

Mastocytosis

Faizi Ali, MD

Hematopathology Fellow

William Beaumont Hospital

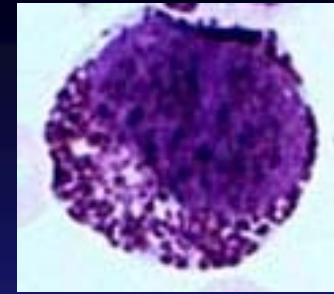
Definition:

“Mastocytosis is a heterogeneous group of disorders characterized by abnormal growth and accumulation of mast cells in one or more organ systems of the body”

Spectrum

Disease manifestations of mastocytosis range from skin lesions that may spontaneously regress, to highly aggressive neoplasm with multisystem involvement and short survival times.

History:



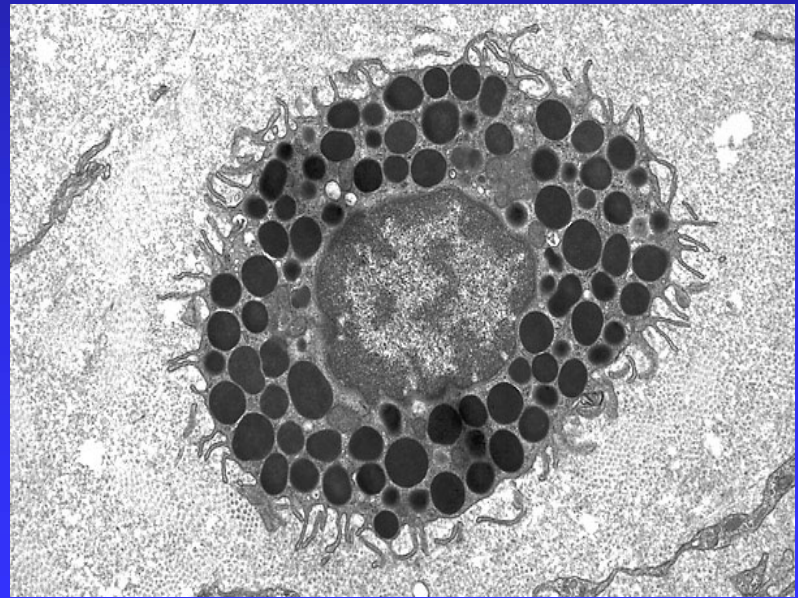
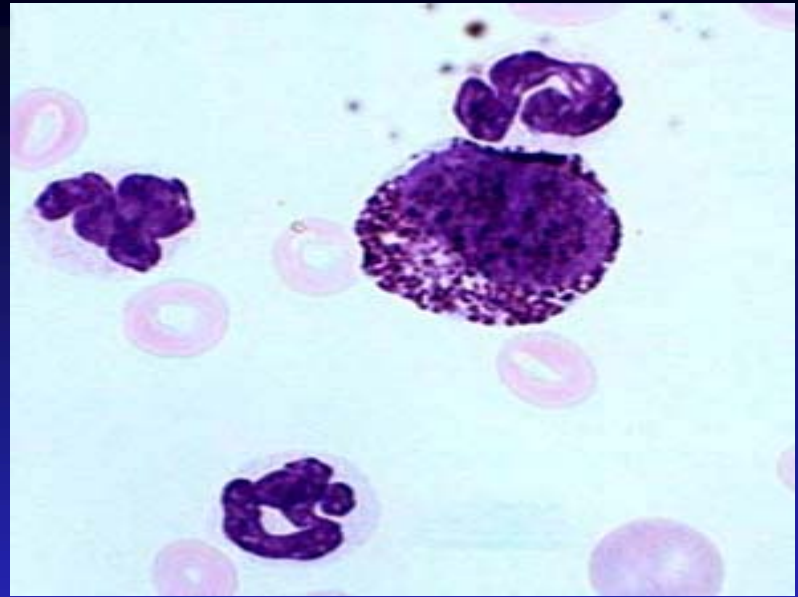
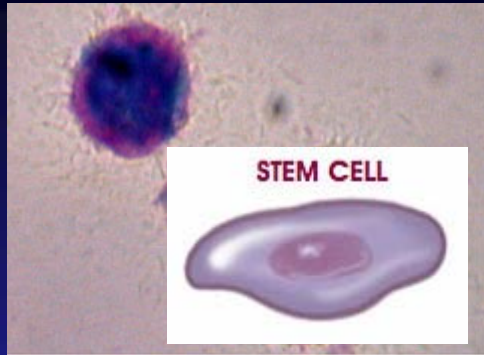
- Paul Ehrlich first described tissue mast cells in 1878 on basis of unique staining characteristics and large granules and named them “mastzellen” meaning “feeding cells”
- Sangster named the entity “urticaria pigmentosa” in 1879 of a disorder encompassing accumulation of numerous mast cells in the skin.
- Ellis first described “systemic disease” of mast cells in 1949 by proving the involvement of internal organs at Autopsy

Origin & Physiology

- Derived from hematopoietic stem cells, specifically from CD34+, and c-kit+ (SCF) progenitor cells in BM
- IL-3 responsible for growth and maturation in BM
- Released into circulation as CD34 precursor cells
- Migrate into loose connective tissue and surround blood vessels, nerves, and lymphatics.
- Distribution depends on content of CT, more mast cells in dermis & subcutaneous than liver, spleen...

Origin & Physiology.....

- Differentiate and mature, form secretory granules that continue to express c-kit, ligand for SCF
- Other sites include mucosa of gastrointestinal tract, upper and lower respiratory tract, and the reproductive tract
- Live in tissues for months before they undergo death
- Express high affinity IgE receptors, when engaged result in degranulation and release of mediators.

