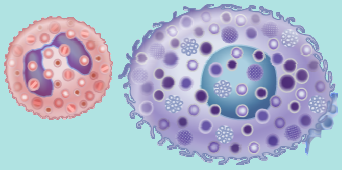
Mass General Brigham



Eosinophilia and Mastocytosis

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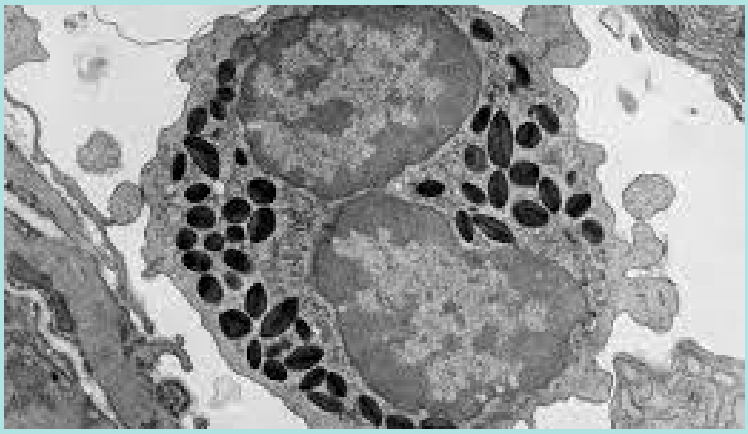
Eosinophilia



Eosinophilia is NOT a diagnosis!

- Eosinophilia is a **laboratory/morphologic finding** that defines higher that normal levels of eosinophils:
  - Peripheral blood:
    - Eosinophilia: 0.5 – 1.5 x 10^9/L or 500 – 1500 cells per µL
    - Hypereosinophilia: > 1.5 x 10^9/L or greater than 1500 cells per µL
  - Bone marrow:
    - >20% of all nucleated cells
  - Other tissues
    - Extensive tissue infiltration in the opinion of a pathologist
    - Marked deposition of eosinophil granule proteins in tissue (IF)
- Eosinophilia by itself is **non-specific** and accompanies many non-neoplastic and neoplastic conditions
  - Each case requires an **extensive** work-up
  - Be VIGILANT!

Eosinophil-associated diseases and disorders

Allergic disorders
- Asthma, allergic rhinitis, atopic dermatitis
- Drug hypersensitivity (eg, drug reaction with eosinophilia and systemic symptoms [DRESS], eosinophilia-myalgia syndrome, interstitial nephritis, eosinophilic hepatitis)

Infectious diseases
- Helminths (eg, strongyloidiasis, trichinellosis, filariasis, toxocariasis, schistosomiasis, hookworm)
- Ectoparasites (eg, scabies, myiasis)
- Protozoans (eg, isosporiasis, sarcocystis myositis)
- Fungi (eg, coccidiomycosis, allergic bronchopulmonary aspergillosis, histoplasmosis)
- Viral (eg, HIV)

Immunologic disorders
- Immunodeficiencies (eg, DOCK8 deficiency, hyper-IgE syndrome, Omenn syndrome)
- Autoimmune and idiopathic disorders (eg, sarcoidosis, inflammatory bowel disease, IgG4 disease, other connective tissue disorders)

Neoplastic disorders
- Primary hypereosinophilic syndromes (eg, *FIP1L1-PDGFRA, -PDGFRB, -FGFR1, PCM1-JAK2* rearrangement)
- Acute or chronic eosinophilic leukemia
- Other myeloid neoplasms (eg, chronic myeloid leukemia, systemic mastocytosis)
- Lymphoid malignancies (eg, B cell lymphoma, B or T lymphoblastic leukemia/lymphoma, adult T cell leukemia/lymphoma, cutaneous T cell lymphoma/Sézary syndrome)
- Solid tumors (eg, adenocarcinoma, squamous carcinoma)

Eosinophilic disorders
- Idiopathic hypereosinophilic syndrome
- Eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome)
- Eosinophilic gastrointestinal disorders

Let's get classification right!

WHO Classification (2016 Revision) – based on pathologic findings

- Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1*, or with *PCM1-JAK2*
- Chronic eosinophilic leukemia, NOS
  - Exclude above + other MPNs
  - Blasts <20%
  - Clonality and/or >2% PB or >5% BM blasts
- Idiopathic HES
  - Exclude above + reactive + LV HE
  - Persistent HE and absence of tissue damage

Working Conference on Eosinophil Disorders and Syndromes (2011) – based on clinical phenotype

- Hereditary (familial) variant of hypereosinophilia
  - AD, mapped to 5q 31-33
- Primary (clonal/neoplastic) hypereosinophilia
- Secondary (reactive) hypereosinophilia
  - Allergic, infectious, etc
  - T-cell LV of HE
- Organ-restricted hypereosinophilia
  - Chronic eosinophilic pneumonia
  - Eosinophilic GI disease
- Hypereosinophilia of undetermined significance

Shomali W, Gotlib J. World Health Organization-defined eosinophilic disorders: 2022 update on diagnosis, risk stratification, and management. Am J Hematol. 2022 Jan 1;97(1):129-148. doi: 10.1002/ajh.26352. Epub 2021 Oct 8. PMID: 34533850.

Diagnostic work-up of patients presenting with HE

Clinical data and physical examination

History and physical examination: skin exam, palpation of spleen, family history of eosinophilia, signs of immunodeficiency

General laboratory data (PB)

CBC with differential
Examination of blood smear (e.g., monocytosis, dysplasia, eosinophilia, circulating blasts)
Comprehensive metabolic panel with uric acid, lactate dehydrogenase, and liver function tests
Serum tryptase, vitamin B12, ESR, and/or CRP
Quantitative serum immunoglobulin (Ig) levels (+IgE)

Biopsy data

BM aspirate and biopsy with IHC for CD117, CD25, and tryptase and reticulin/collagen stains for fibrosis

Flow cytometry data (PB or BM)

Blasts immunophenotyping
T-cell immunophenotyping

Genetic data (PB or BM)

Karyotype
PDGFRA rearrangement (FISH) and/or nested qRT-PCR
Confirmatory FISH if karyotype reveals the following breakpoints: 4q12 (*PDGFRA*); 5q31~33 (*PDGFRB*); 8p11~12 (*FGFR1*); 9p24 (*JAK2*); 9q34 (*ABL1*); 13q12 (*FLT3*)
NGS Myeloid mutation panel
PCR to confirm T-cell clonality when appropriate

Organ damage evaluation

Imaging studies (chest X-ray, ECG, CT/MRI)
Endoscopy, bronchoscopy with biopsy
Pulmonary function tests
Electromyography

Gerds AT, et al. Myeloid/lymphoid neoplasms with eosinophilia and TK fusion genes, version 3.2021. JNCCN J Natl Compr Cancer Netw. 2020;18(9):1248–69.

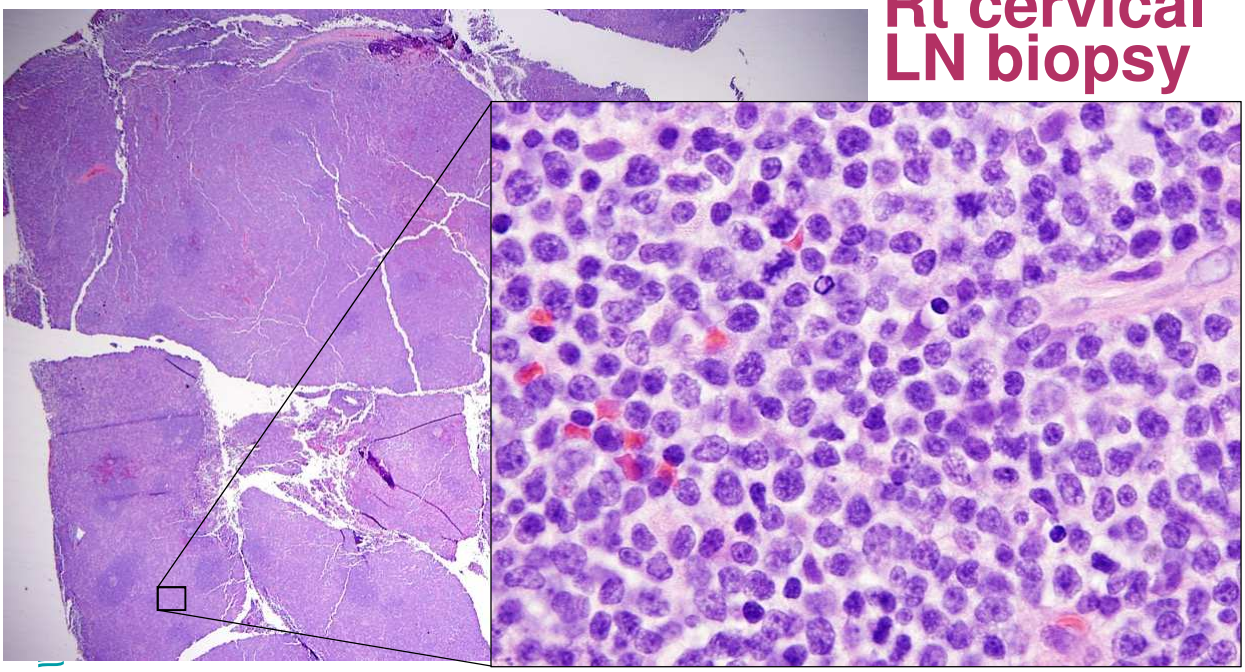
Case 1: 46-year-old man

Diffuse lymphadenopathy:

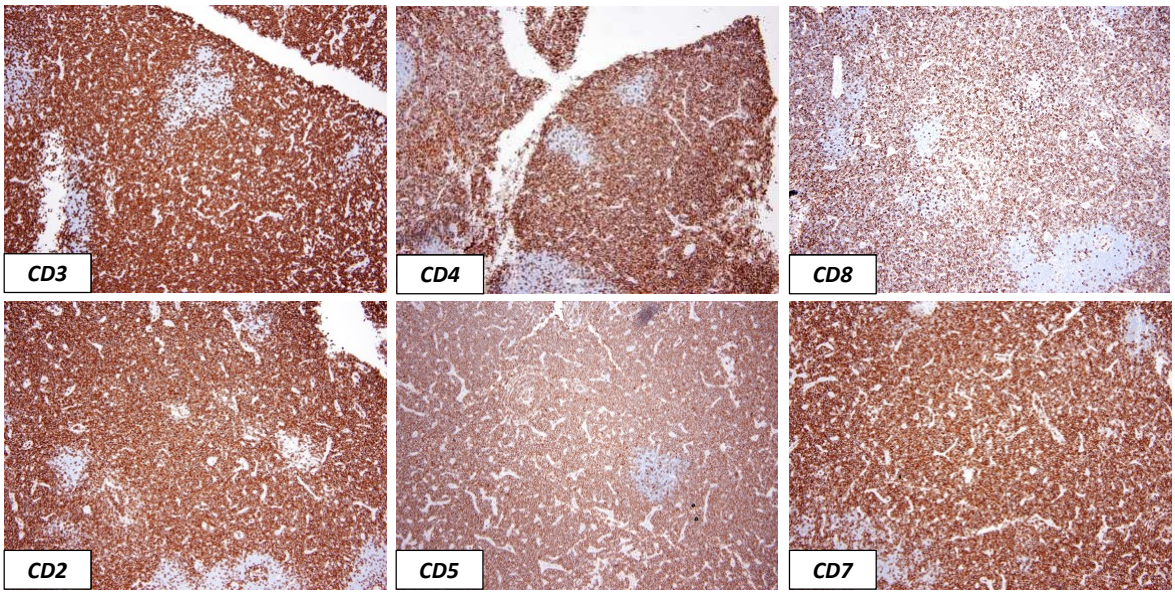
- CT: left axillary lymphadenopathy with lymph nodes measuring up to 3.3 x 2.3 cm, bilateral supraclavicular adenopathy, left periaortic retroperitoneal adenopathy along the iliac chain bilaterally measuring up to 5 cm. There is no splenomegaly.

CBC: WBC 10.8, Hgb 13.6 and PLT 215

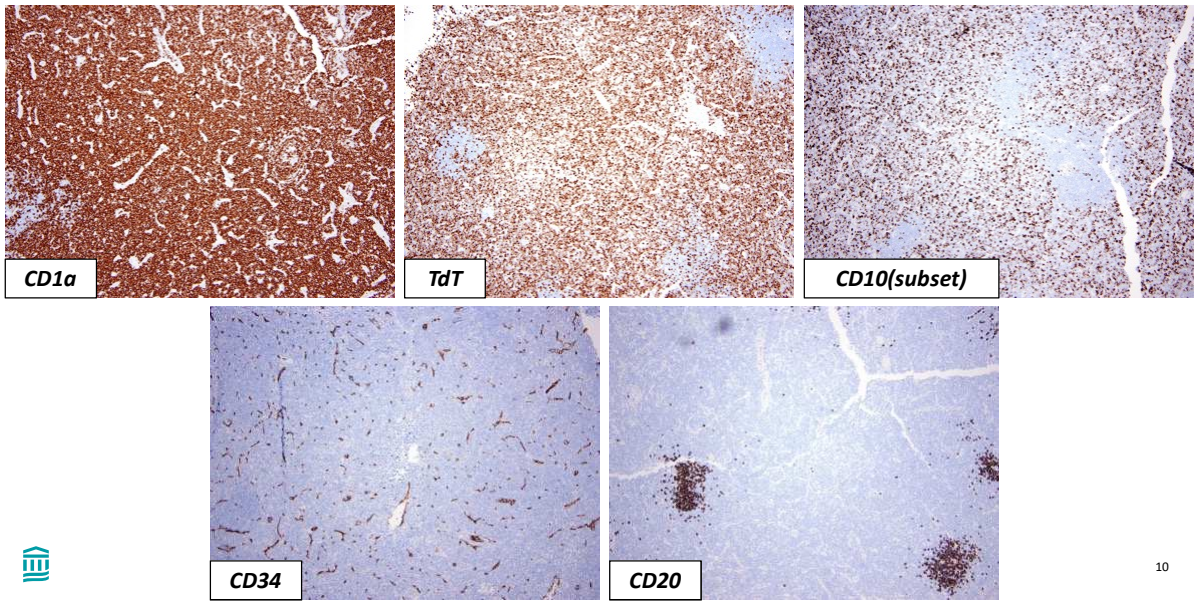
Rt cervical LN biopsy



Positive for many T-cell markers



Positive for markers of immaturity

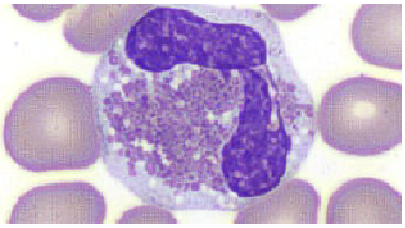


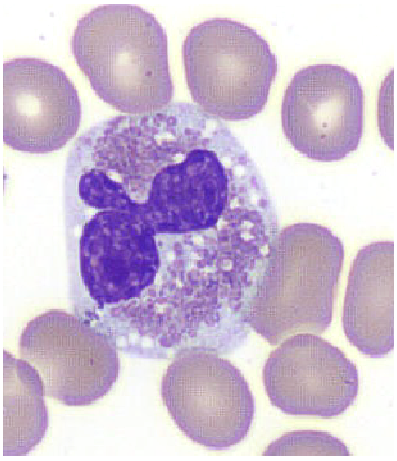
T lymphoblastic lymphoma

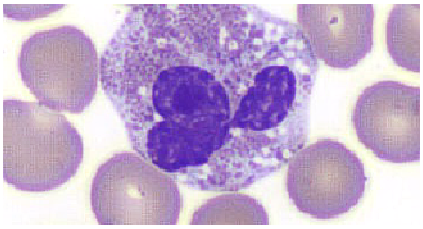
Positive: CD3, CD4, CD8, CD2, CD5, CD7, CD1a, TdT, CD10(subset), CD279(PD-1)

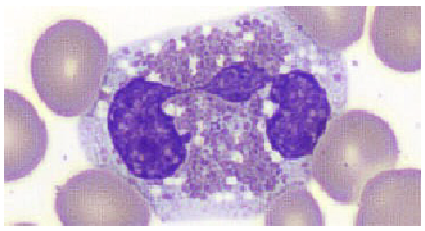
Negative: ALK1, CD34, TCL-1, FoxP3, CD25, CD30, CD20, BSAP

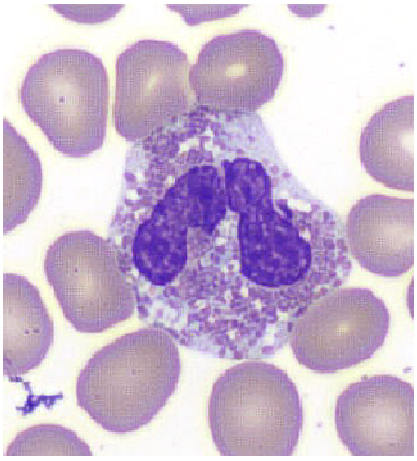
- ✓ WBC = 6.68 K/µL with 45% eosinophils
- ✓ AEC = 3,000/µL
- ✓ No anemia or thrombocytopenia; no blasts
- ✓ Serum tryptase = 82.1 ng/mL



