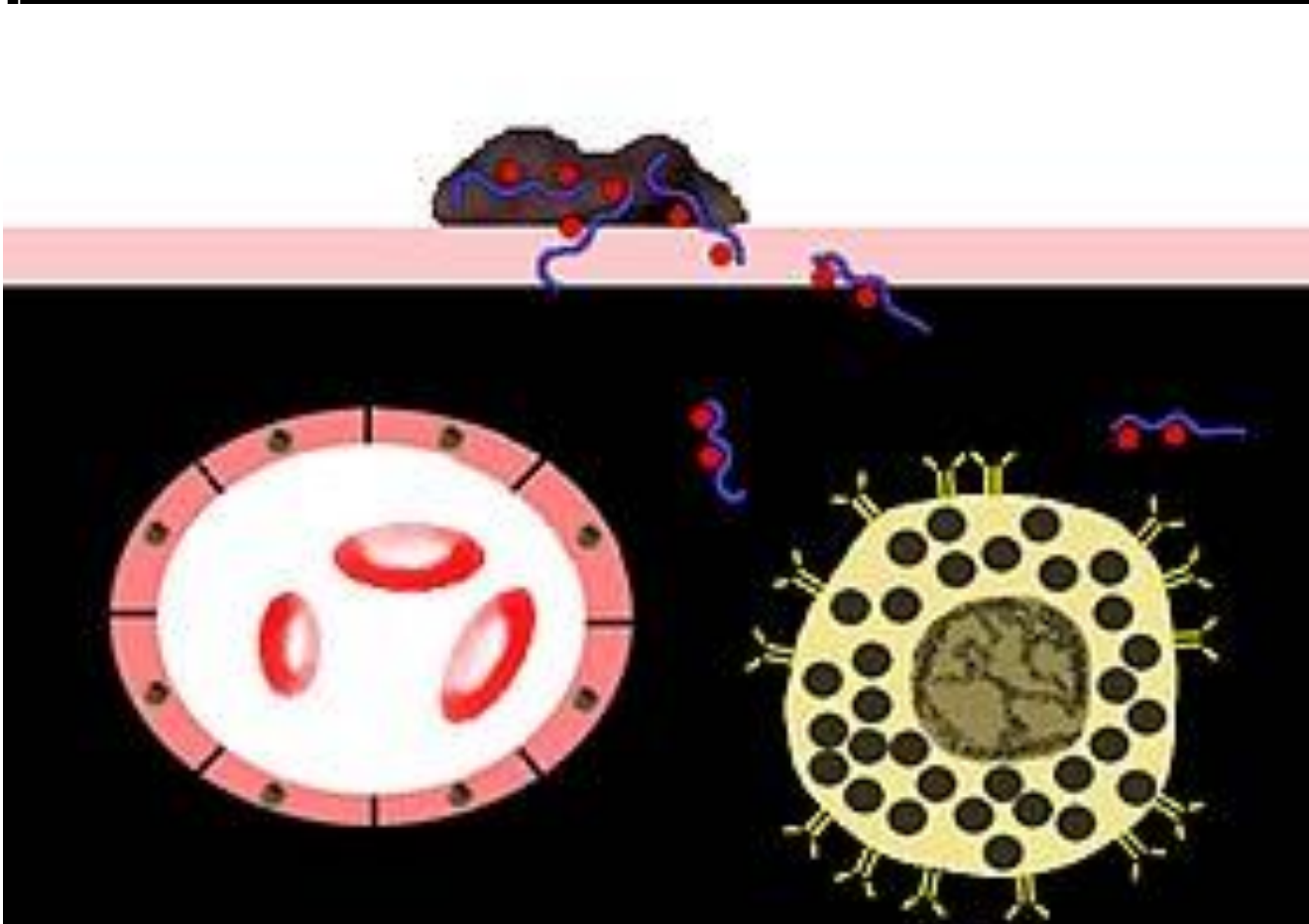


**Systemic mastocytosis: X-ray shows lytic lesions, osteosclerosis, and osteoporosis**

# Etiology

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- The cause of mast cell disease is unknown.
- Rare familial cases are reported.



**Mast cells are covered with IgE and a variety of receptors. When engaged by appropriate antigens, they release their contents, including histamine, heparin, proteases and prostaglandines.**





# Morphology

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- The diagnosis of mast cell disease requires the demonstration of multifocal clusters or aggregates of mast cells in an adequate biopsy specimen.
- Staining of tissue sections with Giemsa or for mast cell tryptase are strongly recommended for confirmation of the diagnosis.

# Morphology

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- The histological pattern of the mast cell infiltrate may vary according to the tissue sampled.
- If the mast cells are loosely scattered without forming aggregates, it may be impossible to establish the diagnosis without additional studies, such as demonstration of an aberrant phenotype, detection of point mutations of *KIT*, or additional biopsies.

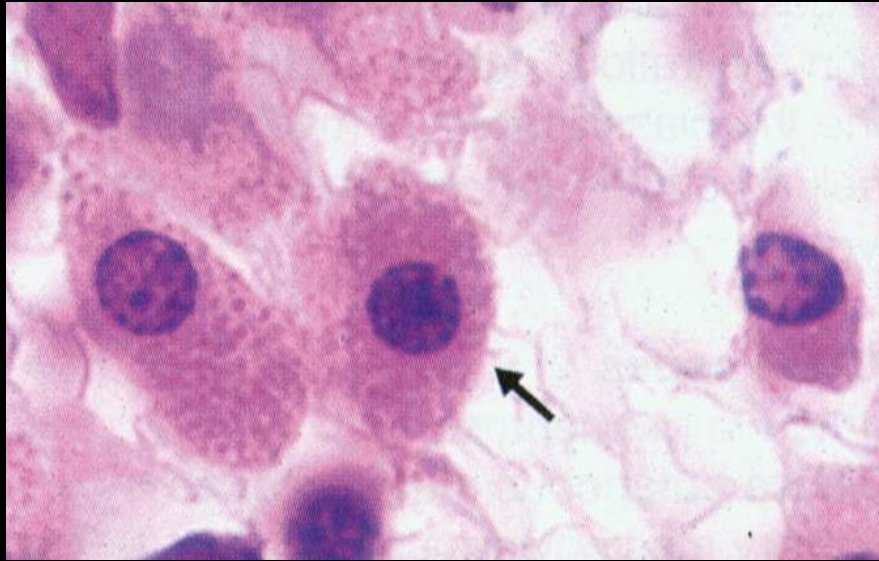
## **Morphology: Normal Mast Cells**

- On H&E, normal mast cells usually display a round to oval nucleus with clumped chromatin, low N/C ratio, and no or indistinct nucleoli.
- They have moderately abundant oval or polygonal-shaped cytoplasm filled with small, faintly visible, slightly eosinophilic granules.
- They are usually sprinkled diffusely in tissues without forming clusters.

