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Case # 228**

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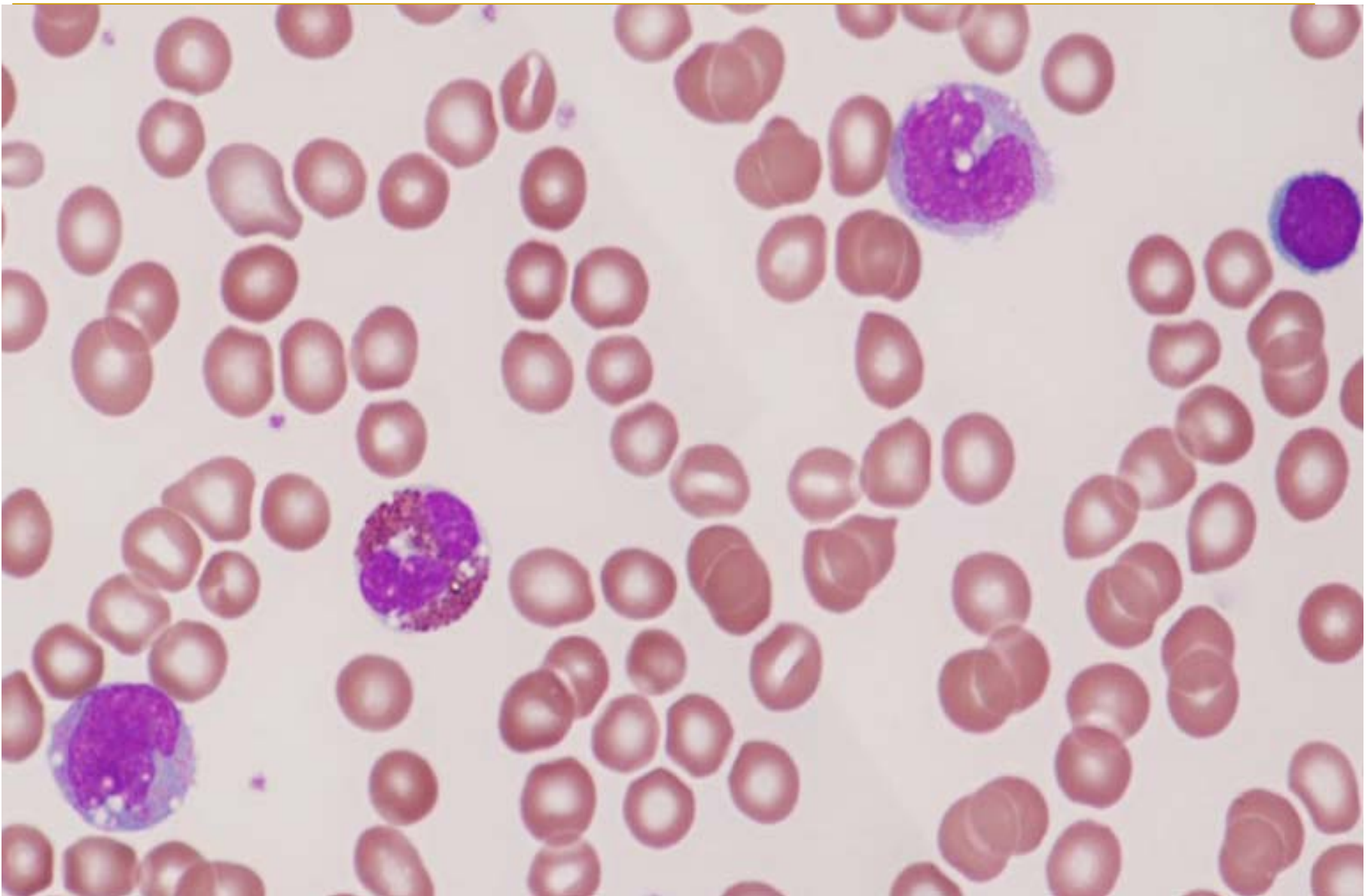
Case 228:

- **Clinical History:**
- This 65 year old female with three month history of abdominal bloating and weakness.
- Labs (CBC): Mild leukocytosis (14k/ul) with monocytosis (2940 absolute monocyte count), mild anemia (HB 11.5) and thrombocytopenia (90 k/ul).
- Bone marrow biopsy: Hypercellular marrow (>75%) with several early myeloid / monocytic elements and few cell clusters with granular cytoplasm
- Physical examination was negative for hepatosplenomegaly and skin rash.

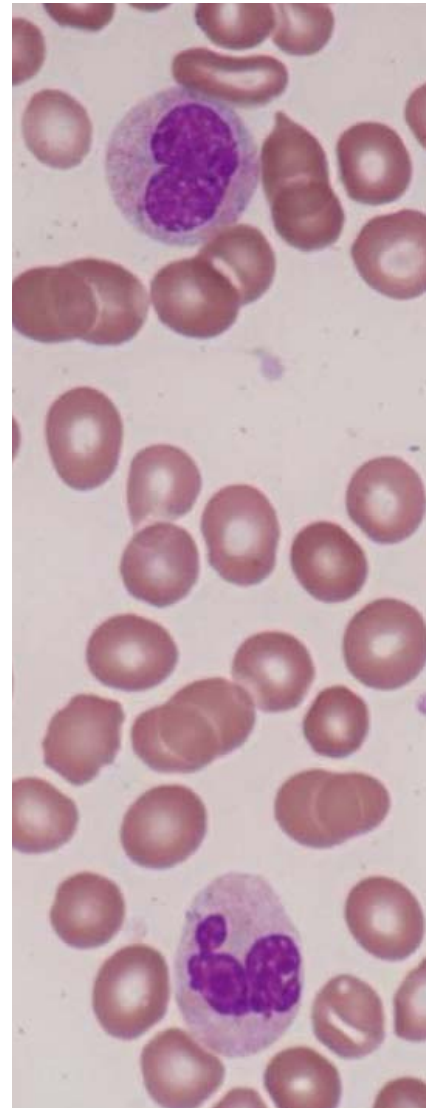
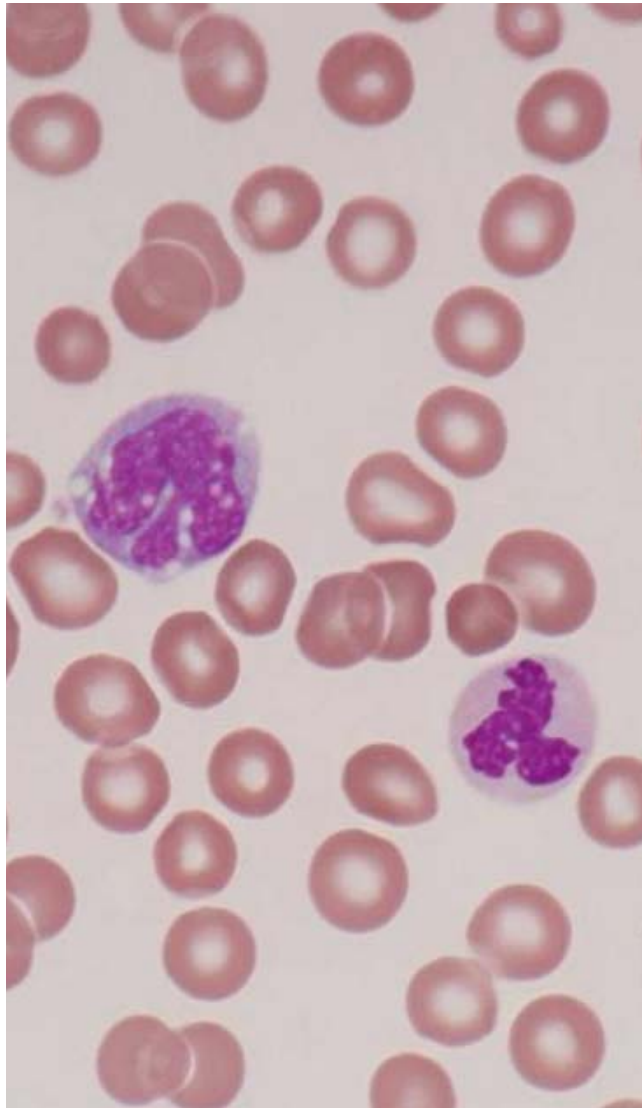
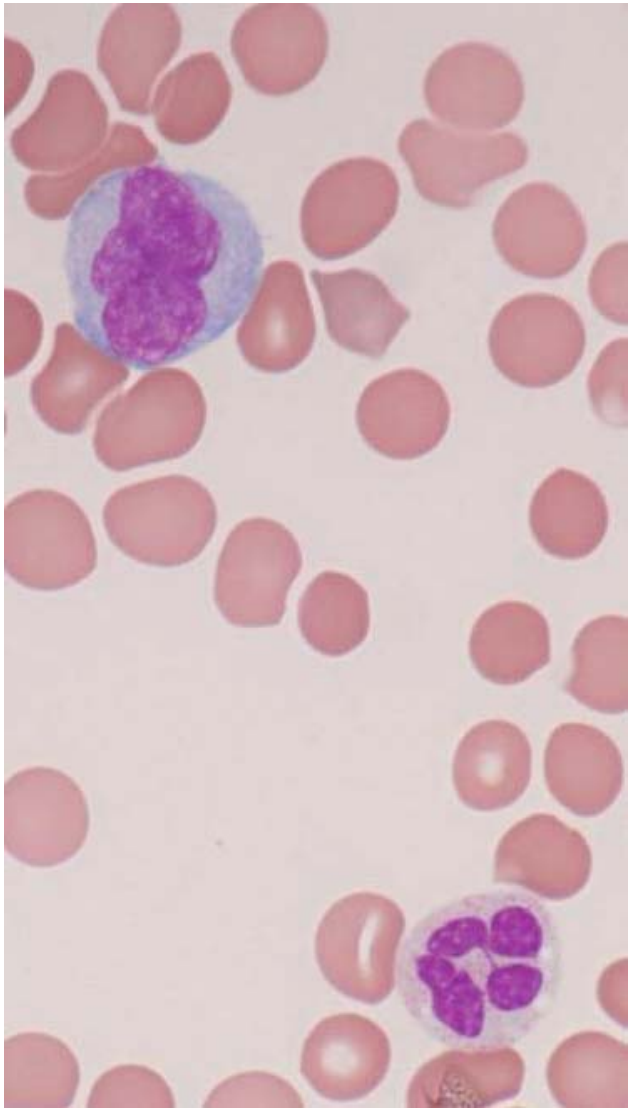
CBC	
WBC	14, 700 / ul
Hb	11.5 gm/dl
HCT	29 %
MCV	103 fl
Platelets	90, 000 / ul