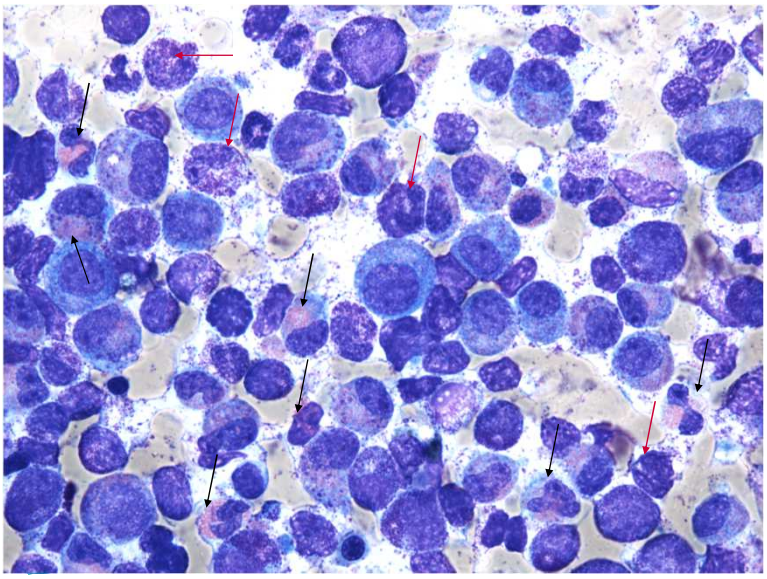






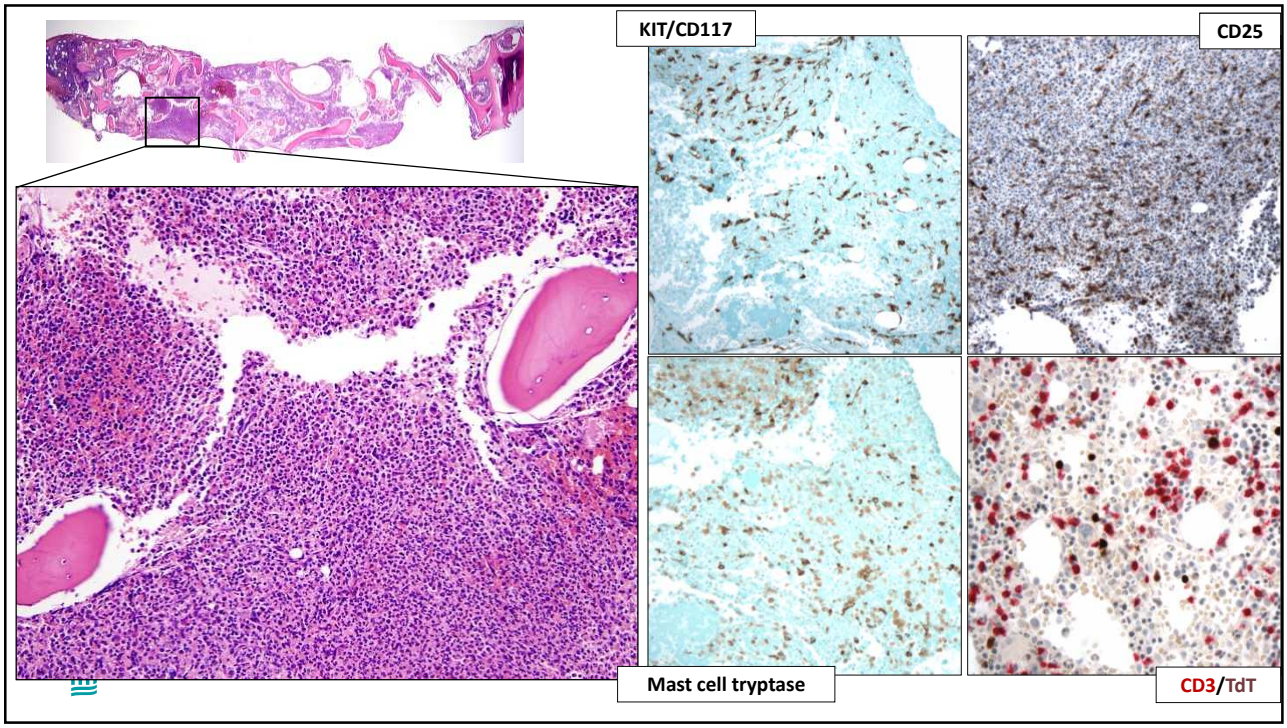


Bone marrow aspirate



Differential count:

Cellularity : Increased
Megakaryocytes : Present
Blasts : -
Promyelocytes : 4%
Myeloid : 78%; markedly increased eos (including immature forms) and some eo-baso forms, neutrophils with prominent granules
Erythroid : 10%
Lymphocytes : 8%
Plasma cells : -
Others : -; ?Mast cells, partially degranulated
M:E ratio : 7.8:1



Genetic analysis

Karyotype:

46,XY[20]

NGS molecular analysis:

Negative for Pathogenic Single Nucleotide Variants and Small Insertions/Deletions

Summary of diagnostic findings (so far …)

CBC

- ✓ Hypereosinophilia (3,000/µL)
- ✓ No anemia or thrombocytopenia; no blasts

Lab tests:

- ✓ Markedly elevated tryptase at 82.1 ng/mL (but absence of *KIT* mutation)

Genetics:

- ✓ Normal karyotype and absence of myeloid-associated pathogenic variants

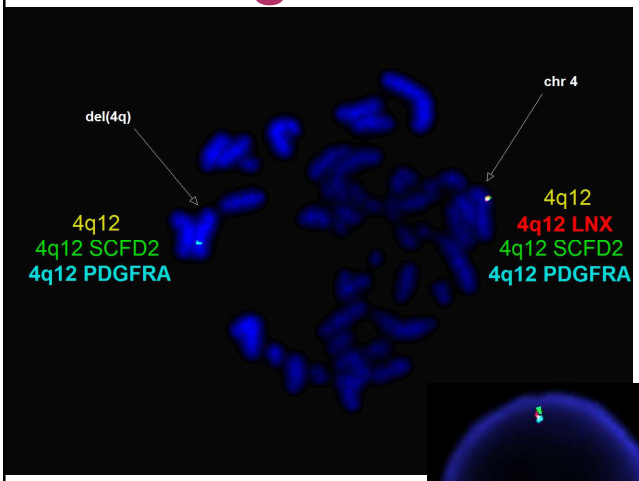
Multiorgan involvement:

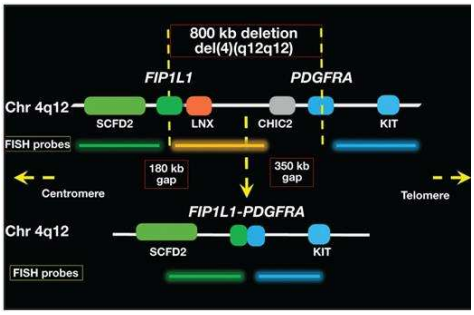
- ✓ LN – T-LBL
- ✓ BM – ?reactive or ?some kind of MPN - ?CEL ?SM ?SM-AHN:
  - ✓ Markedly hypercellular
  - ✓ Marked myeloid hyperplasia (hypergranular)
  - ✓ Marked eosinophilia (partially granulated, cytoplasmic vacuoles, abnormal nuclear segmentation)
  - ✓ Increased mast cells (hypogranular, mostly round, clusters <15 cells, aberrant CD25)

How to tie the findings together?

