Myelodysplastic/Myeloproliferative Neoplasms

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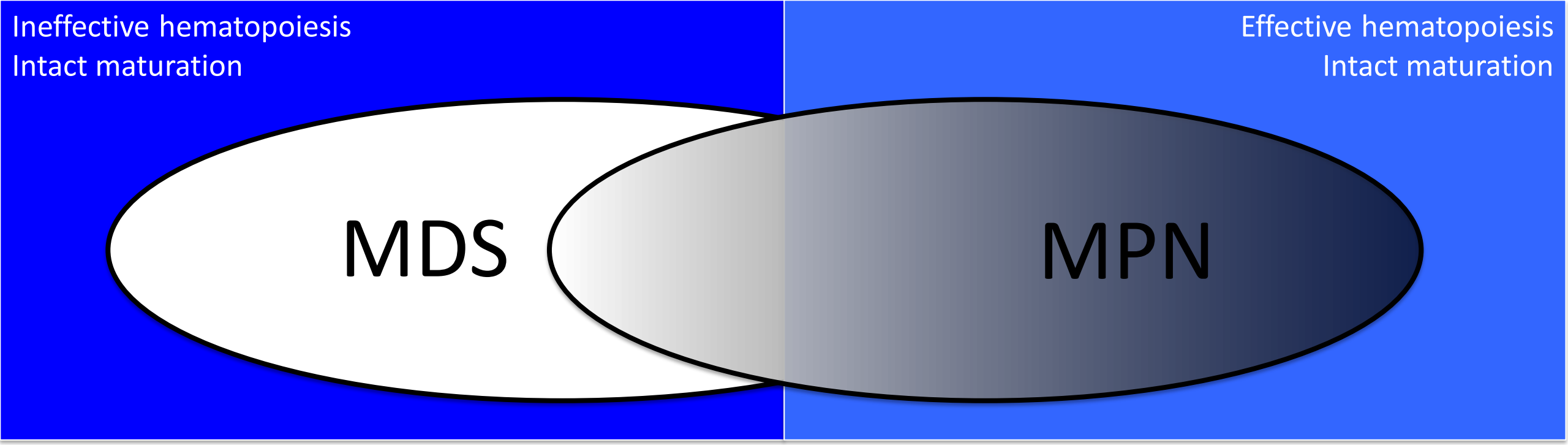
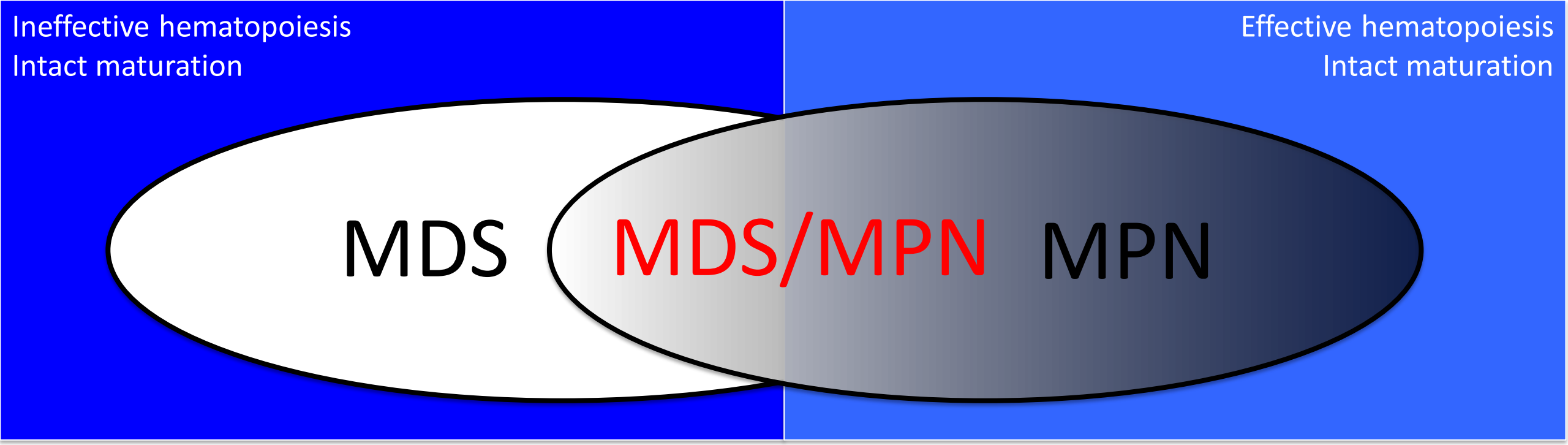


- ***Cytopenias***
  - ***Anemia***
  - ***Thrombocytopenia***
  - ***Neutropenia***
- ***Dysplastic morphology***

- ***Elevated counts***
  - ***Thrombocytosis***
  - ***Leukocytosis***
  - ***Monocytosis***
  - ***Erythrocytosis***
  - ***Eosinophilia***
- ***Non-dysplastic morphology***



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The relationship of MDS/MPN entities to ‘pure’ MDS and MPN entities

- MDS/MPN diseases should exhibit the combined proliferative and dysplastic features at *the initial diagnosis*
- Patients with a previously established diagnosis of MDS or MPN may evolve to a picture mimicking MDS/MPN
  - Persistent monocytosis and/or leukocytosis in MDS
  - Cytopenias, monocytosis, and/or new dysplastic morphology in MPN
  - These changes may be a sign of disease progression or even impending transformation to AML, but generally do not change the diagnosis to an MDS/MPN
    - WHO 5th edition allows prior MDS or MPN for some MDS/MPN entities

‘Dysplastic’ evolution of MPN ≠ MDS/MPN

CML
PMF
CNL
ET
PV

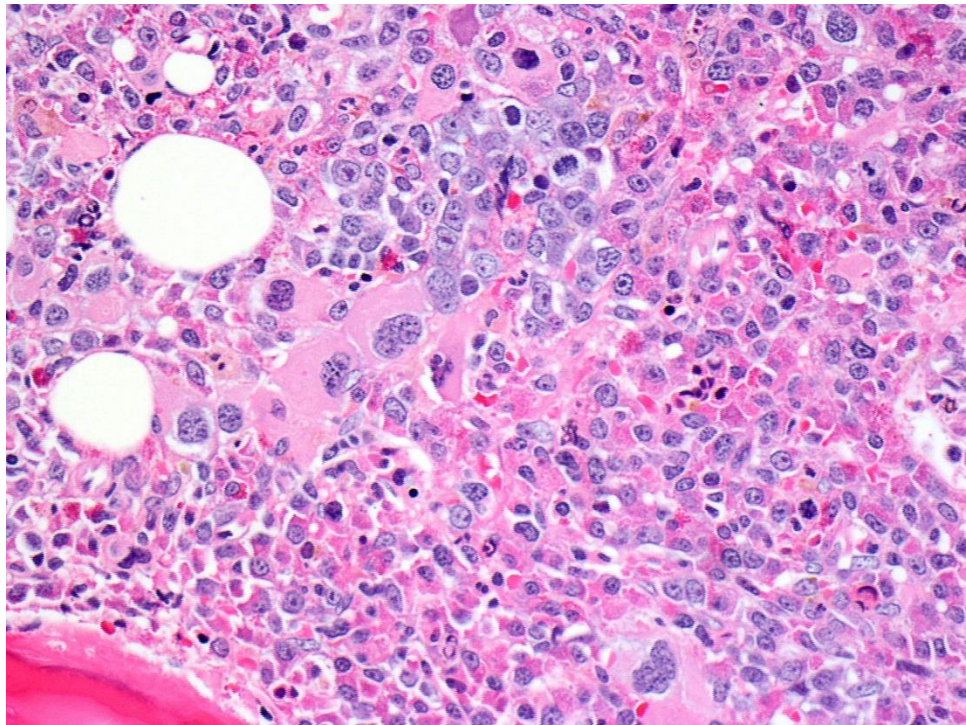
1. Dysplastic morphology
2. Ring sideroblasts
3. Monocytosis

AML

Often accompanied by cytopenias not explained by:

- Marked marrow fibrosis
- Splenomegaly
- Metabolic deficiencies
- Treatment

Primary myelofibrosis with dysmegakaryopoiesis



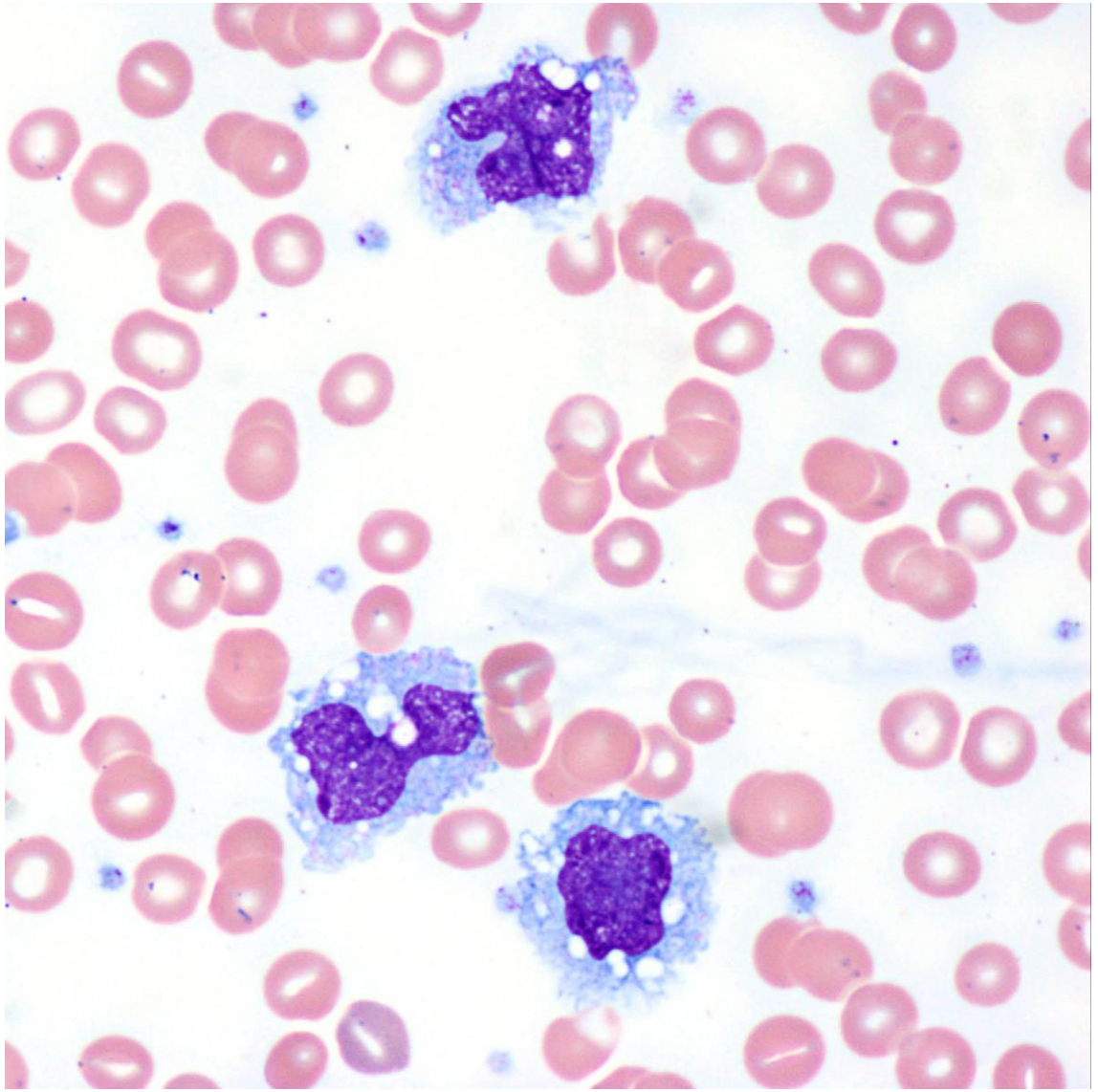
Boiocchi L et al. Mod Pathol 2013;26:204-12, Bain BJ et al. Am J Hematol 2010;85:866, Boiocchi L et al. Hum Pathol 2019;86:1, Chapman J et al. Mod Pathol 2018;31:429

Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)

2022 ICC	2022 WHO	2017 WHO Equivalents
Chronic myelomonocytic leukemia	Chronic myelomonocytic leukemia	Chronic myelomonocytic leukemia
Atypical chronic myeloid leukemia	**MDS/MPN with neutrophilia**	Atypical chronic myeloid leukemia, *BCR-ABL1* negative
MDS/MPN with *SF3B1* mutation and thrombocytosis	**MDS/MPN with *SF3B1* mutation and thrombocytosis**	MDS/MPN with ring sideroblasts and thrombocytosis
MDS/MPN with ring sideroblasts and thrombocytosis, NOS		
MDS/MPN, NOS	MDS/MPN, NOS	MDS/MPN, NOS
MDS/MPN with isolated i(17q)		

Chronic myelomonocytic leukemia (CMML)

- MDS/MPN characterized by excess production of monocytes
- Ineffective hematopoiesis manifesting as one or more cytopenias and dysplasia in non-monocytic lineages



The diverse causes of monocytosis

Reactive

- Recovering bone marrow post-chemotherapy
- G-CSF therapy
- Autoimmune diseases
- Sarcoidosis
- Tuberculosis, brucellosis, leishmaniasis, viral infections
- Endocarditis

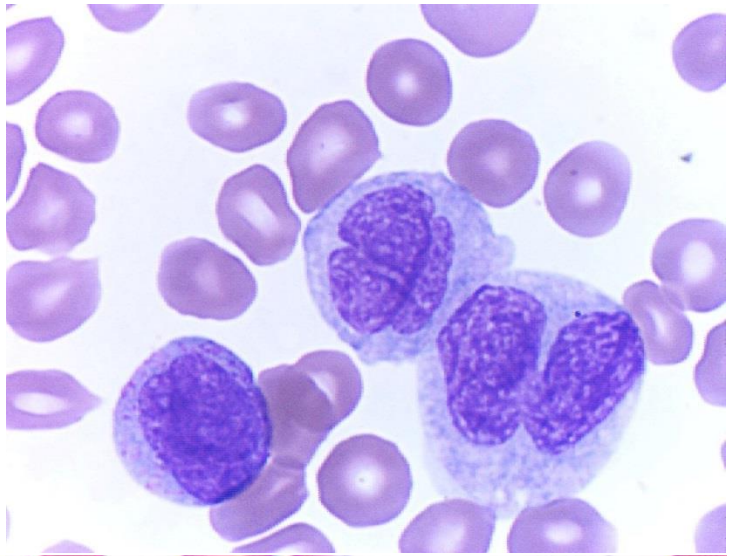
Neoplastic

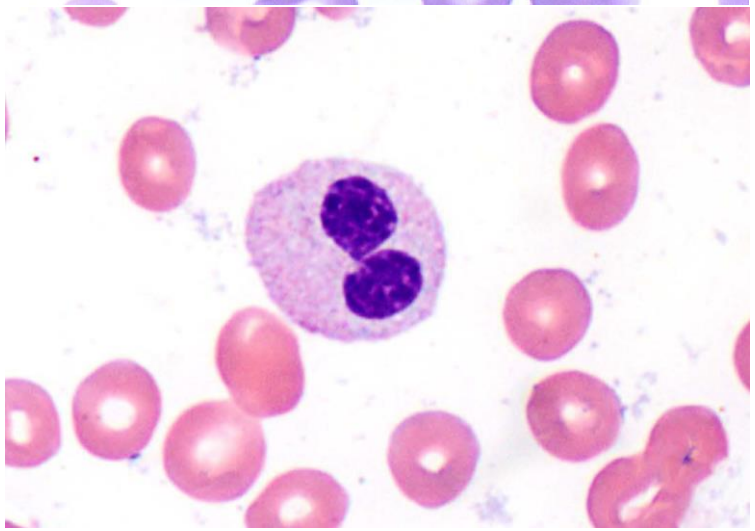
- CMML
- MDS with monocytic progression
- MPN with monocytic progression
- JMML
- AML with monocytic differentiation