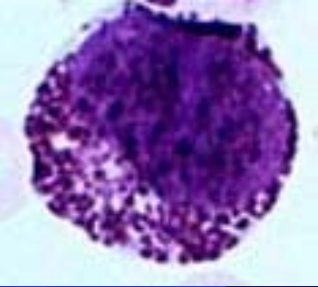


Mast cell Mediators

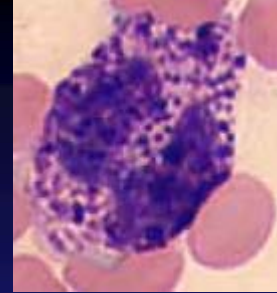
- Preformed granules associated mediators
 - Histamine
 - Heparin
 - Tryptase
 - Chymase
 - Chondroitin sulfate E
 - Cathepsin G
 - Arylsulfatase A
 - Peroxidase
- Arachidonic Acid Metabolites
 - PGD₂, Leukotriene B₄, C₄, D₄, Platelet-activating factor (PAF)
- Cytokines
 - IL-1,2,3,4,5,6,8,10,13, TNF, IFN-gamma, TGF, GM-CSF

Function

- Involved in inflammatory response in immediate anaphylactic and delayed hypersensitivity reaction, release of biogenic amines, potent cytokines and arachidonic metabolites
- Regulation of gastric acid secretion
- Regulation of the microvasculature
- Repair and remodeling of the tissues



Mast cells vs. Basophils



Features	Mast cells	Blood Basophils
Nuclear segmentation	-	+
Occurrence in blood	-	+
Longevity	+ (weeks)	- (8 hours)
Immunohistochemistry		
■ Tryptase	++++	+/-
■ CD117	++++	-
Cytochemistry		
■ Toluidine blue	++++	+++
■ Chloroacetate esterase	++++	-

Pathogenesis

Mast cell hyperplasia

- Transient elevations of SCF or other mast cell growth factors leads to transient mast cell hyperplasia without somatic *kit* mutations

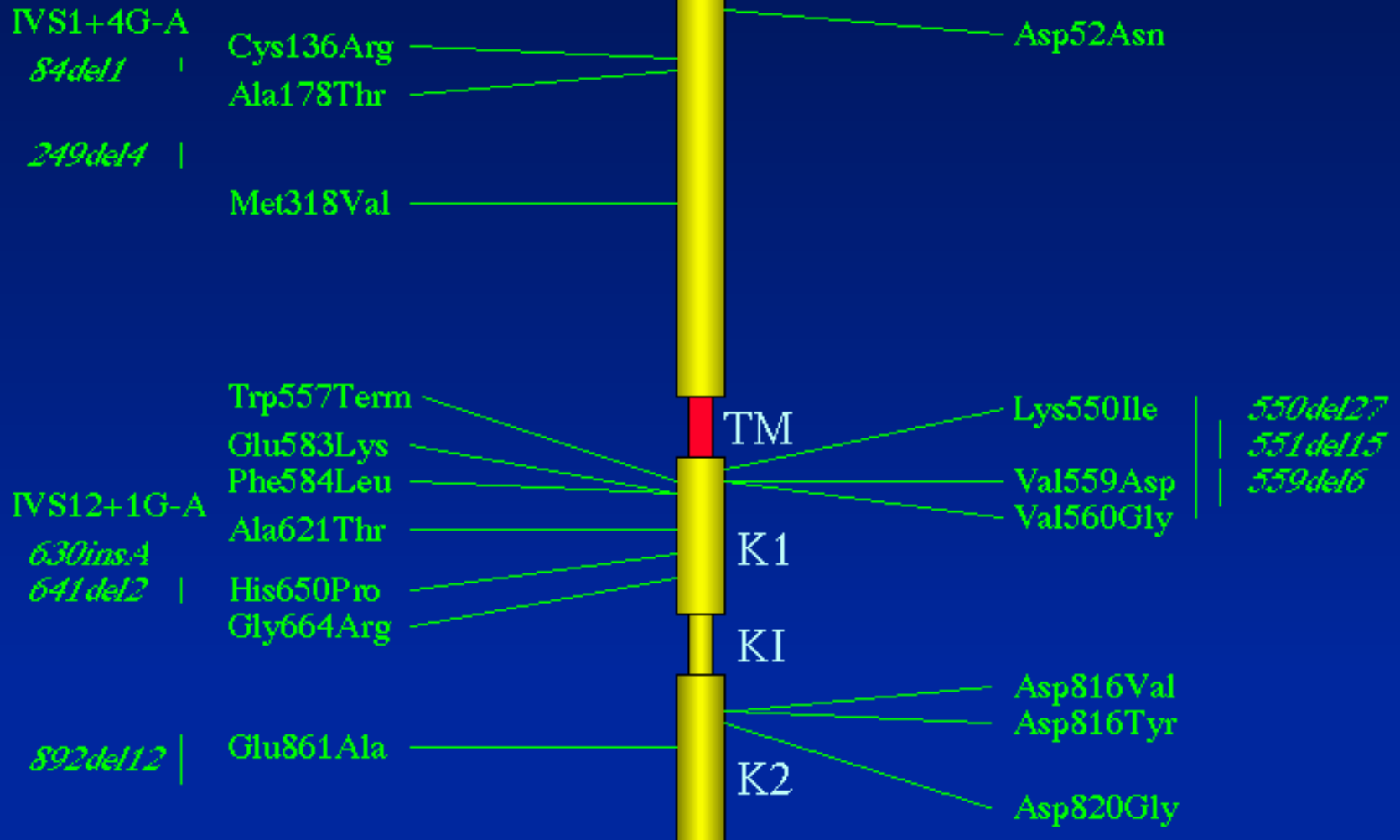
Mastocytosis

- Somatic point mutations on the proto-oncogene *c-kit* (receptor of c-kit ligand, SCF or Mast cell growth factor) is seen in adults with SM or rare pediatric cases of CM.
- Most commonly observed mutation substitutes Val for Asp at codon 816 – activation of *kit* protein (SCF factor)

MUTATIONS AND DELETIONS OF KIT RECEPTOR

LOSS OF FUNCTION

GAIN OF FUNCTION



WHO Classification

- Cutaneous Mastocytosis (CM)
- Indolent systemic mastocytosis (ISM)
- Systemic mastocytosis with associated clonal, hematological non-mast-cell lineage disease (SM-AHNMD)
- Aggressive systemic mastocytosis (ASM)
- Mast cell leukemia (MCL)
- Mast cell sarcoma (MCS)
- Extracutaneous mastocytoma

Cutaneous Mastocytosis

Cutaneous Mastocytosis (CM)

- Mastocytosis confined to the skin, comprising the most common form (80%) of the disease.
- Also most common form of disease in children with 80% of afflicted children demonstrate disease by 6 months of age.
- Skin lesion urticate when stroked (Dreier's sign) and show pigmentation (epidermal).
- Diagnosis requires histologic evidence of skin infiltration by mast cells with absence of systemic involvement such as elevated serum tryptase or organomegaly.