Differential	
Neutrophils	54 %
Monocytes	20%
Lymphocytes	12 %
Bands	4 %
Pro/Mye/Meta	10 %

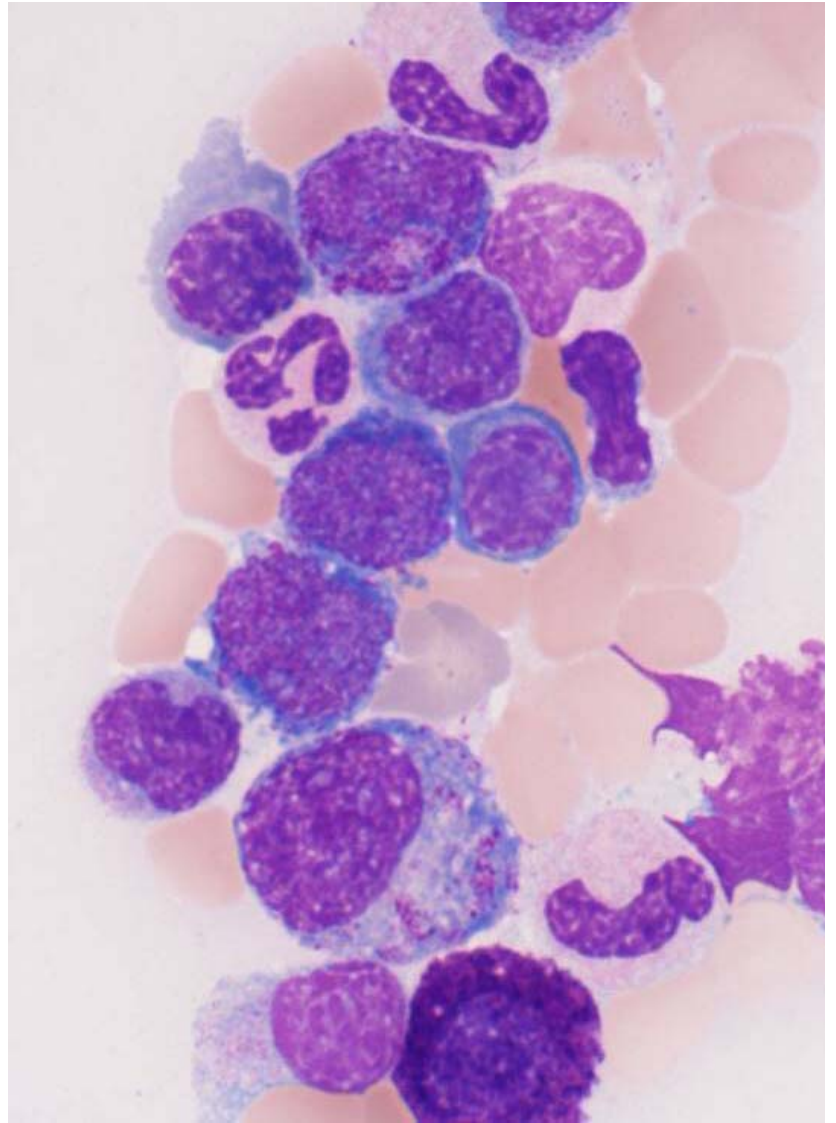
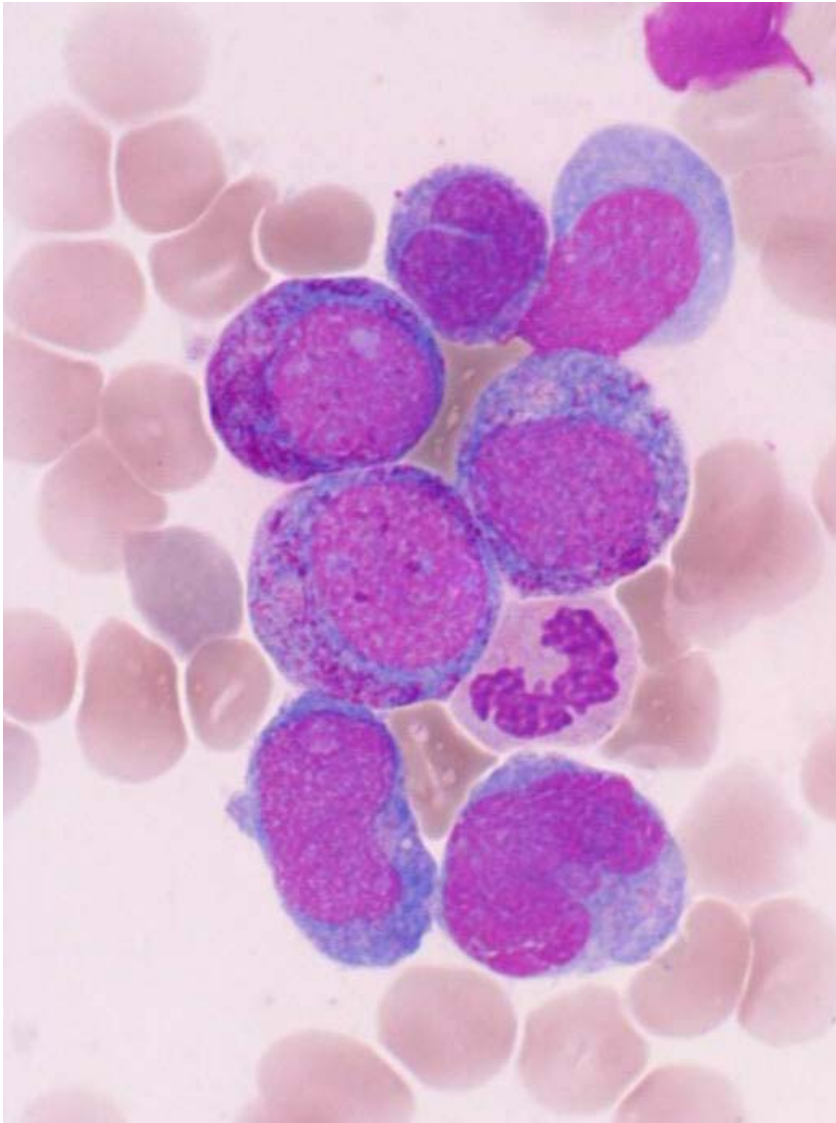
- RBC with moderate anisopoikilocytosis and rare NRBC
- *Few hypogranular / hyposegmented PMN's*
- Monocytosis (absolute count 2940 / cmm)
- Mild myeloid left-shift
- Rare degranulated mast cells (feather edge)



