MYELODYSPLASTIC/ MYELOPROLIFERATIVE OVERLAP NEOPLASMS

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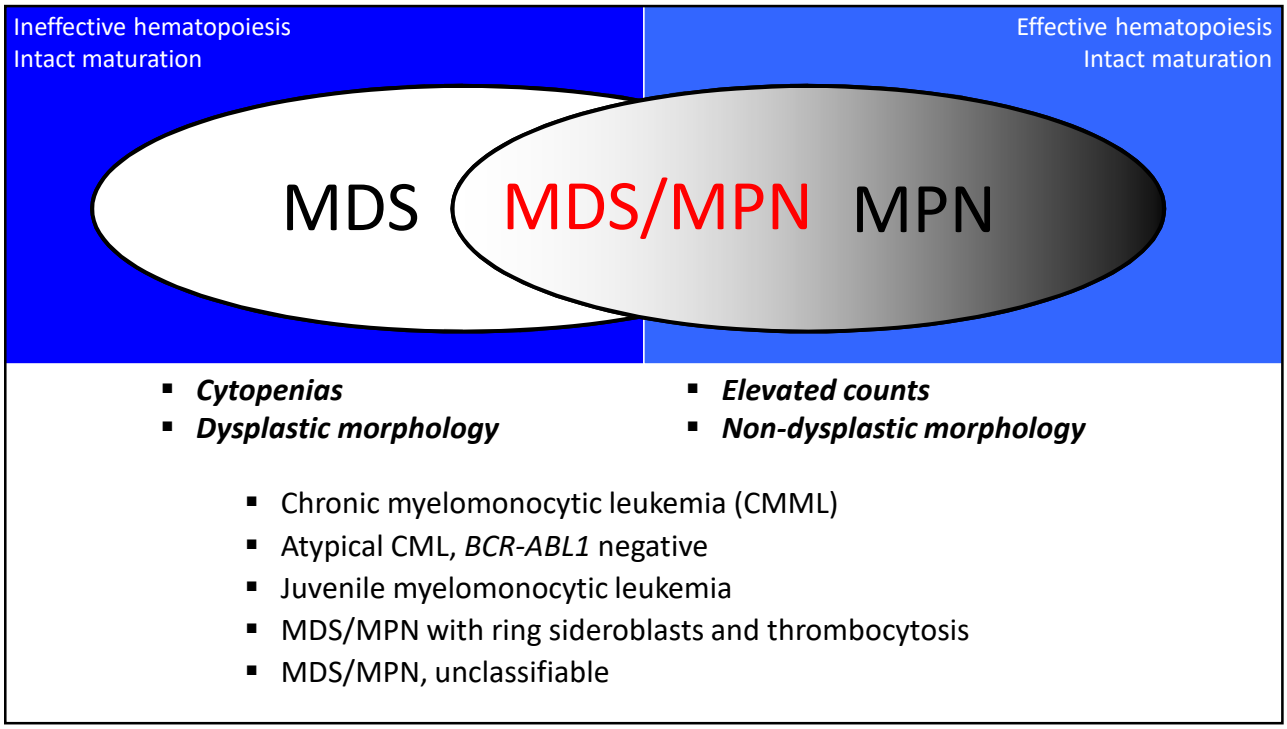
Outline of lecture

- Review the general principles of the 2017 WHO Classification of the MDS/MPN 'overlap' group
- Present the individual MDS/MPN disease entities and explore possible future changes in definitions
- Review the differential diagnosis and diagnostic challenges in MDS/MPN diseases



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 do not change the diagnosis to an MDS/MPN