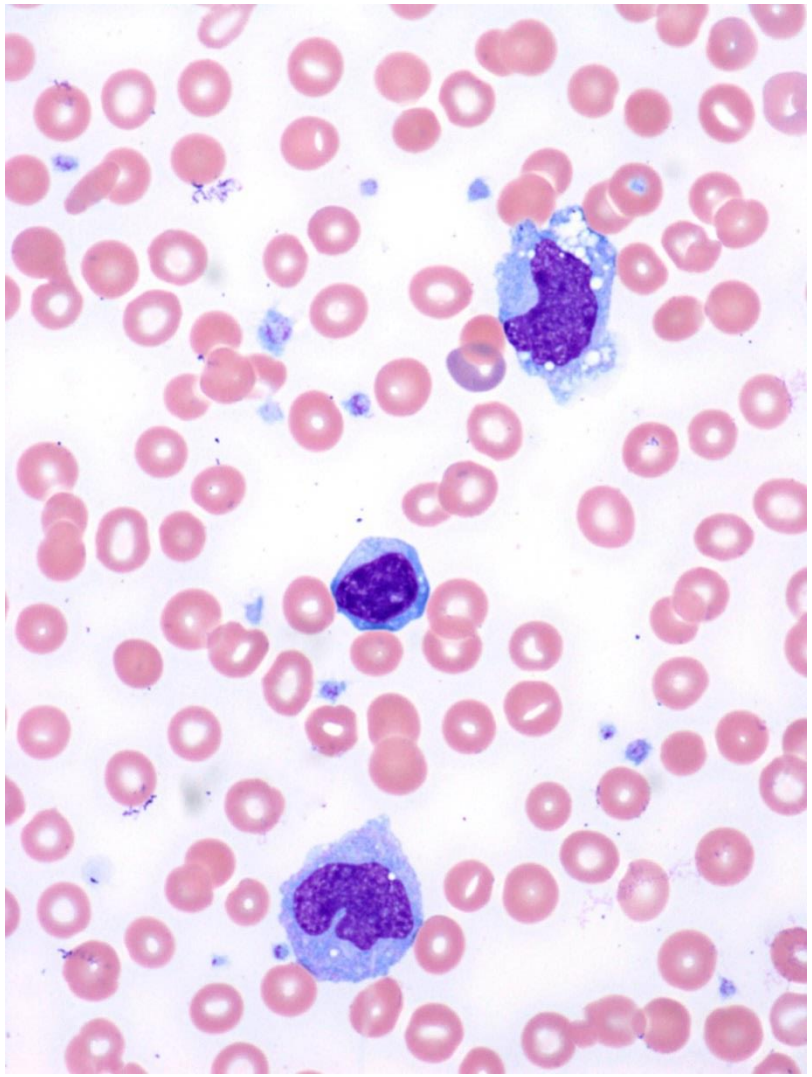
Patnaik MM et al. BJH 2014

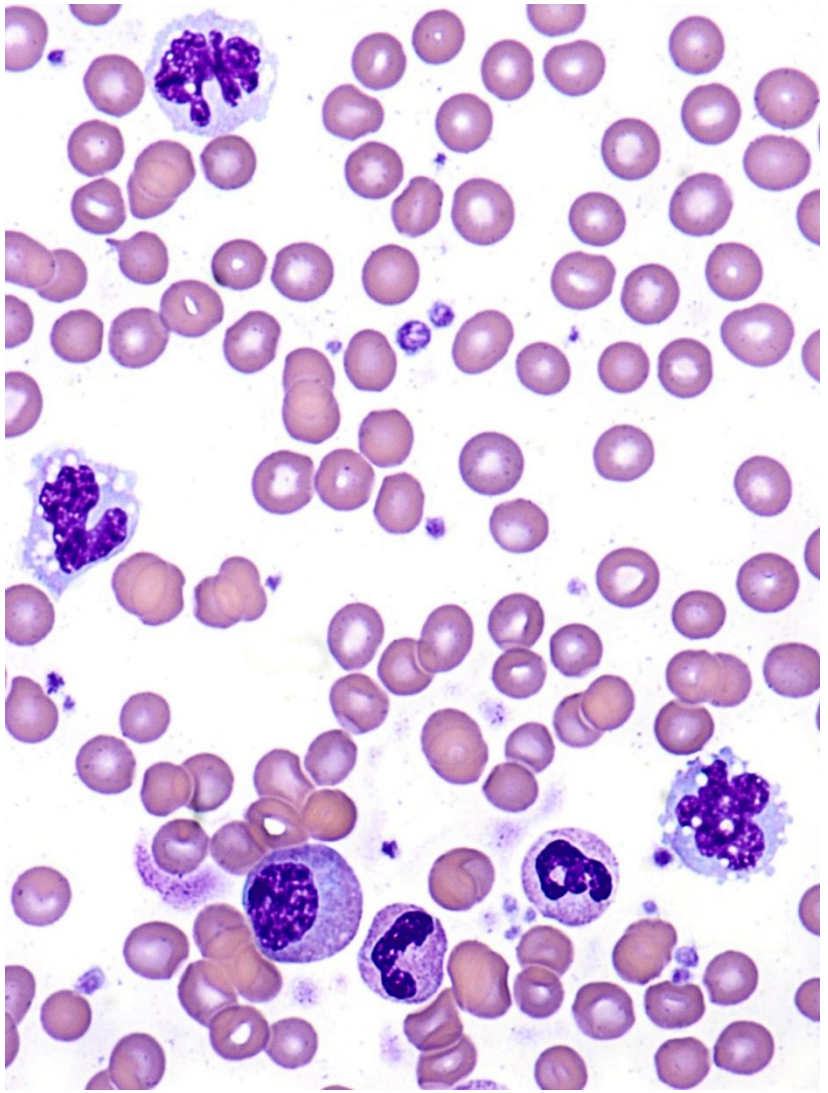
Courtesy of Dr David Steensma

CMML peripheral blood

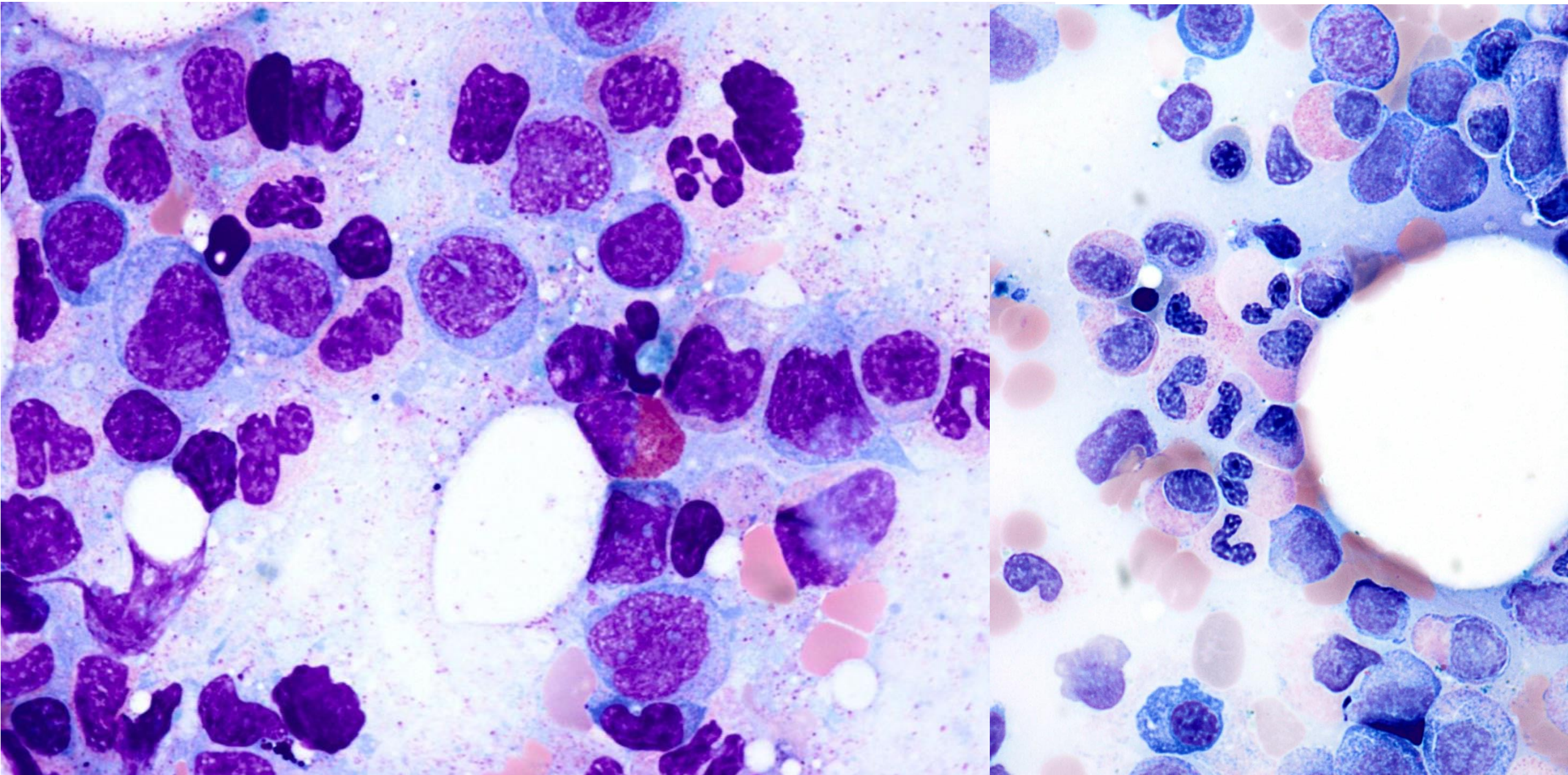




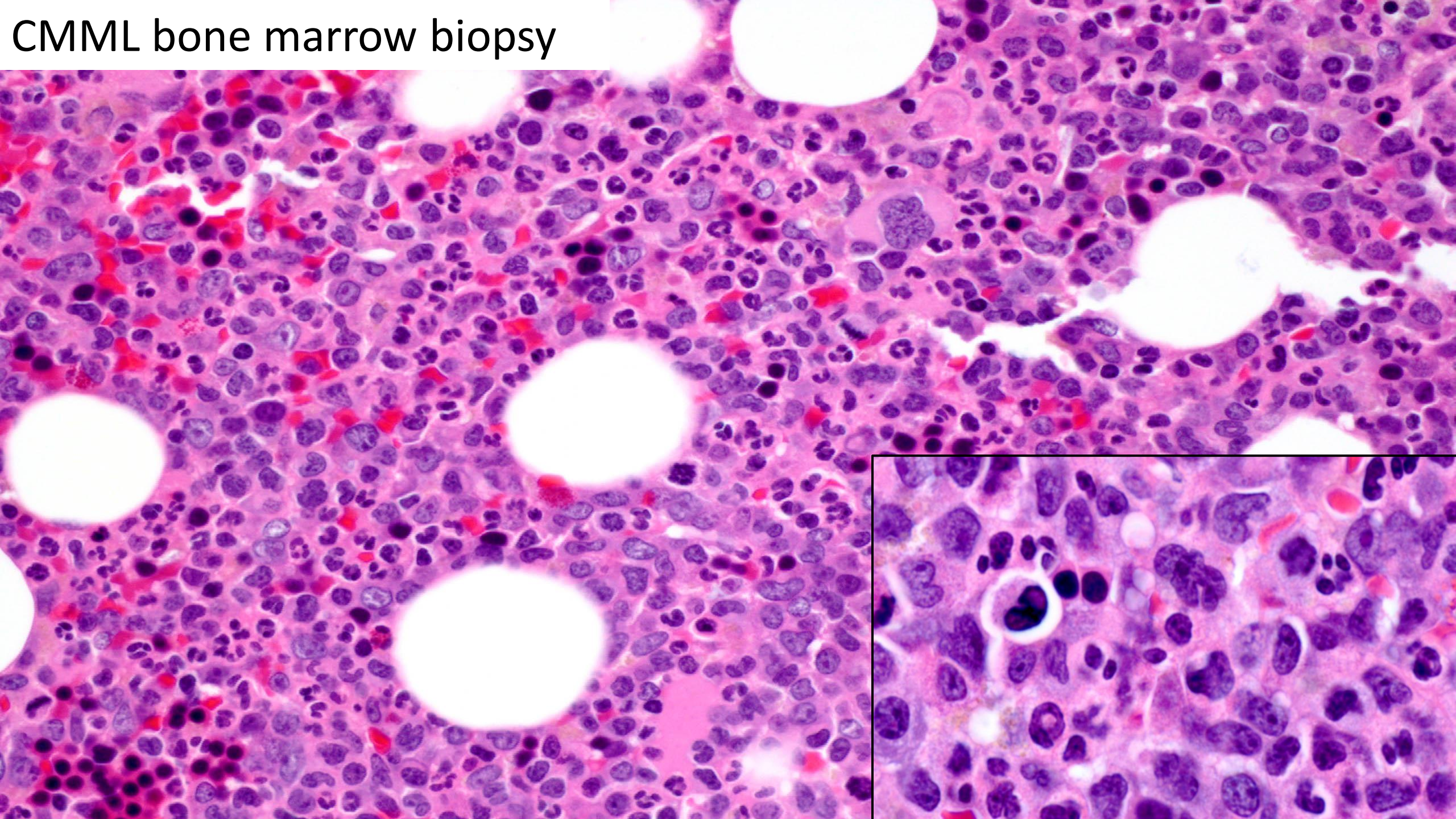




CMML bone marrow aspirate smear



CMML bone marrow biopsy

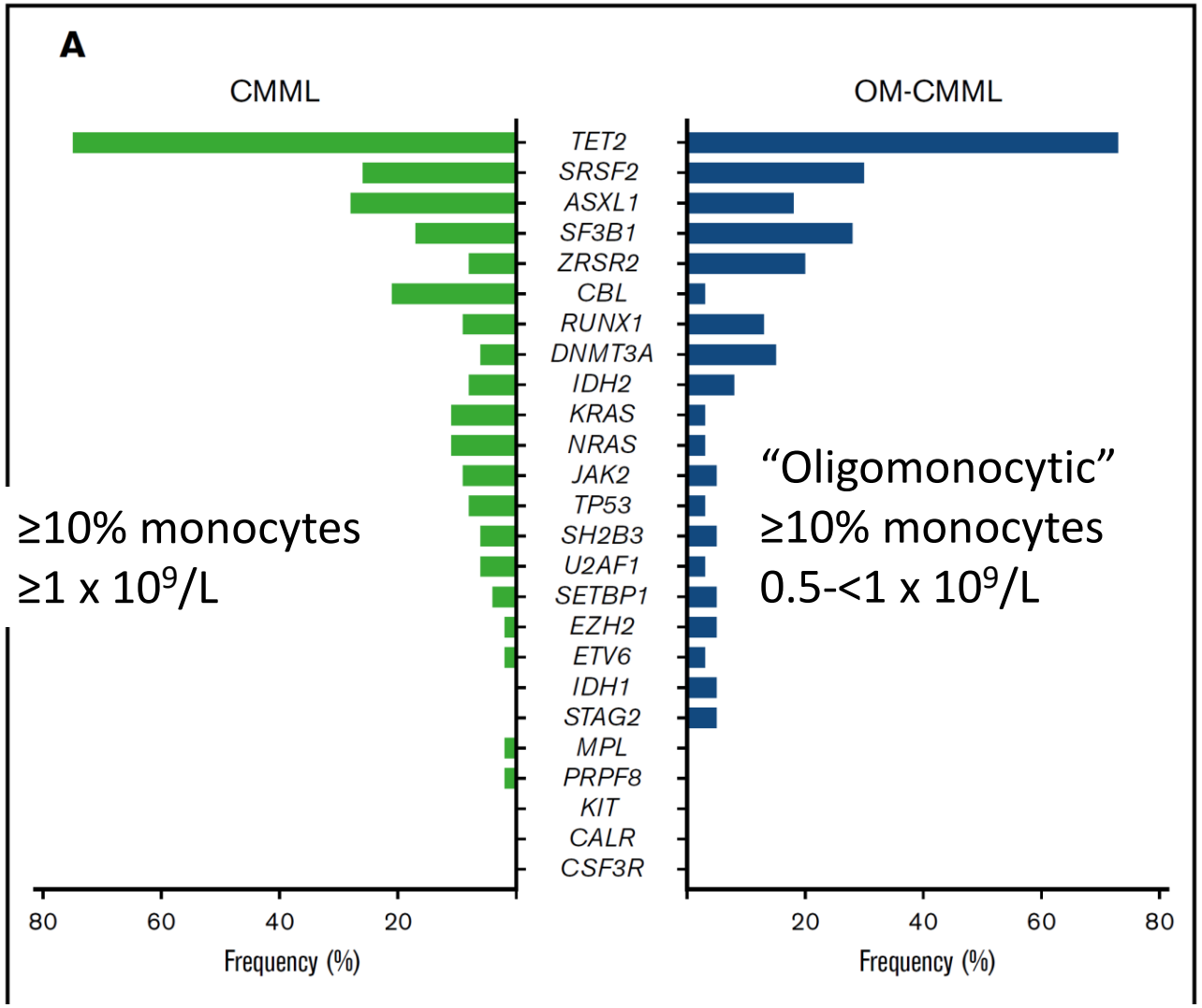


Chronic myelomonocytic leukemia (CMML)

Features	WHO 5th ed	ICC
Cytosis	Persistent monocytes ≥0.5 x 10^9/L and ≥10% of WBC	
Cytopenia	None required	At least 1 cytopenia
Blasts	CMML-1: <10% BM and <5% PB CMML-2: 10-19% BM or 5-19% PB or Auer rods	
Morphology	None specified	BM hypercellularity due to a myeloid proliferation often with increased monocytes
Cases with monocytes ≥1 x 10^9/L	At least one of the following: 1. Dysplasia 2. Abnormal monocyte partitioning* 3. Clonal genetic abnormality	At least one of the following: 1. Dysplasia or increased blasts 2. Abnormal monocyte immunophenotype 3. Clonal genetic abnormality (VAF ≥10%)
Cases with monocytes 0.5-<1 x 10^9/L	Clonal genetic abnormality and dysplasia	Clonal genetic abnormality (VAF ≥10%)
Exclusions	CML, other MPN, MLN-TKF	
Subtyping	Dysplastic (WBC <13 x 10^9/L) and Proliferative (WBC ≥13 x 10^9/L) subtypes	

*>94% CD14 pos/CD16 neg “classical” MO1 monocytes

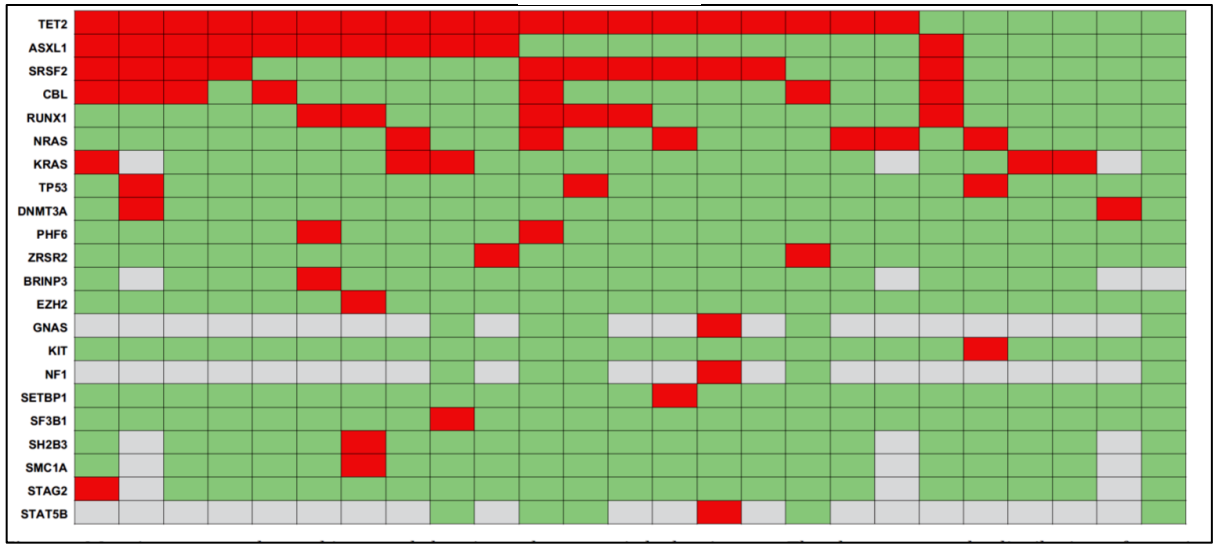
Expanding CMML to include “oligomonocytic” cases