CM.... Subclassification

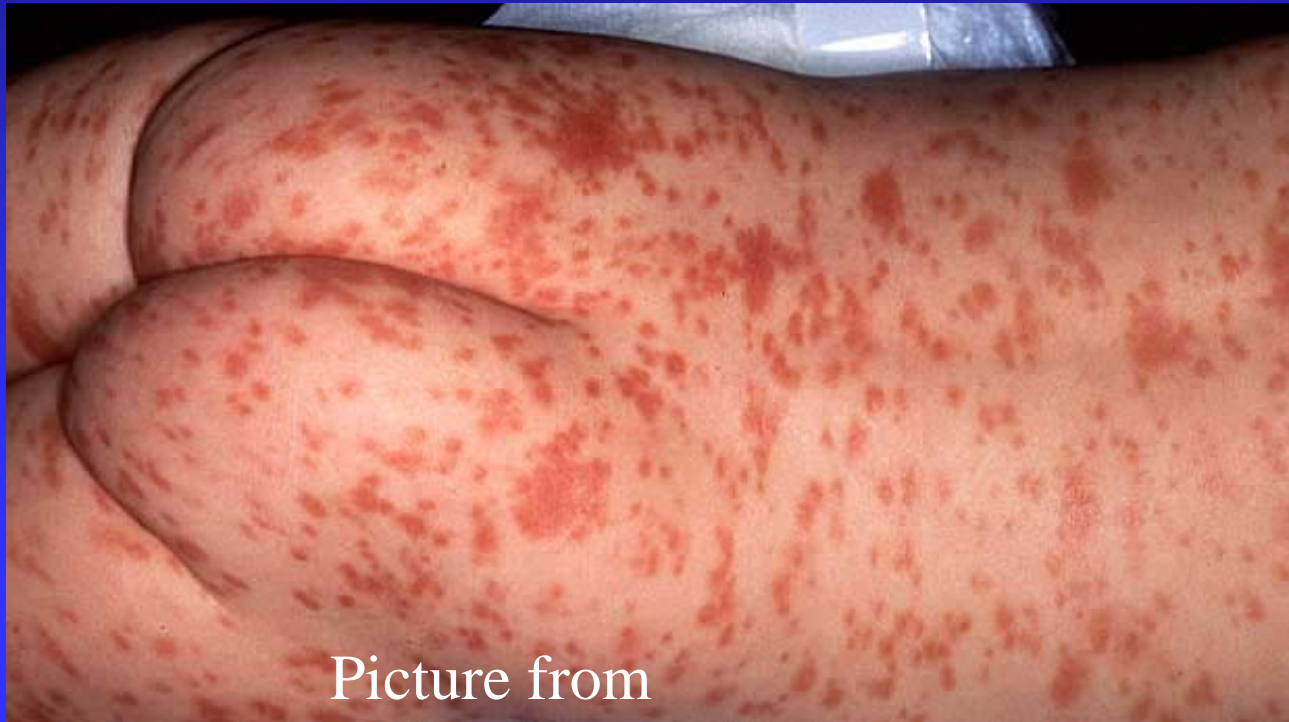
1. Urticaria pigmentosa (UP)/ maculopapular cutaneous mastocytosis (MPCM)
 - Typical UP
 - Plaque form
 - Nodular form
 - Telangiectasia macularis eruptiva perstans
2. Diffuse cutaneous mastocytosis
3. Solitary mastocytoma of skin

Urticaria Pigmentosa (UP)