‘Dysplastic’ evolution of MPN ≠ MDS/MPN

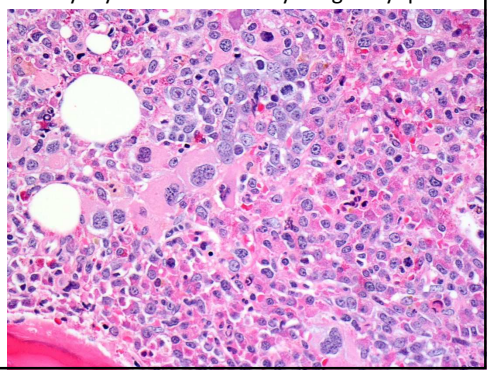
CML
PMF
CNL
ET
PV

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

‘Proliferative’ evolution of MDS ≠ MDS/MPN

MDS

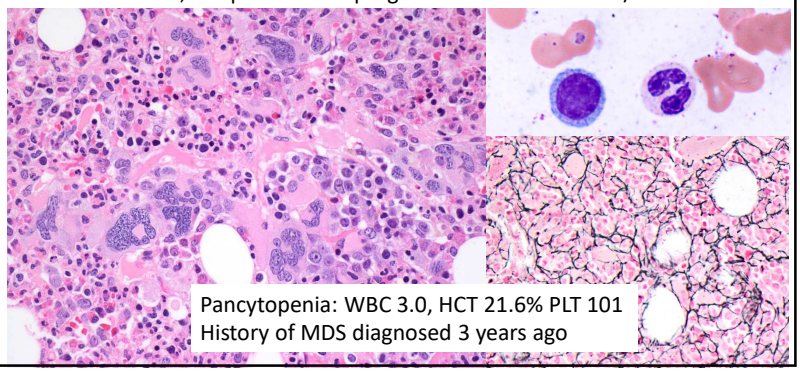
1. Leukocytosis
2. Thrombocytosis
3. Monocytosis

AML

MDS patients may develop transient neutrophilia in response to infection or inflammation

Reticulin fibrosis, JAK2 mutations, and splenomegaly can occur in pure MDS and do not necessarily indicate an MDS/MPN

MDS with fibrosis, not proliferative progression of MDS or MDS/MPN



Pancytopenia: WBC 3.0, HCT 21.6% PLT 101
History of MDS diagnosed 3 years ago

Wang SA Am J Clin Pathol 2006;126:789

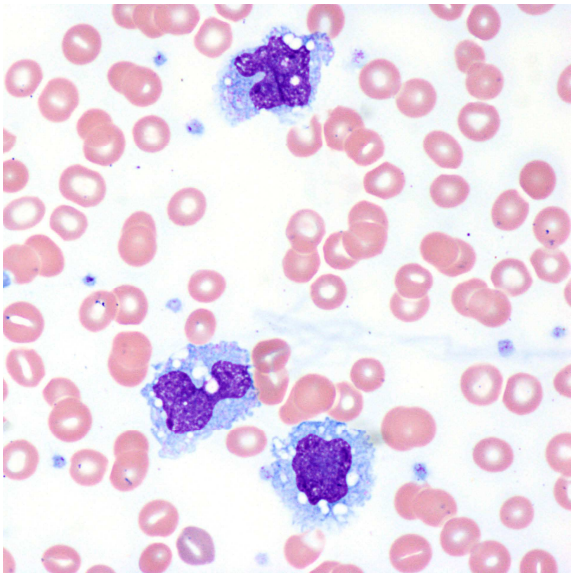
MDS/MPN versus MDS

- Sustained cytoses at the time of disease onset exclude MDS and mandate classification as MDS/MPN
  - Platelet count ≥450 x 10^9/L
    - Exception: if meets criteria for MDS with isolated del(5q)
    - Transient borderline thrombocytosis may be seen in MDS cases with ring sideroblasts
  - WBC ≥13 x 10^9/L
  - Monocytes ≥1 x 10^9/L* (and comprising 10% of leukocytes)

*To be reduced to ≥0.5 x 10^9/L in 2022 International Consensus Classification (="oligomonocytic CMML")

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



CMML definition

- Peripheral blood
  - Persistent absolute monocytosis (≥1 x 10^9/L) and relative monocytosis (≥10% of leukocytes); blasts and promonocytes are <20%
- Bone marrow
  - Hypercellular with dysplasia* in one or more lineages
  - Blasts and promonocytes are <20%
  - Variable marrow monocytosis, often less prominent than in the blood
- Clinical features
  - White blood count may be increased or decreased; other cytopenias are usually present
  - May or may not have splenomegaly

*If dysplasia is absent/minimal, clonality must be proven or monocytosis must last ≥3 months with rigorous exclusion of all possible reactive causes for monocytosis