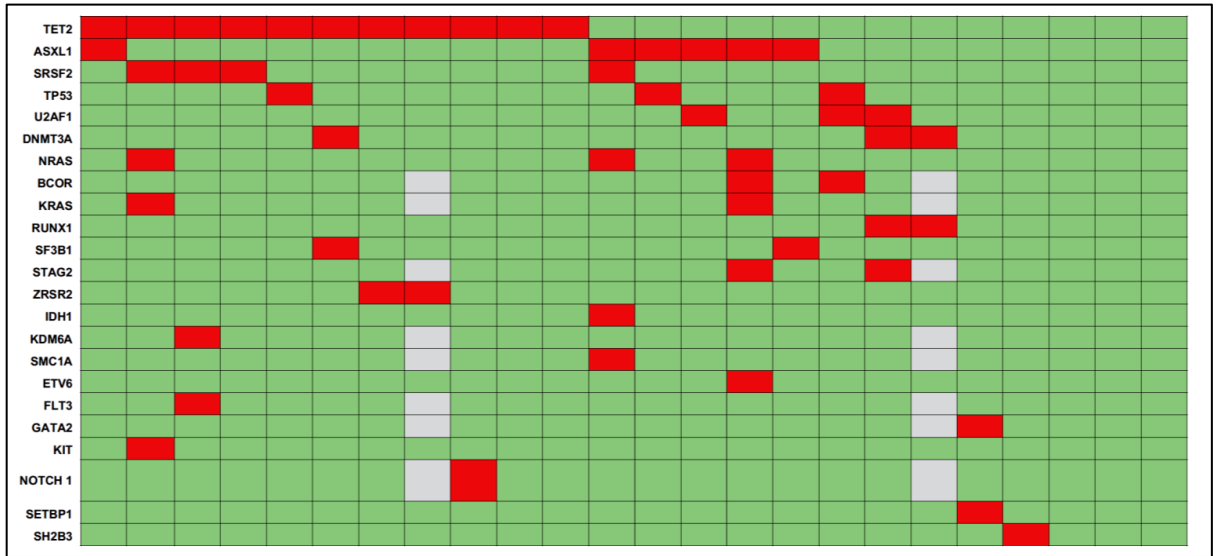
≥10% monocytes
≥1 x 10^9/L

“Oligomonocytic”
≥10% monocytes
0.5-<1 x 10^9/L

CMML



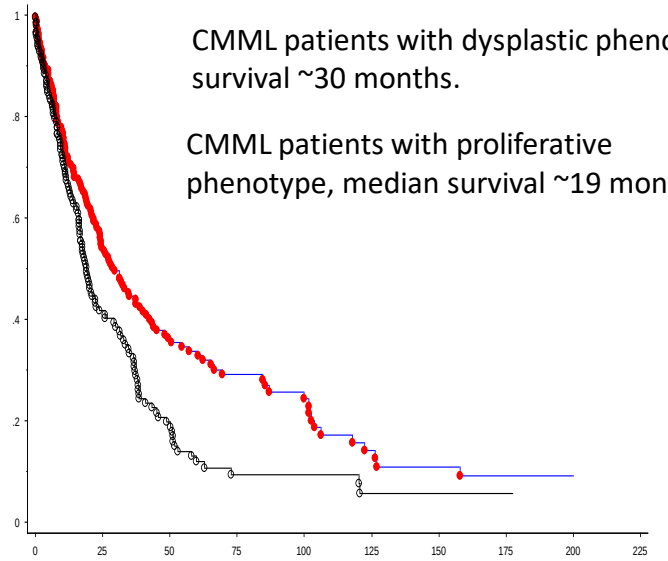
OM-CMML



Calvo X Blood Adv. 2020;4:5285, Geyer JT Mod Pathol 2017;30:1213

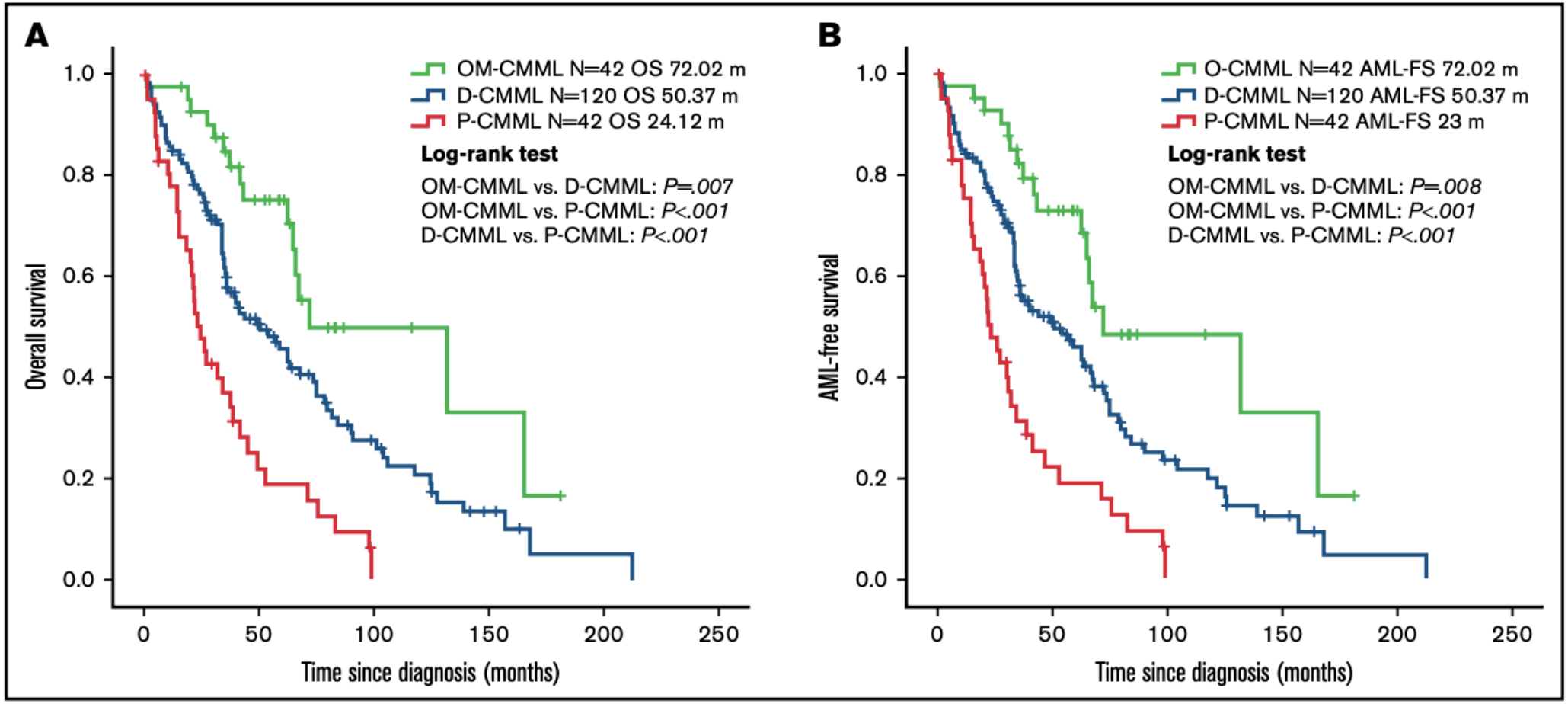
CMML subgroups

- Stratification based on white blood cell count
  - Proliferative type: WBC count ≥13 x 10^9/L
  - Dysplastic type: WBC count <13 x 10^9/L
  - Differences in mutation profile and prognosis
    - RAS pathway mutations more common in proliferative
- Stratification based on blast + promonocyte %
  - ~~CMML-0: <5% BM blasts, <2% PB blasts~~
  - CMML-1: 0-9% BM blasts and 0-4% PB blasts
  - CMML-2: 10-19% BM blasts or 5-19% PB blasts (or any Auer rods)



Schuler E et al. Leuk Res 2014;38:1413, Cervera N et al. Am J Hematol 2014;89:604, Ricci C et al. Clin Cancer Res 2010;16:2246

Is oligomonocytic CMML an early stage of CMML?



Calvo X Blood Adv 2022;6:3921

CMML: Genetic features

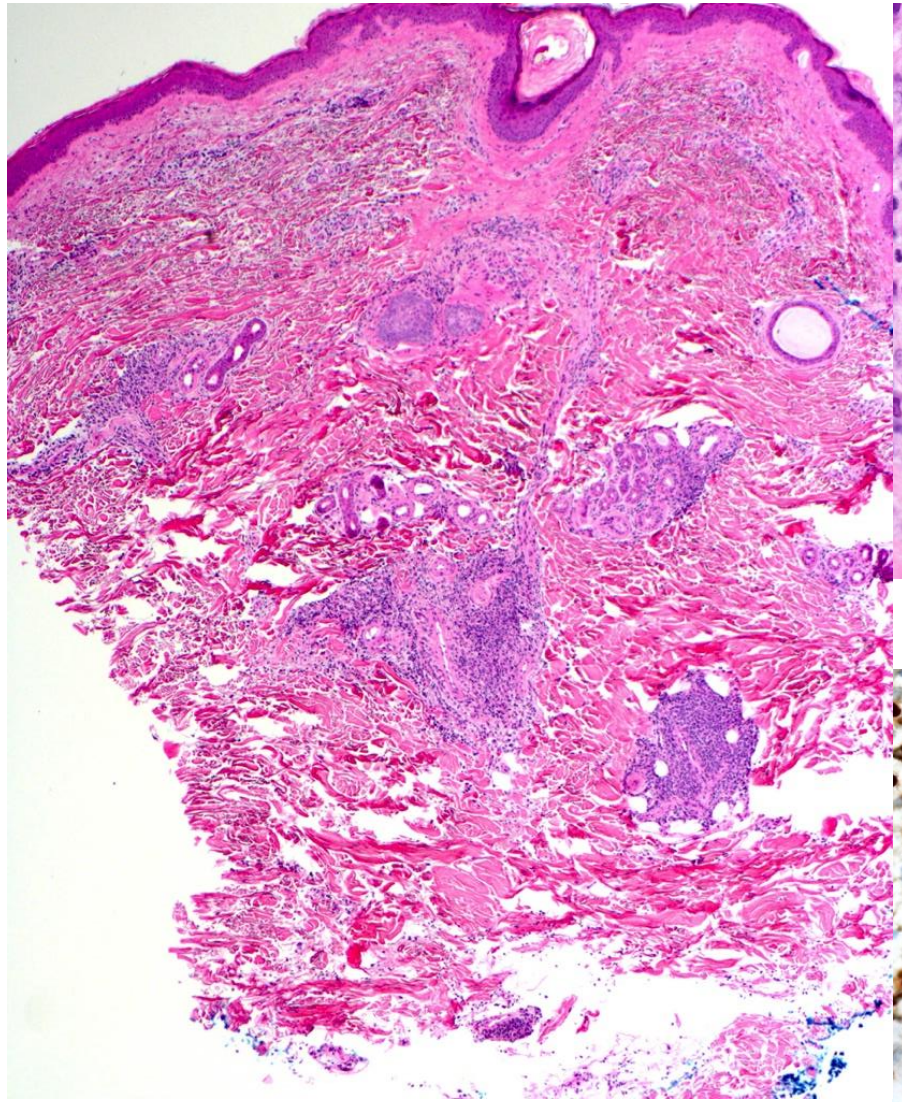
- 60-80% have normal karyotype
  - Must exclude t(5;12)(*PDGFRB* fusion) in cases with eosinophilia
- Distinctive (but not specific) mutation profile
  - *TET2*, *SRSF2*, or *ASXL1* mutated in 80-90% of cases
  - *RUNX1, CBL, KRAS/NRAS,* and other mutations also occur
  - Mutations support the diagnosis, but in the absence of CMML morphology are classified as “clonal monocytosis of undetermined significance” in ICC
- *NPM1* mutation or 11q23 (*KMT2A*) rearrangements may occur in monocytic proliferations mimicking CMML, and are now generally considered to be AML-defining in ICC/WHO5th ed

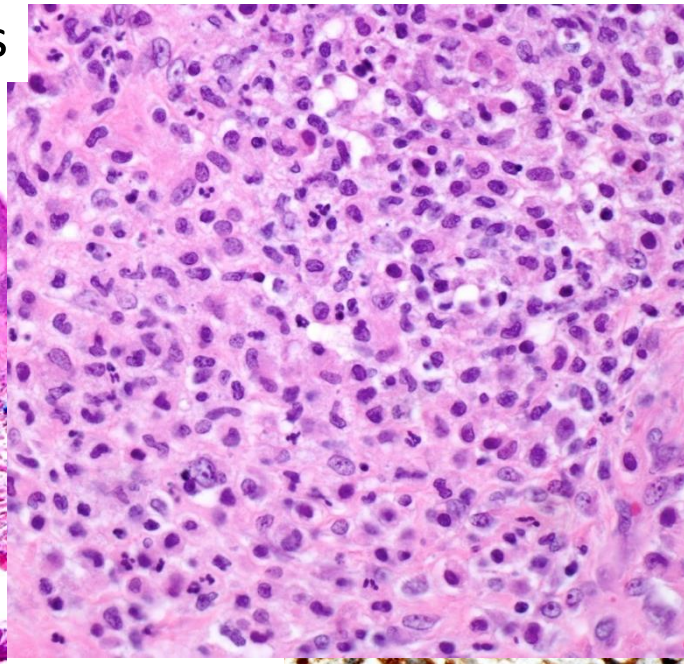
Itzykson R JCO 2013;31:2428. Courville E Mod Pathol 2013;26:751, Goasguen JE Haematologica 2009;94:994-7, Cargo Blood. 2019;133:1325-1334

Diagnostic issues with CMML

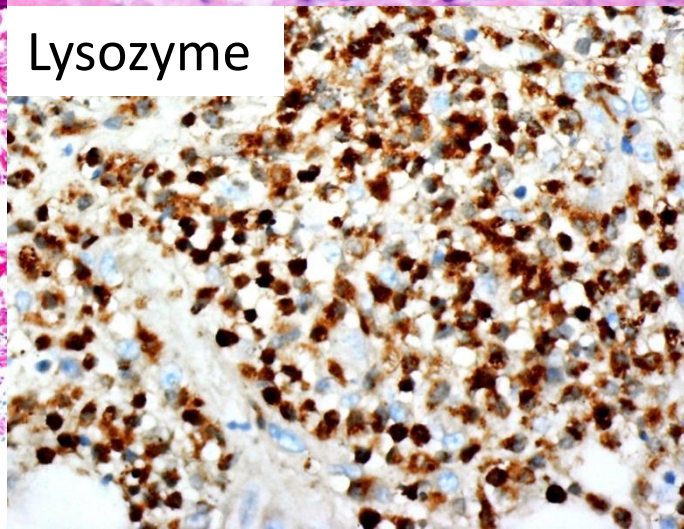
- Extramedullary manifestations
  - Mature monocytic infiltrates in skin, CSF, other sites
  - Plasmacytoid dendritic cell nodules
- Distinguishing blast equivalents (promonocytes) from atypical monocytes
  - CMML-1 versus CMML-2
  - CMML versus AML with monocytic features

Skin infiltration by CMML monocytes





Lysozyme



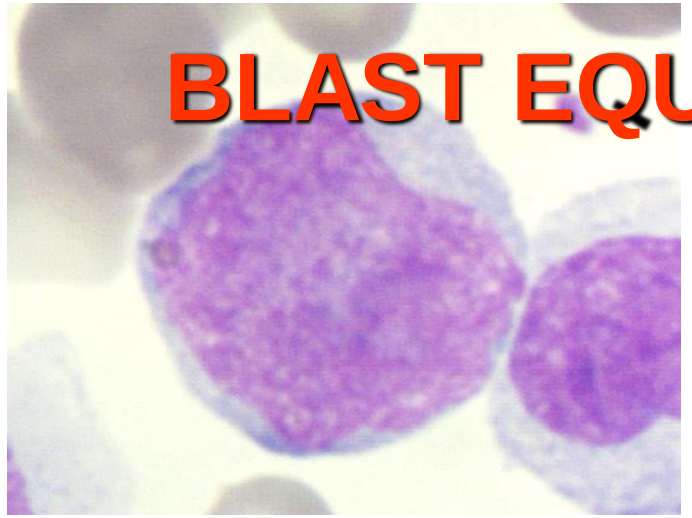
Monocytic cells

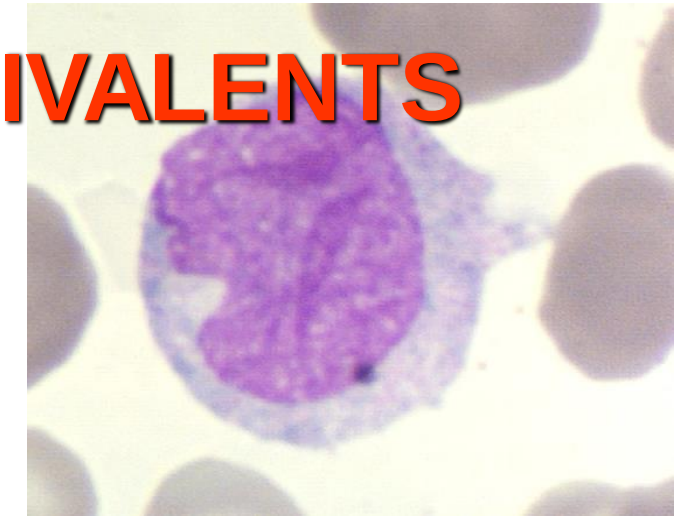
Monoblasts

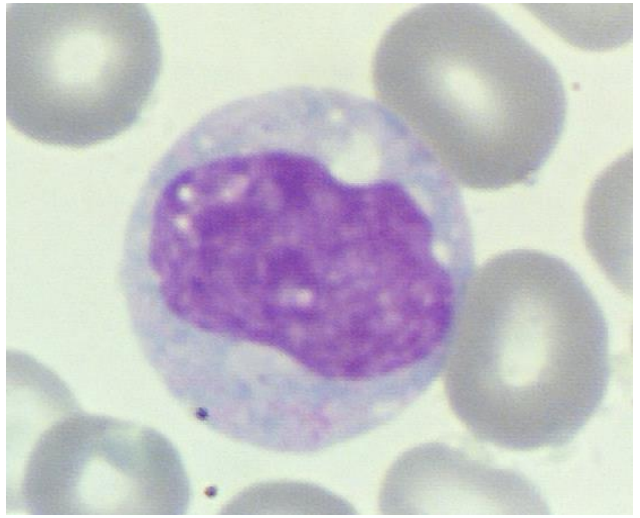
Promonocytes

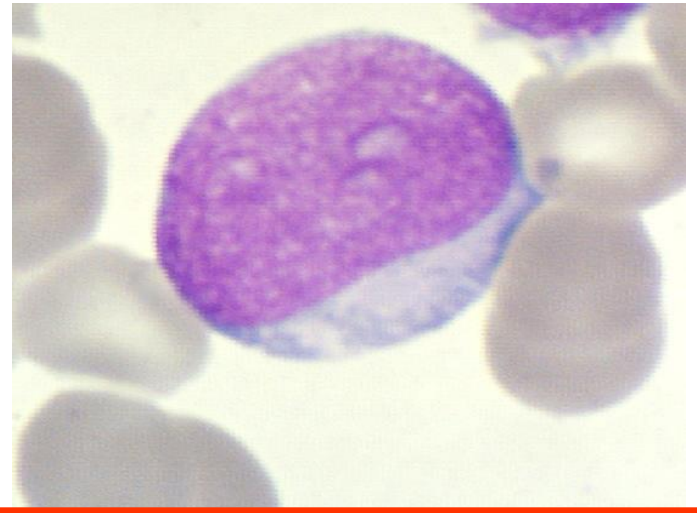
Monocytes

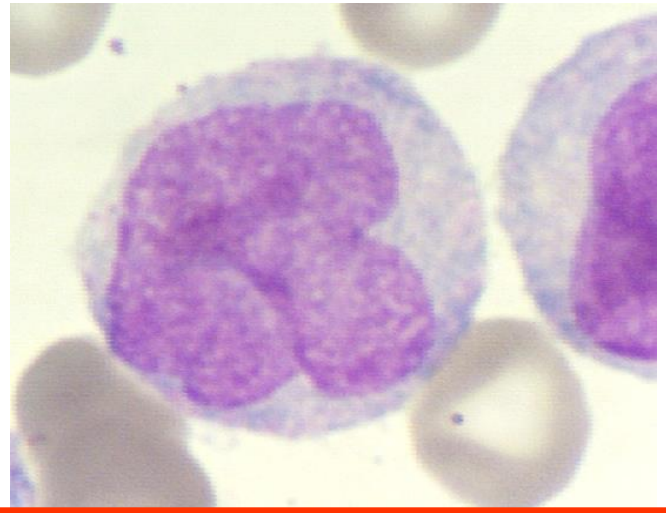
BLAST EQUIVALENTS

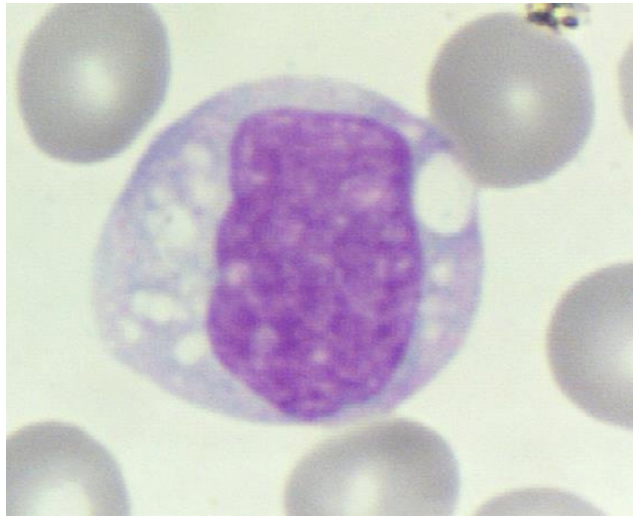




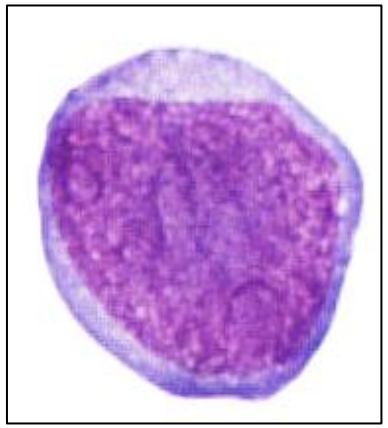


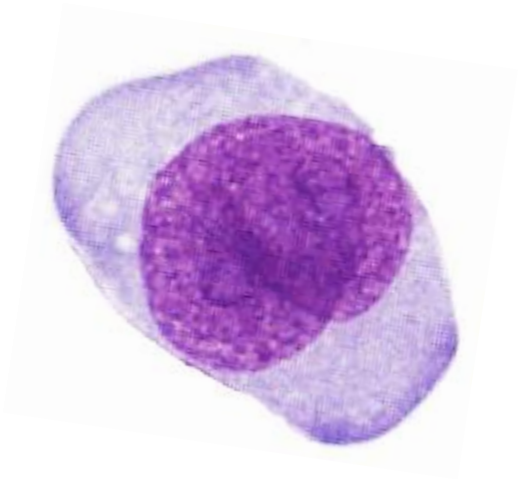




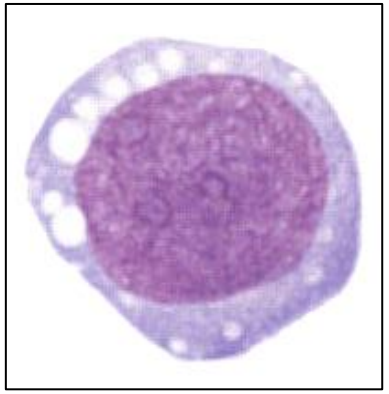


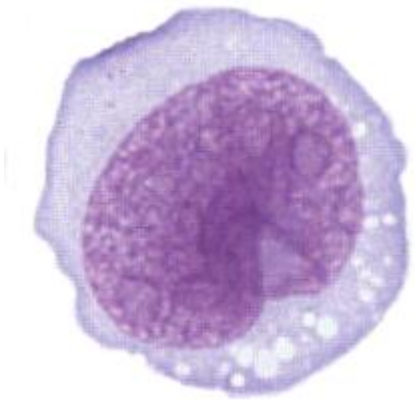
Blasts in CMML: Blasts and Promonocytes (blast equivalents)