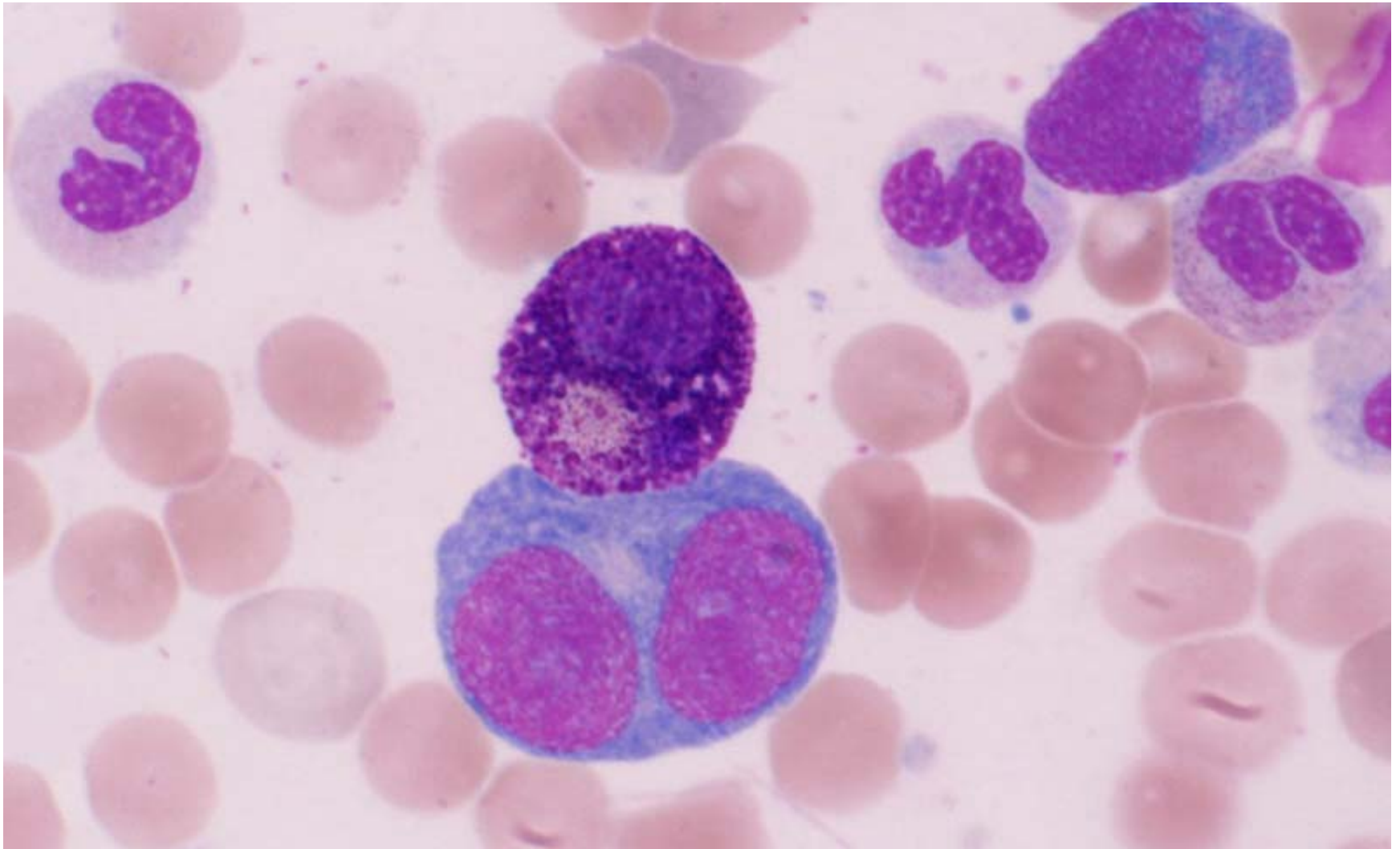
Peripheral Blood



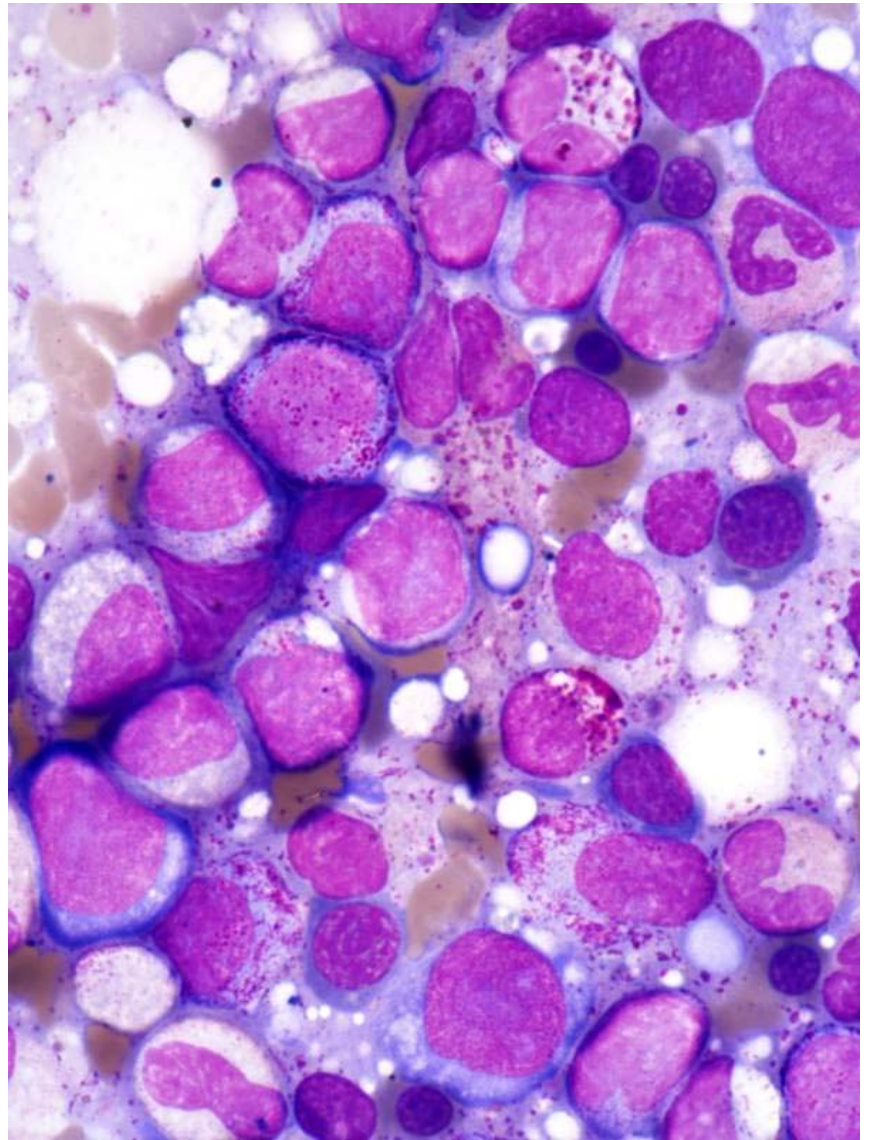
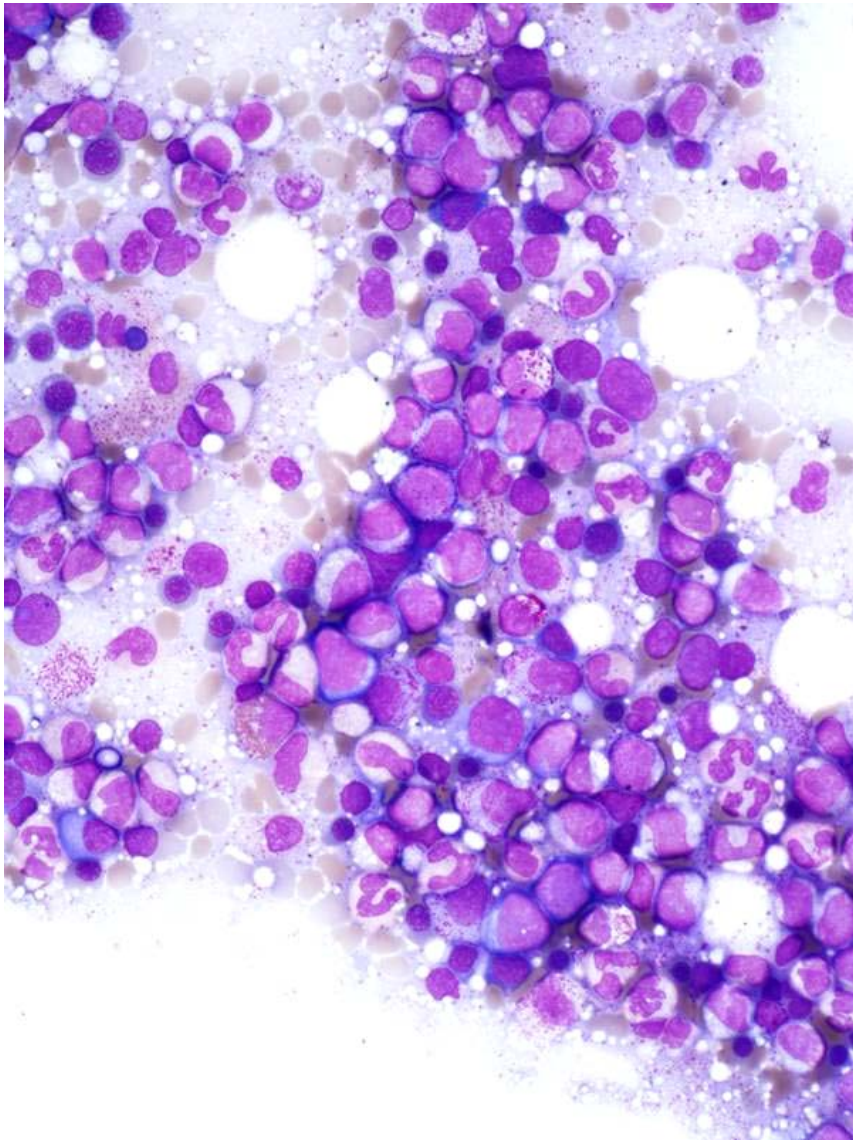
Peripheral Blood