The diverse causes of monocytosis

Reactive

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

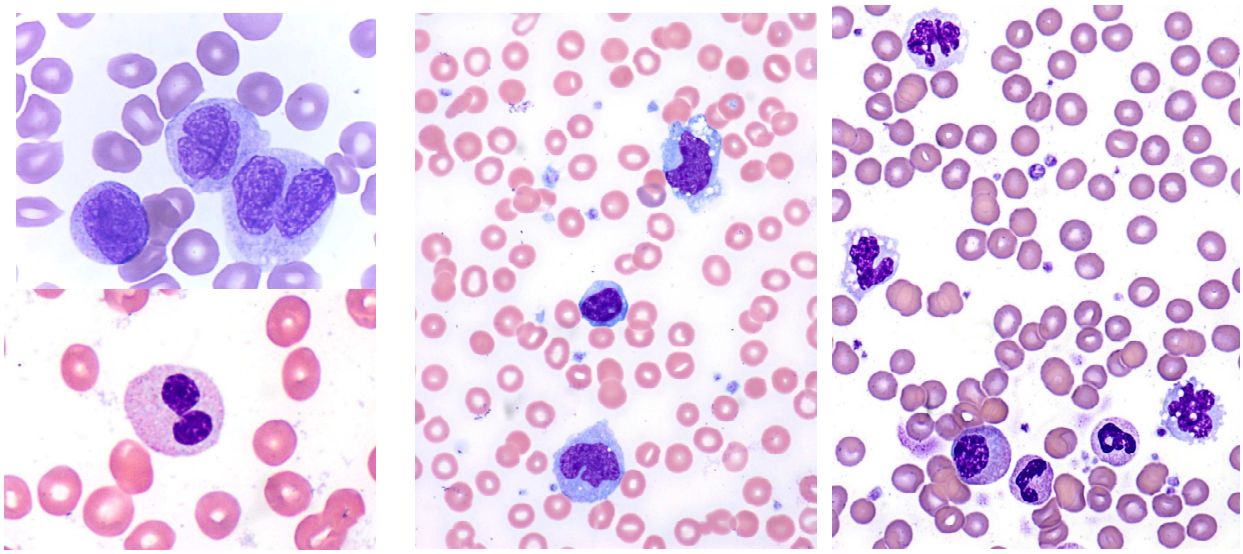
Neoplastic

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

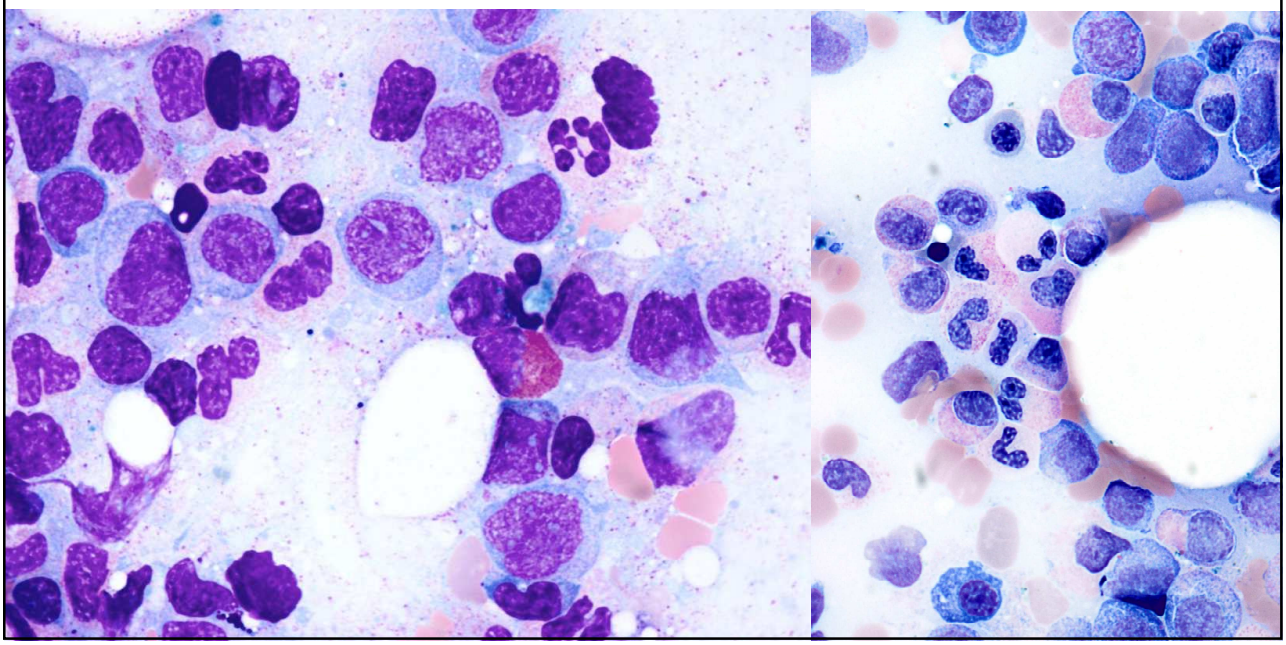
Patnaik MM et al. BJH 2014

Courtesy of Dr David Steensma

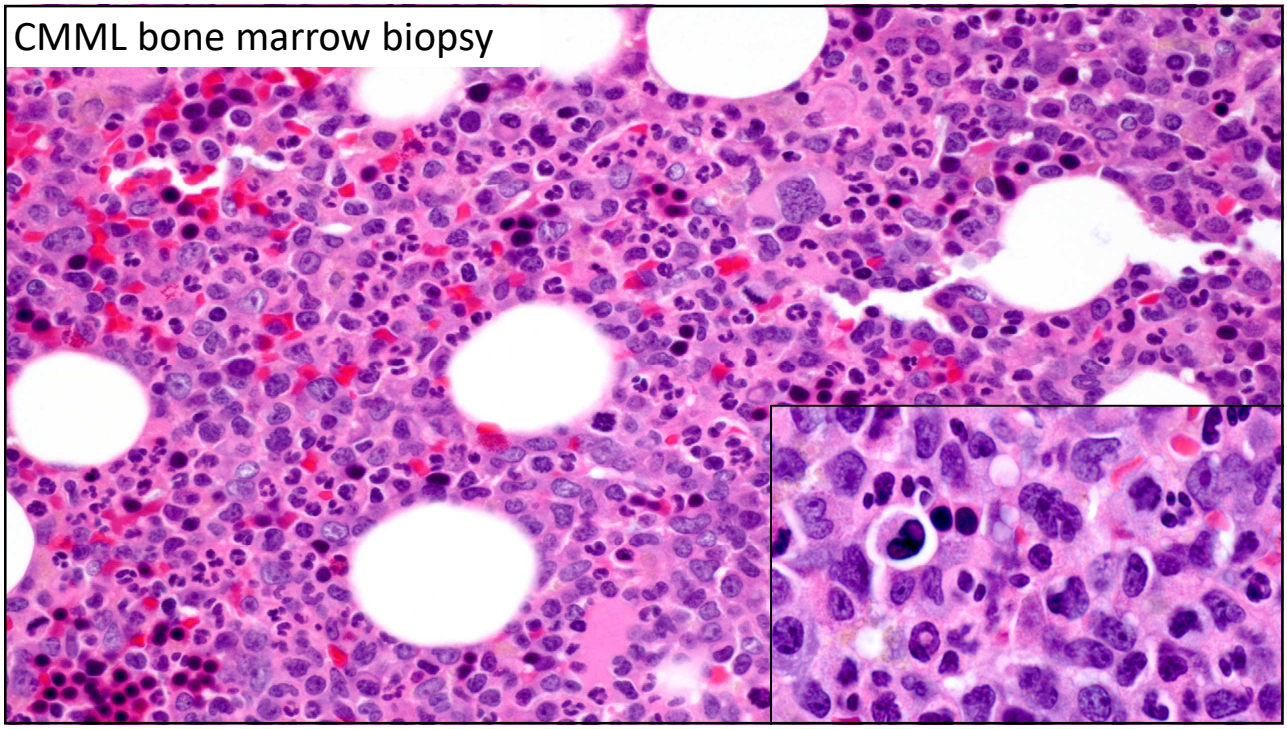
CMML peripheral blood



CMML bone marrow aspirate smear



CMML bone marrow biopsy



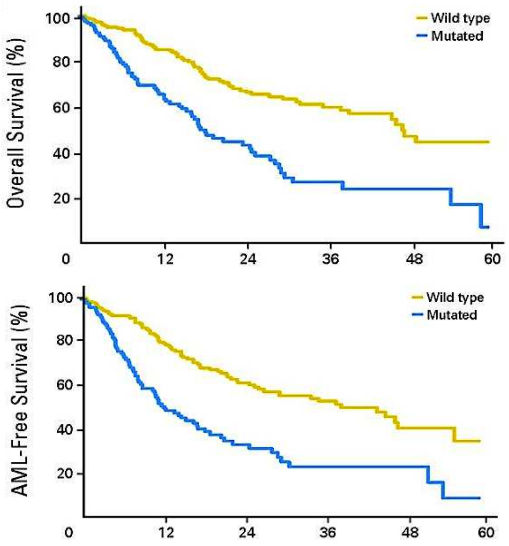
CMML: WHO 2017 subgroups