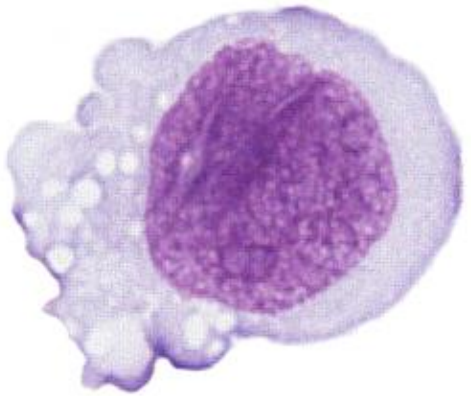




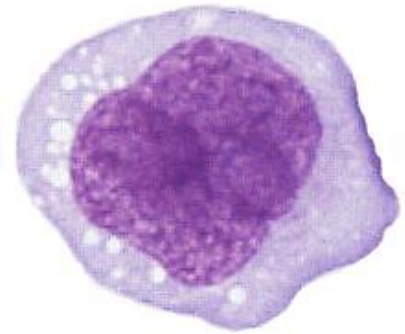
Monoblasts

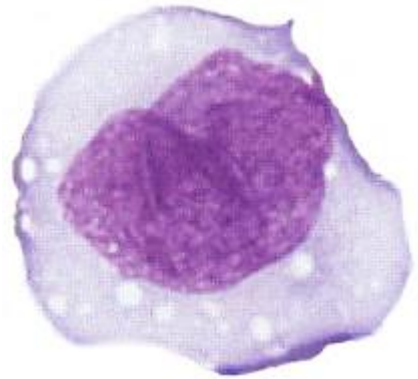




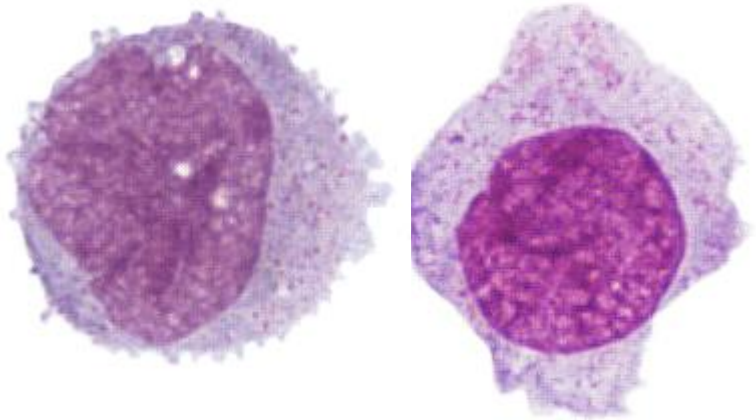


Promonocytes





Promonocytes with granules



Courtesy of Attilio Orazi, Texas Tech University

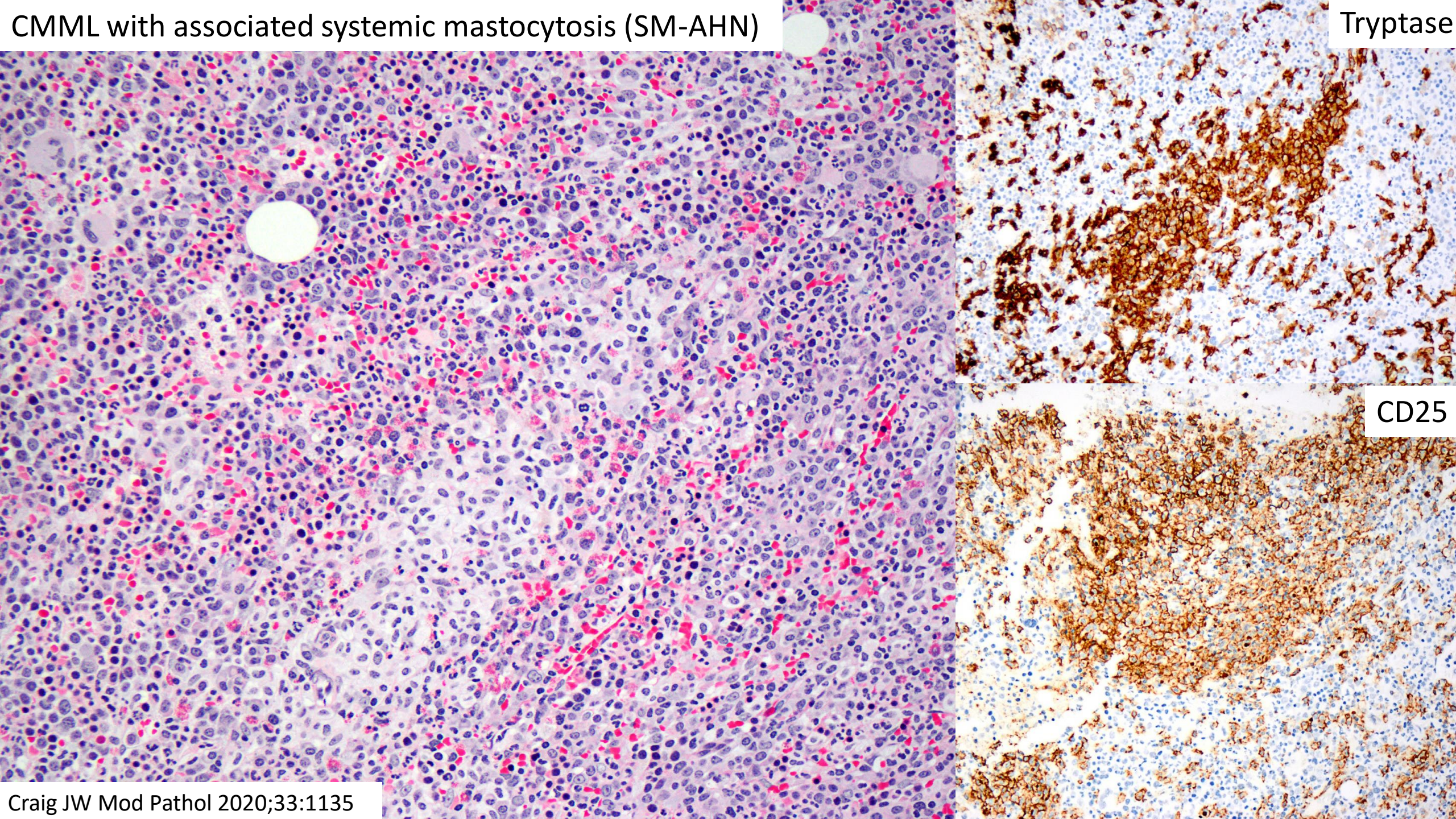
Goasguen J et al. *Haematologica* 2009

Other diagnostic issues with CMML

- Always check the monocyte count before diagnosing MDS!
  - New monocyte threshold of 0.5 x 10^9/L: but should document persistence on multiple measurements over time
  - Marrow monocytes often are NOT increased—definition is based on peripheral blood monocytes
  - Dysplasia in CMML can be subtle or even absent
- Keep an eye out for other myeloid cell proliferations that may accompany CMML in the bone marrow
  - Systemic mastocytosis (may be subtle—consider CD117/tryptase staining!)
    - Detection of a *KIT* mutation by NGS should prompt a re-look for mastocytosis
  - Mature plasmacytoid dendritic cell nodules (CD4+, CD56+, CD123-)

Craig JW Mod Pathol 2020;33:1135, Geyer JT Mod Pathol 2017;30:1213, Calvo X Blood Adv 2020;4:5285

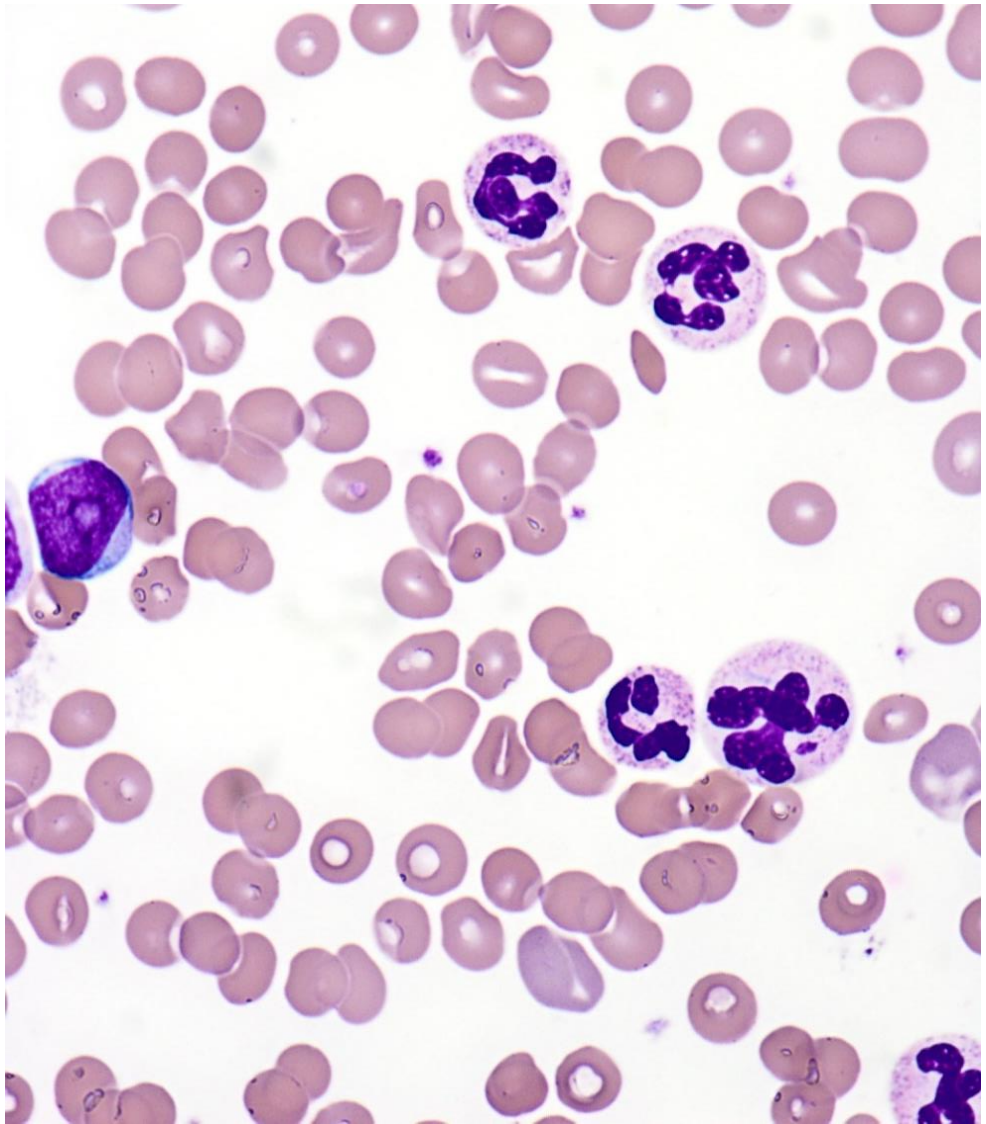
CMML with associated systemic mastocytosis (SM-AHN)



Craig JW Mod Pathol 2020;33:1135

Atypical CML ~~*BCR-ABL1* negative~~ (ICC)
MDS/MPN with neutrophilia (WHO 5th ed)

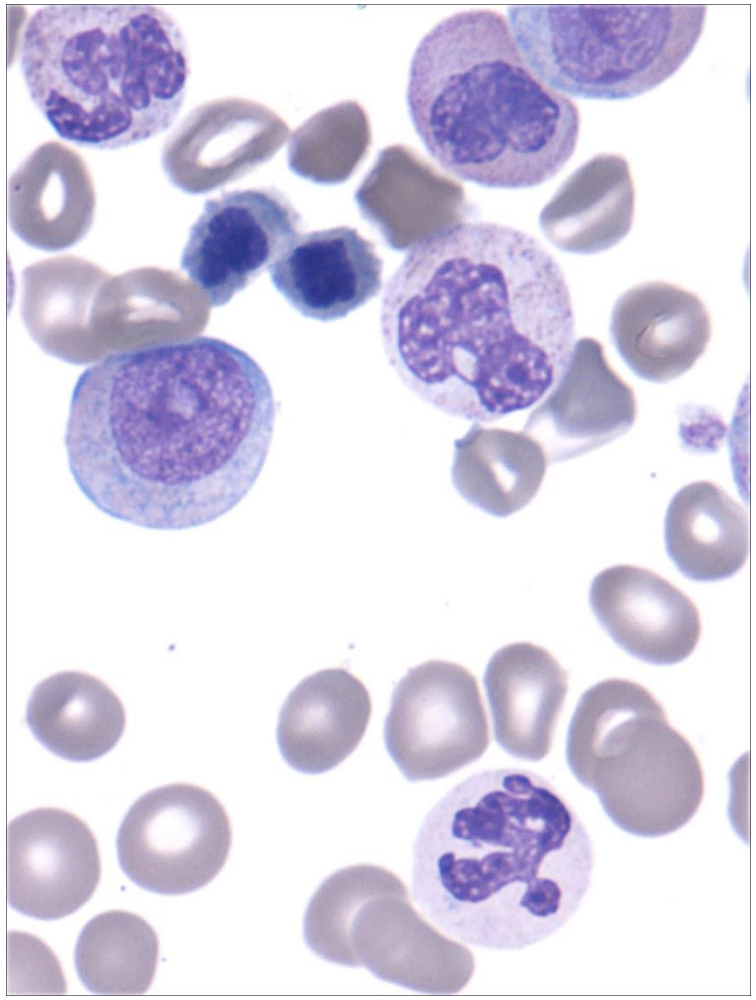
- MDS/MPN characterized by excess production of granulocytes
- Marked granulocytic dysplasia and left-shift in blood
- Can mimic CML in its presentation, but is a completely unrelated disease