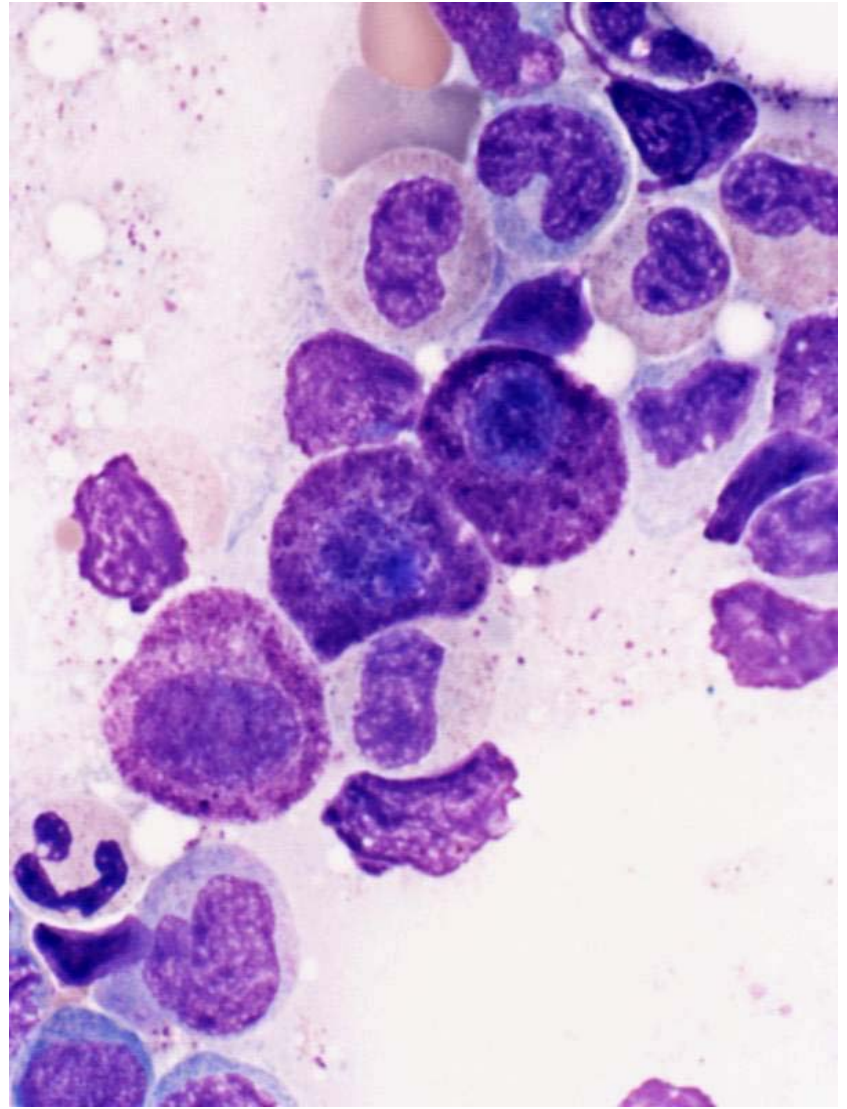
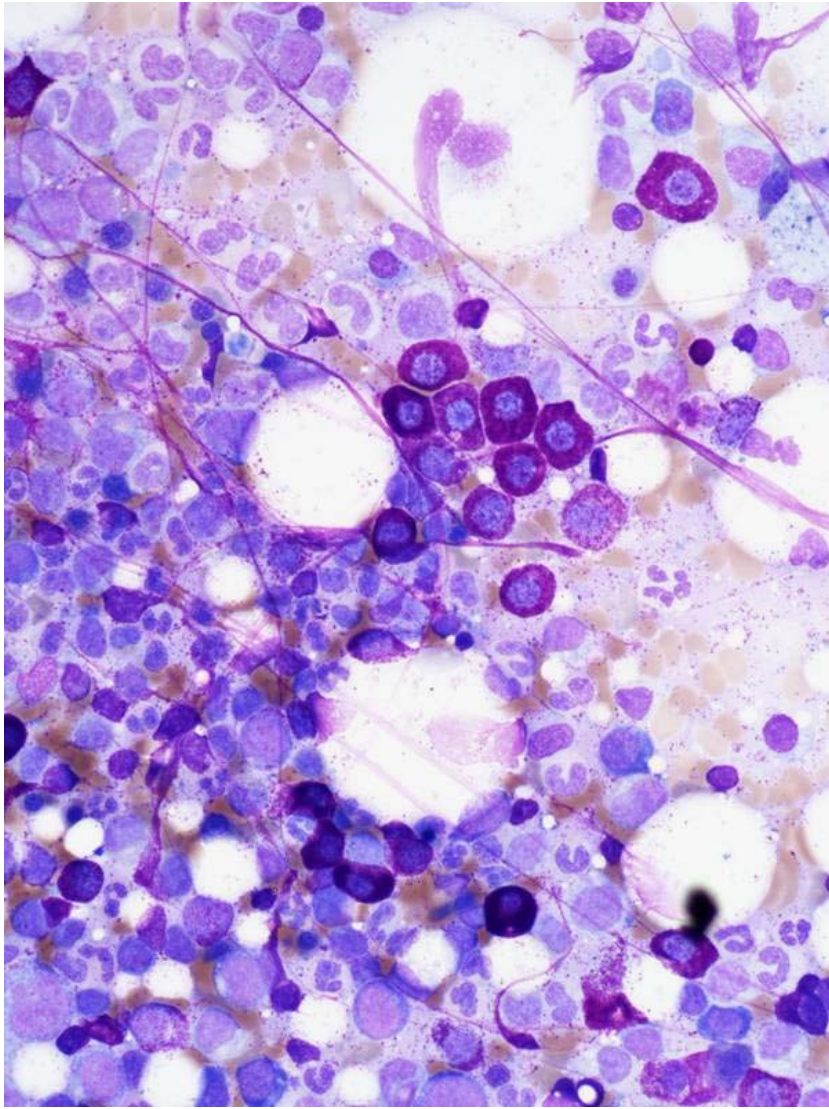
BM Aspirate Smear