- 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
- Stratification based on blast + promonocyte %
  - CMML-0: <5% BM blasts, <2% PB blasts
  - CMML-1: 5-9% BM blasts or 2-4% 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

CMML: Genetic features

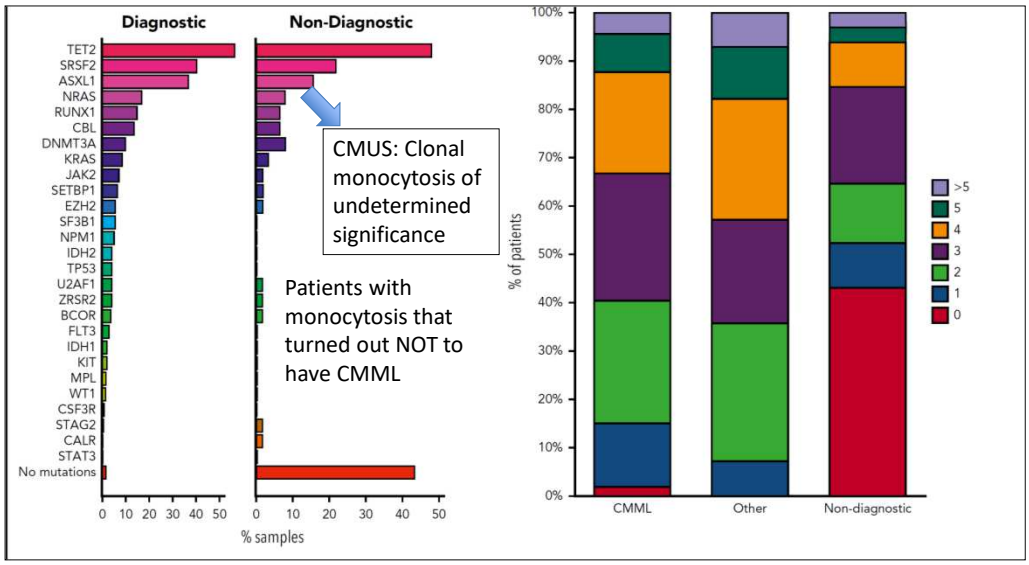
- 60-80% have normal karyotype
  - Must exclude t(5;12) (*PDGFRB* fusion) in cases with eosinophilia
- Distinctive (but not specific) mutation profile
  - *TET2*, *SRSF2*, or *ASXL1* mutated in 80-90% of cases