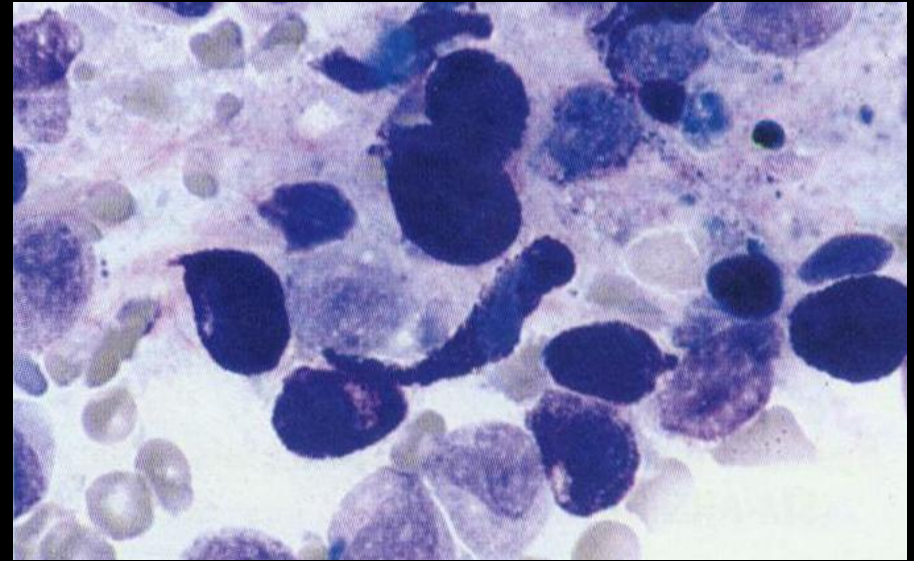
## **Morphology: Normal Mast Cells**

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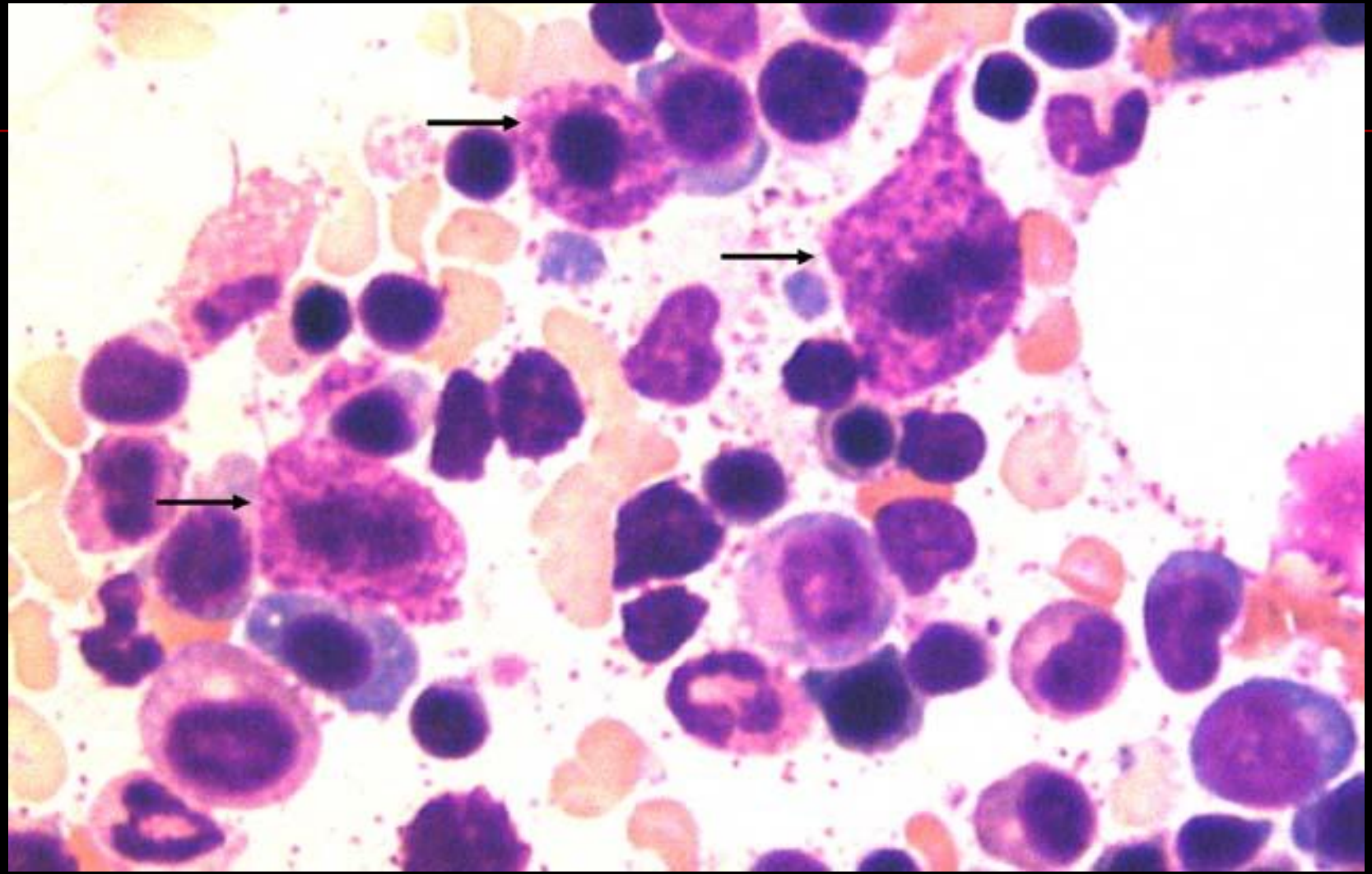
In smear preparations, mast cells are readily visible in Romanowsky stains as round, oval or polygonal cells with cytoplasm densely packed with small, deeply basophilic granules, and round or oval nuclei.

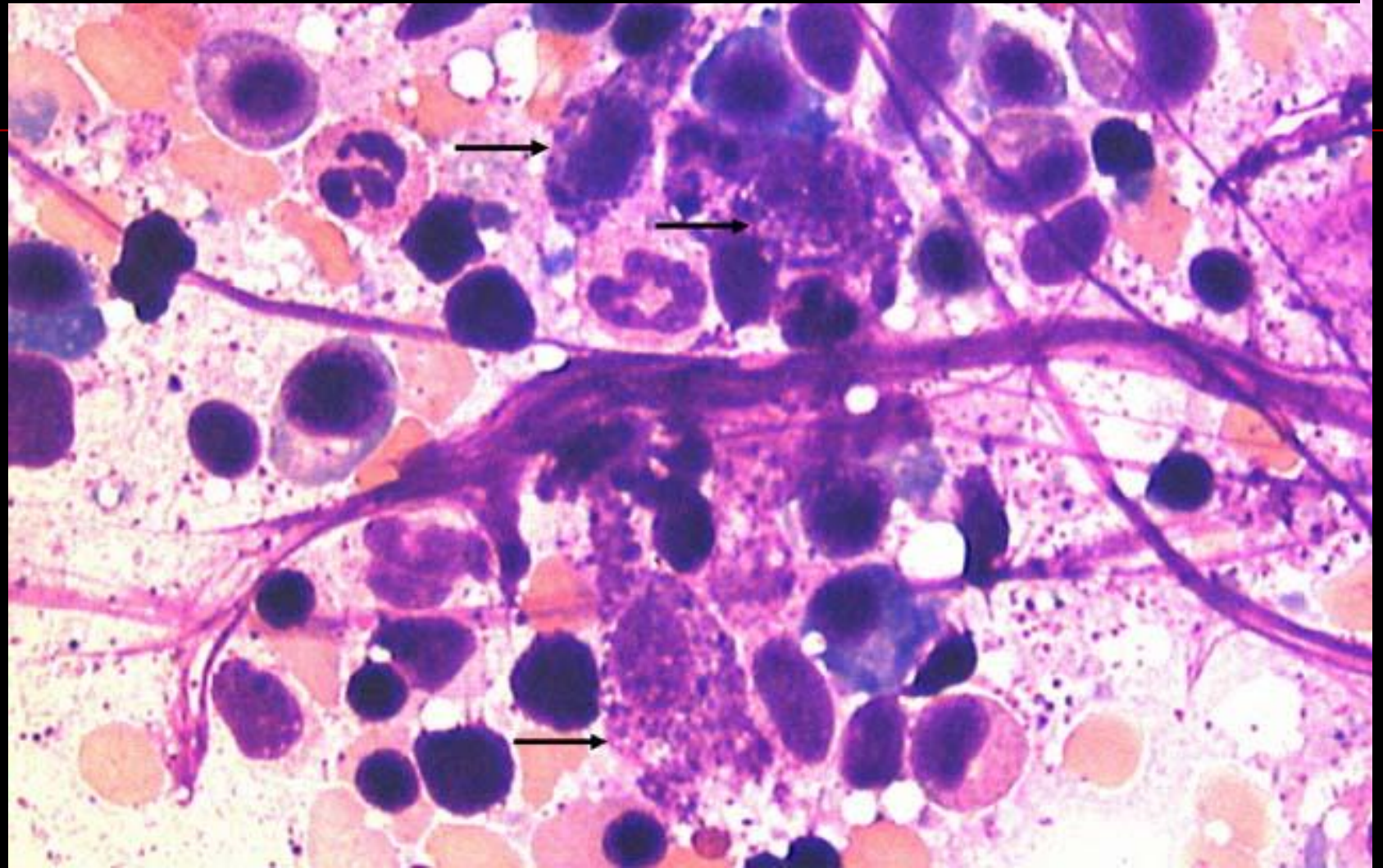


**Normal mast cells, gastric biopsy**



**Mast cell hyperplasia, bone marrow**





## Morphology: Mastocytosis

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- In mastocytosis, the cytology of mast cells is variable.
- In some cases they may closely resemble normal mast cells, but more frequently at least a proportion of the cells have abnormal cytologic features, in that they are more spindle-shaped, and have reniform or indented nuclei.



## Morphology: Mastocytosis

- In some cases, neoplastic mast cells have abundant cytoplasm with sparse granules.
- This feature may be appreciated in tissue sections as pale, almost clear cytoplasm, in which case the mast cells may resemble histiocytes, or the cells of hairy cell leukaemia, monocytoid B cell lymphoma, or other disorders characterised by "clear" cells.

## Morphology: Mastocytosis

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- In smear preparations, mast cells may demonstrate so few granules that their mast cell origin may not be readily appreciated even in the Romanowsky stains.
- This is particularly true of immature mast cells ("nonmetachromatic" and "metachromatic" blasts) seen in the high grade lesions, such as mast cell leukemia.

## Morphology: Mastocytosis

- The finding of mast cells with bi- or multi-lobated nuclei usually indicates an aggressive mast cell proliferation, and although they are commonly observed in mast cell leukemia, they may be seen in other subtypes of the disease as well.
- Mitotic figures are generally scarce, even in the aggressive variants.