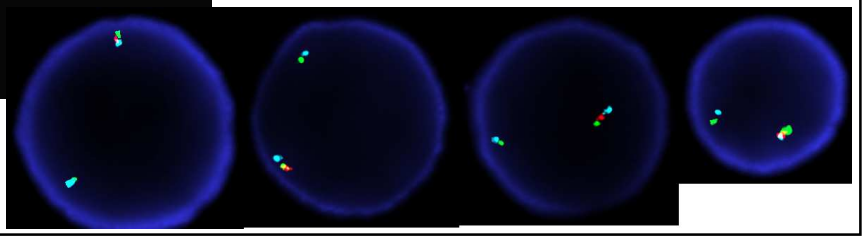
	Secondary eosinophilia due to T-LBL (or another undiagnosed condition)	
a)	CEL and T-LBL	P R I M A R Y
a)	SM with eosinophilia and T-LBL	
a)	SM with AHN	
a) b)	MLN-eos associated with *PDGFRA, PDGFRB, FGFR1 or PCM1-JAK2* rearrangement	
c)	all detected by karyotype but *PDFGRA*	

FISH for *PDGFRA* rearrangement





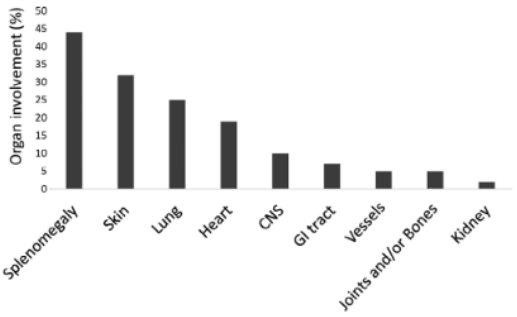
Positive in 69%



Patients	N = 151
Male	143 (96)
Age at diagnosis	49 +/– 12
Number of organs involved	
Asymptomatic	26 (17)
1	41 (28)
2	36 (24)
3 or more	31 (21)
CBC	
Eosinophils (/mm3)	10 309 +/– 5960
Hemoglobin (g/dl)	13 +/– 2
Platelets (/mm3)	195 700 +/– 63 600
Neutrophils (/mm3)	6850 +/– 5330
Lymphocytes (/mm3)	2650 +/– 1120
Basophils (/mm3)	240 +/– 270
Monocytes (/mm3)	640 +/– 415
F/P transcript screening	
PCR	140/140 (100)
FISH	87/87 (100)
Other	
High B12 levels	74/79 (94)
Median (IQR) serum B12 levels (pmol/l)	1741 (1170-2080)
High tryptase levels	45/57 (79)
Median (IQR) serum tryptase levels (ng/mL)	23 (14-43)
High CRP levels	34/118 (29)
Median (IQR) serum CRP levels (mg/L)	19 (9-30)
High total IgE levels	12/86 (14)
Median (IQR) serum IgE levels	20 (8-168)

Exclusively sensitive to imatinib!
OS: 1-year 99%, 5-year 95% and 10-year 84%
None developed accelerated phase

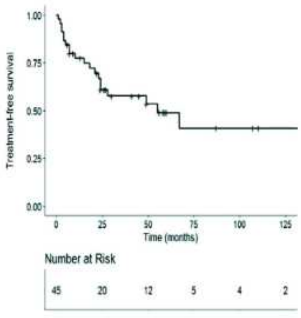
Frequency of organ involvement



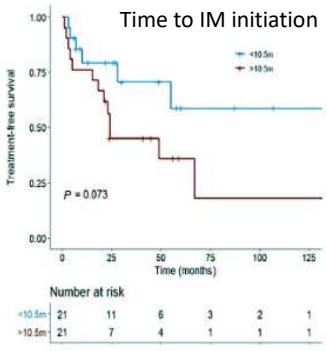
Rohmer J et al. Am J Hematol. 2020 Nov;95(11):1314-1323PMID: 327

Predictors of relapse after imatinib (IM) treatment withdrawal (n=46 pts)

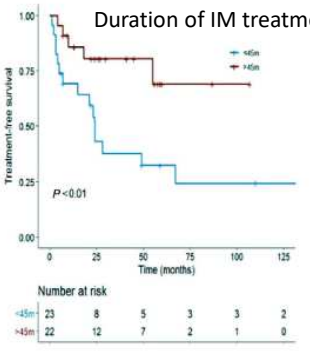
All pts



Time to IM initiation



Duration of IM treatment



	Univariate analysis			Multivariate analysis		
	HR	CI95%	P-value	HR	CI95%	P-value
Treatment with IM						
Time to IM initiation (months)	**1.01**	**[1.00–1.03]**	**.01**	**1.01**	**[0,99–1.03]**	**.05**
Sudden withdrawal	1.16	[0.48-2.85]	.74			
Total IM treatment duration	**0.97**	**[0.95–0.99]**	**.002**	**0.97**	**[0.95–0.99]**	**.001**
IM starting dose	1	[0.99–1.00]	.77			
Last IM dose before withdrawal	1	[0.99-1.01]	.95			

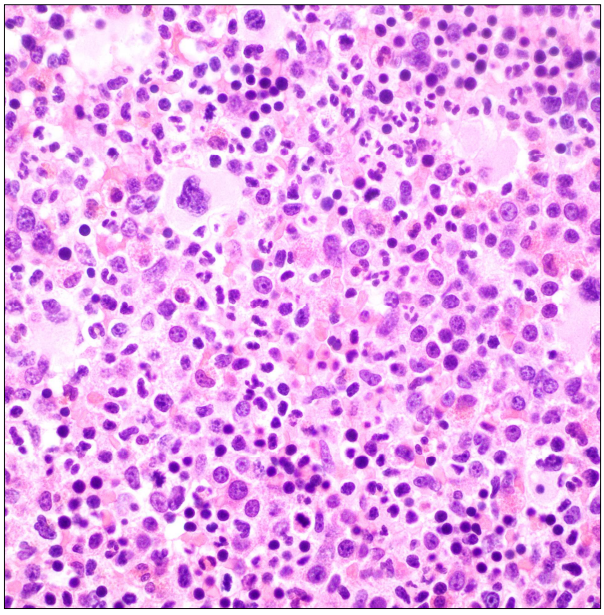
Rohmer J et al. Am J Hematol. 2020 Nov;95(11):1314-1323PMID: 327

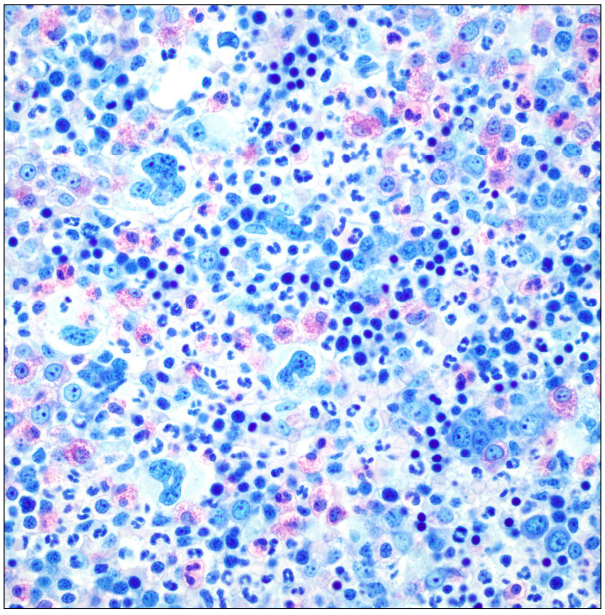
Myeloid/lymphoid neoplasms with *PDGFRA* rearrangement

- >90% of *PDGFRA* rearrangements are cytogenetically **cryptic**
  - *FIP1L1::PDGFRA* – cryptic 4q12 deletion
  - Other partners (7): *BCR* (22q11), *ETV6* (12p13), *KIF5B* (10p11), *CDK5RAP2* (9q33), *STRN* (2p22), *TNKS2* (10q23), *FOXP1* (3p13)
  - *PDGFRA* mutation
- **Diverse** morphologic spectrum usually with hypereosinophilia
  - CEL, AML, ALL and SM
  - abnormal eosinophil morphology (uneven granulation, hypo- or hypersegmentation)
- ~20% of cases present **without** PB eosinophilia
  - Some have variant *PDGFRA* rearrangements other than *FIP1L1*; may show abnormal karyotype
  - Some show myeloid/eosinophilic proliferations in biopsies that can be a clue
- **Extramedullary** presentation is common ~50% of cases and it can be the primary site of *PDFGRA*-rearranged neoplasm
  - LN is the most common site of involvement
  - MPN with eosinophilia is the most common pattern (but can vary)
- ~40% of cases show aberrant mast cell proliferations in the absence of a *KIT* mutation (**helpful feature!**)
- If *PDGFRA* FISH is negative and suspicion is high use **other** molecular methods
  - RNAseq, SNP-CN microarray
- Consider a **trial** of TKI in cases with hypereosinophilia not responsive to conventional therapy and perform comprehensive retrospective testing in responders

Pozdnyakova O et al. Am J Clin Pathol. 2021 Feb 4;155(2):160-178 PMID: 33367495.