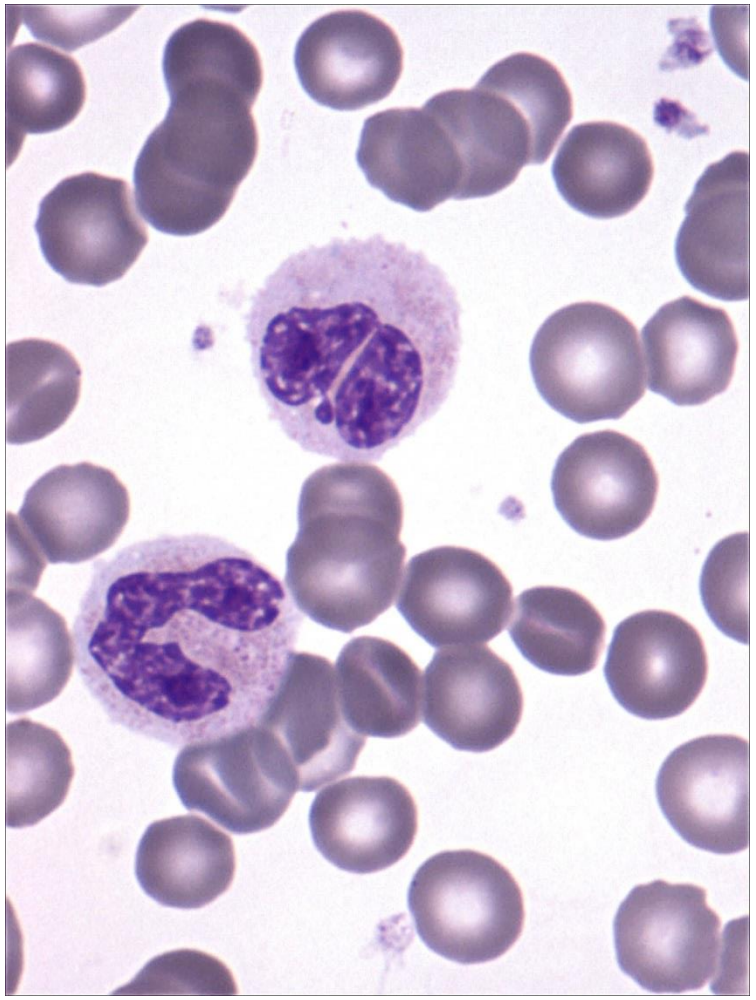


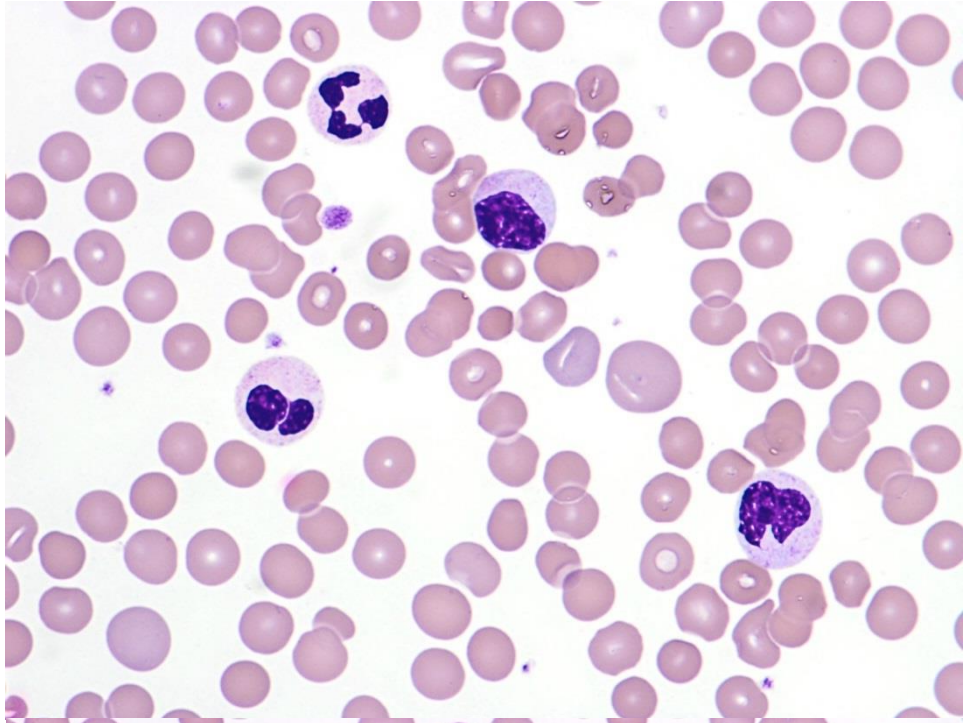
Atypical CML definition

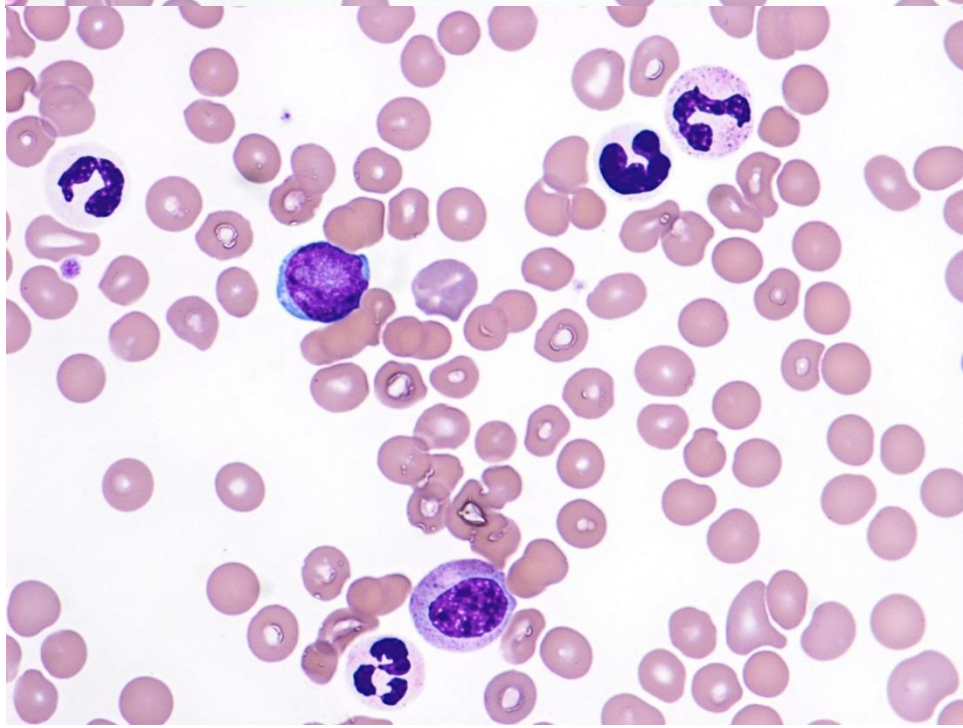
- Leukocytosis (WBC ≥13 x 10^9/L) with ≥10% immature granulocytic forms
- Dysgranulopoiesis in blood and marrow
- Exclusion of common mimics
  - CML
  - Chronic neutrophilic leukemia (CNL)
  - CMML
  - Genetically-defined eosinophilic neoplasms

Atypical CML peripheral blood

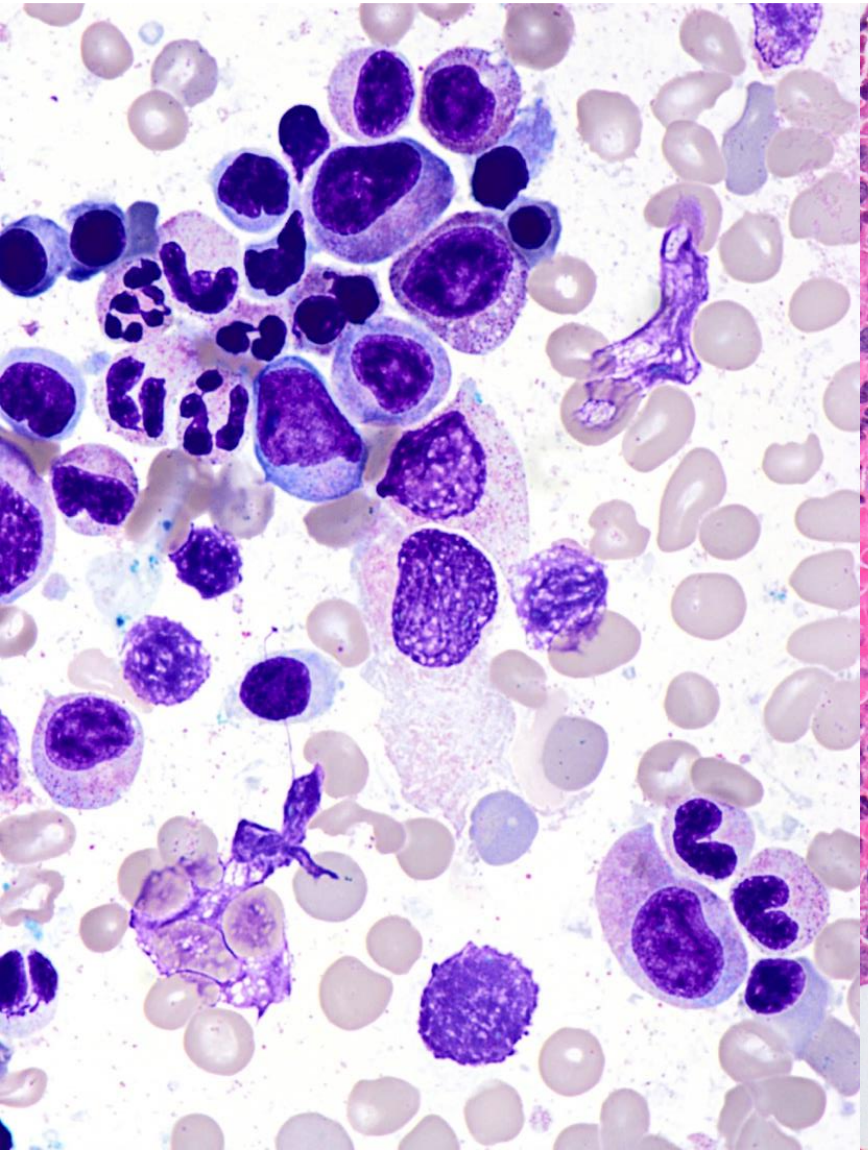


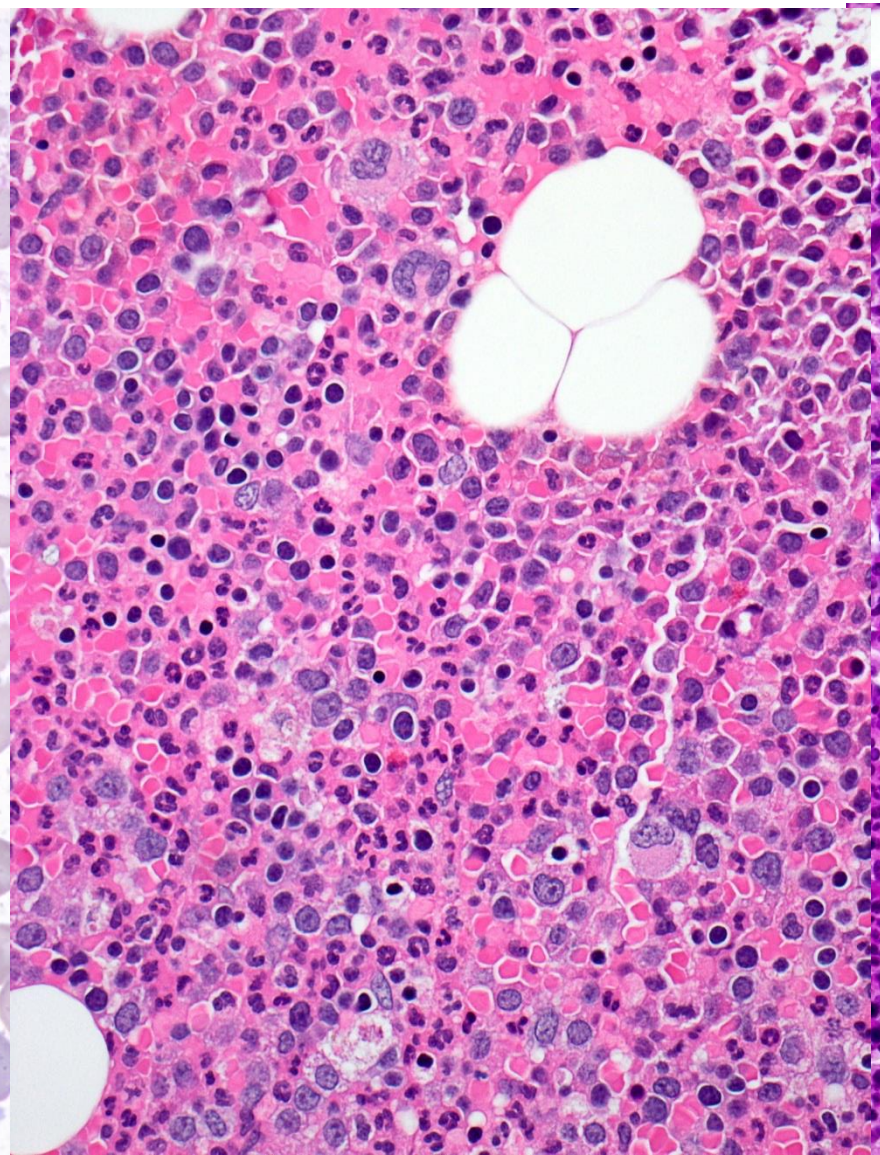


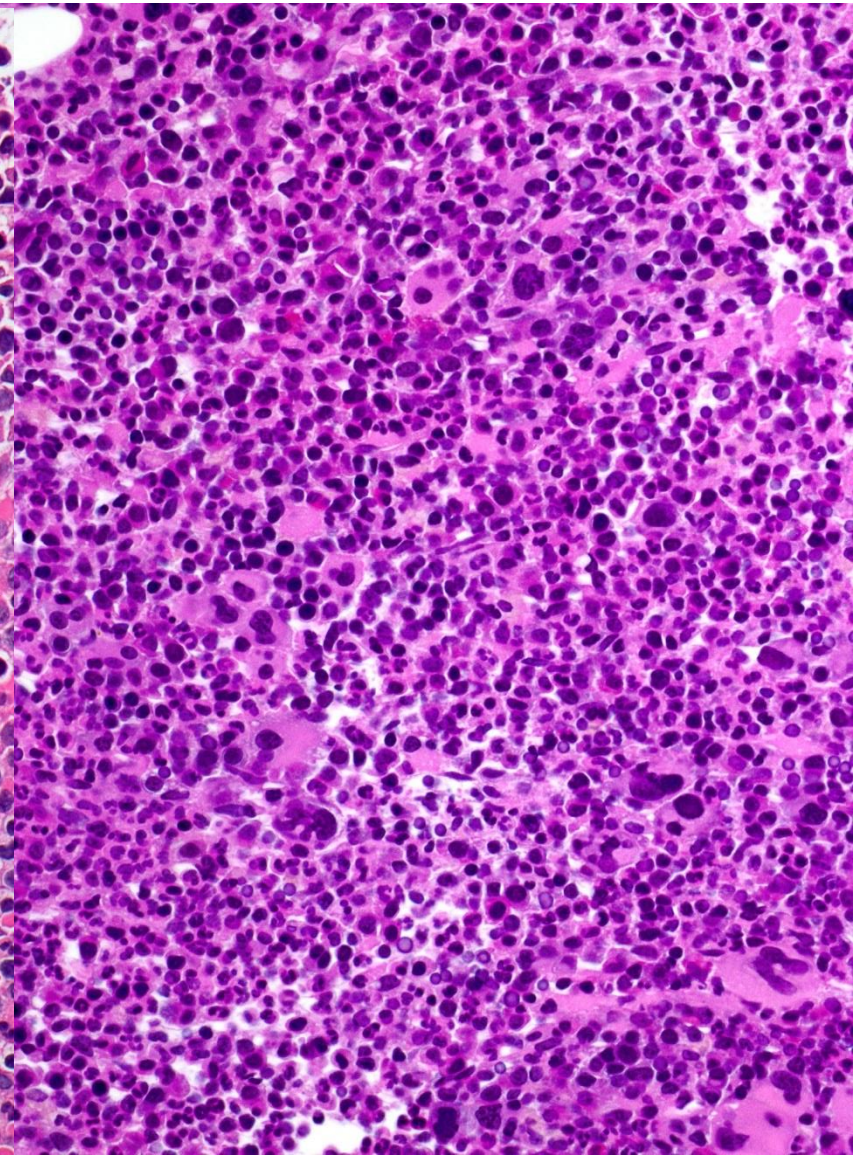




Atypical CML bone marrow





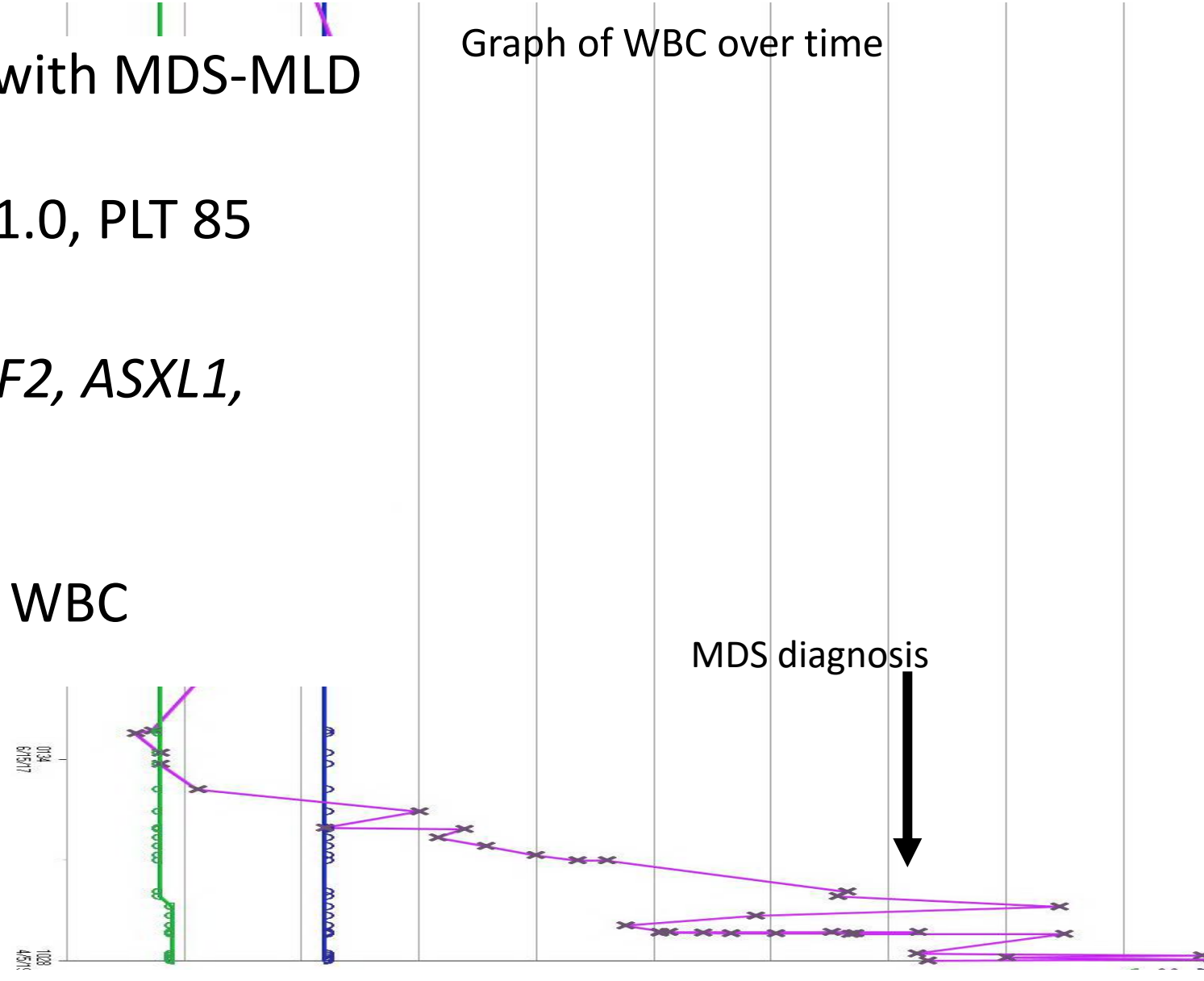


Atypical CML – MDS/MPN with neutrophilia

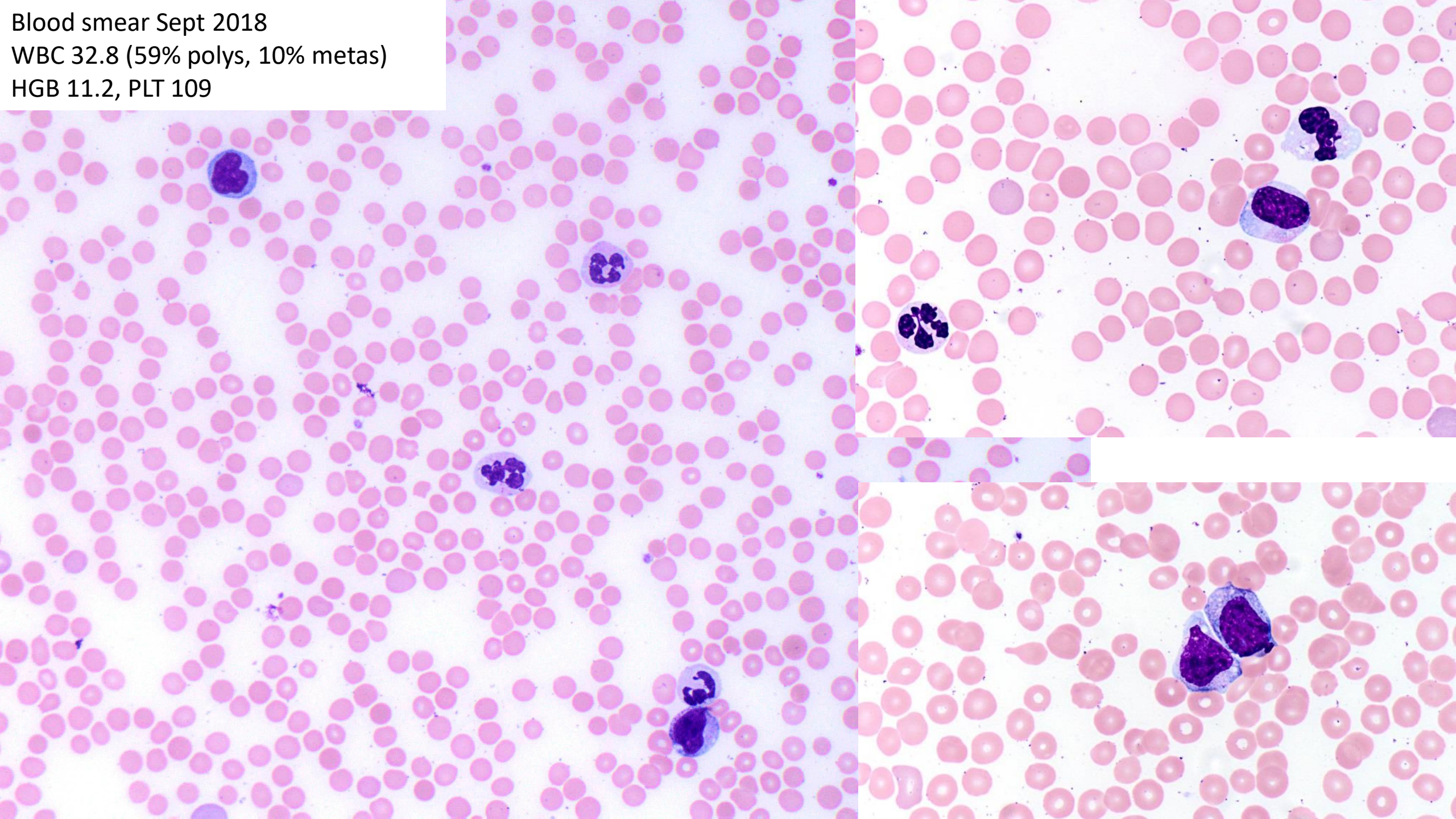
Features	WHO 5th ed	ICC
Cytosis	WBC ≥13 x 10^9/L Neutrophilia Promyelocytes, myelocytes and metamyelocytes ≥10% of leukocytes	
Cytopenia	No cytopenia required	At least 1 cytopenia
Blasts	<20% in PB and BM	
Morphology	Hypercellular bone marrow with granulocytic predominance and granulocytic dysplasia	
Genetics	Usually *SETBP1* or *ETNK1*	Usually *SETBP1* and *ASXL1*
Exclusions	Monocytes <10% of WBC CML, other MPN, MLN-TKF Usually absence of *JAK2, MPL, CALR, CSF3R*	
Exclusions	MDS/MPN-*SF3B1*-T	Eosinophils <10% of WBC