  - *RUNX1, CBL, KRAS/NRAS,* and other mutations also occur
  - Mutations support the diagnosis, but are not sufficient to diagnose CMML in isolation (beware of CHIP!)
- *NPM1* mutation or 11q23 (*KMT2A*) rearrangement may herald rapid progression to AML and patient should be followed closely



CMML patient outcomes based on *ASXL1* mutation

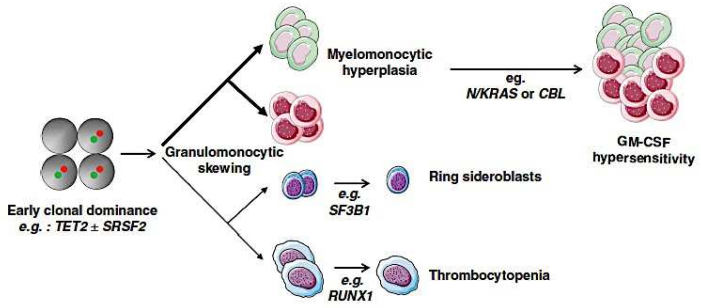
Itzykson R JCO 2013;31:2428. Courville E Mod Pathol 2013;26:751, Schnittger S Leukemia 2011;25:615, Goasguen JE Haematologica 2009;94:994-7