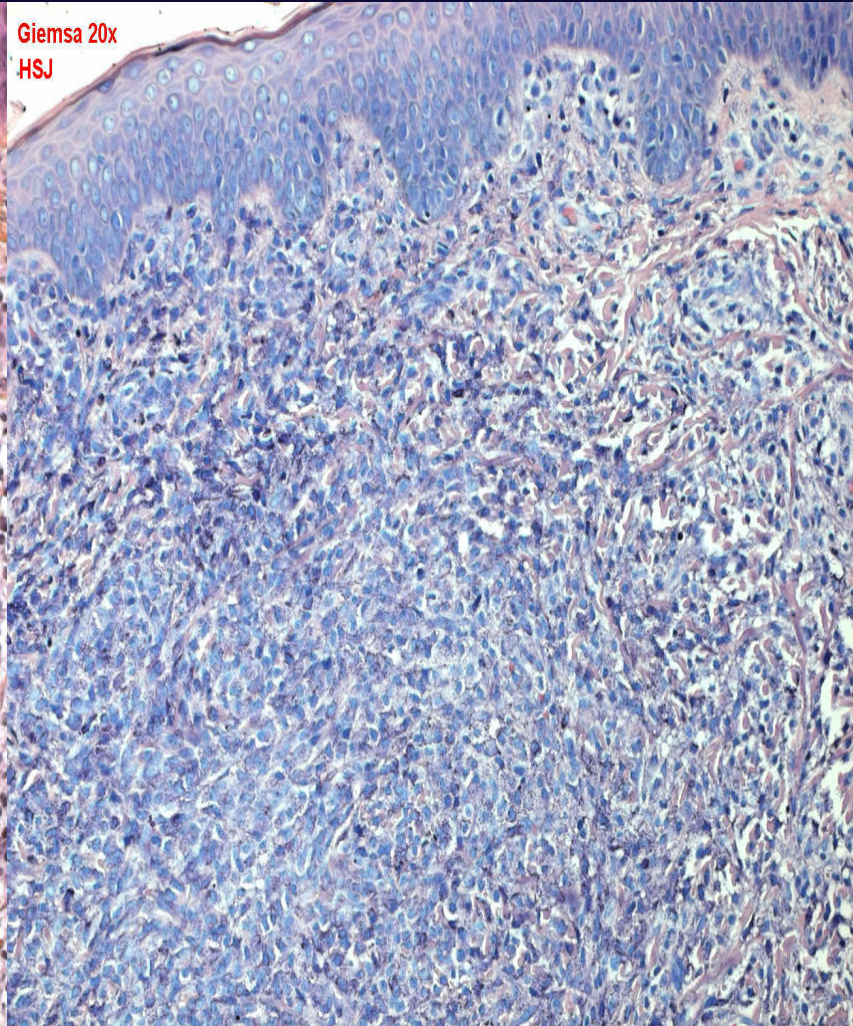
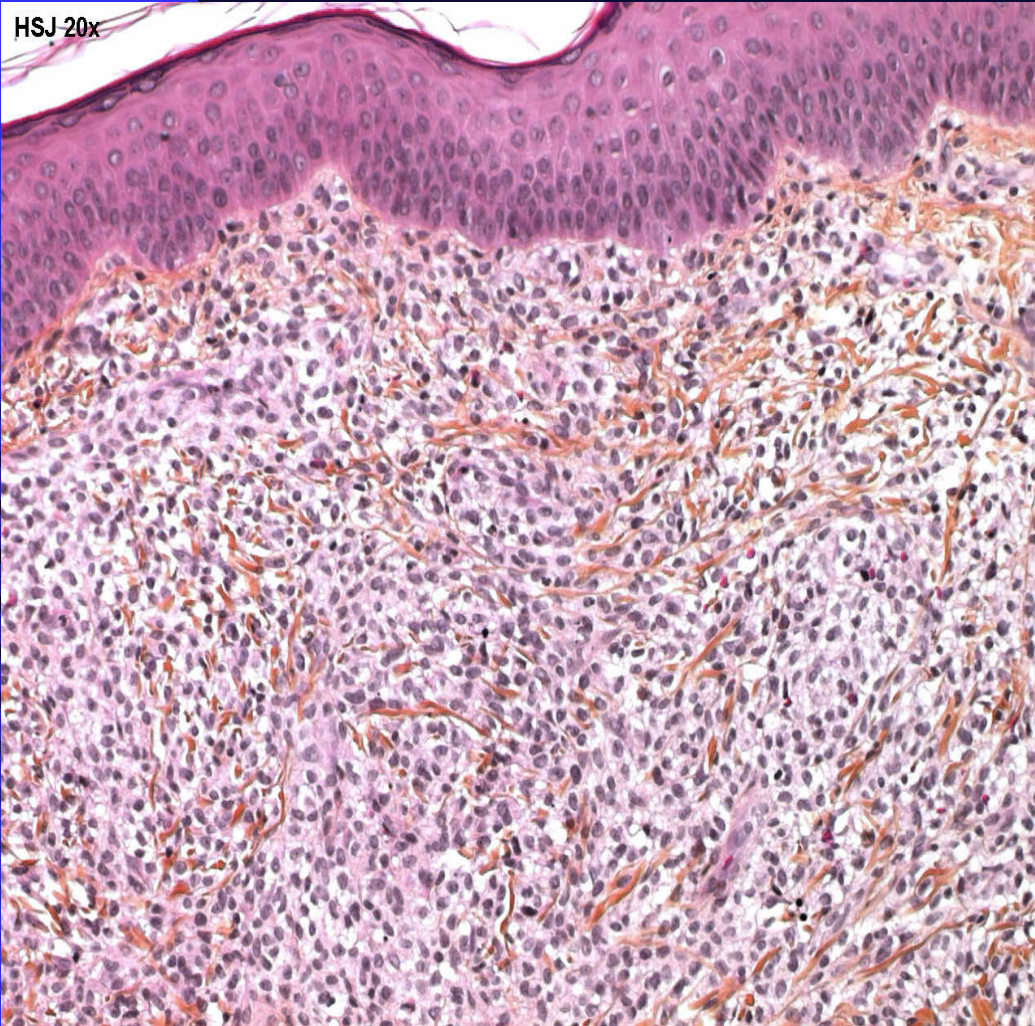
- Most frequent form of CM
- Characterized by aggregates of elongated or oval mast cells which typically fill the papillary dermis and extend as sheets and aggregates into the reticular dermis around the B. vessels.
- confined strictly to the dermis.
- >70% subside with puberty in children.
- benign disease of chronic course

Urticaria Pigmentosa.....

- diagnosis of UP should be confirmed by careful search to exclude involvement of other organs



Picture from
Robbins



Pictures from Robbins

Telangiectasia macularis eruptiva persistans (TMEP)

- Rare Subtype of UP seen in adults
- Small hyperpigmented lesions
- shows minimal or no increase in number of mast cells
- Examination of multiple sections for aggregates of mast cells or biopsies of multiple lesions may be necessary to establish diagnosis.

Diffuse Cutaneous Mastocytosis

- Less frequent than UP
- seen almost exclusively in children
- lack typical maculopapular rash
- have smooth, red or thickened skin (peau chagrin, grain leather skin)
- histologically, a band-like infiltrate of mast cells is seen in the papillary and reticular dermis.

Mastocytoma of Skin (Mast cell nevus)

- Limited to first three years of life, usually present at birth
- Predilection for trunk and wrist
- Solitary nodule with sheets of mast cells in the papillary and reticular dermis extending into the subcutaneous tissues with no cytologic atypia.
- Spontaneous regression within 1 to 2 years
- excision recommended since only way of confirming diagnosis

Systemic Mastocytosis and Variants

Systemic Mastocytosis

- Major criteria

Multifocal, dense infiltrates of mast cells (15 or more mast cells in aggregates) detected in sections of bone marrow and/or other extracutaneous organs, and confirmed by immunohistochemistry

- Minor criteria

- a. More than 25% of mast cells in the infiltrate are spindle shaped or have atypical morphology in bone marrow or other extracutaneous sites

Minor Criteria.....