Atypical CML-like progression of MDS

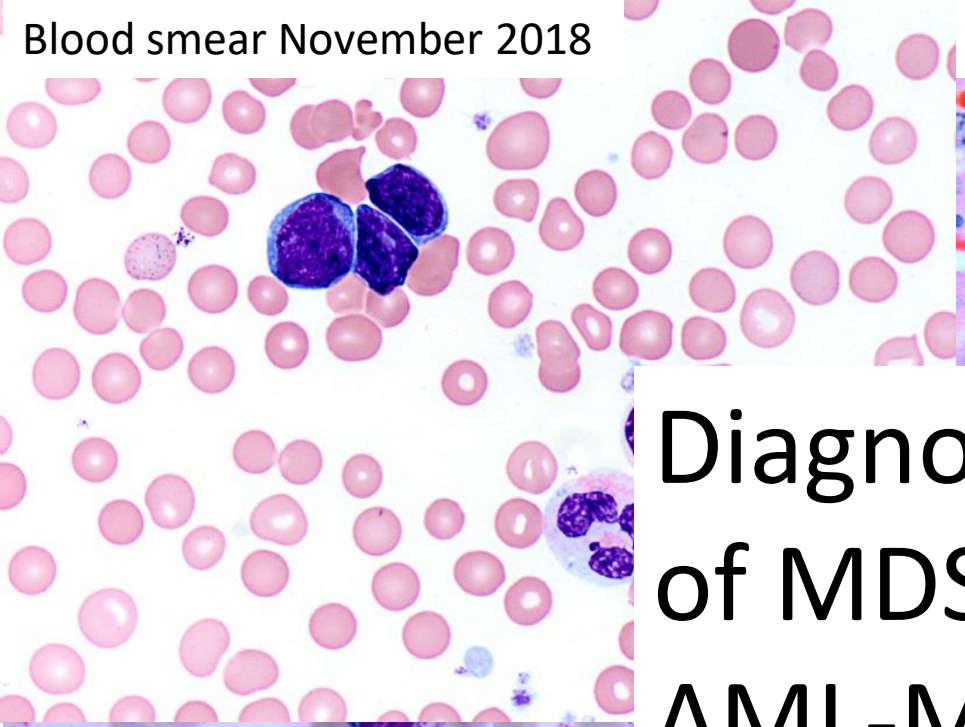
- 84 year-old woman diagnosed with MDS-MLD in July 2017
  - WBC 4.0 (54% polys), HGB 11.0, PLT 85
  - Normal karyotype
  - *NRAS*, 2 x *KRAS, RUNX1, SRSF2, ASXL1, STAG2, TET2* mutations
- Not treated
- Marked progressive increase in WBC



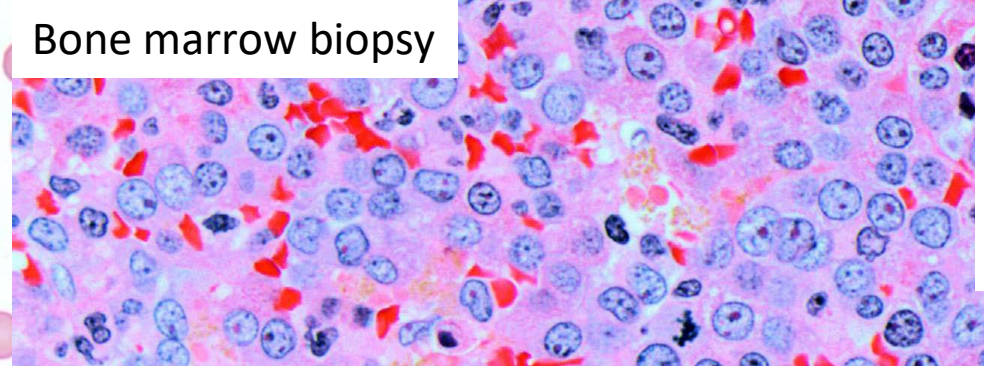
Blood smear Sept 2018
WBC 32.8 (59% polys, 10% metas)
HGB 11.2, PLT 109



Blood smear November 2018

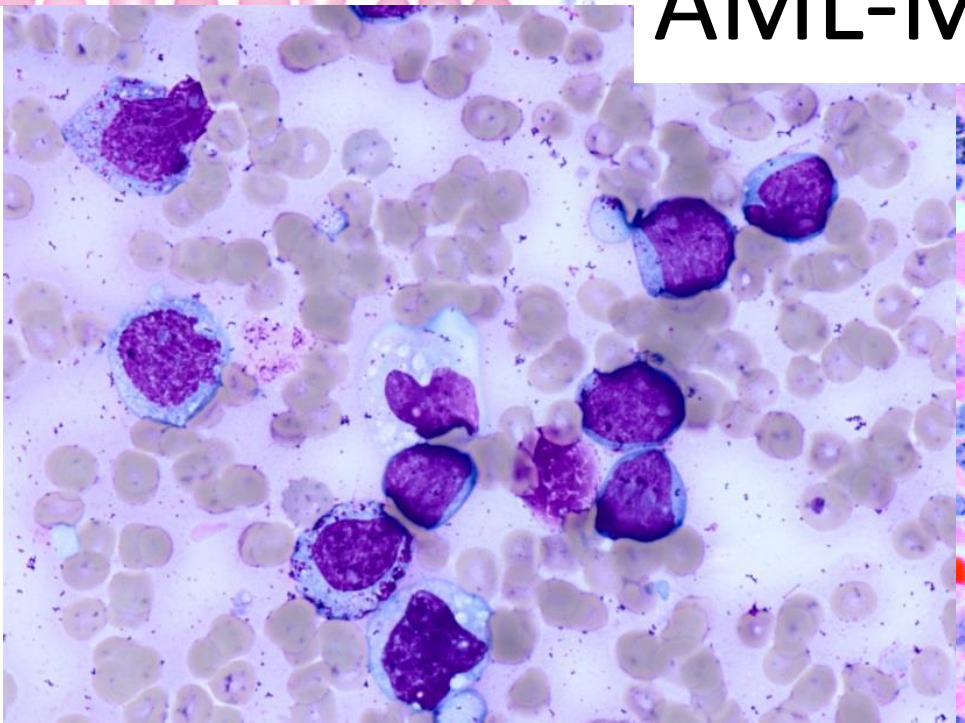


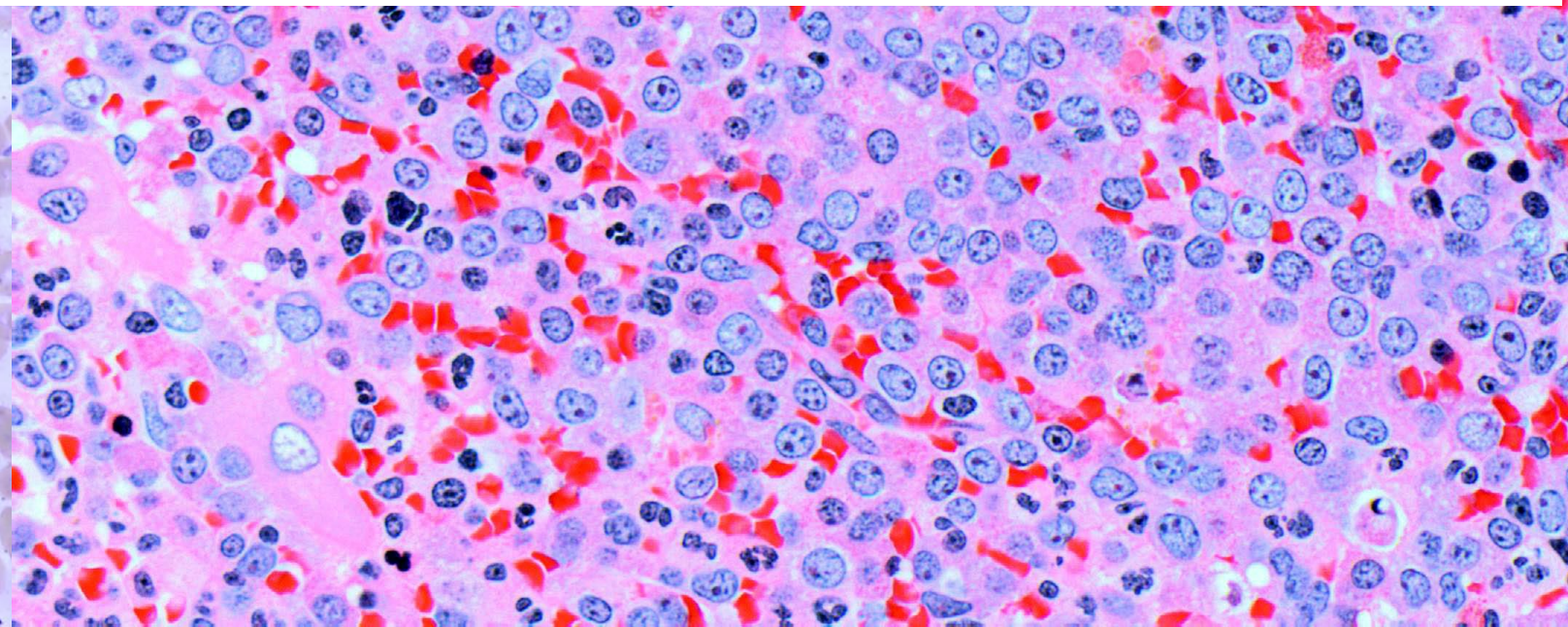
Bone marrow biopsy



WBC 48.3 (25% blast
HGB 10.4
PLT 154

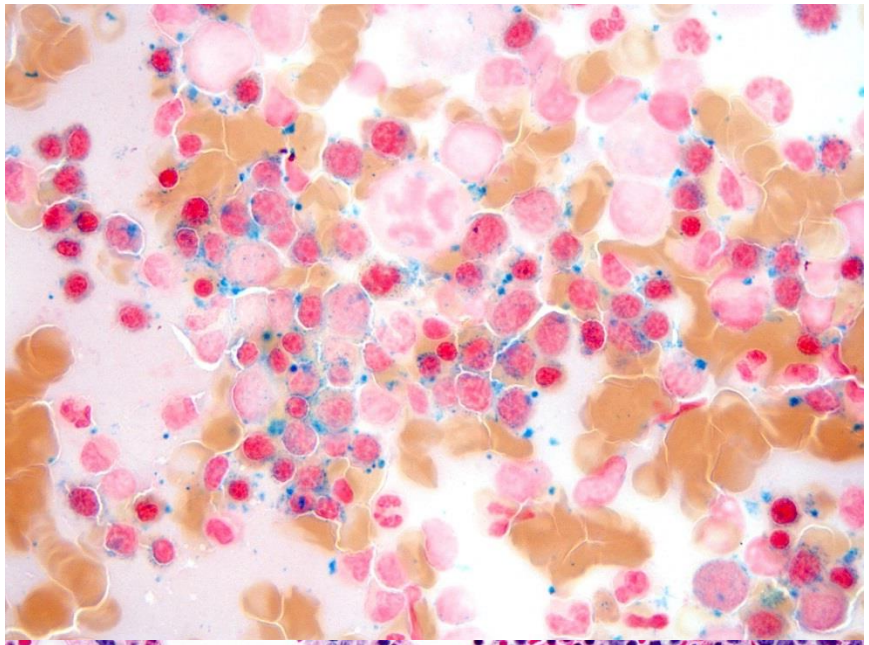
Diagnosis: atypical CML-like progression of MDS and subsequent progression to AML-MRC

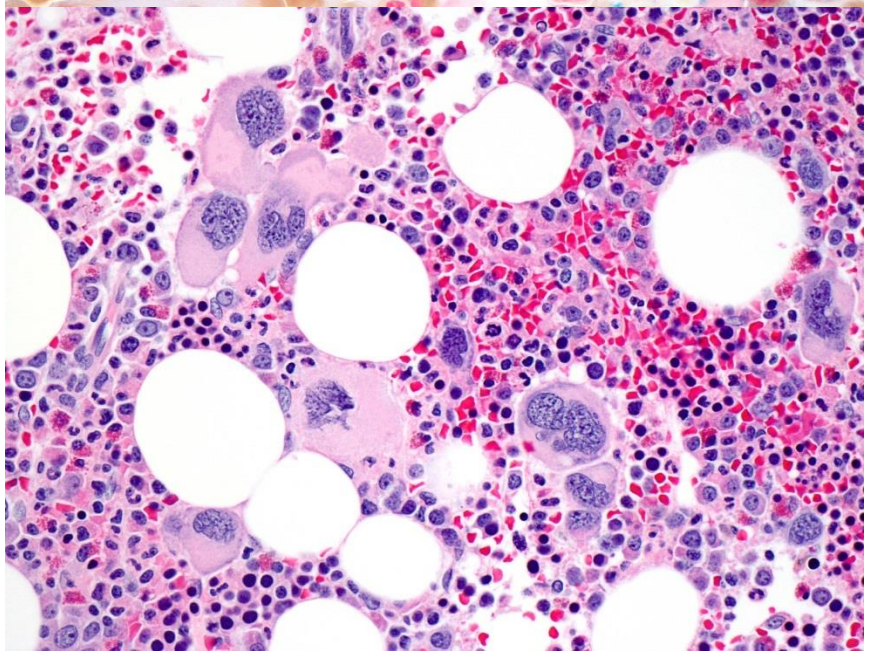




MDS/MPN with *SF3B1* mutation and thrombocytosis

- MDS/MPN characterized by overexuberant production of platelets and ineffective production of red cells
- Anemia due to the presence of ring sideroblasts
- Replaces most cases (85%) of revised 4th edition WHO "MDS/MPN with ring sideroblasts and thrombocytosis" or 2008 WHO "RARS-T"