Myeloid/lymphoid neoplasms with *PDGFRB* rearrangement





Myeloid/lymphoid neoplasms with *PDGFRB* rearrangement

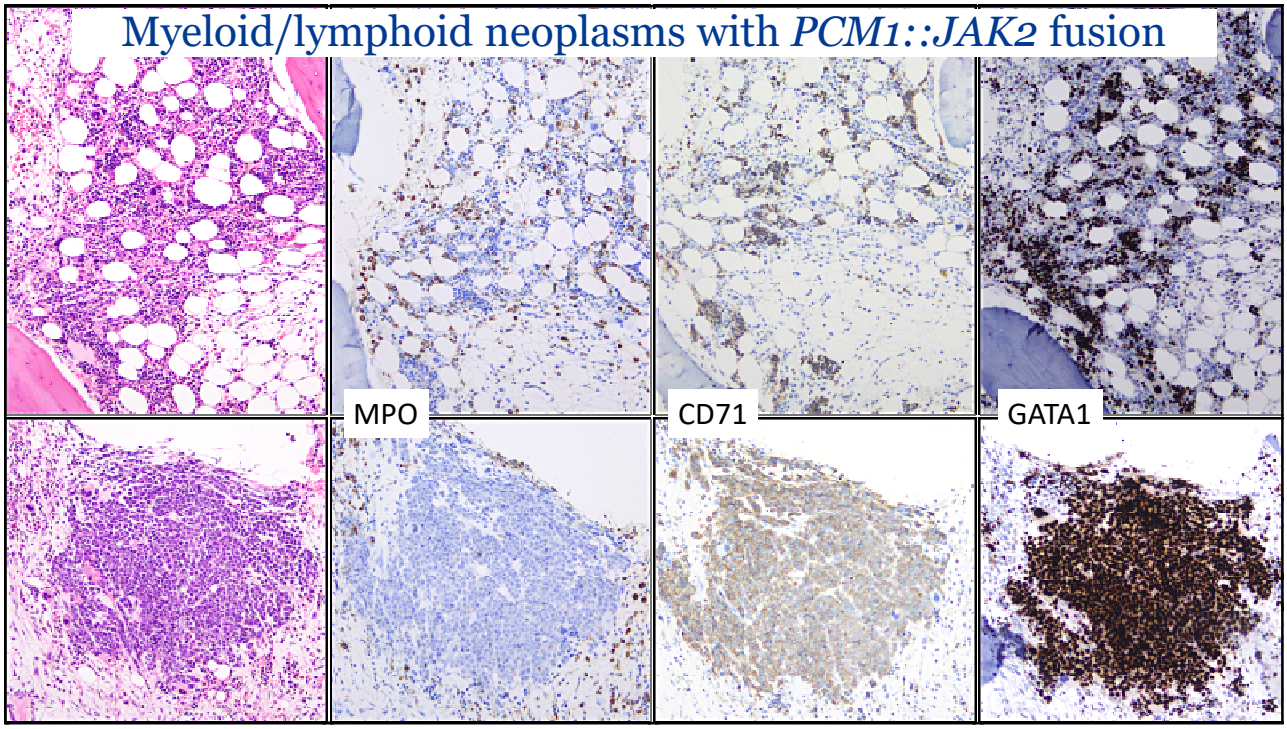
- >90% *PDGFRB* gene rearrangements are detected on karyotype
  - *PDGFRB* gene is located at 5q31~33, and more than 30 partner genes have been described to date
  - t(5;12)(q32;p13.2)/*ETV6::PDGFRB* is the most common genetic variant
  - *PDGFRB* FISH or RNA-seq needed, when cryptic
- Diverse morphologic spectrum usually with hypereosinophilia (similar to PDGFRA)
  - **CMML**, CEL, AML, ALL and SM
  - abnormal eosinophil morphology (uneven granulation, hypo- or hypersegmentation)
  - Various degree of monocytosis is very common
  - Combination of monocytosis and eosinophilia are suggestive of this category
- ~25% of cases present without eosinophilia
- Aberrant mast cell proliferations in the absence of a *KIT* mutation are a helpful feature
- A differential diagnosis between Ph+ B-ALL and MPN-Eo with PDGFRB based on antecedent history
- Extremely sensitive to TKI

Pozdnyakova O et al. Am J Clin Pathol. 2021 Feb 4;155(2):160-178 PMID: 33367495.

Myeloid/lymphoid neoplasms with *FGFR1* rearrangement

- 100% *FGFR1* gene rearrangements are detected on karyotype
  - 8p11 abnormalities with 14 gene partners described to date
  - Karyotype is imprecise and FISH maybe needed
- Complex morphologic presentation usually with hypereosinophilia. WHO defines as:
  - MPN or MDS/MPN with prominent eosinophilia and sometimes with neutrophilia or monocytosis, *or*
  - AML, T-ALL or B-ALL, or mixed-phenotype acute leukemia (usually associated with peripheral blood or bone marrow eosinophilia), *and*
  - Presence of t(8;13)(p11.2;q12) or a variant translocation leading to *FGFR1* rearrangement, demonstrated in myeloid cells, lymphoblasts or both
- Hypereosinophilia is almost always present (unlike *PDGFRA/B*)
- Somatic mutations, involving *RUNX1* or others, are very common (unlike other entities in MLN-Eo group
- Very poor prognosis
  - No TKI therapy
  - FGFR inhibitor clinical trial is ongoing

Pozdnyakova O et al. Am J Clin Pathol. 2021 Feb 4;155(2):160-178 PMID: 33367495.

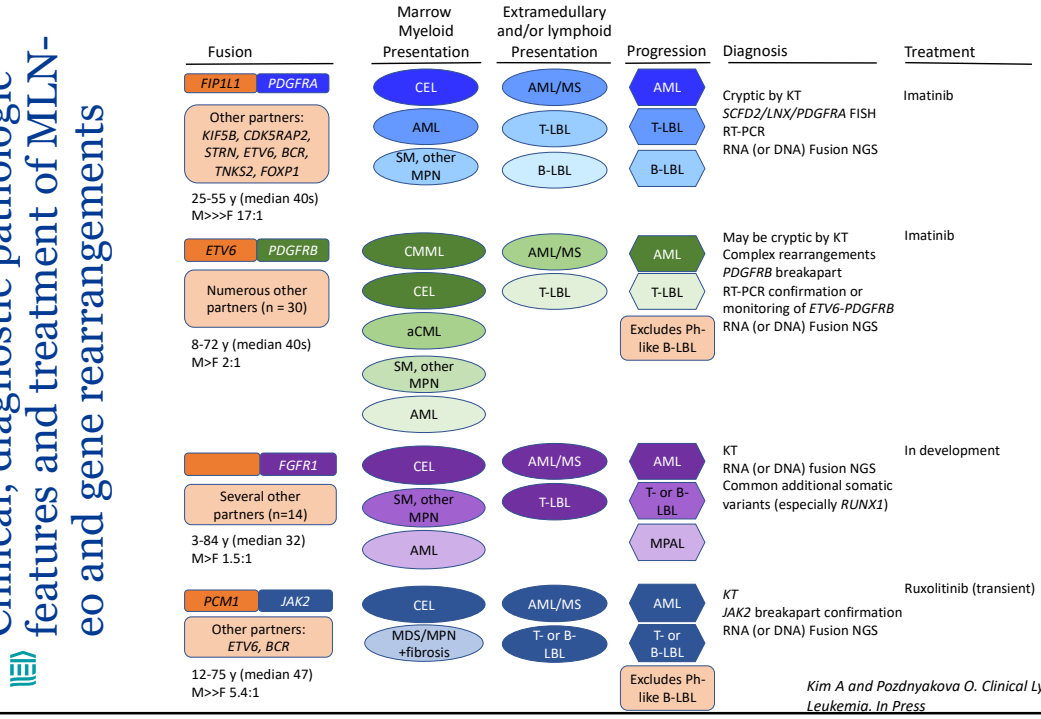


Myeloid/lymphoid neoplasms with *PCM1::JAK2* fusion

- t(8;9)(p22;p24); *PCM1::JAK2* fusion is detected on karyotype
  - FISH could be used but not necessary
  - *ETV6::JAK2* and *BCR::JAK2* may be considered variants
- Usually presents as MPN/CEL with hypereosinophilia and BM "triad":
  - (1) Hypercellular marrow with an eosinophilic infiltrate, (2) large aggregates of immature erythroid precursors and (3) myelofibrosis
  - Similar morphologic findings are present in extramedullary sites
  - MDS/MPN with prominent eosinophilia and sometimes with neutrophilia or monocytosis
- Hypereosinophilia and neutrophilia with left-shift are almost always present
- Somatic mutations are uncommon
- Clinical course is variable
  - JAK2 inhibitor therapy
  - No response to imatinib

Pozdnyakova O et al. Am J Clin Pathol. 2021 Feb 4;155(2):160-178 PMID: 33367495.

Clinical, diagnostic pathologic features and treatment of MLN-eo and gene rearrangements



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Kim A and Pozdnyakova O. Clinical Lymphoma, Myeloma and Leukemia. In Press

What happens when we excluded MLN-eo with gene rearrangements and other MPNs?