# Morphology: Stains

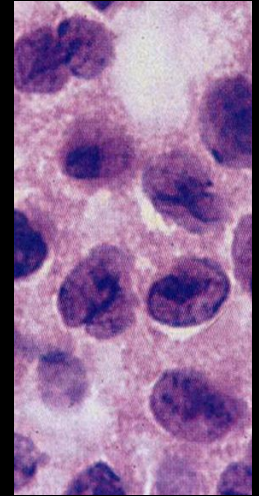
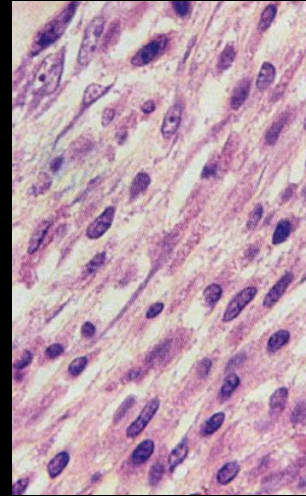
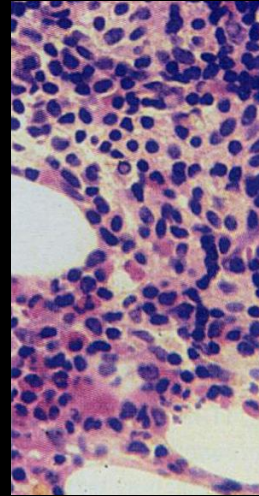
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- All mast cell proliferations should be confirmed by special stains. Metachromatic stains (Giemsa, toluidine blue) are strongly recommended as routine stains for mast cells.
- Fixation methods commonly employed for bone marrow biopsies, however, may result in no or diminished toluidine blue staining.

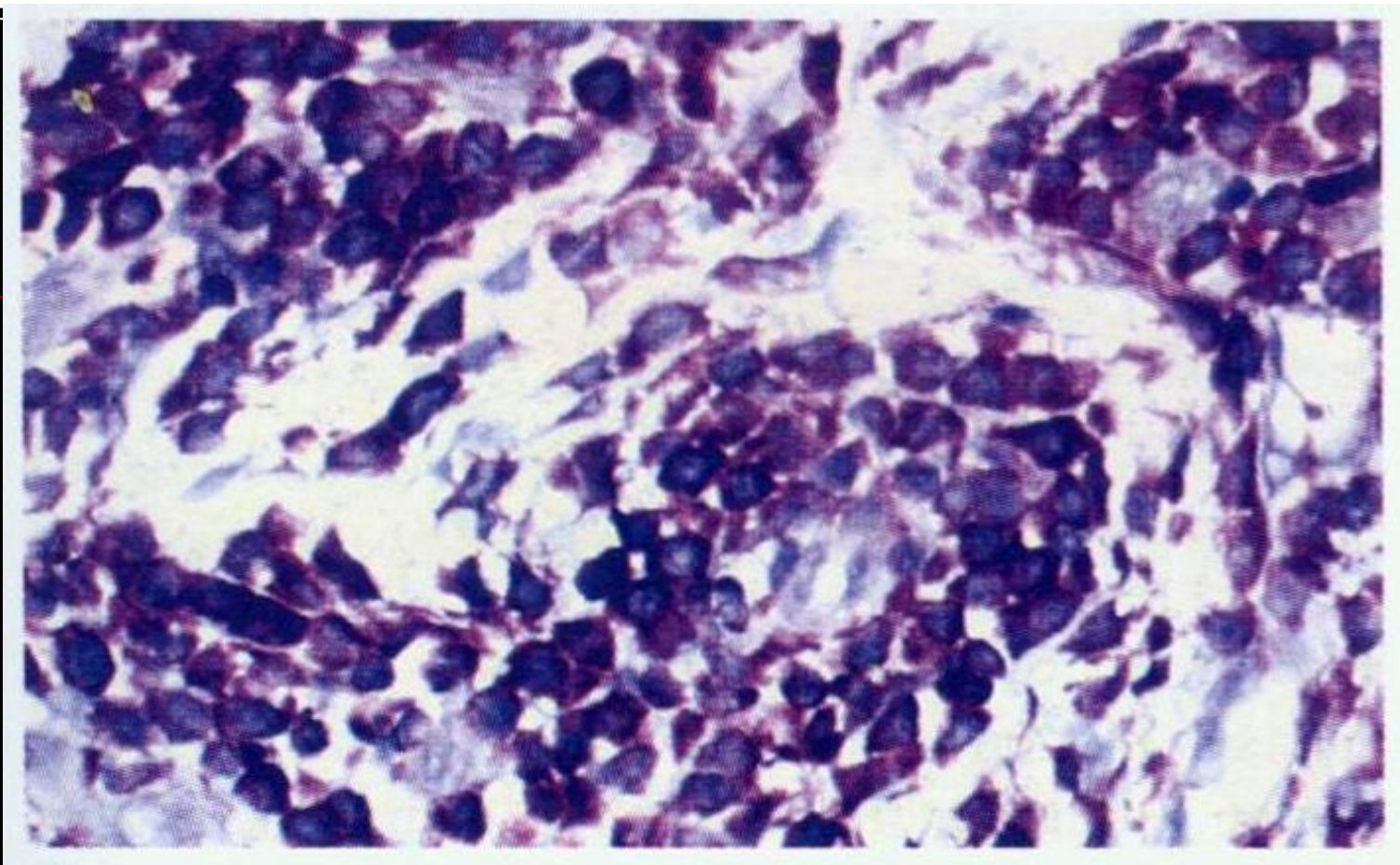
# Morphology: Stains

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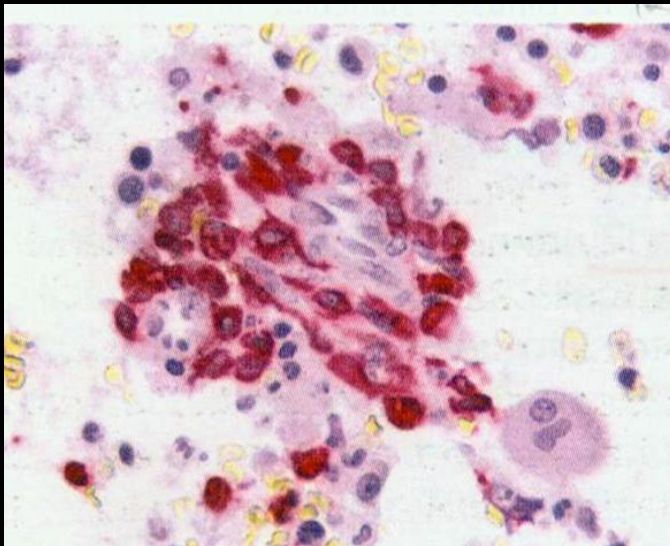
- The most specific method for identification of mast cells in all tissues is immunohistochemical staining for mast cell tryptase.
- Naphthol ASD chloroacetate esterase and CD117 are also characteristic markers of mast cells, but they are not specific.
- In contrast to normal mast cells, CD2 and CD25 are reportedly expressed on the surface of neoplastic mast cells.