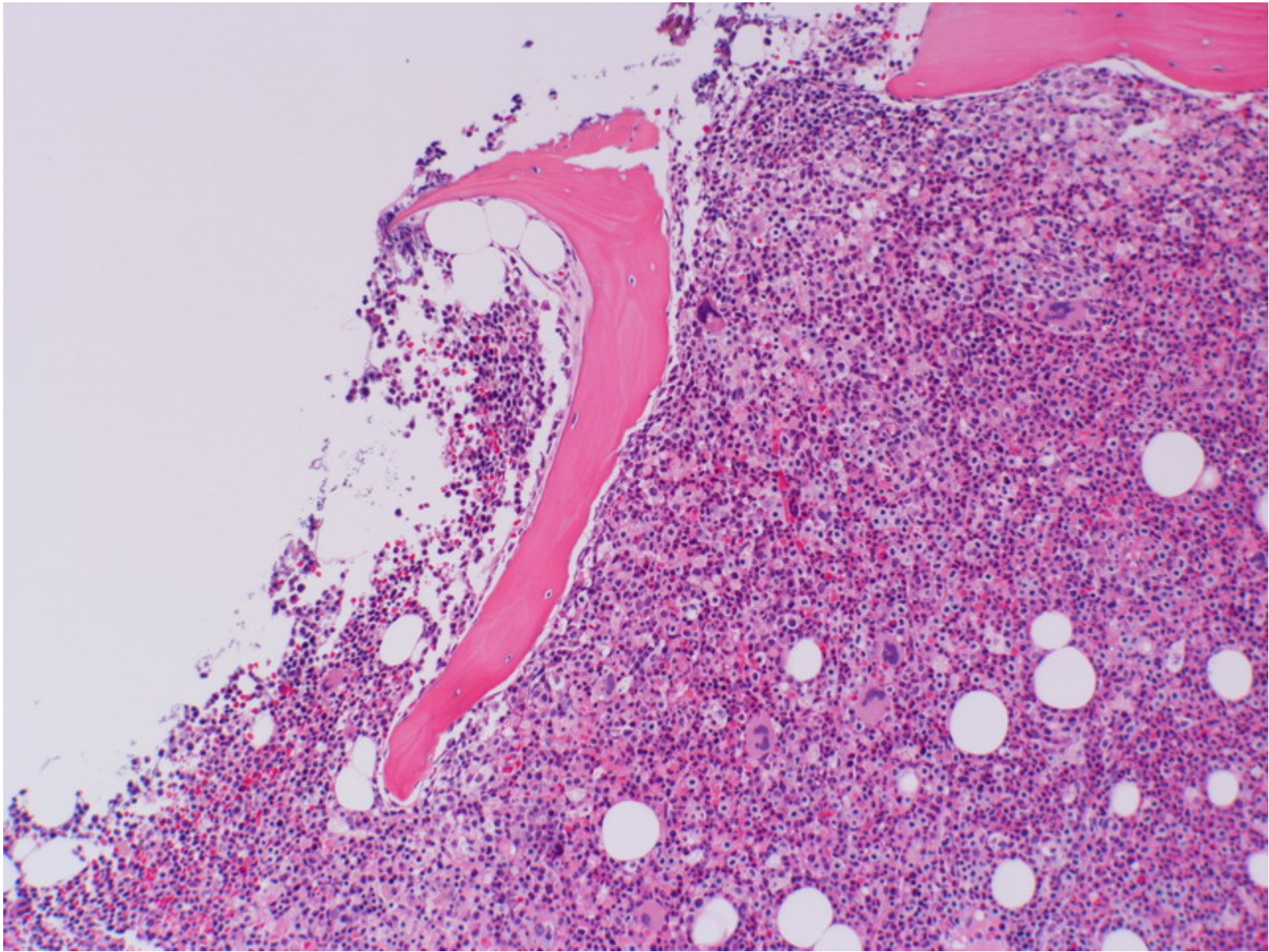
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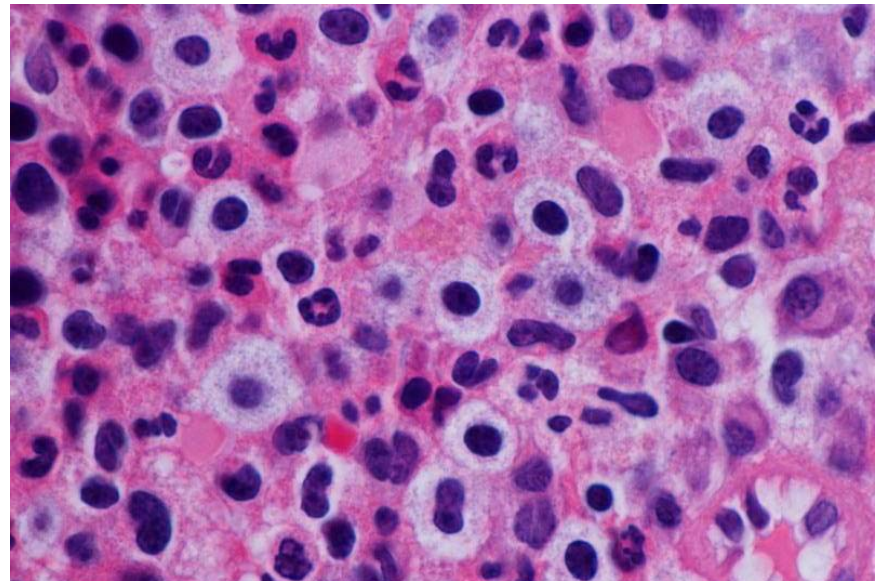
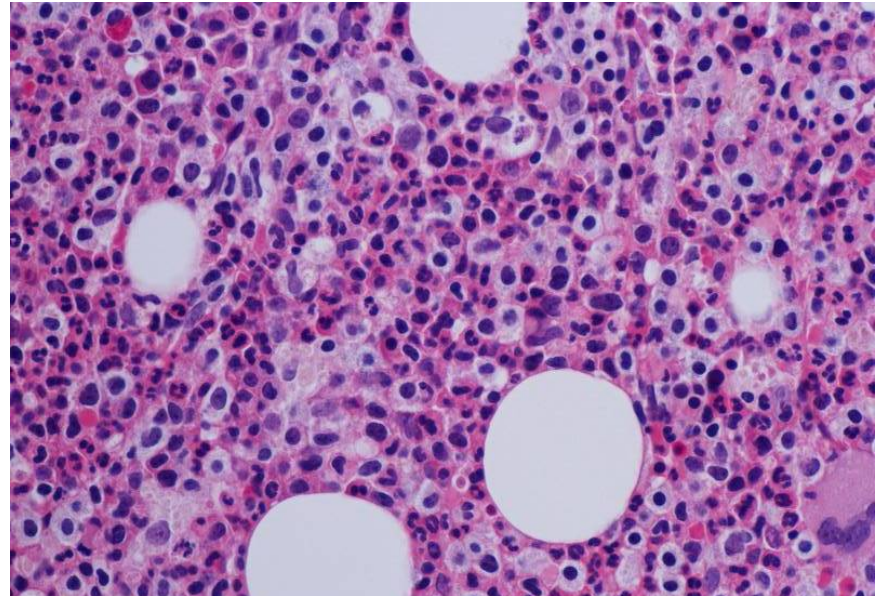
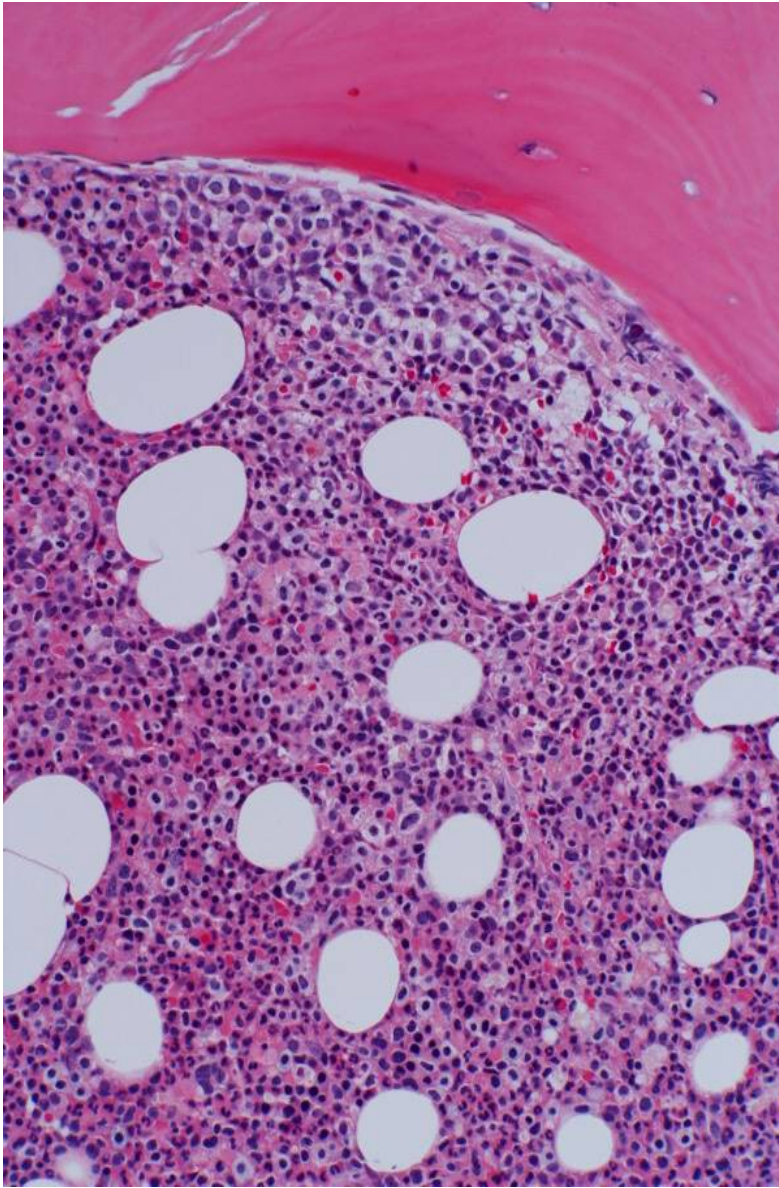
BM Biopsy Imprint