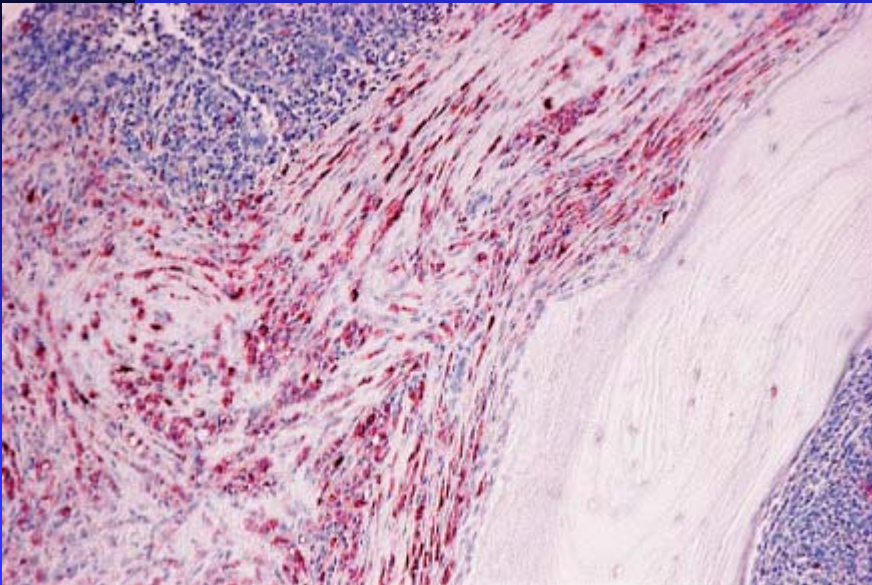
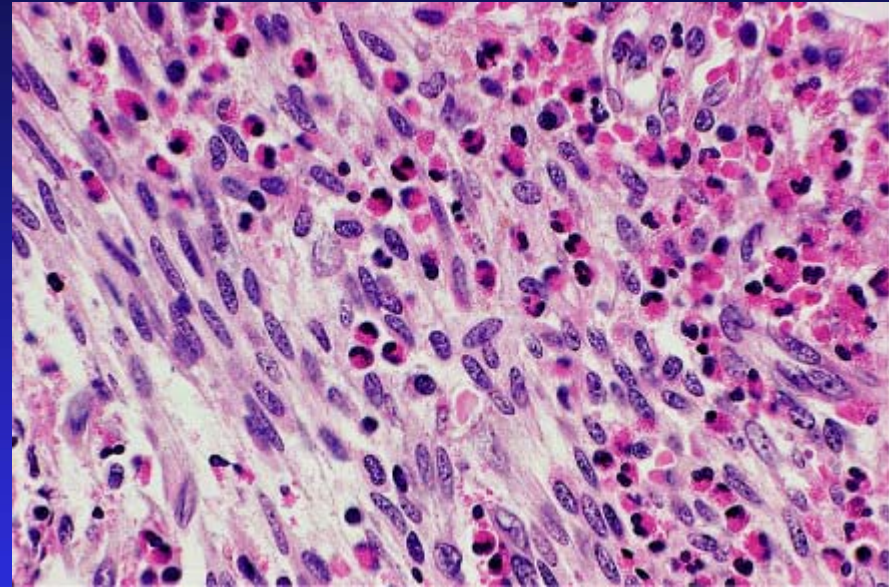
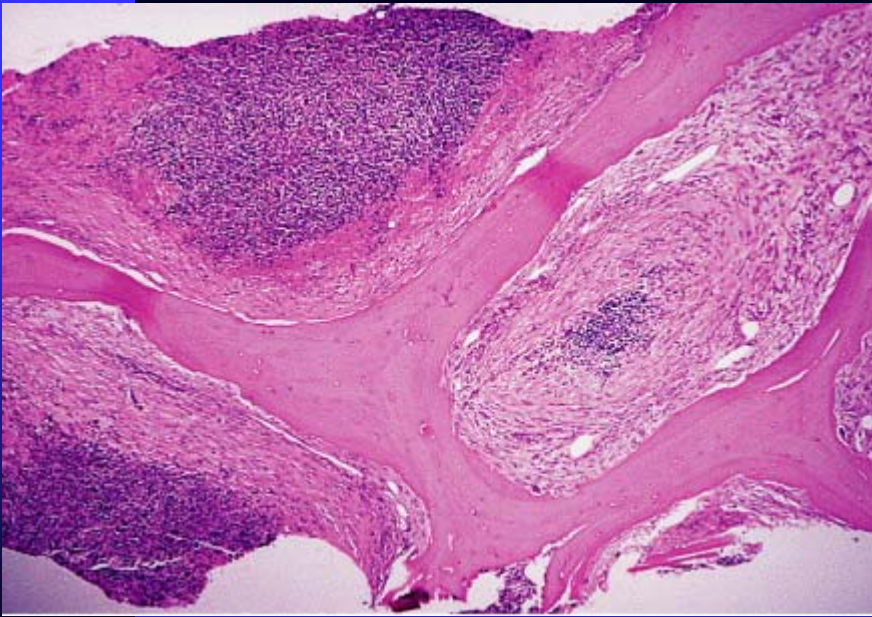
- b. Detection of KIT point mutation at codon 816
 - c. Mast cells that co-express CD117 with CD2 and or CD25
 - d. Serum total tryptase persistently >20 ng/ml (unless there is an associated clonal myeloid disorder)
- The diagnosis of SM made if one major and one minor criterion or 3 minor criteria are fulfilled.

Symptoms & Signs

- Constitutional: fatigue, malaise, lethargy, weight loss & fever.
- Cardiopulmonary: shortness of breath, chest pain, Palpitation, dizziness, & syncope.
- Gastrointestinal: Nausea, vomiting, epigastric pain, abdominal cramps, diarrhea.
- Skin: Urticaria, pruritis, flushing & bullae formation.
- Neurologic: Headache, Cognitive disorganization
- Skeletal: Bone pain, fractures.

Bone Marrow Findings

- One of the major sites of involvement
- 96% infiltration of mast cells is seen
- Important diagnostic criterion
- Multifocal, sharply demarcated infiltrates, in peritrabecular or perivascular location or disseminated comprising of fusiform to spindle shaped mast cells.
- Accompanied by fibrosis and/or osteosclerosis



Pics from
Ackerman's

Bone Marrow Findings.....

- Diagnosis missed because of small numbers of mast cells in aspirate smears, due to presence of marrow fibrosis
- Reliable diagnosis only possible on basis of bone marrow biopsy and IHC stain e.g Tryptase should be used to confirm the Dx.

Lymph Node Involvement

- Detectable in 15% of cases.
- Mast cell infiltrates seen in cortical and paracortical areas
- Mast cells surround vessels and sinuses
- Follicles only partially infiltrated by mast cells
- Cells have a clear cytoplasm with few metachromatic granules
- May be accompanied by eosinophils

Spleen Involvement

- Splenomegaly in 27-41% of SM patients.
- May involve any compartment of spleen, red pulp or white pulp
- Eosinophilia, fibrosis, and Plasmacytosis are frequently seen in areas of mast cell infiltration.
- Frequently hypersplenism with pancytopenia in peripheral blood is observed.