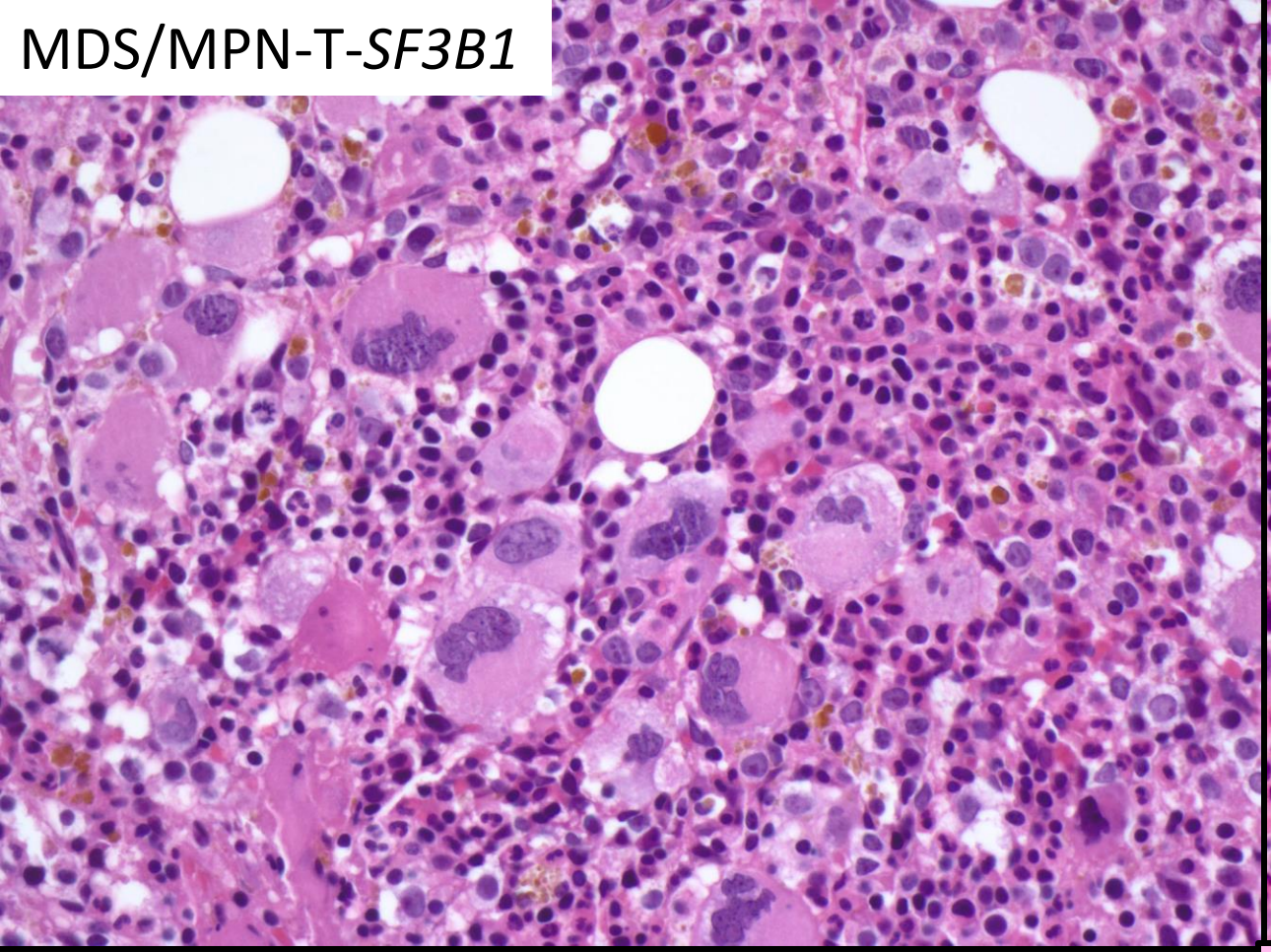


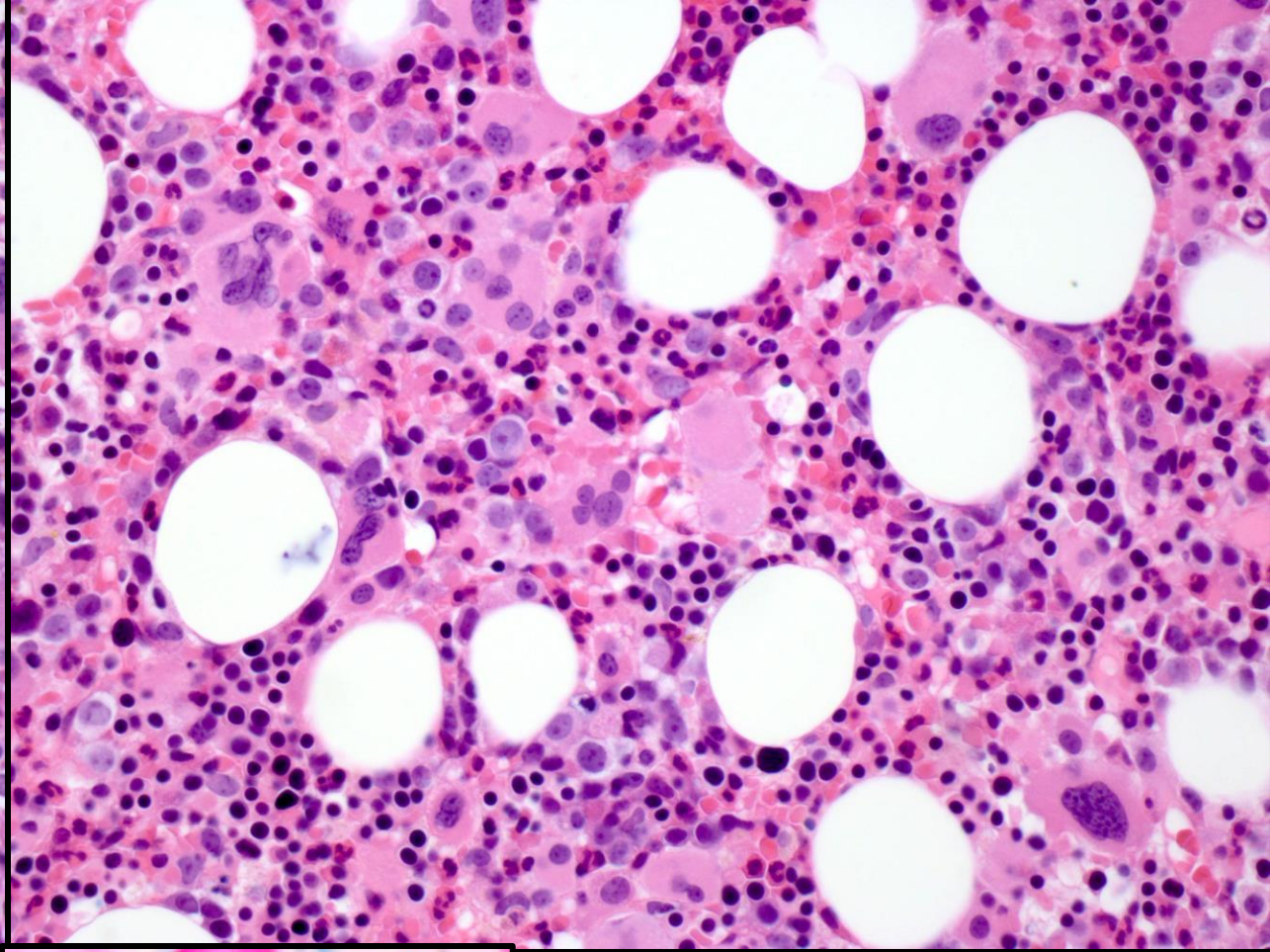


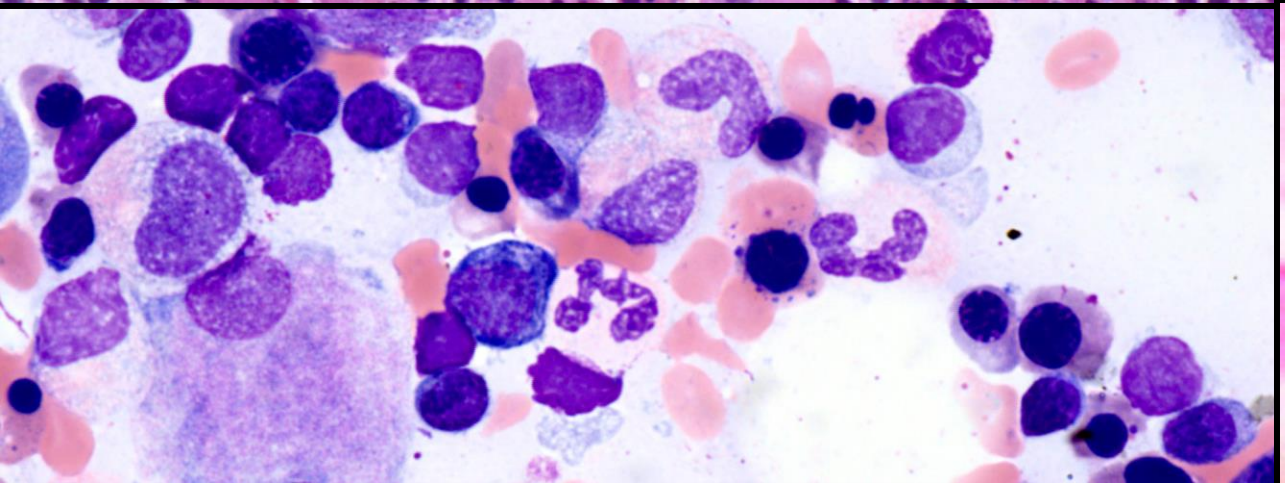
Morphologic and genetic features

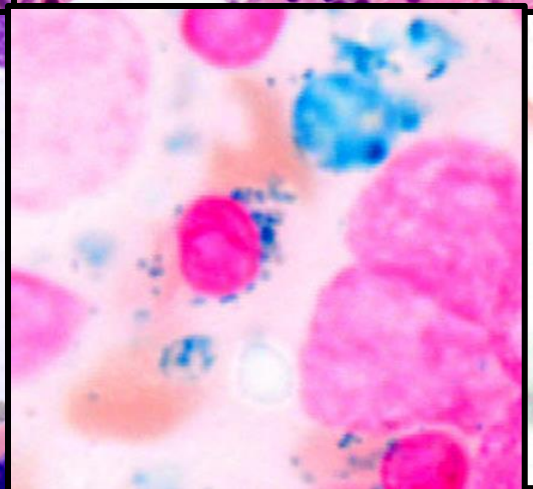
- Anemia with erythroid lineage dysplasia
  - May or may not have granulocytic or megakaryocytic dysplasia
- *SF3B1* mutation (cases with no *SF3B1* mutation and ≥15% ring sideroblasts classified separately as“MDS/MPN-RS-T-NOS” in ICC, but are included in WHO 5th edition entity)
- Thrombocytosis with platelet count ≥450 x 10^9/L
  - Megakaryocytes usually resemble those seen in the ‘pure’ MPN, but may also include some small, MDS-like forms
- *JAK2* co-mutation is common; *MPL* and *CALR* co-mutations occur infrequently

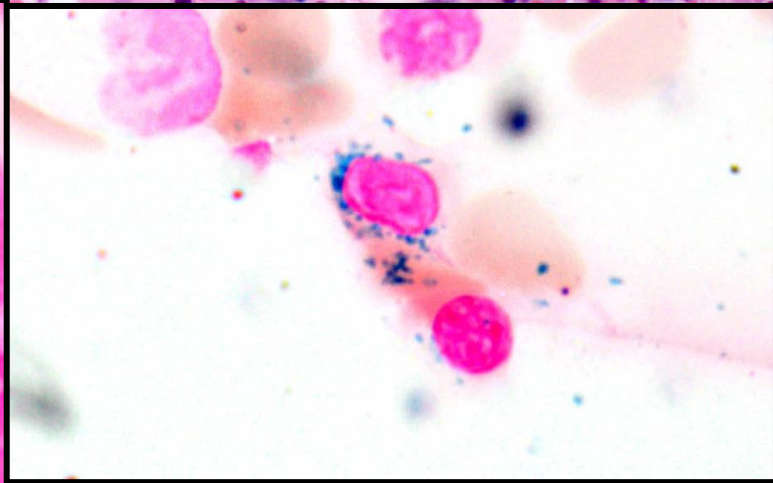
MDS/MPN-T-*SF3B1*











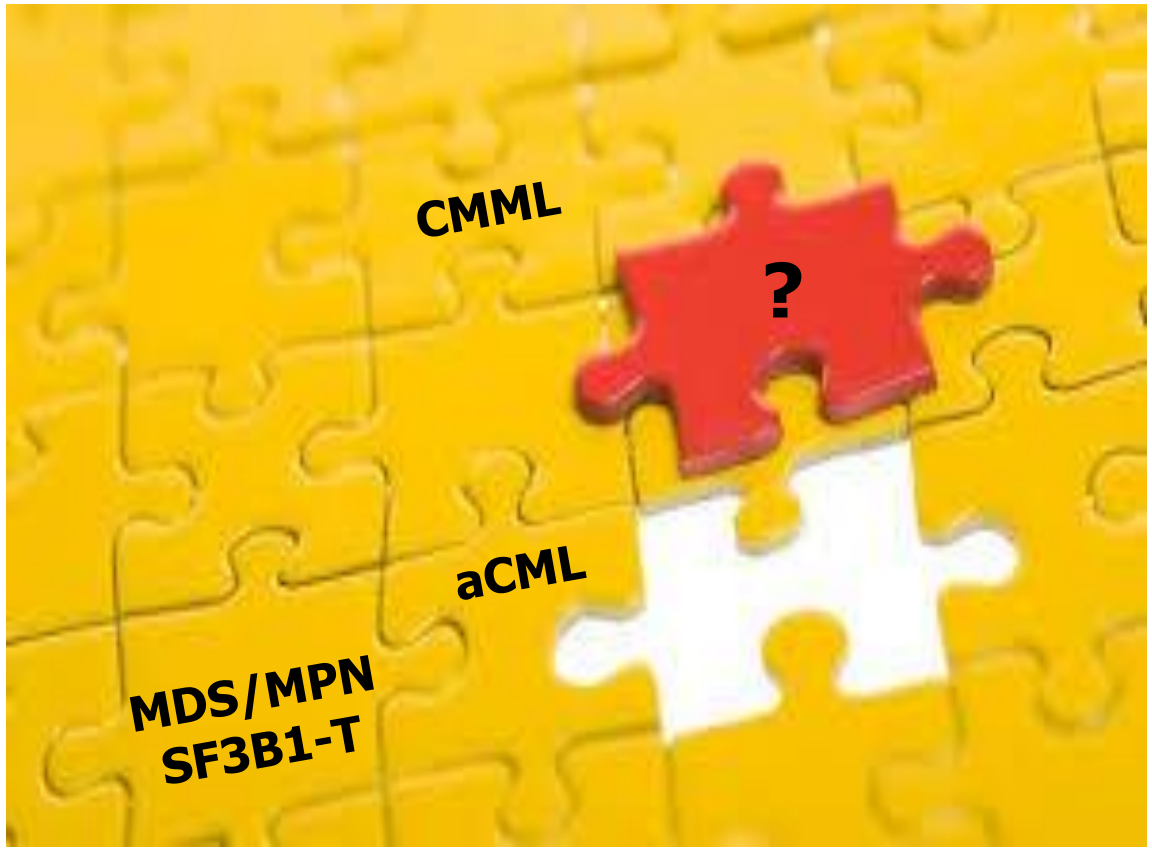
MDS/MPN with *SF3B1* mutation and thrombocytosis

Features	WHO 5th ed	ICC
Cytosis	Platelets ≥450 x 10^9/L	
Cytopenia	Anemia	
Blasts	Rare (<1%) in PB and <5% in BM	
Morphology	Dysplasia, especially dyserythropoiesis with ring sideroblasts	Dysplasia, especially dyserythropoiesis, usually with ring sideroblasts
Genetics	*SF3B1* mutation or ≥15% ring sideroblasts *JAK2, MPL*, or CALR mutation (or sustained 3 months thrombocytosis)	*SF3B1* mutation* (VAF ≥10%) Usually *JAK2*, *MPL*, or *CALR* mutation
Exclusions	CML, MLN-TKF, MDS del(5q), inv(3)/t(3;3)	
Exclusions	Therapy-relatedness Bi-allelic *TP53*	History of prior MDS, MPN, or other MDS/MPN

*Cases lacking SF3B1 mutation with ≥15% ring sideroblasts are classified separately as **MDS/MPN with ring sideroblasts and thrombocytosis** in ICC

MDS/MPN-NOS ~~unclassifiable~~

- MDS/MPN that cannot be placed into another category
- Often due to:
  - Thrombocytosis + anemia and erythroid dysplasia, without *SF3B*1 mutation
  - MDS/MPN with *SF3B1* and thrombocytosis, but with excess blasts
  - Neutrophilia lacking granulocytic dysplasia, but with dysplasia in another lineage



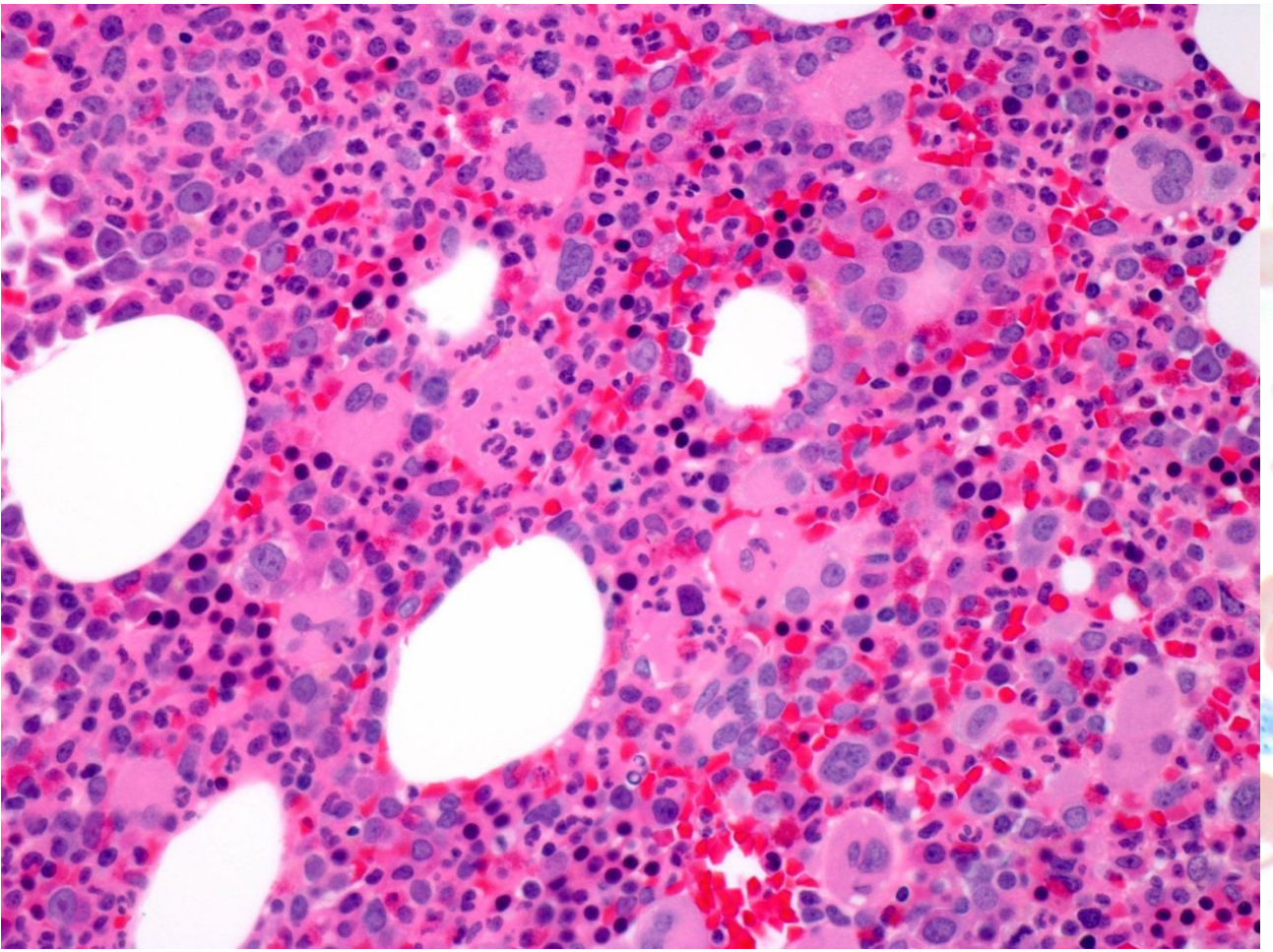
MDS/MPN, not otherwise specified

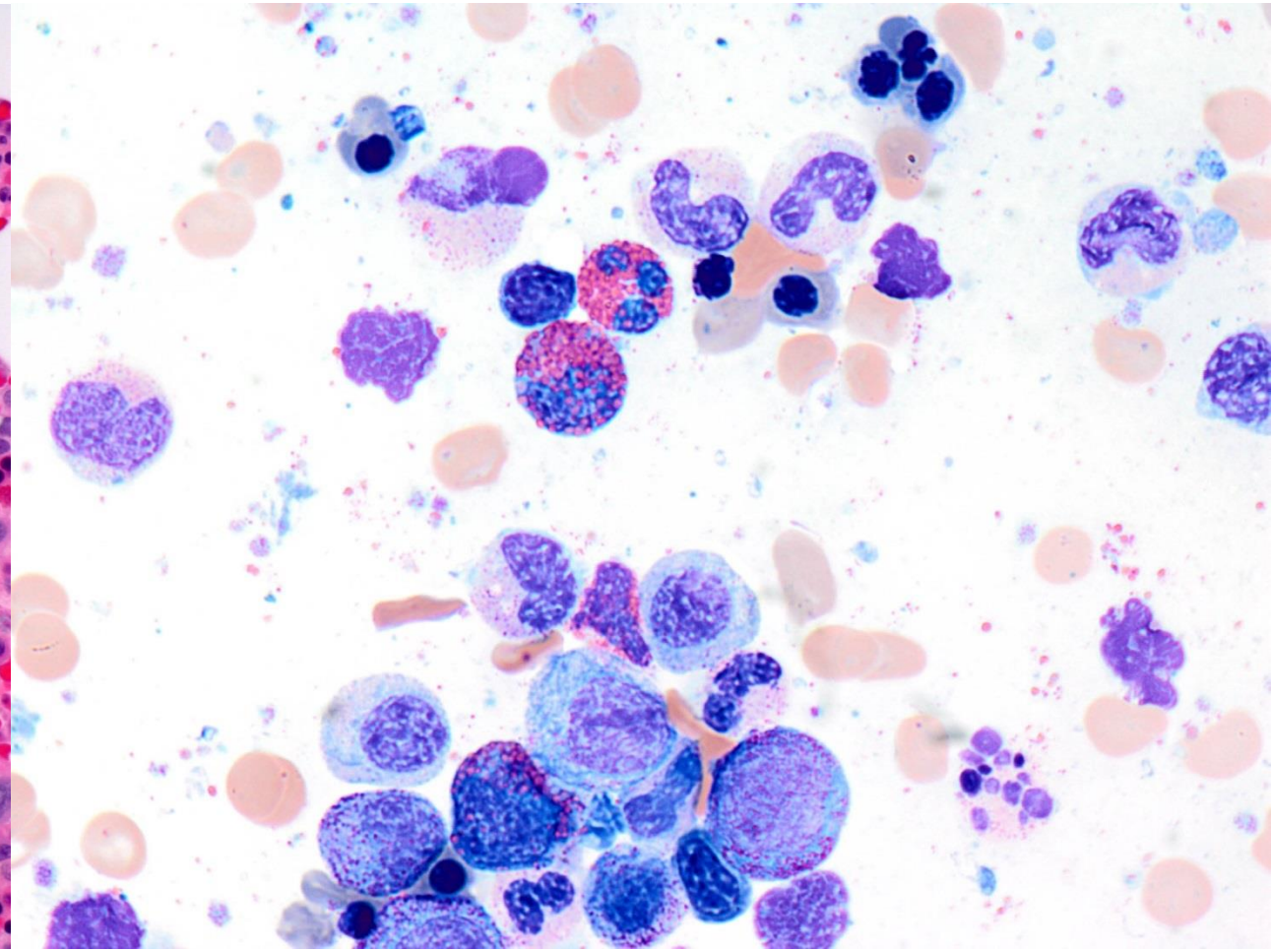
Features	WHO 5th ed	ICC
Cytosis	Platelets ≥450 x 10^9/L or WBC ≥13 x 10^9/L	
Cytopenia	At least one	
Blasts	<20% in PB and BM	
Morphology	Dysplasia and proliferative features	No specific morphologic features required
Genetics	Combination of mutations seen in MDS and MPN	Clonality or persistence of unexplained cytosis and cytopenia
Exclusions	CML, MLN-TKF, MDS del(5q), inv(3)/t(3;3), other MDS/MPN	
Exclusions	Therapy-relatedness	History of prior MPN Usually absence of *JAK2, MPL, CALR, CSF3R* Absence of hypereosinophilia