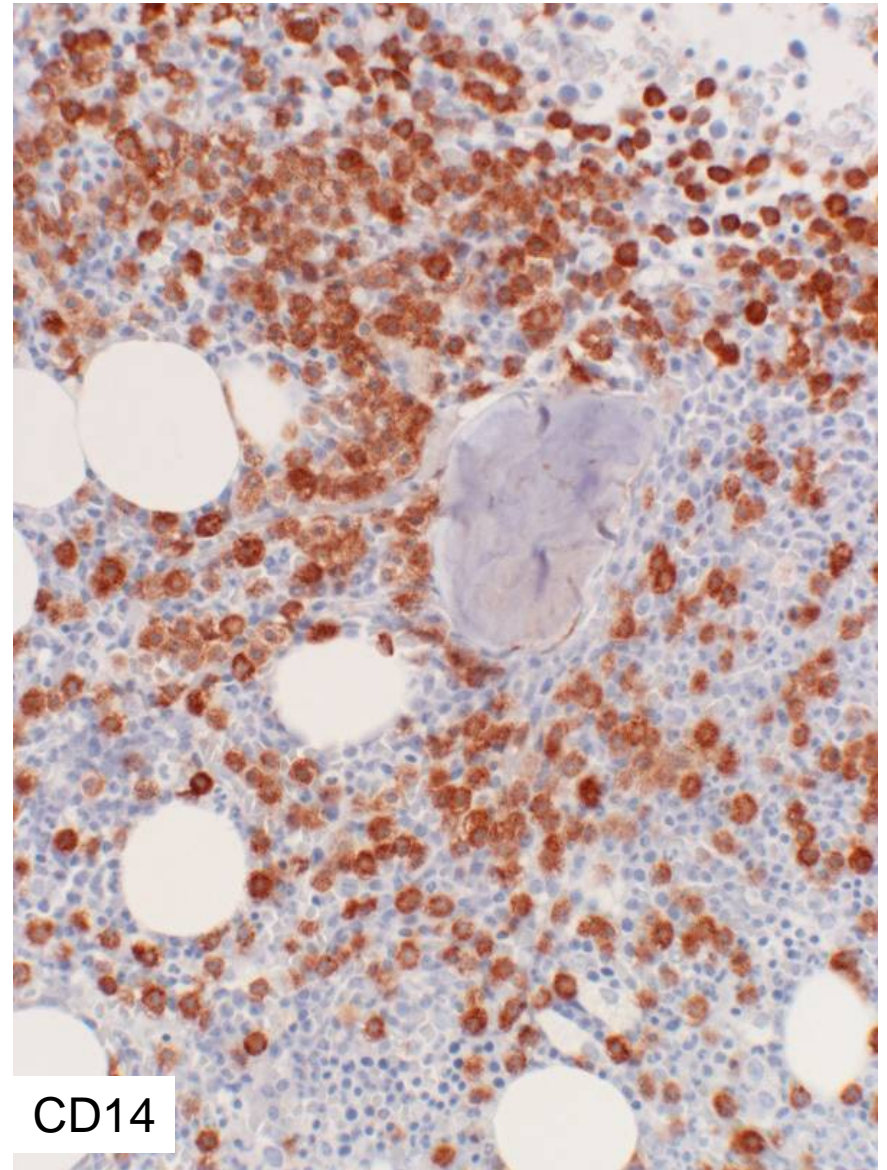
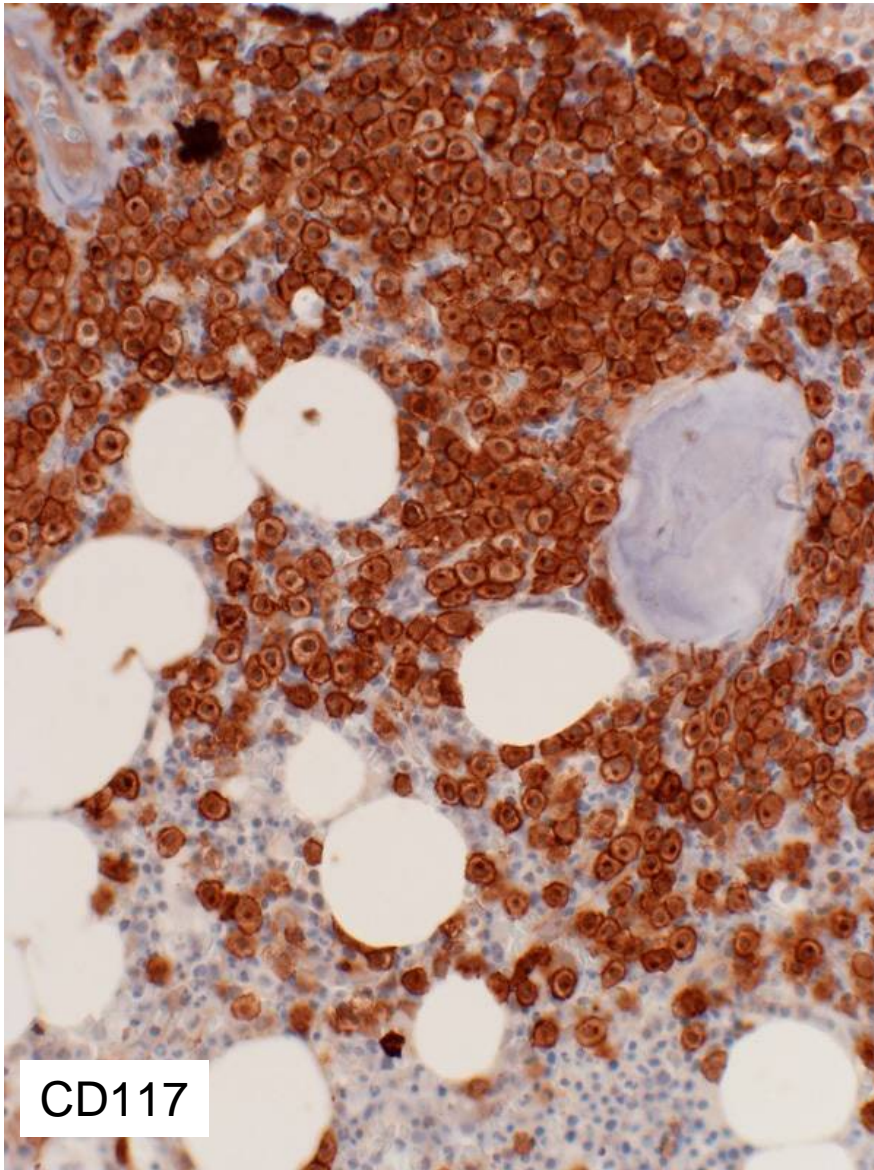
BM Biopsy Imprint