Gastrointestinal Symptoms

- Seen in 15% of patients
- Abdominal pain, diarrhea, nausea, vomiting
- Melena or hematemesis in < 10 %
- Histologically, mast cell infiltration rarely seen

Liver and Bone Lesions

■ Liver

- Seen in 66% of patients.
- Mast cells found in sinuses or in periportal areas.
- Fibrosis present in 20% but fully developed cirrhosis only in 2% of all cases.

■ Bone

- Osteosclerosis in 80% of cases
- Osteoporosis in 30%
- Bone pain or arthralgias in 20%

Hematological Findings

- Usually, completely normal hematological findings
- If present, anemia is most frequent
- Leukocytosis in 15%, eosinophilia in 13%, and monocytosis in 6%

SM variants...Additional Criteria

■ “B” Findings

- 1: BM showing >30% infiltration by mast cells and or serum tryptase > 200ng/ml
- 2: Dysplasia or proliferation in non mast cells lineage but insufficient for Dx of hematopoietic neoplasm
- 3: Hepatomegaly without liverfunction impairment and or splenomegaly without hyprsplenism and or palpable lymphadenopathy.

■ “C” Findings

- 1: BM dysfunction manifested with one or more cytopenia but no frank non-mast cell malignancy.
- 2: Hepatomegaly with impairment of liver function, ascites or portal hypertension.
- 3: Splenomegaly with hypersplenism
- 4: Malabsorption with weight loss due to GI mast cell infiltrates.

Indolent Systemic Mastocytosis (ISM)

- First describe by Ellis
- Median age at onset: 38 years
- Median age at time of diagnosis: 45 years
- ISM – disease of adults, rarely seen in infants
- Confusing clinical manifestations with a broad spectrum of symptoms, probably the main cause of false diagnosis

Indolent Systemic Mastocytosis...

- Meets criteria for SM
- No “B” or “C” findings
- No evidence of associated hematological clonal disorder/ malignancy

Systemic mastocytosis with associated Clonal hematological non-mast cell lineage disease (SM-AHNMD)

- Meets criteria for Systemic mastocytosis and
- Associated, clonal hematological non-mast cell lineage disorder e.g (MDS, CMPD, AML, Lymphoma or other hematologic neoplasm that meets the criteria for a distinct entity in the WHO classification)
- Neoplastic mast cells positive for c-kit point mutation.
- Malignant SM disorder with prognosis dependent on underlying hematological disorder.

Aggressive Systemic Mastocytosis(ASM)

- Meets criteria for Systemic mastocytosis and
- One or more “C” findings
- No associated clonal hematological disorder
- No evidence of mast cell leukemia.
- WHO classification has added a provisional sub variant

“Lymphadenopathic mastocytosis with eosinophilia”

-Progressive lymphadenopathy

ASM.....

- Peripheral blood eosinophilia
- Extensive bony involvement,
- Hepatosplenomegaly & usually no skin lesions.
- Malignant SM disorders with a poor prognosis.

Mast cell leukemia

- Meets criteria for SM and
- Mast cells account for >10% or more of peripheral blood white cells
- Bone marrow aspirate shows >20% mast cells
- BM Biospy shows diffuse infiltration, in interstitial pattern, by atypical, immature mast cells.
- Variant: Aleukemic mast cell leukemia- as above, but <10% of WBCs as mast cells in PB.
- Clinical features of SM with hepatosplenomegaly without skin involvement.
- Poor prognosis with short survival.

Mast cell Sarcoma

- Exceedingly rare entity
- Localized mast cell tumor
- No evidence of SM
- No skin lesions
- Destructive growth pattern
- High grade cytology
- Leukemic phase may occur.

Extracutaneous Mastocytoma

- Rare entity with most reported cases localized in the lung.
- Localized mast cell tumor
- No evidence of SM
- No skin lesions
- Non-destructive growth pattern
- Low-grade cytology

Prognosis and Predictive Factors

- No cure for SM & prognosis - depends on the disease category, skin involvement +/-, associated hematological disorder.
- Favorable Prognosis (Benign): CM, ISM
- Unfavorable Prognosis (Malignant):
SM-AHNMD, ASM, Mast cell leukemia & sarcoma and extracut. mastocytoma.

Lab. Diagnosis of Systemic Mastocytosis

- Tryptase is concentrated in mast cells and used as a clinical marker of mast-cell mediated diseases
- Tryptase level is usually normal in cutaneous disease, enabling to distinguish from systemic mastocytosis
- Tryptase levels assessed by immunoassays and has two subunits alpha & beta.
- Elevated beta subunit is associated with systemic mastocytosis
- The specificity >98% and sensitivity >83% for total : Beta tryptase ratio > 20.

Tryptase Levels in Serum

	Total (a +b-Tryptases)	b-Tryptase	Ratio (Total:b-tryptase)
■ Normal	1-15 ng/mL	<1ng/mL	na
■ Systemic Anaphylaxis	Increased markedly	Occasional small increase	< 10 ng/mL
■ Systemic Mastocytosis	Increased	+/- Increased	> 20 ng/mL

Cytochemistry & Flowcytometry

Normal Mast Cells

MPO - , CAE +

Express CD45, CD33, CD34, CD68, and c-kit (CD117)

Lack CD14, CD15, CD16, & B and T cell markers.

Neoplastic Mast Cells

MPO -, CAE -/+

Similar antigenic profile but in contrast to normal mast cells, demonstrate expression of CD2 and CD25.

Genetics

- Somatic point mutation of KIT proto-oncogene which encodes the tyrosine kinase receptor for stem cell factor (SCF or mast cell growth factor) are recurring genetic abnormalities.
- Most common mutation in SM, involves substitution of Val for Asp at codon 816, resulting in spontaneous activation of the KIT protein.
- Majority CM lack this codon 816 mutation.

Treatment

- Symptomatic:

- Epinephrine, Corticosteroids, H1&H2 blockers, & anticholinergics.