**Systemic mastocytosis, bone marrow aspirate and biopsy**



**Toluidine blue**



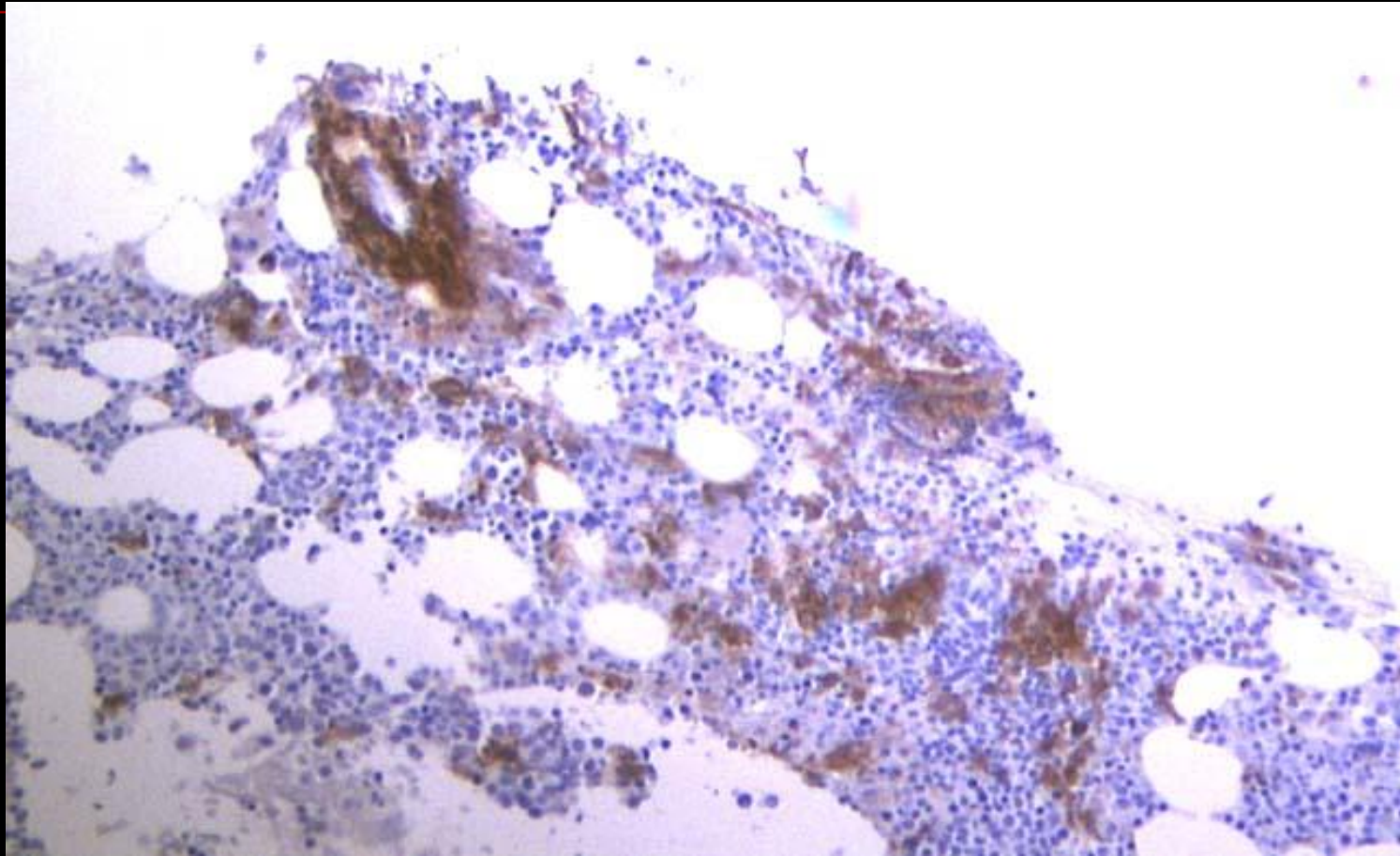
**Tryptase, bone marrow**



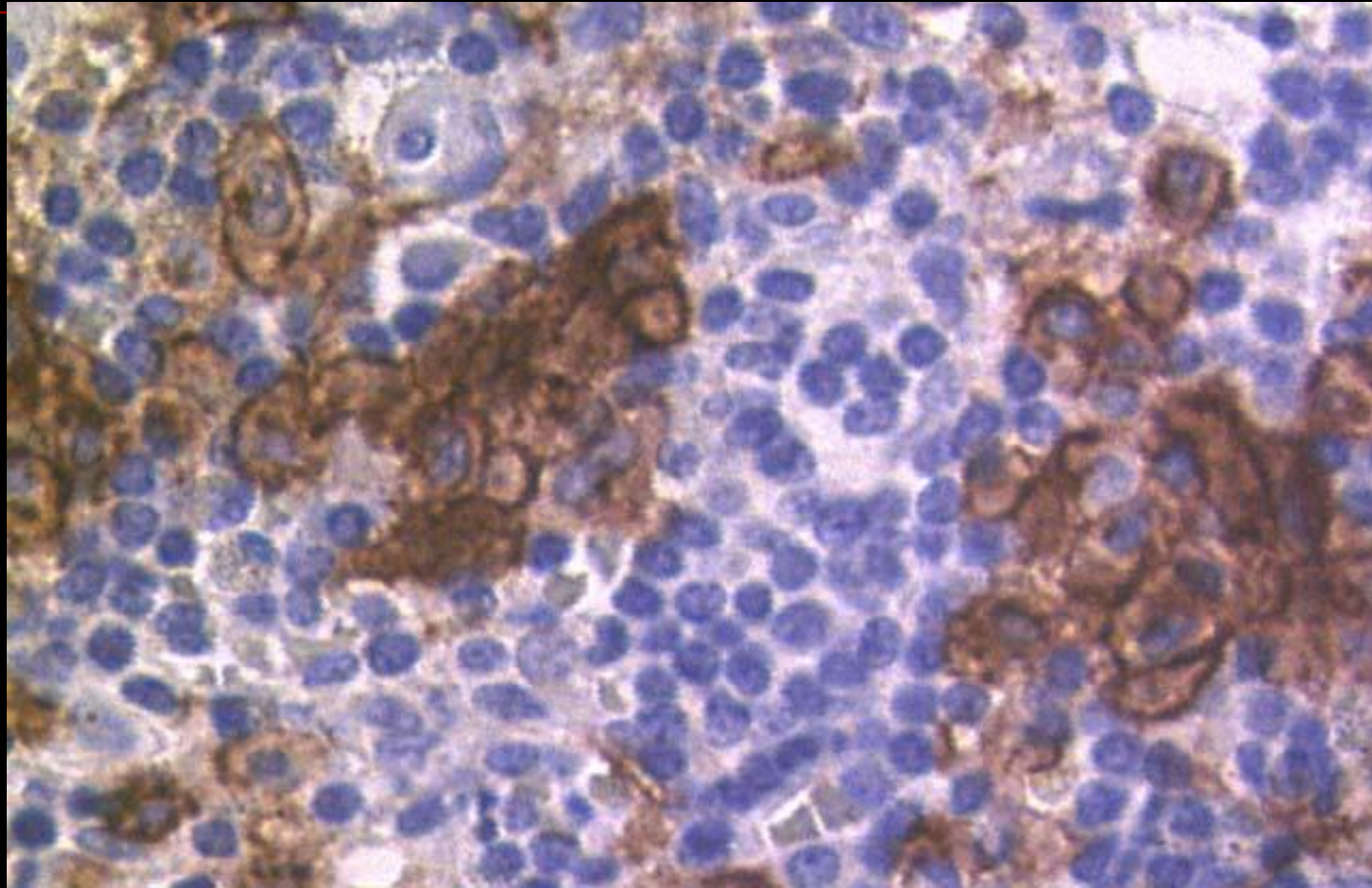
**Urticaria pigmentosa, skin**



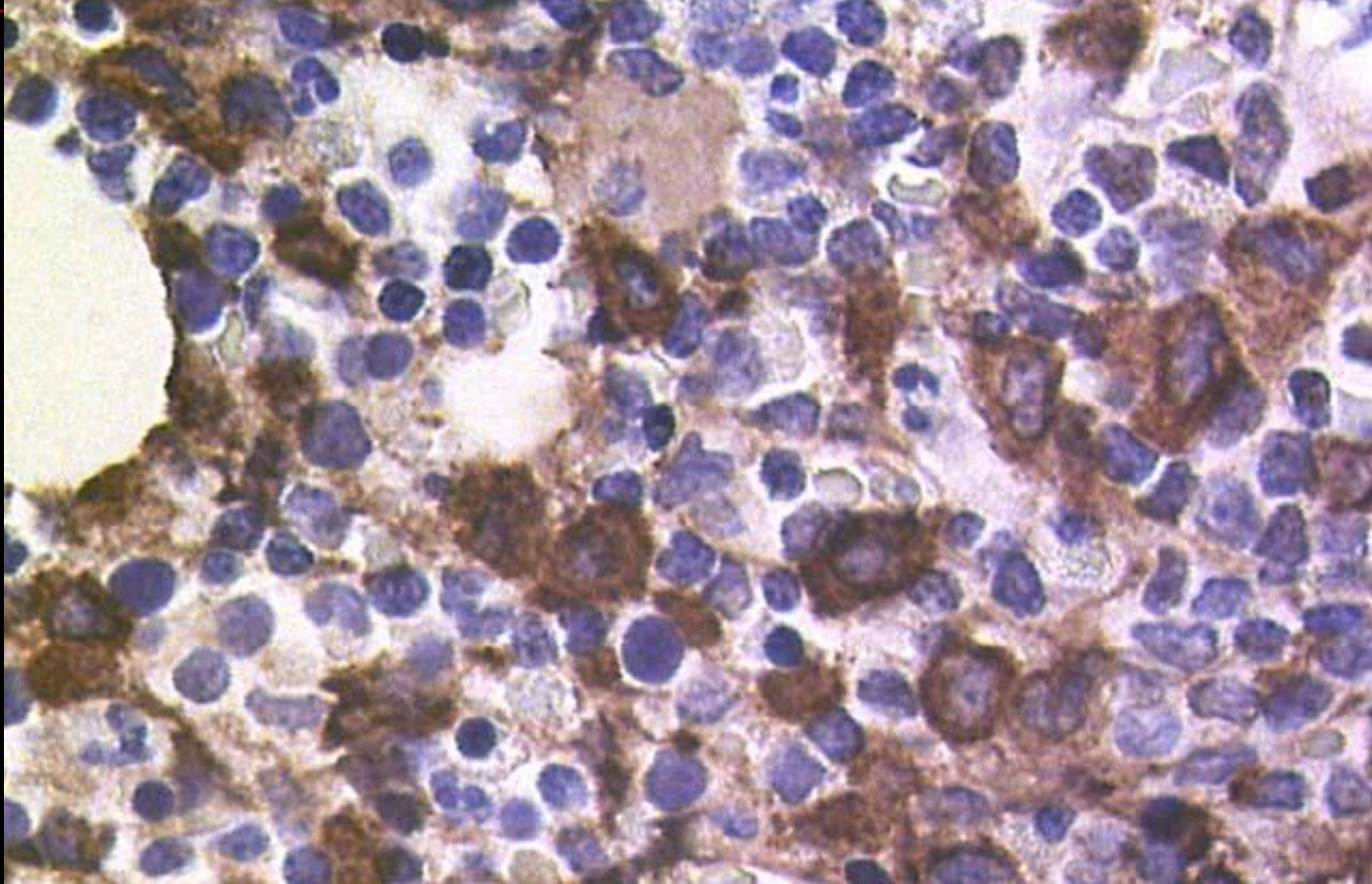
# C-kit (CD117)



# c-kit (CD117)



# Tryptase



# Cutaneous mastocytosis

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- The diagnosis of CM requires the demonstration of typical clinical findings and histological evidence of infiltration of the skin by mast cells.
- In cases of pure cutaneous mastocytosis, there is no evidence for any systemic involvement, such as elevated levels of total serum tryptase or organomegaly.
- Three major variants of CM are recognized