99% of bona fide CMML patients have at least one pathogenic mutation on NGS



Cargo Blood. 2019;133:1325-1334

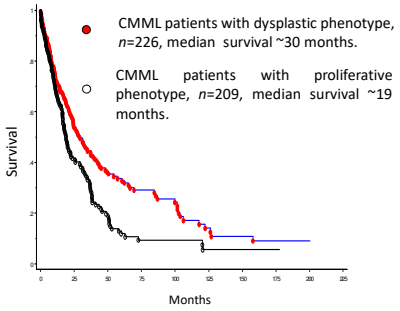
Biologic basis of CMML subtypes

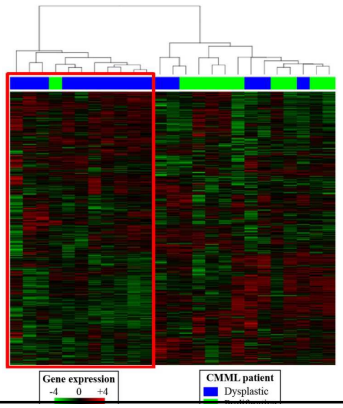


Dysplastic subtype CMML

Proliferative subtype CMML

RAS pathway mutations
JAK2
SETBP1

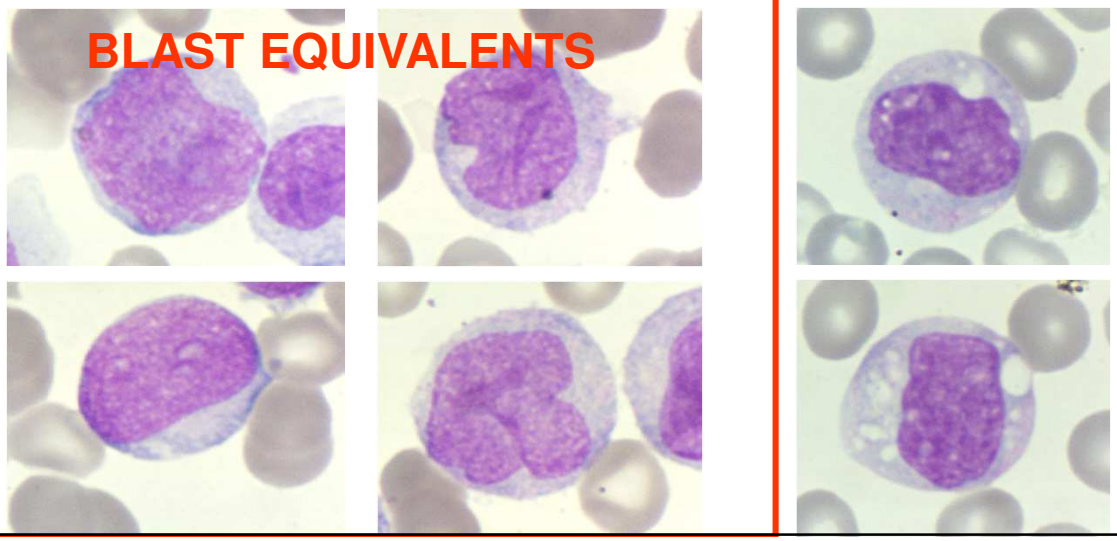




Itzykson R and Solary E. Leukemia 2013; 27:1441, Patniak N Hematology 2016

Monocytic cells

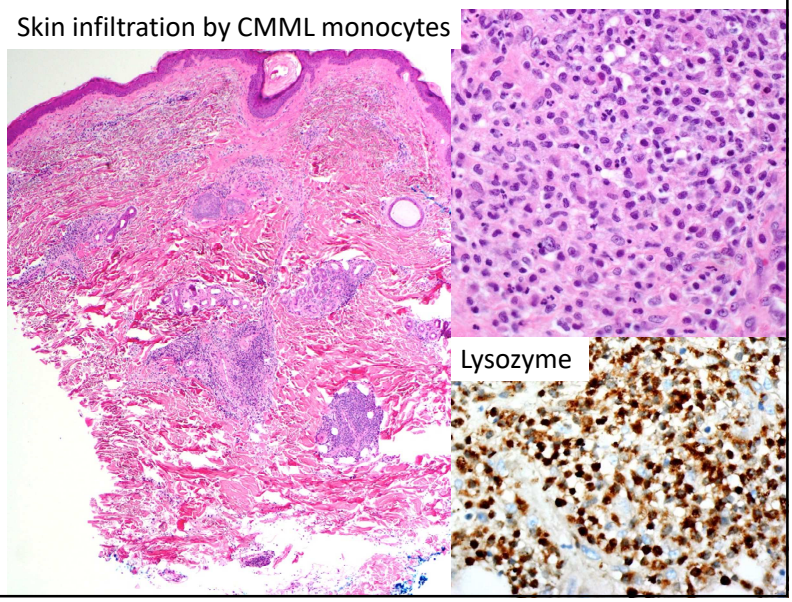