- Chemotherapy

- Alpha Interferon

- 2-Chlorodeoxyadenosine

- Tyrosine kinase inhibitor, Imatinib mesylate (Gleevac)

- Allogenic Bone marrow transplantation, considered experimental and being pursued currently in many NIH trials.

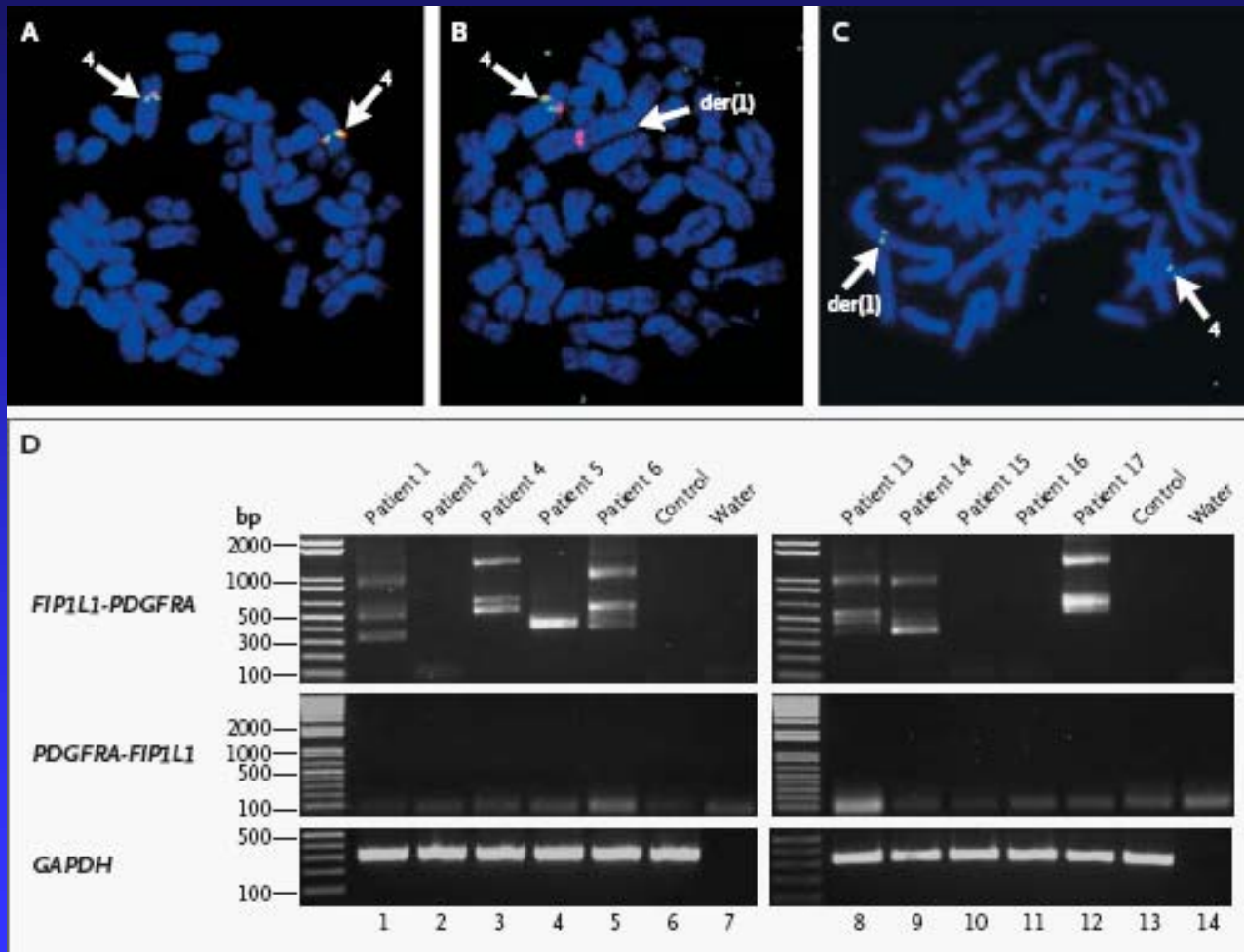
What's Up in Mastocytosis?

Tyrosine kinase generated by FIP1L1-PDGFR α gene Fusion

Cools & Gotlib J, et al. A tyrosine kinase created by fusion of the *PDGFR α* and *FIP1L1* genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. *N Engl J Med.* 2003;348: 1201-1214

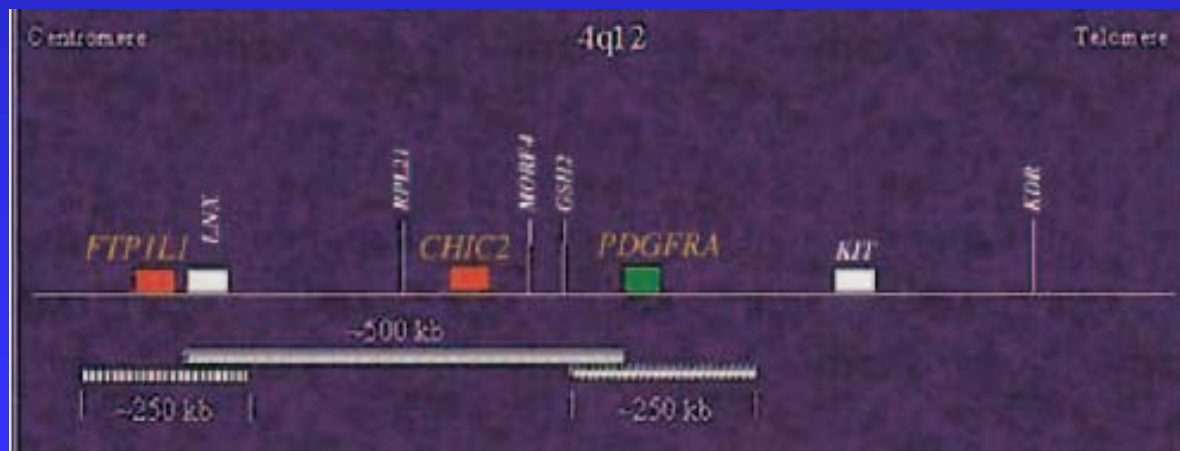
- Discovered a novel Tyrosine kinase generated by fusion of FIP1-Like1 (FIP1L1) gene & Platelet derived growth factor alpha gene (PDGFR α) gene due to an interstitial deletion on chromosome 4q12, identified in 9 out of 16 pts. with Hypereosinophilic syndrome (HES).
- FIP1L1-PDGFR α is a constitutively activated tyrosine kinase with gain of function that transforms hematopoietic cells and that is inhibited by imatinib.