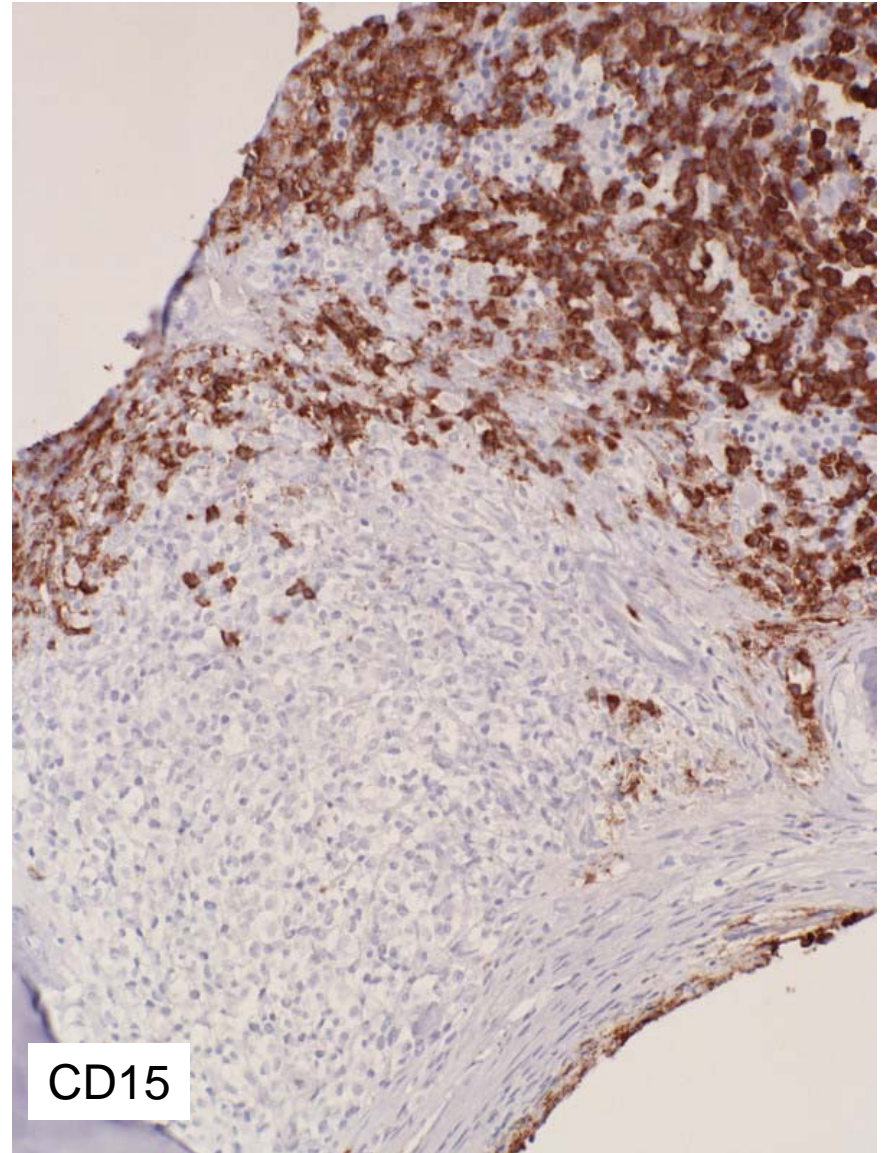
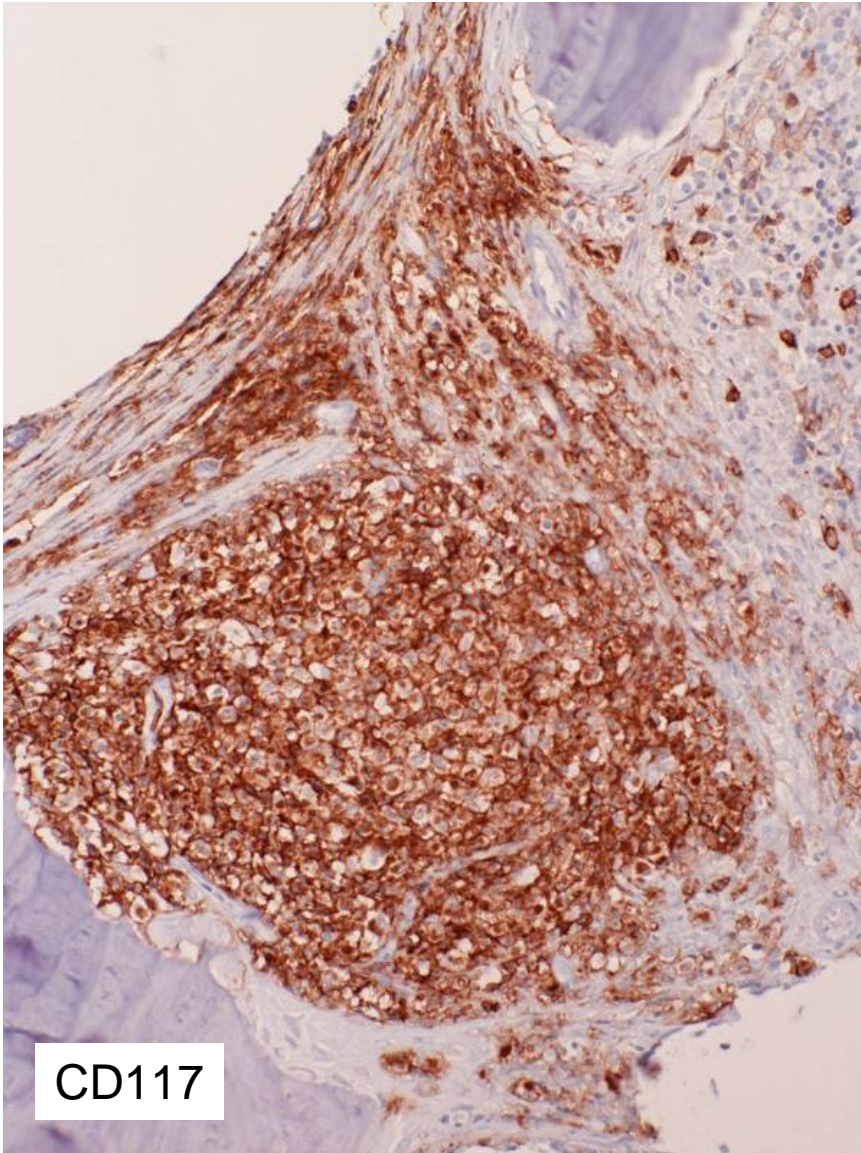
BM Biopsy



BM Biopsy



BM Biopsy



BM Biopsy

Bone Marrow Morphology

- Marrow cellularity 80-90%
 - Marked myeloid left-shift and focal immature cell clusters
 - Mast cells (aggregates and diffuse scattering)
 - Mild dyserythropoiesis and normal megakaryocytic morphology
 - Focal paratrabecular fibrosis
 - Benign lymphoid aggregate
-
- Serum tryptase levels increased (outside lab report)

Bone Marrow Aspirate

Blasts	7 %
Pro/Mye/M/PMN	40 %
Monocytes	9 %
Eosinophils	5 %
Erythroid	21 %
Mast cells	~15 %

Flow Cytometry

Mast: CD117+, CD33dim+

My/Mo: CD33/CD13+, CD14+, CD117+

Immunohistochemistry

Mast cells: CD21+, CD117+, CD34-, CD2- CD25-, *Tryptase*+

Mono: NSE+, CD14

Myeloid: MPO+, CD117+, CD15+

Case: 228

■ **Differential Diagnosis:**

- Myelodysplastic syndrome ? CMML
- Reactive mastocytosis

■ **Diagnosis:** Systemic Mast cell Disease with Associated clonal Hematologic non-Mast Cell Lineage Disease (SM-AHNMD)