# Cutaneous mastocytosis

*Urticaria pigmentosa (UP) /  
Maculopapular Cutaneous  
Mastocytosis (MPCM).*

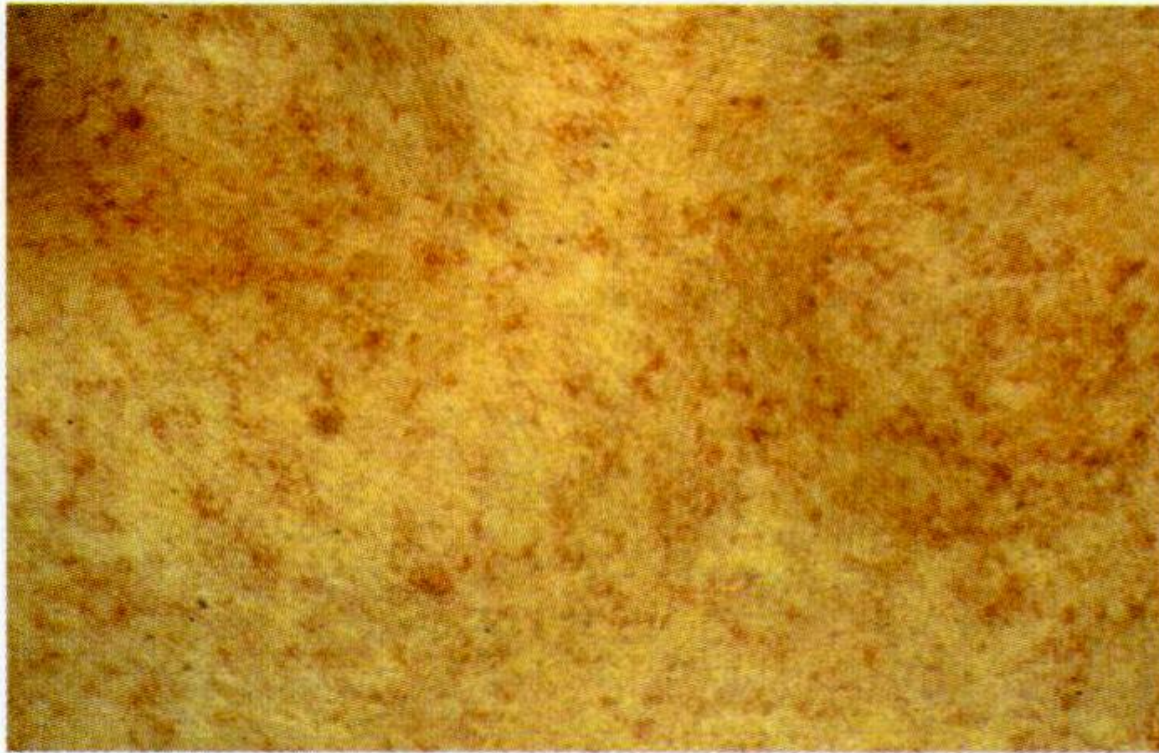
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- This is the most frequent form of CM.
- In children, the lesions of UP tend to be papular, and are characterised by aggregates of elongated or spindle-shaped mast cells which typically fill the papillary dermis and extend as sheets and aggregates into the reticular dermis, often following the vasculature.
- A subvariant is a non-pigmented, plaque-forming lesion that most often occurs in infants.

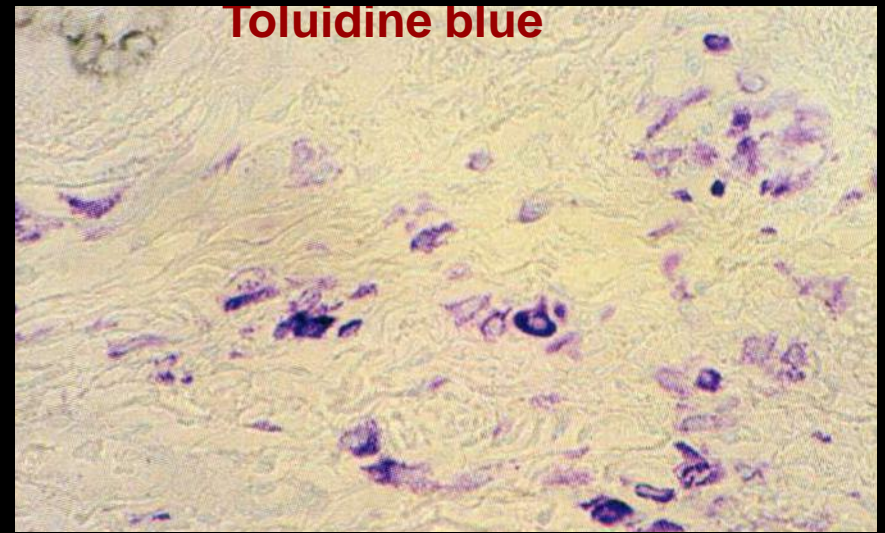
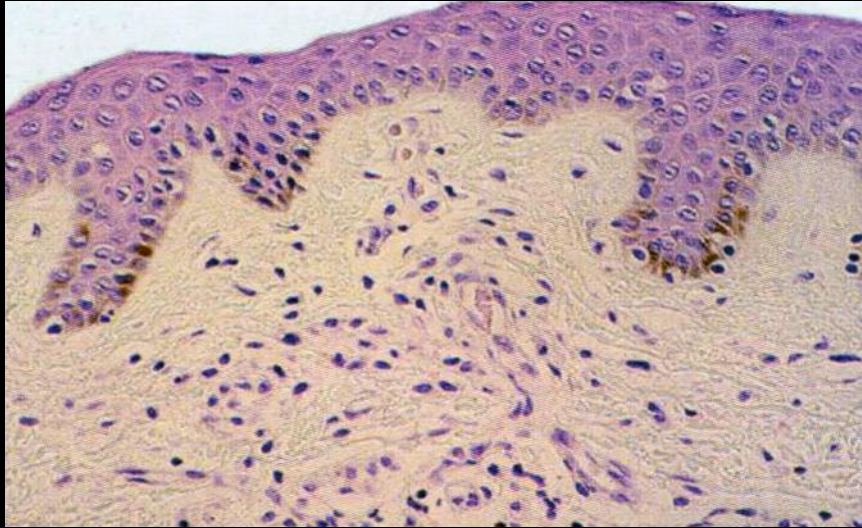
## **Cutaneous mastocytosis** *Urticaria pigmentosa (UP) / Maculopapular Cutaneous Mastocytosis (MPCM).*

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- In adults the lesions tend to be macular, more darkly pigmented, and sometimes associated with telangiectasia.
- Some authorities refer to the small hyperpigmented macular lesions of adult-type UP as the telangiectasia macularis eruptiva perstans subvariant (TMEP).
- Others reserve TMEP for a more rare form characterised by a small number of larger lesions (>1cm) which are lightly pigmented, telangiectatic macules with minimal or no increase in the number of mast cells.



**Telangiectasia macularis eruptive perstans (TMEP), skin**



**Telangiectasia macularis eruptive perstans (TMEP), skin**



# Cutaneous mastocytosis

*Urticaria pigmentosa (UP) /  
Maculopapular Cutaneous  
Mastocytosis (MPCM).*

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- Adult UP tends to have fewer mast cells than the lesions in children, and in some macular lesions the number of mast cells may overlap with the upper range seen in normal or inflamed skin.
- In such cases, examination of multiple sections for aggregates of mast cells or biopsies of multiple lesions may be necessary to establish the diagnosis.

# Cutaneous mastocytosis:

## *Diffuse Cutaneous Mastocytosis*

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- This lesion is less frequent than UP, and is seen almost exclusively in children.
- Patients lack the typical maculopapular lesions of UP, and may have relatively smooth skin, red skin, or skin which is greatly thickened (peau chagrine, grain leather skin).