Typical example of MDS/MPN-NOS

WBC 10.7 x 10^9/L HGB 11.3 g/dL PLT 766 x 10^9/L
No ring sideroblasts, no monocytosis

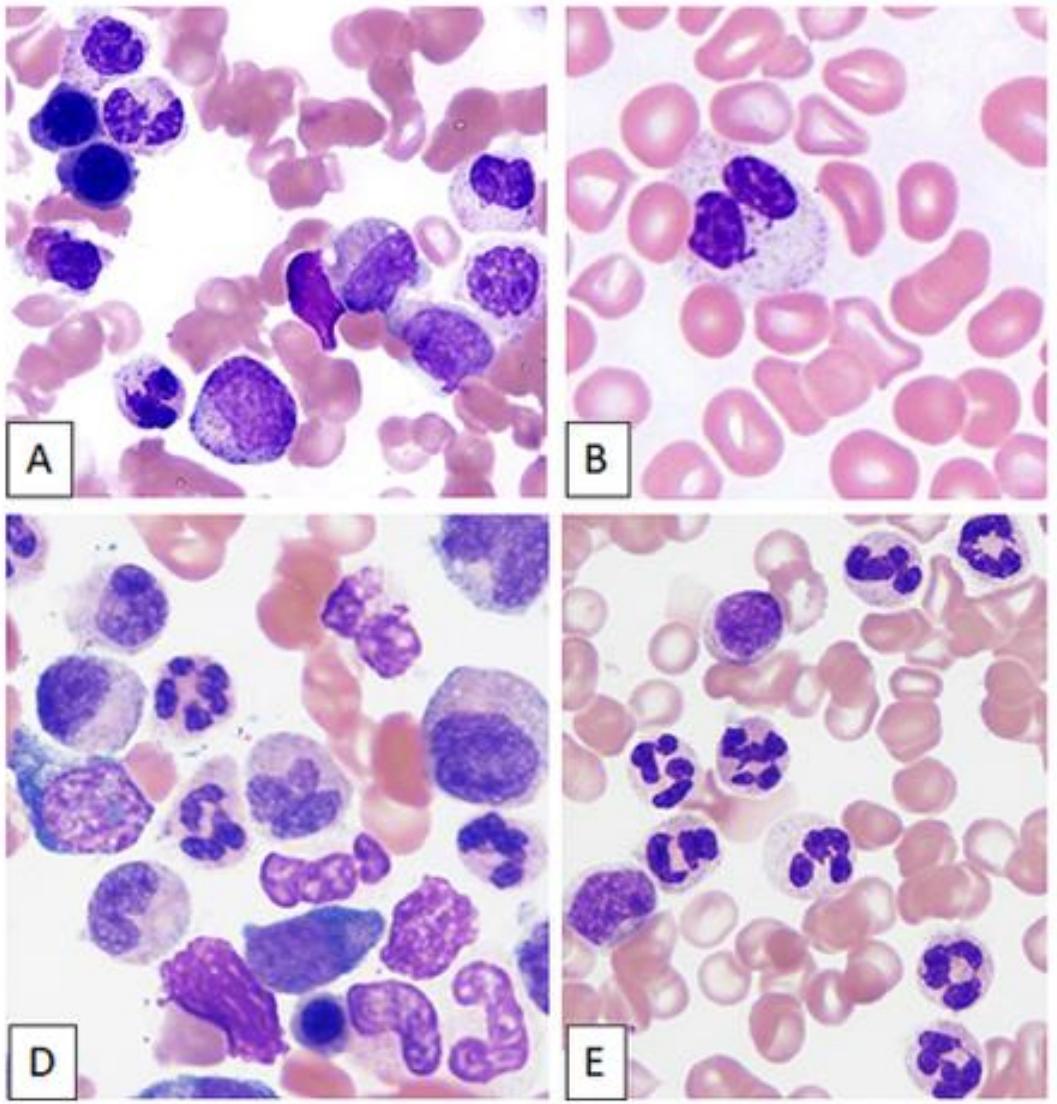
Normal karyotype
SETBP1, CSF3R, GATA2, ASXL1 mutations





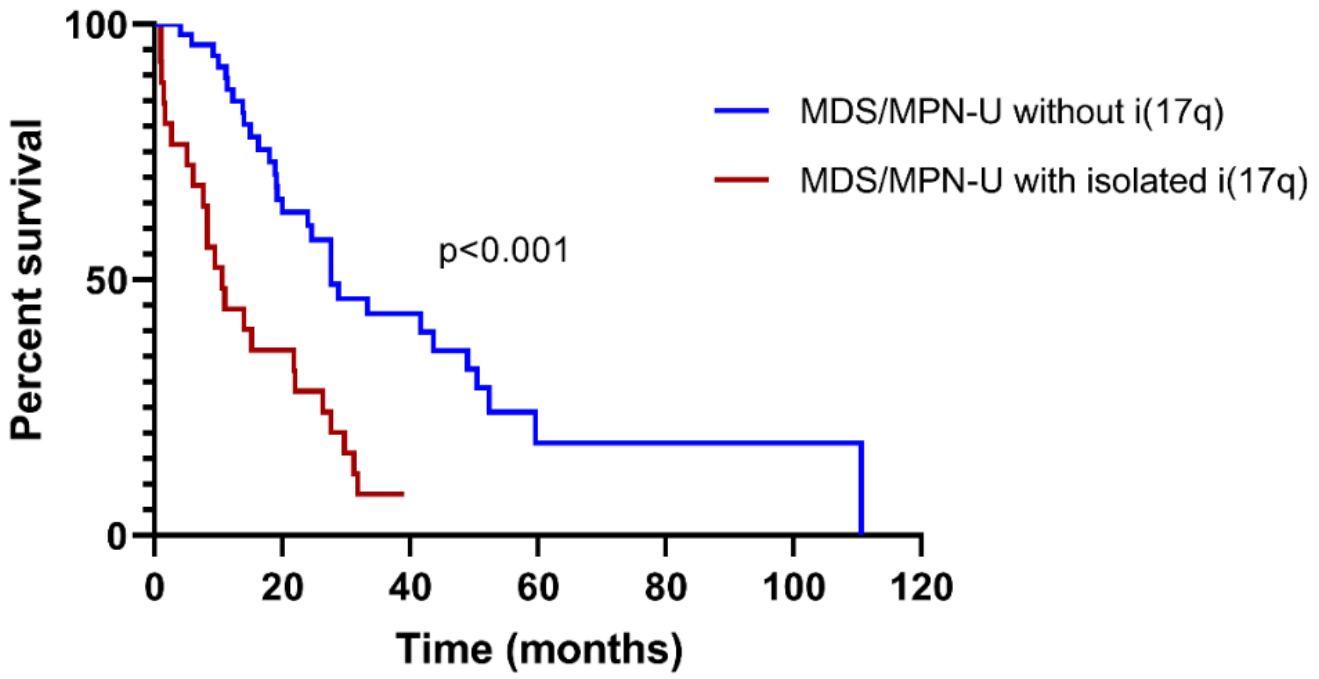
MDS/MPN with isolated isochromosome (17q) (provisional entity in ICC)

- Leukocytosis ≥13 x 10^9/L + cytopenia
- Blasts <20% of the cells in blood and bone marrow
- Dysgranulopoiesis with non-segmented or Pseudo-Pelger-Hüet neutrophils
- i(17q), either isolated or occurring with one other additional abnormality [other than -7/del(7q)]
- No *BCR::ABL1* or MLN-TKF
- Absence of MPN-associated mutations (*JAK2, CALR* and *MPL*)
- No history of recent cytotoxic or growth factor therapy that could explain the MDS/MPN features



Kanagal-Shamanna R et al. Mod Pathol 2022;35:470

MDS/MPN with i(17q) has poorer prognosis than MDS/MPN-NOS



Multivariable analysis (Cox proportion hazards model) for overall survival

Parameters	Co-efficient	Hazard Ratio	Standard Error	Z	p-value
Isolated isochromosome i(17q)	1.304478	3.686	0.585	2.231	**0.02571**
Splenomegaly	1.943008	6.98	0.7	3.187	**0.00144**
Platelet Count	0.001554	1.001	0.001	1.343	0.17928
PB Blast%	0.188571	1.207	0.105	1.792	**0.07309**
BM Blast%	0.022547	1.023	0.076	0.296	0.7673

Kanagal-Shamanna R Mod Pathol 2020;33:1409, Kanagal-Shamanna R Mod Pathol 2022;35:470

Conclusions

- The MDS/MPN overlap group is a repository for cases displaying mixed myelodysplastic and myeloproliferative features
  - Most often 1 cytosis + 1 cytopenia + morphologic dysplasia
  - Generally no history of prior MDS or MPN
- CMML has been expanded by the incorporation of ‘oligomonocytic cases’ (OM-CMML), and simplified by the elimination of CMML-0
  - Further study is needed on the prognostic significance of OM-CMML and its separation from MDS cases that may display borderline monocytosis
- Mutation profile can be helpful in supporting specific MDS/MPN entities and resolving their differential diagnoses
  - *SRSF2/TET2/ASXL1* in CMML
  - *SETBP1* in aCML / MDS/MPN-neutrophilia
  - Usual absence of *JAK2, CALR*, or *MPL* mutations

Reference slide: MDS/MPN entities (ICC/WHO 5th ed)

	CMML	aCML	MDS/MPN-*SF3B1*-T	MDS/MPN-NOS	MDS/MPN-i(17q)
Dysplasia	Any lineage	Granulocytic	Erythroid + ring sideroblasts	Any lineage	Granulocytic
Cytopenia	Yes (any)	Yes (any)	Anemia	Yes (any)	Yes (any)
Cytosis	Monocytes **≥0.5 x 10^9/L**	WBC ≥13 x 10^9/L	Platelets ≥450 x 10^9/L	Platelets ≥450 x 10^9/L or WBC ≥13 x 10^9/L	WBC ≥13 x 10^9/L
Median OS	31 months	12 months	88-120 months	22-28 months	11 months
Genetics	*TET2* 50% *ASXL1* 45% ***SRSF2*** **40%** *RUNX1* 15% *CBL* 15% *SETBP1* 10% *ETNK1* 2%	*TET2* 30% ***SETBP1*** **25%** *ASXL1* 25% *NRAS* 20% *EZH2* 15% **ETNK1** **9%** *CBL* 8%	***SF3B1*** **100%** ***JAK2*** **60%** *TET2* 25% *DNMT3A* 15% *MPL* 10% *ASXL1* 10%	*TET2* 30% *SRSF2* 24% *SETBP1* 14% *NRAS* 10% *CBL* 10% *EZH2* 10%	*SETBP1* 69% *ASXL1* 67% *SRSF2* 63%
Prognostic factors	Karyotype *ASXL1* mutation Blasts ≥10%	Karyotype Higher WBC Increased blasts	*JAK2* mutation	Karyotype Increased blasts	Unknown

Such E et al. Blood 2013;121:3005, Wang SA et al. Blood 2014;123:2645, Zoi K et al. Int J Hematol 2015;101:229, Meggendorfer M et al. Leukemia 2013;27:1852, Broseus J et al. Leukemia 2013;27:1826, Gambacorti-Passerini CB et al. Blood 2015;125:499, Kangal-Shamanna et al. Mod Pathol 2022;35:470

Discussion on Case #4

- 62 year-old female with splenomegaly, systemic symptoms
- HGB 10.9 g/dL, WBC 16K (15% monos, 4% blasts), PLT 393K
  - Leukoerythroblastosis, elevated LDH
- Bone marrow markedly hypercellular, myeloid predominance, dysplastic and “proliferative” megakaryocytes with some clustering, myeloid predominance
  - Increased reticulin fibrosis
  - Increased monocytes
  - Mature plasmacytoid dendritic cell nodules
- Normal karyotype
- *MPL* mutation detected; other NGS not available
- Later developed mature PDC nodules in lymph nodes

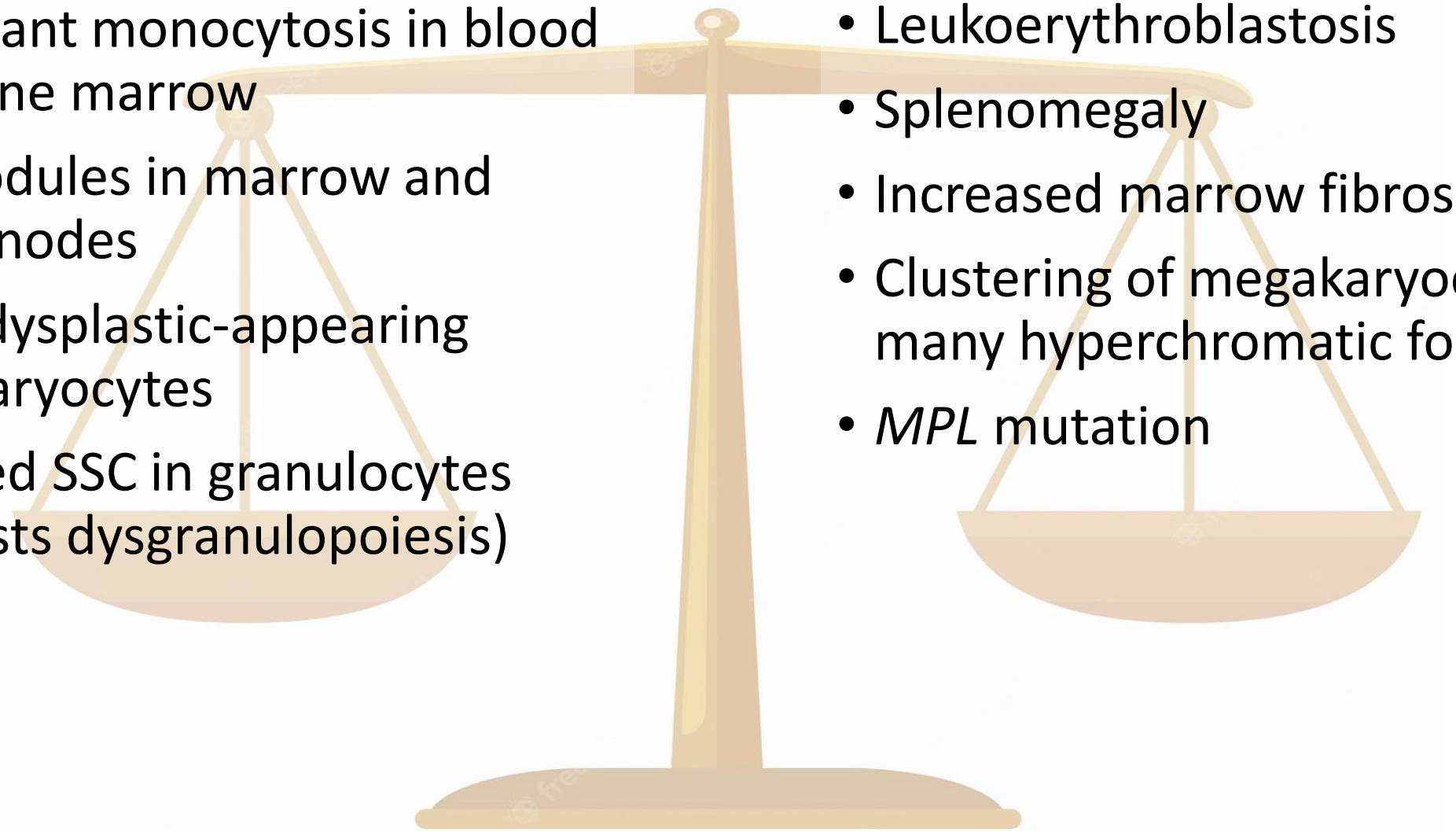
Differential diagnosis

CMML, proliferative subtype

- Significant monocytosis in blood and bone marrow
- PDC nodules in marrow and lymph nodes
- Some dysplastic-appearing megskaryocytes
- Reduced SSC in granulocytes (suggests dysgranulopoiesis)

Primary myelofibrosis

- Leukoerythroblastosis
- Splenomegaly
- Increased marrow fibrosis
- Clustering of megakaryocytes, with many hyperchromatic forms
- *MPL* mutation



How to diagnose?

- Descriptive diagnosis
  - “Myeloid neoplasm with increased fibrosis and monocytosis”
  - May be a true intermediate case between CMML and PMF, as described in the series of Chapman J et al. Mod Pathol 2018
- How to resolve?
  - Additional NGS studies
    - Presence of *SRSF2/TET2/ASXL1* mutations could support CMML
    - Low *MPL* VAF (<15%) could be more in keeping with CMML
  - Flow cytometry for monocyte partitioning
    - Increased (>94%) CD14+/CD16- monocytes could support CMML

Chapman J eMod Pathol 2018;31:429, Hu Z Hum Pathol 2019;85:290, Patnaik MM Blood Cancer J 2017;7: e584


THANK YOU!