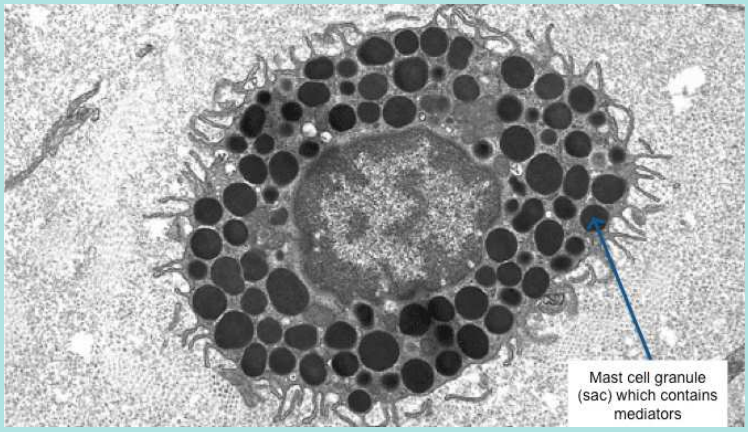
Chronic eosinophilic leukemia, NOS

- Clonality and/or
- 2-19% PB or 5-19%% BM blasts

Idiopathic HES

- Exclude above + reactive + LV HE
- Persistent HE and absence of tissue damage

Mastocytosis



Classification of mastocytosis is complicated!

Variant	Risk of Progression to Higher-Grade Neoplasm	Risk of Anaphylaxis
Cutaneous Mastocytosis (CM)*		
Maculopapular CM	Very low	Intermediate
Diffuse CM	Very low	High
Mastocytoma of skin	Very low	Low
Systemic Mastocytosis (SM)		
*Bone Marrow Mastocytosis***	Very low	High
Indolent SM	Low	Intermediate to High
Smoldering SM	Intermediate	Intermediate
SM with an AHN	High	Low
Aggressive SM	High	Low
Mast Cell Leukemia	Intermediate	Low
Mast Cell Sarcoma	Very high	Low

*All adults with CM should undergo BM examination to exclude SM
**Provisional entity

Criteria for systemic mastocytosis diagnosis

Major: Multifocal dense infiltrates of mast cells (≥15 mast cells in aggregates) in bone marrow biopsies and/or in sections of other extracutaneous organ(s)

Minor: 1) >25% morphologically atypical mast cells, 2)* activating *KIT* mutation at codon 816, 3)* aberrant expression of CD2 and/or CD25, 4) baseline serum tryptase >20ng/mL

SM = 1Majoir + 1minor *or* SM = 3 minor

2)* any other critical activating *KIT* mutation
3)* CD30

B findings: 1) >30% involvement and serum tryptase >200ng/mL, 2) signs of myeloproliferation and/or dysplasia , 2) organomegaly without organ function impairment

B = disease **burden**

C findings: 1) ≥ cytopenia, 2) organomegaly with organ function impairment, 3) skeletal involvement, 4) malabsorption and weight loss due to GI involvement

C = SM-induced organ damage requiring **cytoreduction**

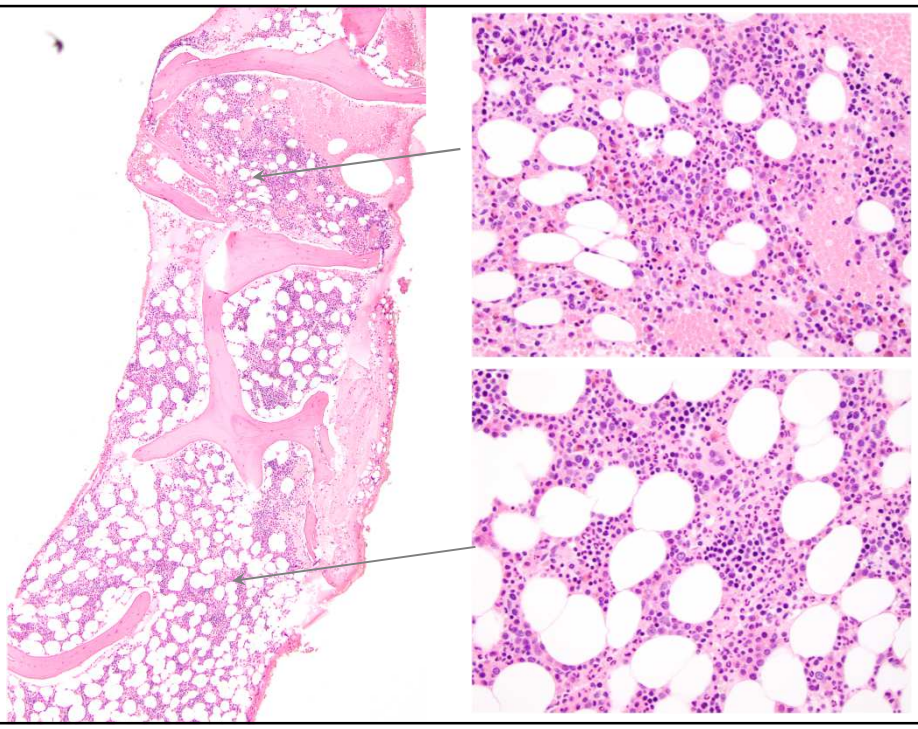
Case 2. 48-year-old man presenting with flushing associated with tachycardia, dyspnea and hypotension

CBC: WBC 4.96, Hgb 14.6, MCV 84.3, PLT 205

WBC differential: N 68%, L 24.4%, M 5.2%, E 1.7%

Serum tryptase: 4.8 ng/mL

LFTs: WNL



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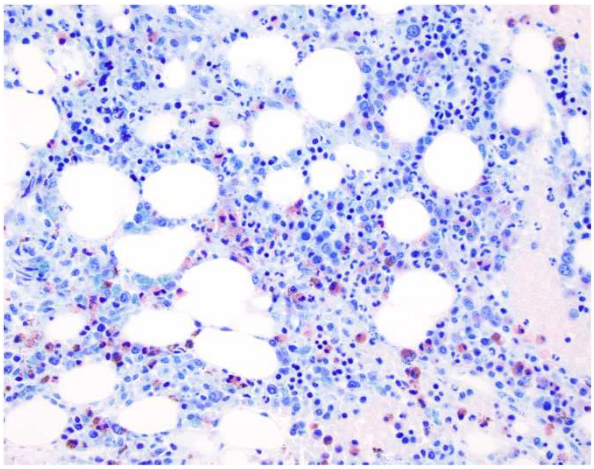

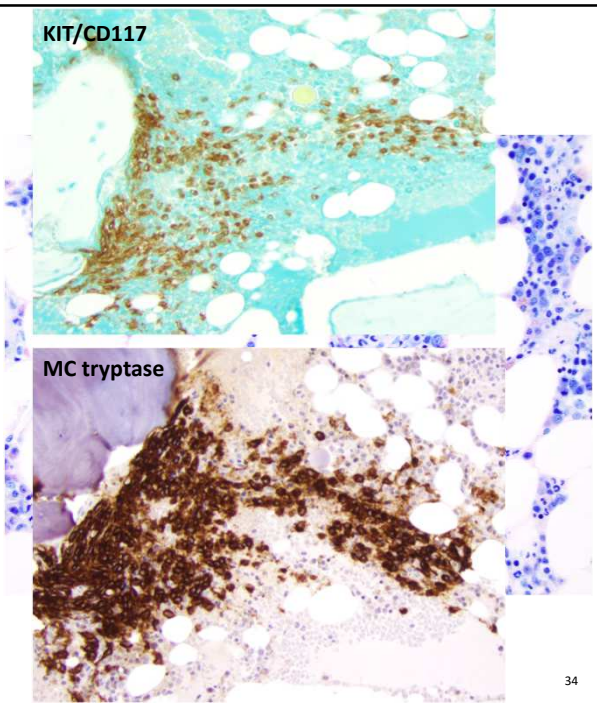

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Summary of pathologic and lab findings

Bone marrow biopsy:

- ~5% involvement by mast cell (hypogranular) with clusters **(M),** spindled morphology **(m)**, paratrabecular localization, and associated eosinophilia
- Aberrant CD25 expression **(m)**
- Maturing trilineage hematopoiesis
- Normal bone trabeculae

Flow cytometry: no aberrant population of CD117 bright mast cells

Serum tryptase: normal

Cytogenetics: 46,XY[20], normal karyotype

NGS: No pathogenic variants

- ddPCR not performed

No skin lesions

SM classified as Bone Marrow Mastocytosis

Proposed criteria for BM mastocytosis and separation from indolent and smoldering SM

Variant	Criteria
BMM	SM criteria fulfilled
	No skin lesions
	No B-finding(s)
	No C-finding(s)
	Basal serum tryptase <125 ng/mL
	No dense SM infiltrates in an extramedullary organ
	No signs/criteria for MCL
	No signs/criteria for an AHN
(Typical) ISM	SM criteria fulfilled
	Typical skin lesions
	No or one B-finding
	No C-finding
	No signs/criteria for MCL
	No signs/criteria for an AHN
ISM without skin lesions	SM criteria fulfilled
	No skin lesions
	No or one B-finding[a] and/or:
	Basal serum tryptase ≥125 ng/mL and/or:
	Dense SM infiltrates in an extramedullary organ
	No C-finding
	No signs/criteria for MCL
	No signs/criteria for an AHN
SSM	SM criteria fulfilled
	Two or 3 B-findings
	No C-finding
	No signs/criteria for MCL
	No signs/criteria for an AHN[b]

Why important?