# Cutaneous mastocytosis:

## *Diffuse Cutaneous Mastocytosis*

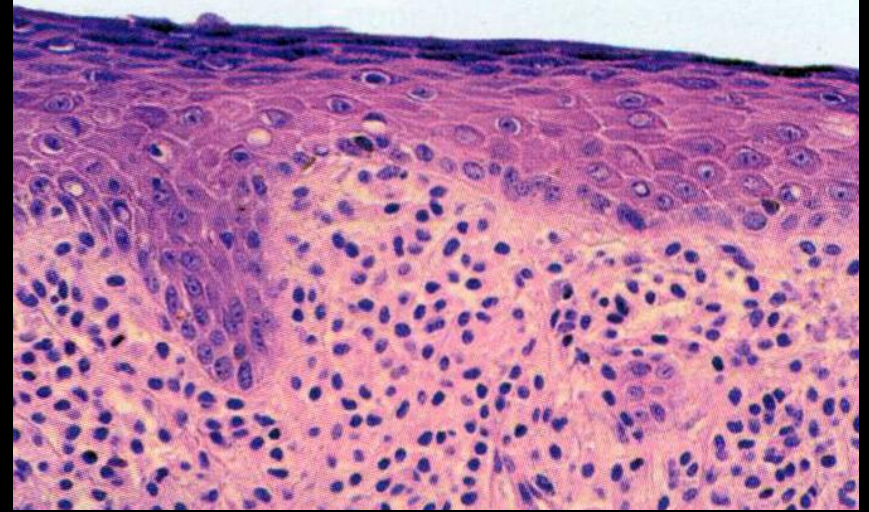
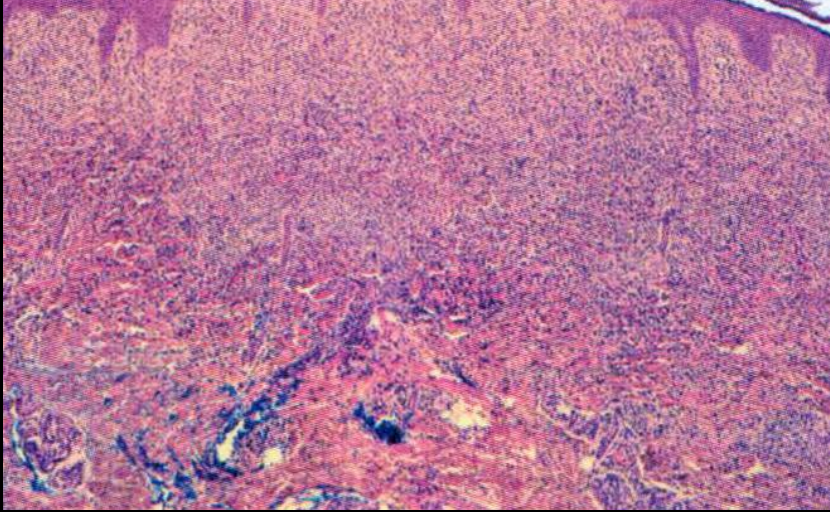
- Histologically, in patients with less clinically obvious infiltration of the skin, the biopsy may show a band like infiltrate of mast cells in the papillary and upper reticular dermis.
- In nodular, plaque-like or greatly infiltrated skin lesions, the histological picture may be identical to that seen in solitary mastocytoma.

# Cutaneous mastocytosis:

## *Mastocytoma of Skin*

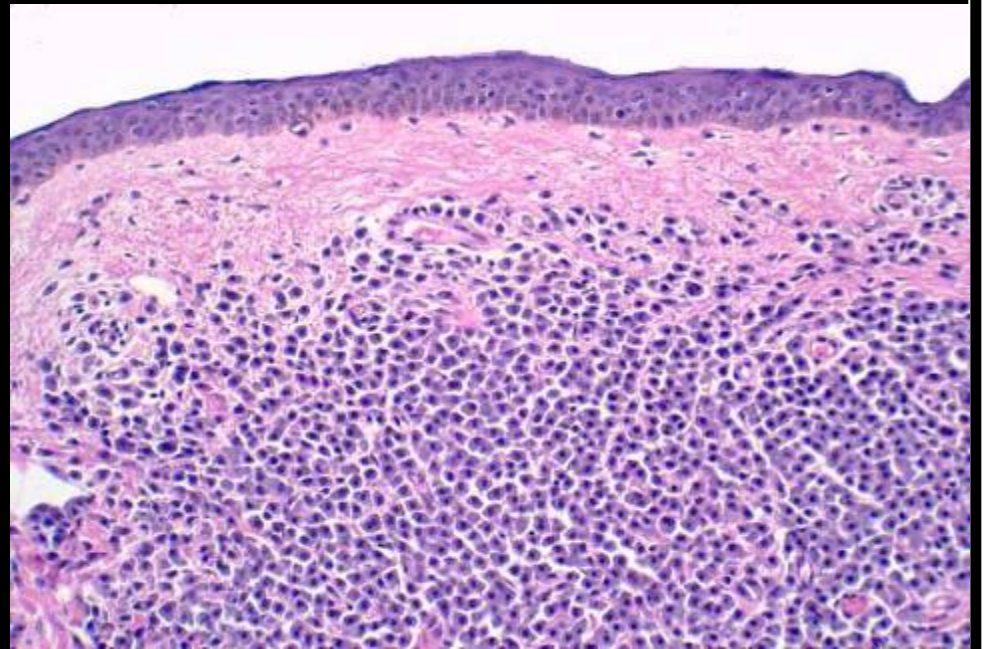
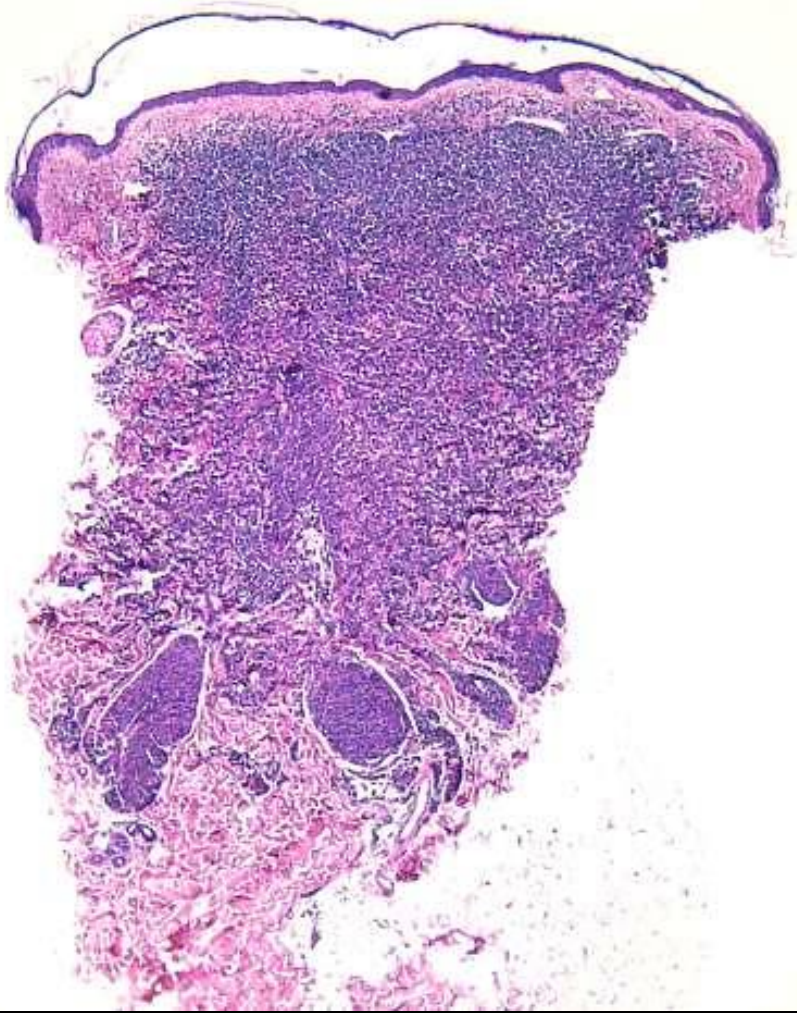
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- This occurs as a single lesion, usually in infants, with a predilection for the trunk and wrist.
- Sheets of mast cells with abundant cytoplasm fill the papillary and reticular dermis, and may extend into the deep dermis and subcutaneous tissues.
- There is no cytologic atypia.



**Mastocytoma, skin**

# Solitary mastocytoma



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# **Systemic Mastocytosis (SM)**

## **Bone Marrow**

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### **-Distribution:**

**Multifocal, peritrabecular perivascular, random**

**-Central core of lymphocytes**

**mast cells in peripheral**

**reactive Eos in marginal**

**-Monomorphic spindle cells, streaming along trabecular**

**bones or diffuse resembling fibrosis**



## BM

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Careful inspection of BM in other areas for:

-Hypercellular marrow: Neutrophil, Eos

-Coexisting hematopoietic neoplasms:

AML, MPD, MDS, LPD

Hypercellularity and abnormal maturation: unfavorable outcome

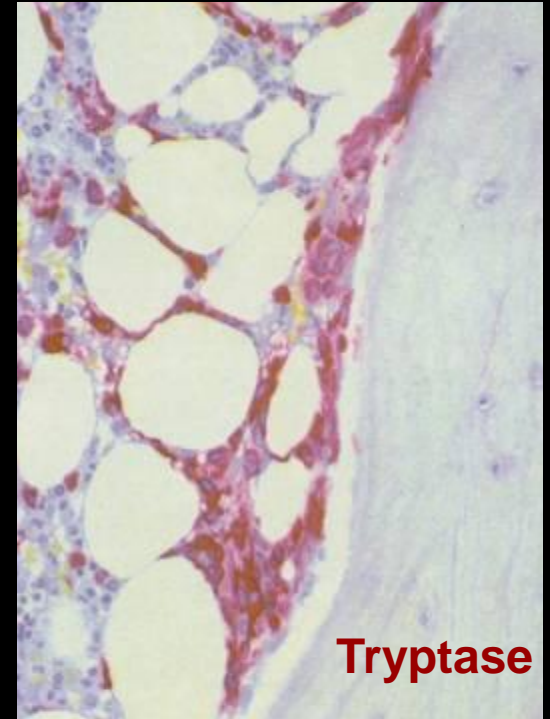
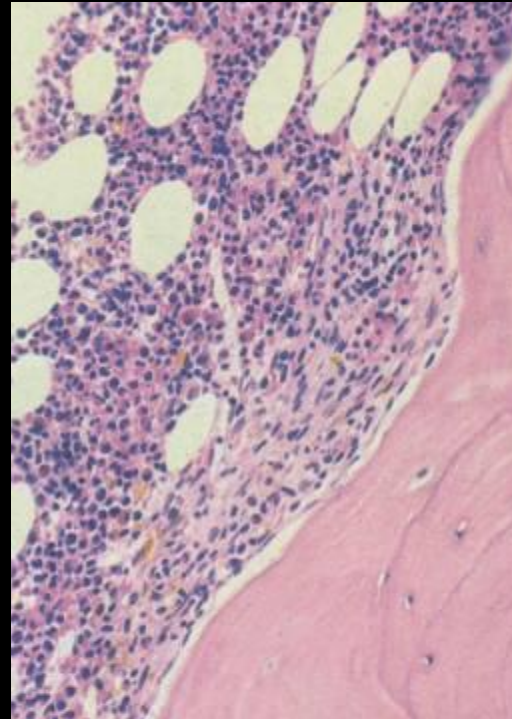
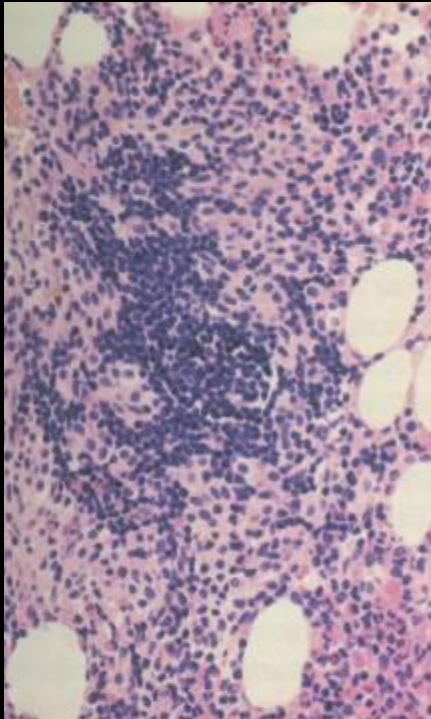
Reactive non-clonal mast cells: no cytological atypia,  
sprinkled interstitially

Diagnostic: core bx

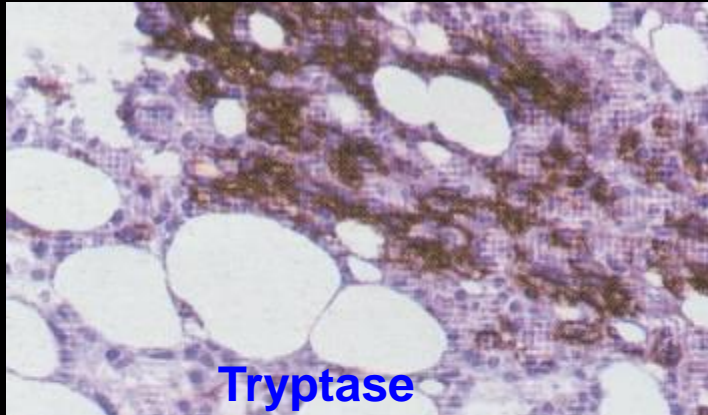
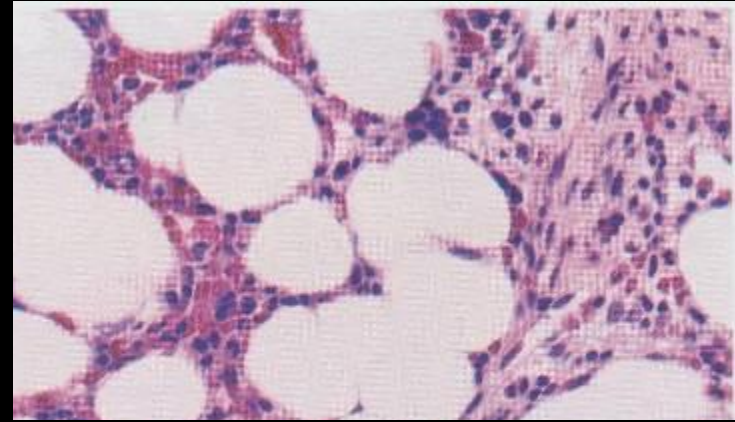
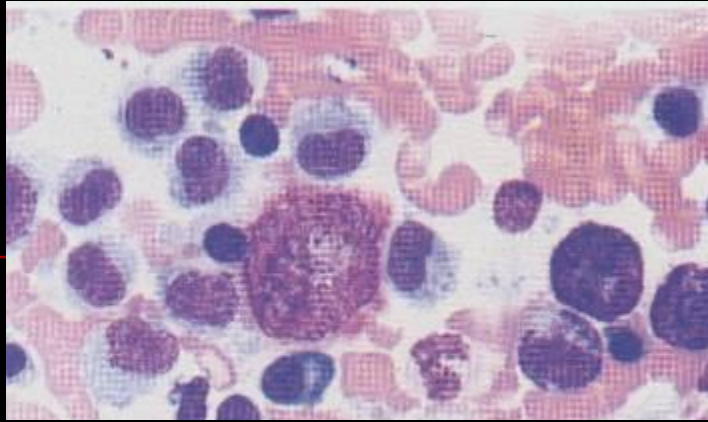
aspirate could be underrepresented

mast cell leukemia: sheets, irregular nuclei, prominent nucleoli

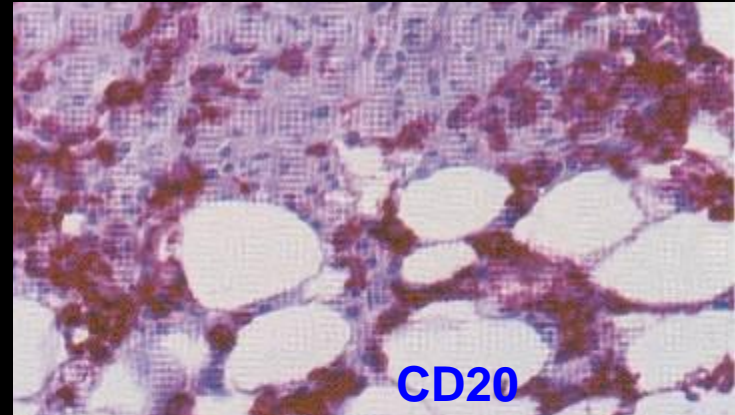
poorly granulated, 20% or more in BM, 10% or more in PB smear



**Systemic mastocytosis, bone marrow**

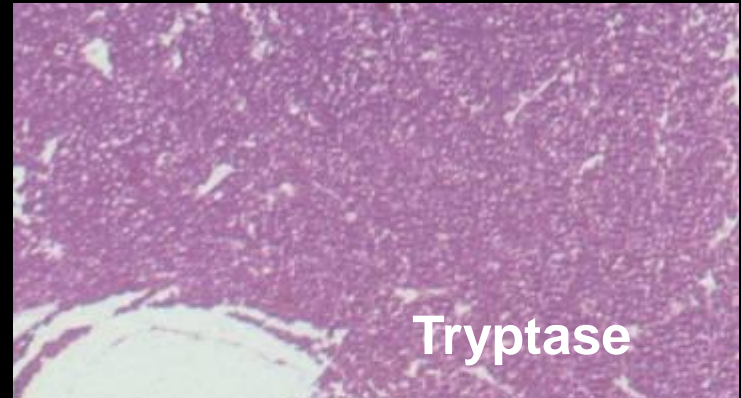
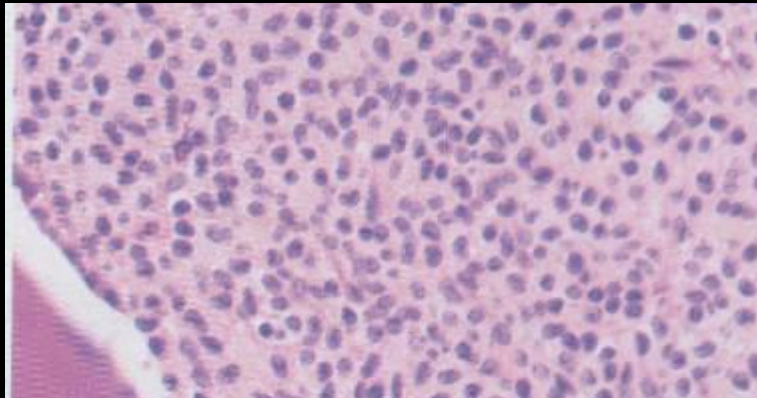
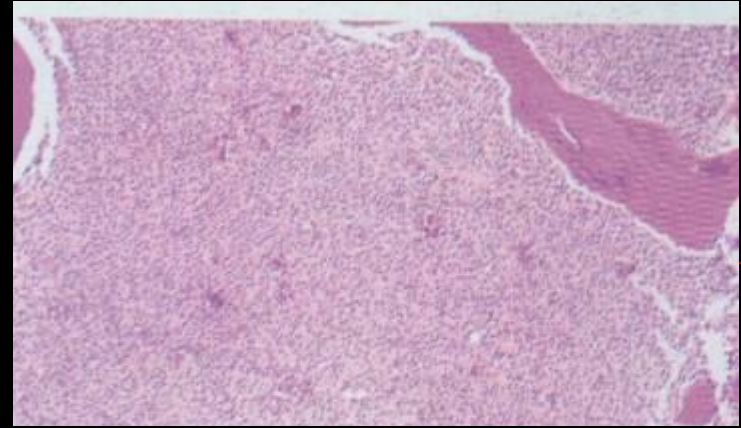
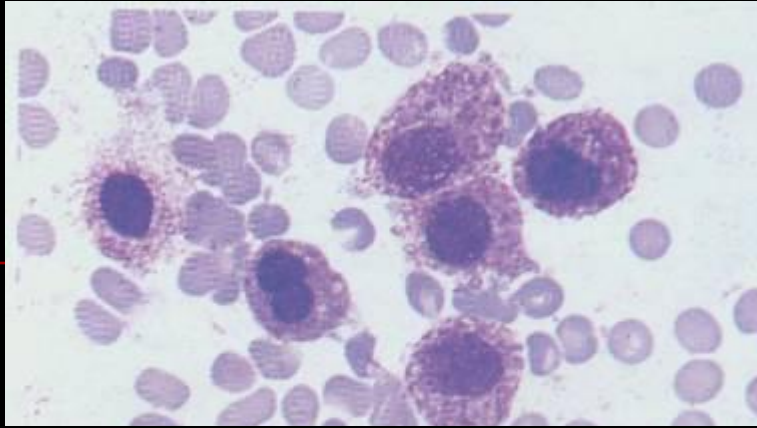