Cools and Gotlib et. al.....



CHIC2 deletion, a surrogate for FIP1L1-PDGFR α fusion, occurs in Systemic mastocytosis with eosinophilia and predicts response to imatinib mesylate therapy.

- Pardnani and Tefferi et al. 2003
- Documented the deletion of this locus and expression of the FIP1L1-PDGFR α fusion in bone marrow and PB eosinophils, neutrophils by both FISH and RT-PCR.

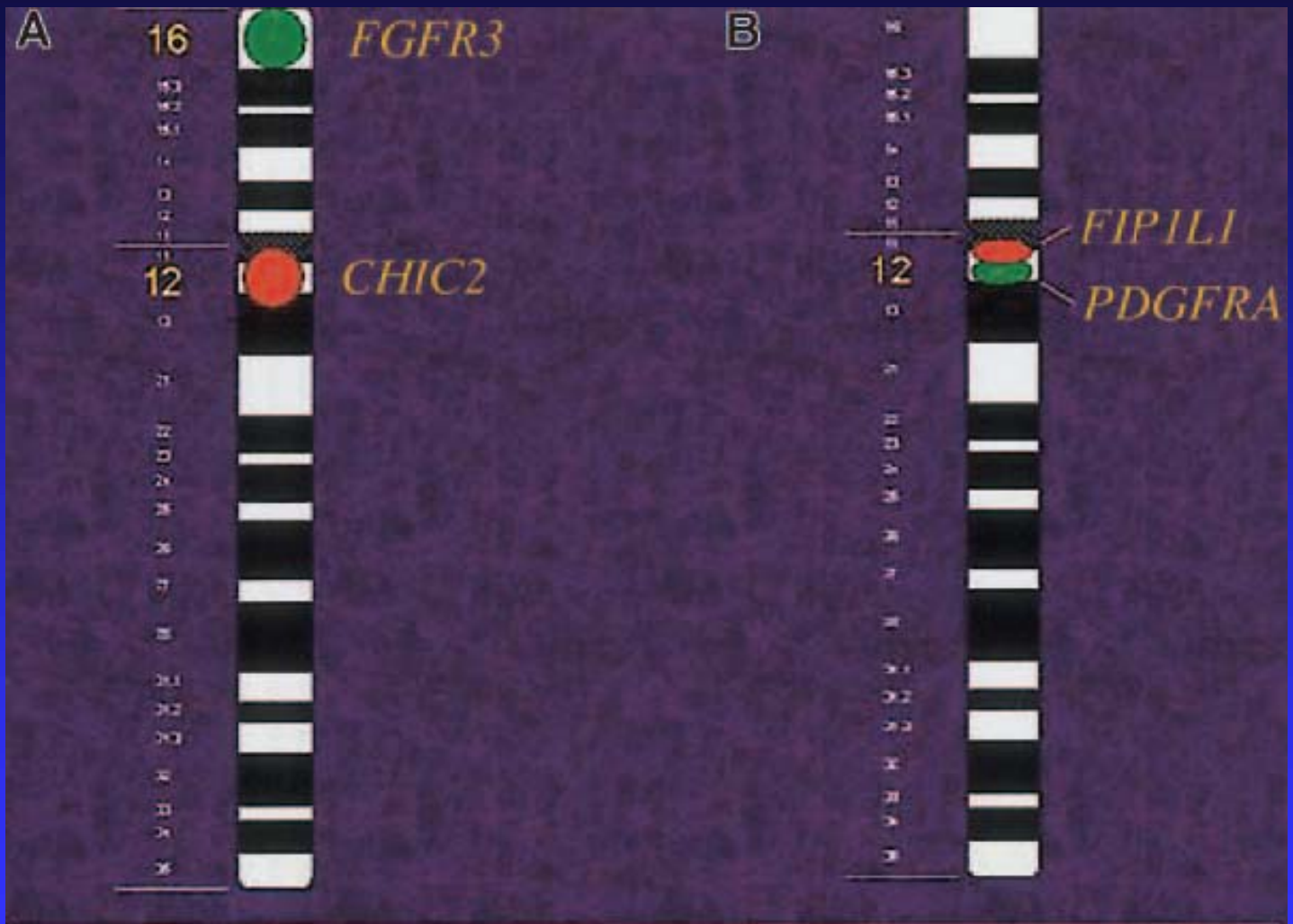


CHIC2 deletion, a surrogate for FIP1L1-PDGFRFA.....

- Used FISH to detect deletion of CHIC2 locus at chromosome 4q12 as a surrogate for FIP1L1-PDGFRFA fusion in 5 cases of systemic mastocytosis with eosinophilia.
- Concluded that Molecular pathogenesis is similar for a subset pts. of Systemic Mastocytosis with eosinophilia and HES pts and screening for FIP1L1-PDGFR rearrangement will advance rational therapy decisions in SM.

FIP1L1-PDGFR α Fusion: clinicopathologic correlates in 89 consecutive patients with moderate to severe eosinophilia.....Pardnani & Tefferi et. Al, 2004

- Used FISH based techniques to study a cohort of 89 patients with absolute eosinophil count > 1.5 to detect FIP1L1-PDGFR α fusion in bone marrow cells.
- Results:
 - None (0%) of 8 Pt.s with reactive eosinophilia showed abnormality
 - 3 (5%) of 57 pt.s with HES (hypereosinophilic syndrome) showed abnormality.
 - 10 (56%) of 19 pts.with Systemic mast cell disease assoc. with eosinophilia (SMCD-eos) showed CHIC2 deletion and showed complete remission with low dose Imatinib.



Conclusion of New Studies?

- Advocating clinical molecular classification of Systemic Mastocytosis ?

1: CHIC2 deletion or FIP1L1-PDGFR fusion
POSITIVE group

2: CHIC2 deletion or FIP1L1-PDGFR fusion
NEGATIVE group

Need to study CHIC2 deletion in Sytemic Mastocytosis pts. Without eosinophilia...

Thank you!!!!