- Patients with BMM have much better prognosis than typical SM
- Defined as:
  - <30% BM cellularity; tryptase <125ng/mL
  - Absence of skin lesions
  - No B or C findings
- Absence of skin lesions is often observed in advanced SM:
  - Need to exclude C-findings and MCL
- Our patient
  - On antihistamines with no symptoms

Valent P. et al. Hemasphere. 2021 Oct 13;5(11):e646. PMID: 34901755.

78-year-old man with MDS-MLD presenting with weakness

MDS diagnosed 6 years ago and treated with Procrit with good response

- BM biopsy: hypercellular marrow (80% cellular) with erythroid and megakaryocytic dysplasia
  - no IHC or Giemsa stains; no mentioning of mast cells
- Normal karyotype
- NGS not performed
- Serum tryptase levels not performed

Splenomegaly for many years (!)

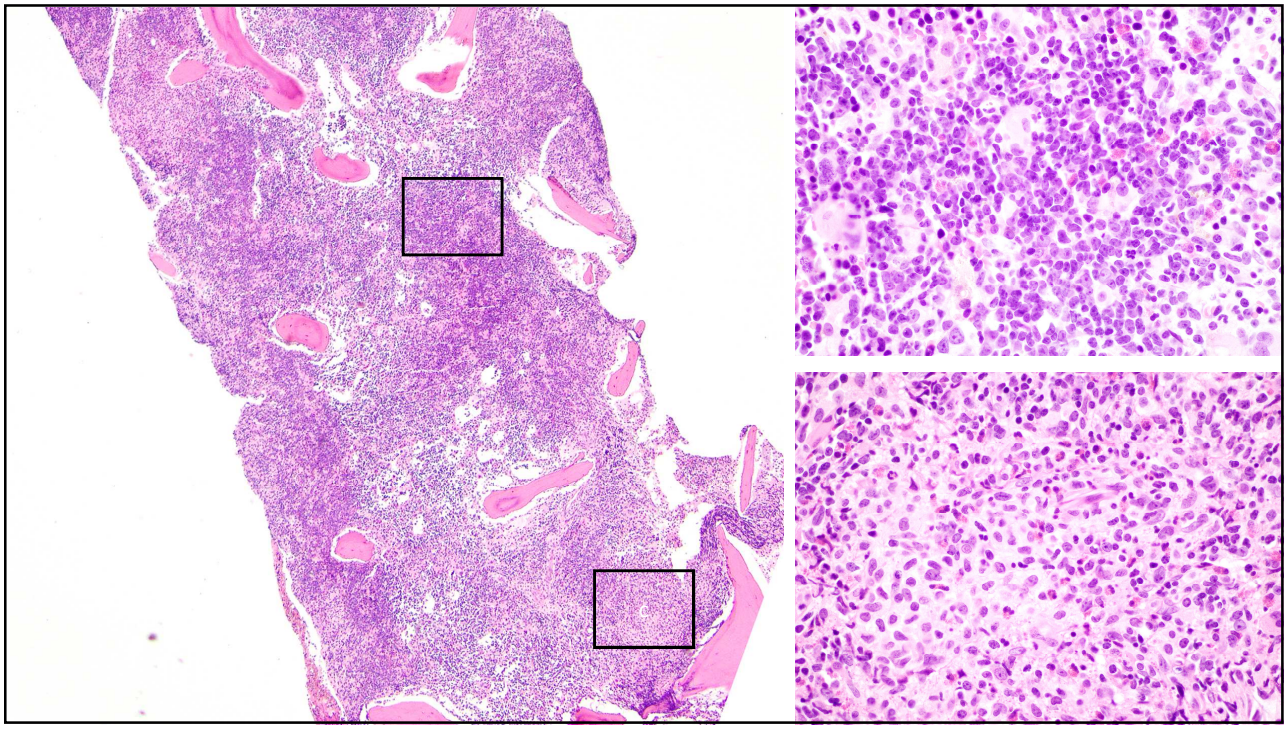
<u>At presentation:</u>

CBC: WBC 33.57 (HH), Hgb 8.2 (L), MCV 91.6, PLT 185

WBC differential: N 28% (L), L 22%, E 1%, B 2%, Blasts 47% (HH)

Abdominal CT: hepatosplenomegaly

- Prior MDS diagnosis was questioned due to splenomegaly (?MPN)



Additional Studies

Bone marrow biopsy:

- >95% cellular with >90% blasts
- MTH markedly reduced
- Absence of extensive fibrosis or osteosclerotic changes
- No IHC performed

BM aspirate:

- 72% MPO+ blasts
- Trilineage dysplasia

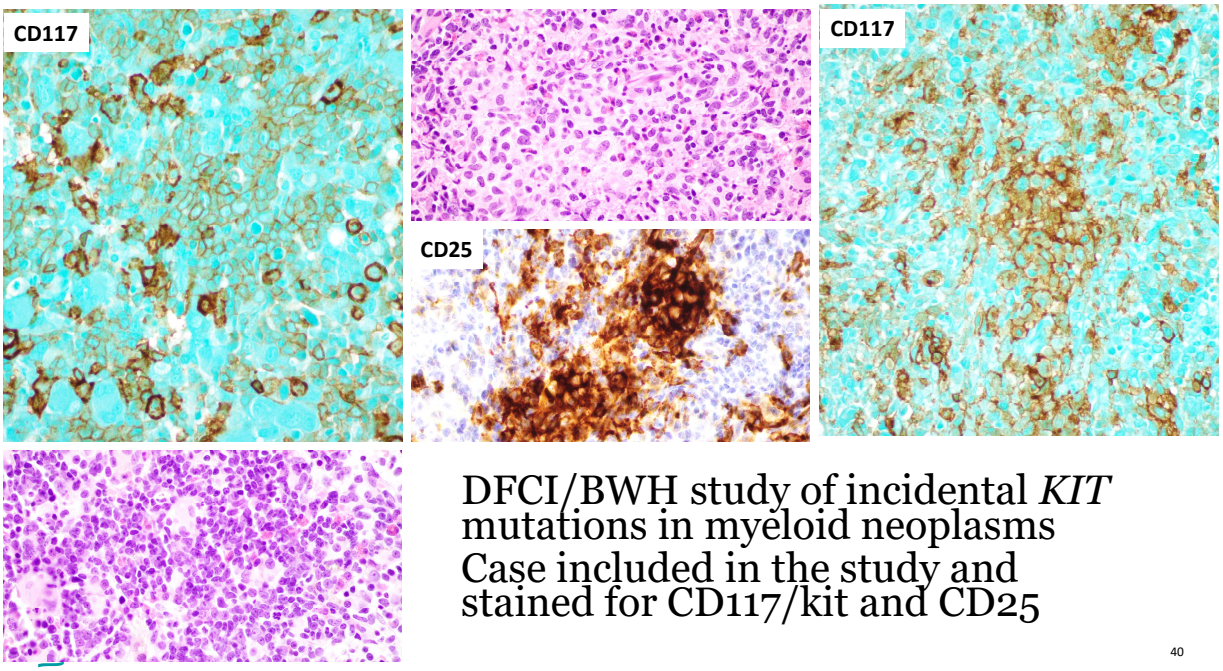
Dx: AML-MRC

Flow cytometry: CD34+CD117+HLA-DR+ blasts

Cytogenetics: 46,XY[20], normal karyotype

NGS:

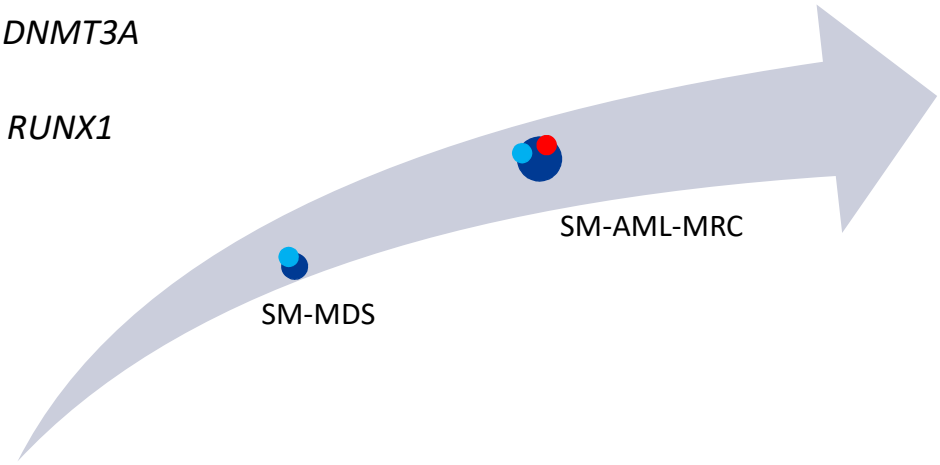
ASXL1 48%, *DNMT3A* 35% , *RUNX1* 10%, *CEBPA* 16% , *KIT* D816V 4%



DFCI/BWH study of incidental *KIT* mutations in myeloid neoplasms
Case included in the study and stained for CD117/kit and CD25

Likely chain of molecular events

- *ASXL1, DNMT3A*
- *KIT*
- *CEBPA, RUNX1*



How often do we detect unsuspected SM?