Tryptase



CD20

**Systemic mastocytosis associated with hairy cell leukemia, bone marrow**

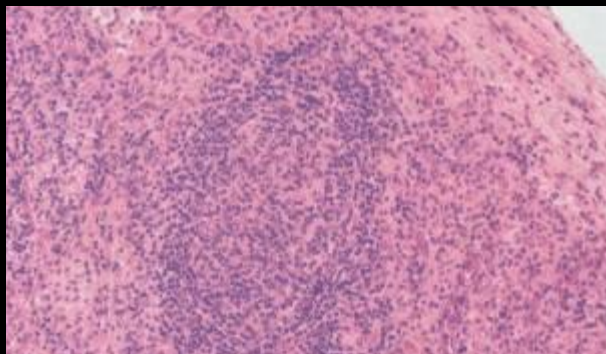
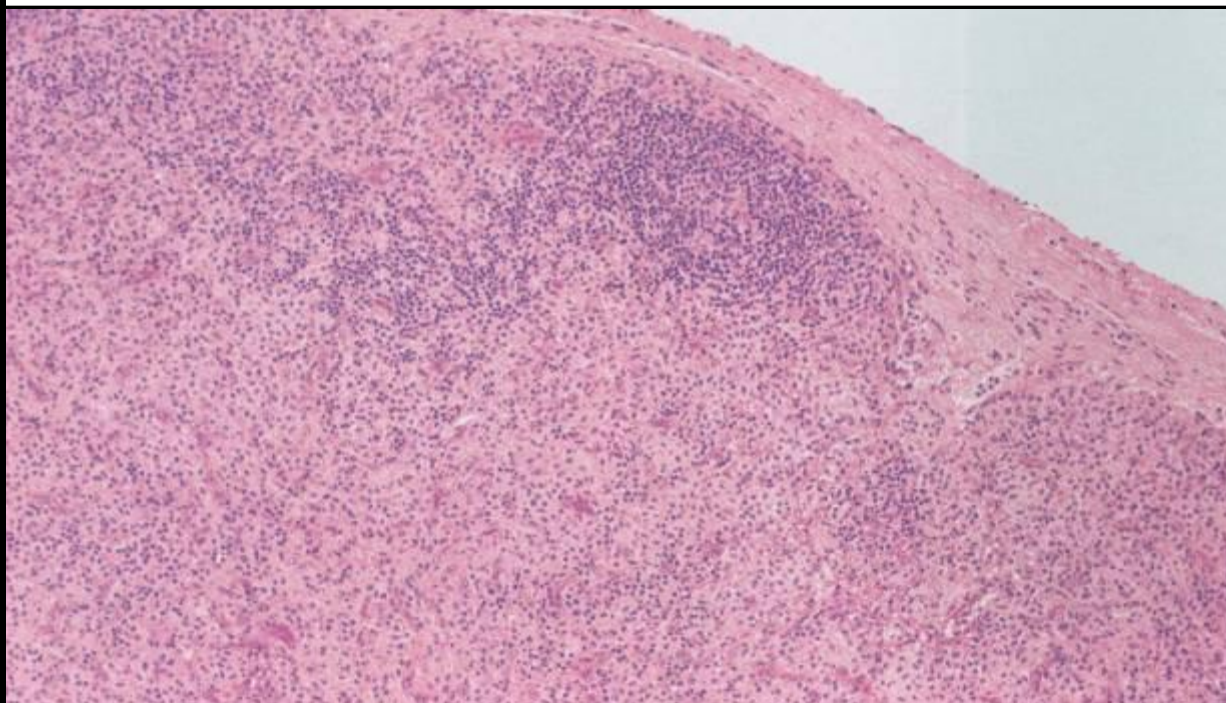


**Mast cell leukemia, bone marrow**

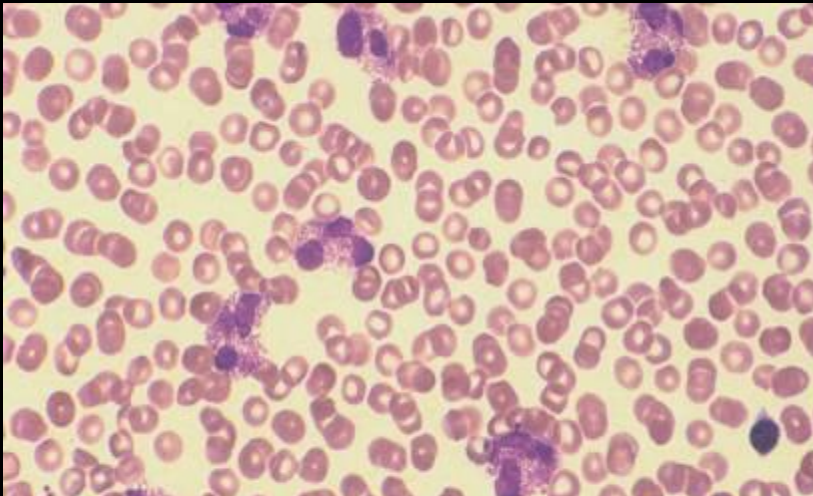
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## Lymph node

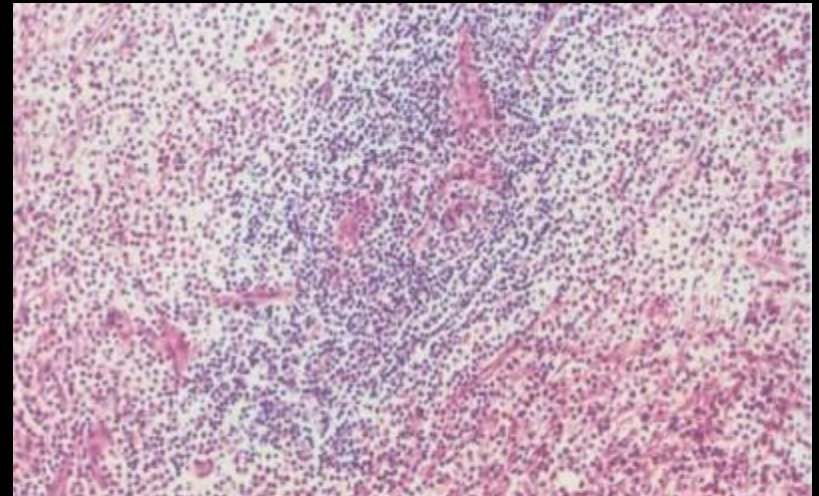
- Infiltrate paracortical but any compartment
- Often accompany:
  - hyperplastic germinal centers and vessels
  - eosinophilia, plasmacytosis, fibrosis



**Systemic mastocytosis, lymph node**



Peripheral blood



Lymph node

**Systemic mastocytosis with eosinophilia**

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## **Spleen**

Any compartment, focal and diffuse, para-follicular  
or -trabecular

Eosinophilia, fibrosis and plasmacytosis



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## **Liver**

- Small foci of atypical mast cells
- Sinuses, periportal areas
- Fibrosis, 20%
- Occasional full cirrhosis

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## **Skeletal lesions**

Osterosclerosis: most common

Lytic lesions and osterosclerosis concurrently

# Mast cell sarcoma

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- Exceedingly rare
- Localized destructive growth
- Highly atypical, immature mast cells
- Distant spread possible
- Leukemic phase

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# Extracutaneous mastocytoma

- Localised, mature mast cells
- Very rare
- Most reported cases were in lung

# Cytochemistry/immunophenotype

## **Positive:**

- Chloroacetate esterase(except of poorly differentiated)
- CD45,33,68,117
- Mast cell tryptase
- Chymase (subpopulation)

## **Negative:**

- CD14,15,16 and T or B Ags  
(except CD2 and CD25, contrast to normal mast cells)

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# Genetics

C-Kit: vast majority of adults with SM  
Rare cases of pediatric CM, atypical

# Prognosis and predictive factors

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## **Favorable:**

Cutaneous mastocytosis in children

SM with CM

Indolent SM, no impact on survival

## **Unfavorable:**

Adults, CM rarely regress, often related with SM

Mast cell leukemia, weeks or months

Mast cell sarcoma

SM without CM

Hematological neoplasms