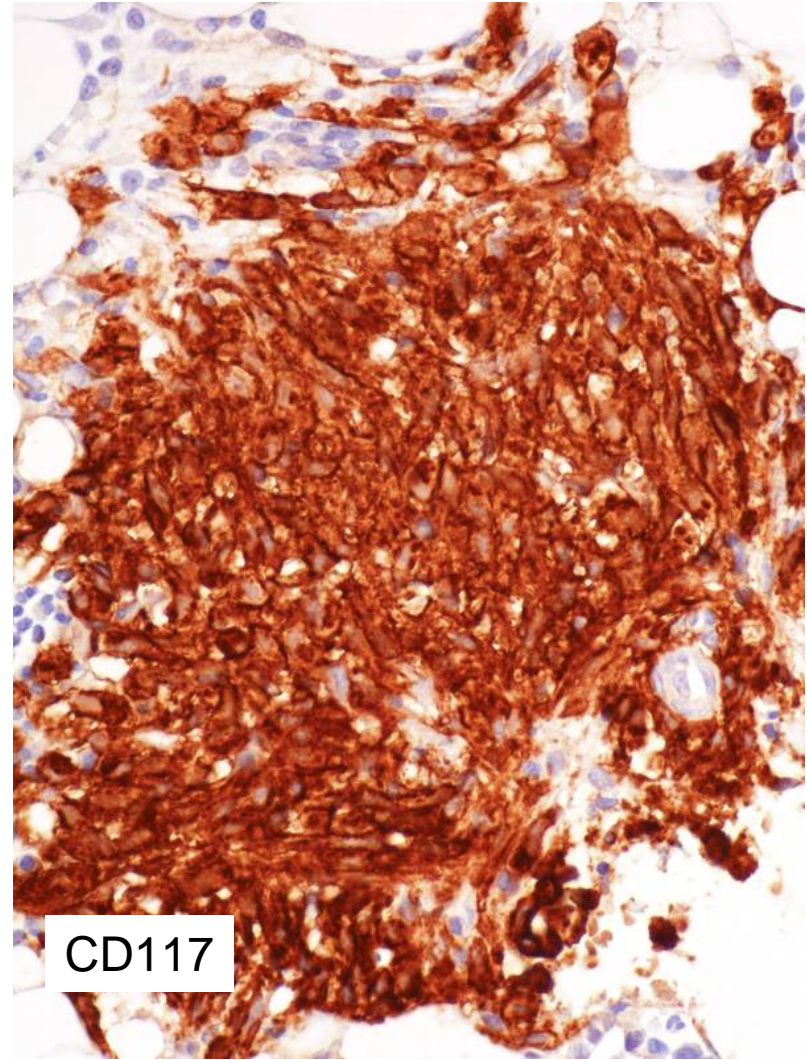
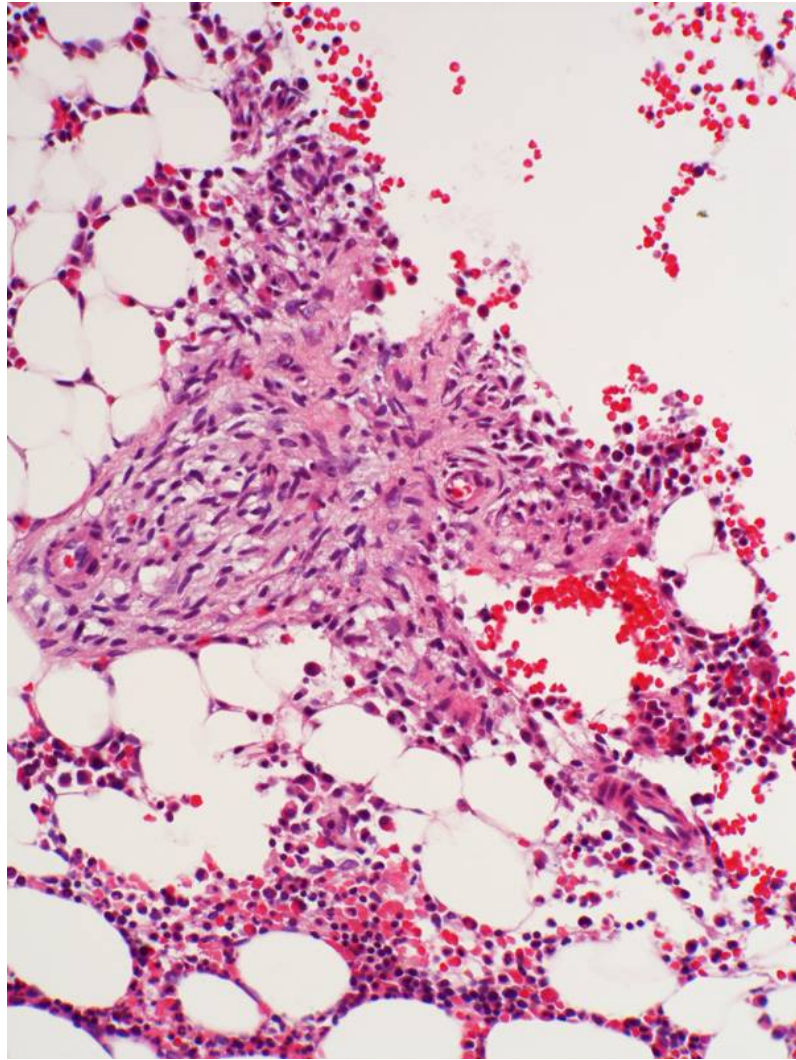
■ **Panel Diagnosis:** Differential diagnosis includes SM/mast cell leukemia and SM-AHNMD

- Studies by panel: WT c-kit CD25-

MC Characteristics in Mastocytosis

- Mature MC with variant morphology in indolent SM
 - MC with cytoplasmic extensions
 - Oval to spindle nuclei, hypogranular / degranulated cytoplasm and normal appearance
- BM histological patterns
 - Type I = Focal infiltrates
 - Type II = Focal infiltrates / hypercellular marrow in non MC areas and osteoclerosis (SM-AHNMD)
 - Type III = Diffuse infiltration (ASM or MCL)
- Immature MC (promastocytes / blasts) seen in aggressive SM and mast cell leukemia
- Immunophenotype
 - Immature = CD34+, CD13+ and CD117+
 - MC in SM = CD117+, CD2+ and CD25+

Indolent Systemic Mastocytosis



WHO Classification of Mastocytosis

Cutaneous mastocytosis	CM
• Maculopapular CM	MPCM
• Diffuse CM	DCM
• Mastocytoma of skin	
Indolent systemic mastocytosis	ISM
Smoldering SM	SSM
• Isolated bone marrow mastocytosis	BMM
Systemic mastocytosis with an associated clonal hematologic non MC lineage disease	SM-AHNMD
Aggressive systemic mastocytosis	ASM
• With eosinophilia	
Mast cell leukemia	MCL
• Aleukemic MCL	
Mast cell sarcoma	MCS
Extra-cutaneous mastocytoma	

SM-AHNMD

- Clonal hematopoietic non-MC neoplasms associated with systemic mast (SM) cell disease
- AML, CMML, MDS, CML^{ph+}, HES etc.
- In most cases SM is obvious, however, in some it may be masked by *non-MC neoplasm*
- Clues
 - MC aggregates
 - Variant MC morphology (spindle, lobed nuclei and lack of granules) *Bm touch imprint > aspirate smear*
 - CD2+/CD25+ (IPOX)
 - C-kit mutation for confirmation

SM-AHNMD

- Second most frequent subtype of SM
- >80% are myeloid – MDS/MPS, AML, CEL and CML (CMML is the most common association)
- Associated lymphatic malignancies (10-20%)
 - Plasma cell myeloma
 - ALL, CLL and hairy cell leukemia (rare cases)
 - CD25+ in hairy cells ?
 - No case reports with Hodgkin lymphoma

- BM Presentation
 - Hypercellular marrow
 - Normo or hypocellular areas
 - “Occult” mastocytosis unmasked after chemotherapy

- Prognosis depends on the “*AHNMD component*”
- Type of MDS/MPD or AL type
- 5 year survival: SM-AHNMD 17-28%, compared to MCD alone 75% and 61% (*Travis et al*)

Pullarkat VA et al Am J Hem. 2003;73:12-17

Agis H et al, Leuk Res. 2005;29:1227-1232

Horny HP et al. Pathobiology 2007;74:121-132

Diagnostic Workup

- Tissue biopsies (BM, skin & other tissues)
 - Routine H&E, Giemsa and toluidine blue (pH 1.5-2.5)
 - Reactive increase in MPD and lymphoproliferative disorders
- Flow / Immunohistochemistry
 - CD2, CD25, CD117, CD35, CD14, CD15, CD33 and CD34
 - Flow – Quick processing, stain lyse method over Ficoll separation, double step acquisition i.e. all nucleated cells followed by selective gating on CD117
- Serum
 - Elevated tryptase levels (note: higher levels are also seen in AML, MDS, MPD & hypereosinophilic syndrome)
- Molecular
 - C-kit (D816V), bcr/abl and FIPL1-PDGFR
- Pediatric patients
 - Skin biopsy > tryptase levels and D816V
- Adults
 - Bone marrow biopsy > serum tryptase and c-kit mutation ?

Case 228 – 6 month followup

- White blood cell count 55.1/ul with 15 bands, 7 myelocytes, 4 metamyelocytes, 9 lymphocytes and 10 monocytes. No circulating blasts. Hemoglobin 10.3 and platelet count had decreased to 78,000.
- Continued diarrhea and weight loss
- Chemotherapy (outside follow-up, no details about the exact treatment regimen)



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