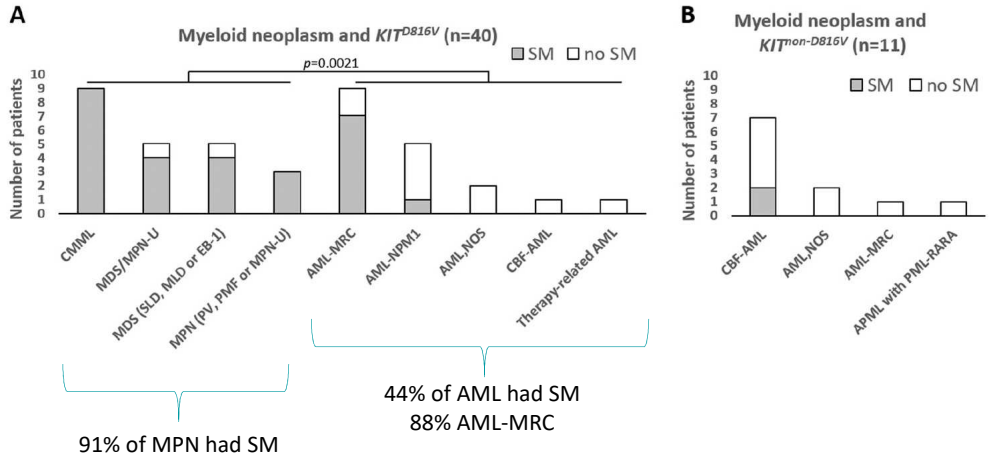
9 out of 30 patients with no clinical or morphologic suspicion for SM
- 7 cases were diagnosed upon IHC performed during the study
- 2 cases were diagnosed on deeper tissue levels

Average extent of involvement by SM was 10% (5-30%)

AHN component
- 2 patients with MDS
- 2 patients with CMML
- 2 patients with MDS/MPN-U
- 2 patients with AML-MRC
- 1 patient with MPN-U

Craig JW et al. Mod Pathol. 2020 Jun;33(6):1135-1145. PMID: 3189

Patients with myeloid neoplasms and *KIT* mutations



Craig JW et al. Mod Pathol. 2020 Jun;33(6):1135-1145. PMID: 3189

Clinical characteristics and outcome of 40 patients with *KIT* D816^{mut}/CBF^{neg} SM-AML

De novo SM-AML - 11/40 (28%) patients
Secondary SM-AML - 29/40 (73%) patients

n	Variables	
	No. of patients (*n*)	40
	Age in years, median (range)	65 (28–83)
	Males, *n* (%)	29 (73)
29	**Diagnosis prior to SM-AML**	
	ISM, *n* (%)	5 (17)
	SM-AHN, *n* (%)	24 (83)
24	**AHN-subtypes**	24 (83)
	MDS/MPN-u, *n* (%)	8 (33)
	CMML, *n* (%)	6 (25)
	MDS, *n* (%)	5 (21)
	MPN-eo, *n* (%)	5 (21)
29	Time to progression to SM-AML in months, median (range)	24 (2–116)
	SM-related findings	
21	Mast cell infiltration in BM histology, %; median (range)	10 (5–65)
27	Serum tryptase, µg/L; median (range)	92 (13–885)
	>100 µg/L, *n* (%)	13 (48)
32	Alkaline phosphatase, U/L; median (range)	145 (52–1428)
	>150 U/L, *n* (%)	16 (50)
36	Splenomegaly, *n* (%)	23 (64)
36	Ascites, *n* (%)	9 (25)
	Outcome	
	Follow-up, months, median (range)	5 (0–91)
	Death, *n* (%)	30 (75)

AHN associated hematologic neoplasm, *BM* bone marrow, *MDS/MPN-u* myelodysplastic/myeloproliferative neoplasm unclassifiable, *CMML*

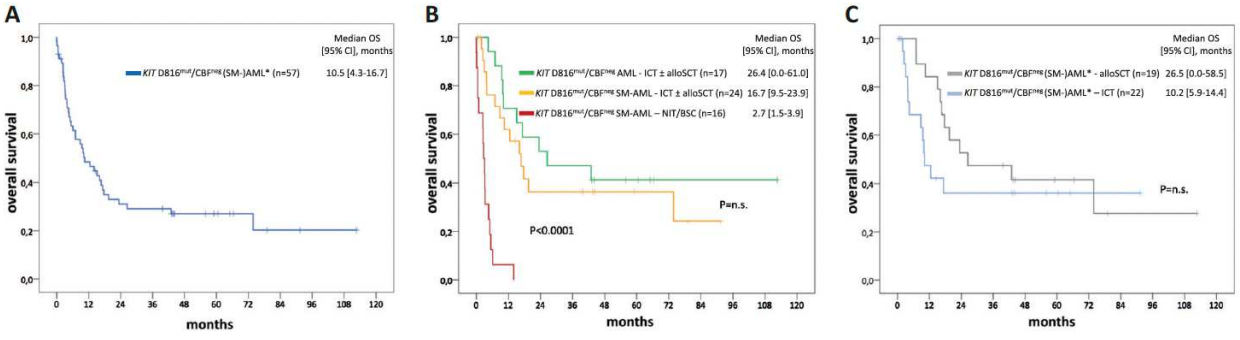
Jawhar M et al. Leukemia. 2019 May;33(5):1124-1134. PMID: 30635631

Longitudinal genetic profile of 16 *KIT* D816^{mut}/CBF^{neg} SM-AML pts

Case #	Diagnosis: SM with associated	Time to progression (months)	Molecular evolution: *SRSF2*	*RUNX1*	*TET2*	*ASXL1*	*NPM1*	*DNMT3A*	*IDH1/2*	*N/KRAS*	*BCOR*	*SETBP1*	*TP53*	*JAK2*	Karyotype evolution: Normal karyotype	Aberrant karyotype
15	MPN-eo AML	13														
20	CMML AML	19														
23	MDS/MPN-u SM-AML	37														
38	ASM AML	110														
39	MDS/MPN-u SM-AML	8														
9	CMML AML	14														
5	ISM AML	22														
1	CMML AML	29														
2	CMML AML	5													*	
3	MDS/MPN-u AML	4														
6	ISM AML	22														
29	ISM AML	74														
7	CMML AML	41													*	
36	MPN-eo AML	12														**
12	MDS AML	24														**
13	CMML AML	48														

Jawhar M et al. Leukemia. 2019 May;33(5):1124-1134. PMID: 30635631

Why is SM-AML diagnosis important to recognize?



Jawhar M et al. Leukemia. 2019 May;33(5):1124-1134. PMID: 30635631

Systemic Mastocytosis with Associated Hematologic Neoplasm

SM-AHN comprises 60-70% of AdvSM:

- SM-AML (2^{o}) progresses from SM-AHN by acquisition of additional mutations

Difficult to diagnose (but important!):

- AHN component can obscure SM (our case) or *vice versa*

Molecular testing:

- NGS for AHN component (low sensitivity for *KIT* but detects non-D816V)
  - Was crucial in case 3
- ddPCR/ASO-qPCR for *KIT* (highly sensitive but detects only D816V)
  - Could have been helpful in Case 2?

Always perform IHC for SM component or deeper levels when *KIT* is detected

Poor prognosis

Treatment options are unclear

- Avapritinib (selective KIT inhibitor) or midostaurin (multi-kinase inhibitor) for SM component
- Intensive chemotherapy for AHN component
- Improve prognosis if accurately diagnosed?

Presence of *KIT** mutations in AML

CBF-AML	AML-MRC
de novo	secondary
no/rare SM	SM
up to 40%	incidence unknown (<5%?)
changes prognosis	poor prognosis

*D816V and non-D816V

VIP: Very important points!

01

(Hyper)eosinophilia is NOT a diagnosis but a lab value

02

Mastocytosis is an ENCOMPASSING term containing many diagnostic entities

03

Both require extensive work-up and could be CLUES to guiding testing

QUESTIONS?