Monoblasts | Promonocytes | Monocytes



Diagnostic issues with CMML

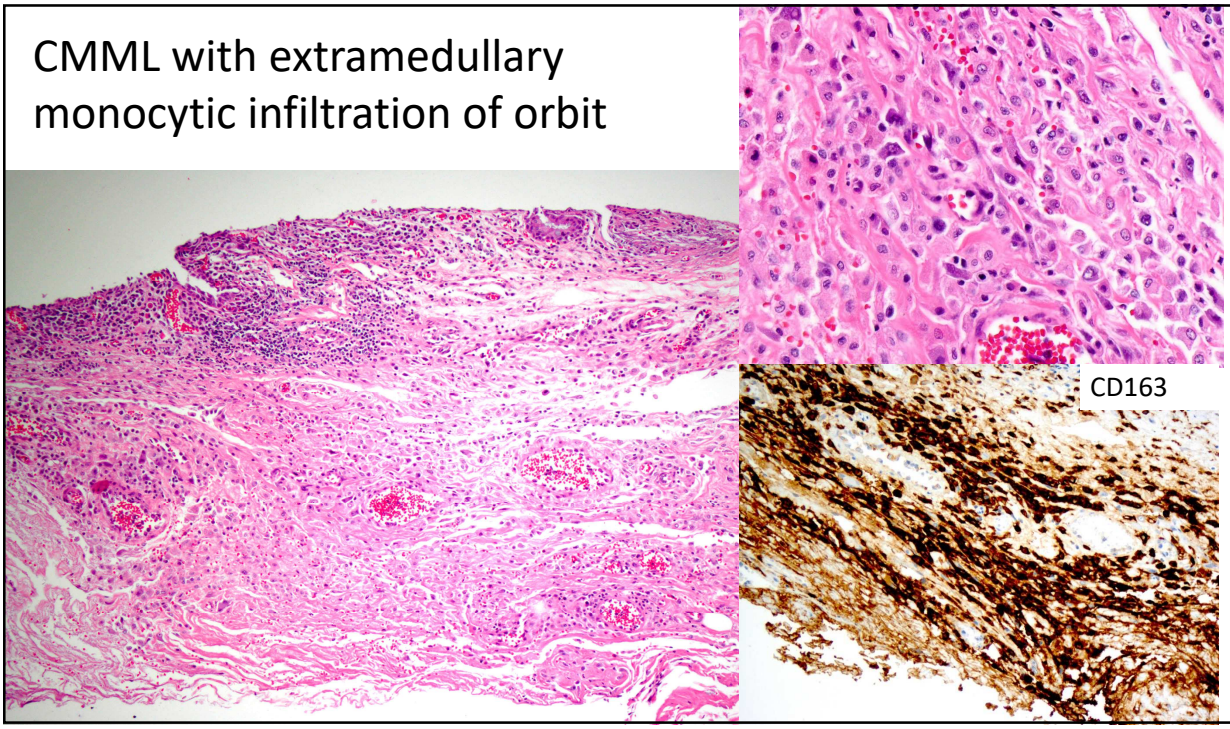
- Extramedullary manifestations
  - Mature monocytic infiltrates in skin, CSF, other sites
  - Plasmacytoid dendritic cell nodules
- Distinguishing blast equivalents (promonocytes) from atypical monocytes
  - CMML-0/CMML-1/CMML-2
  - CMML versus AML with monocytic features

Skin infiltration by CMML monocytes



Lysozyme

CMML with extramedullary monocytic infiltration of orbit



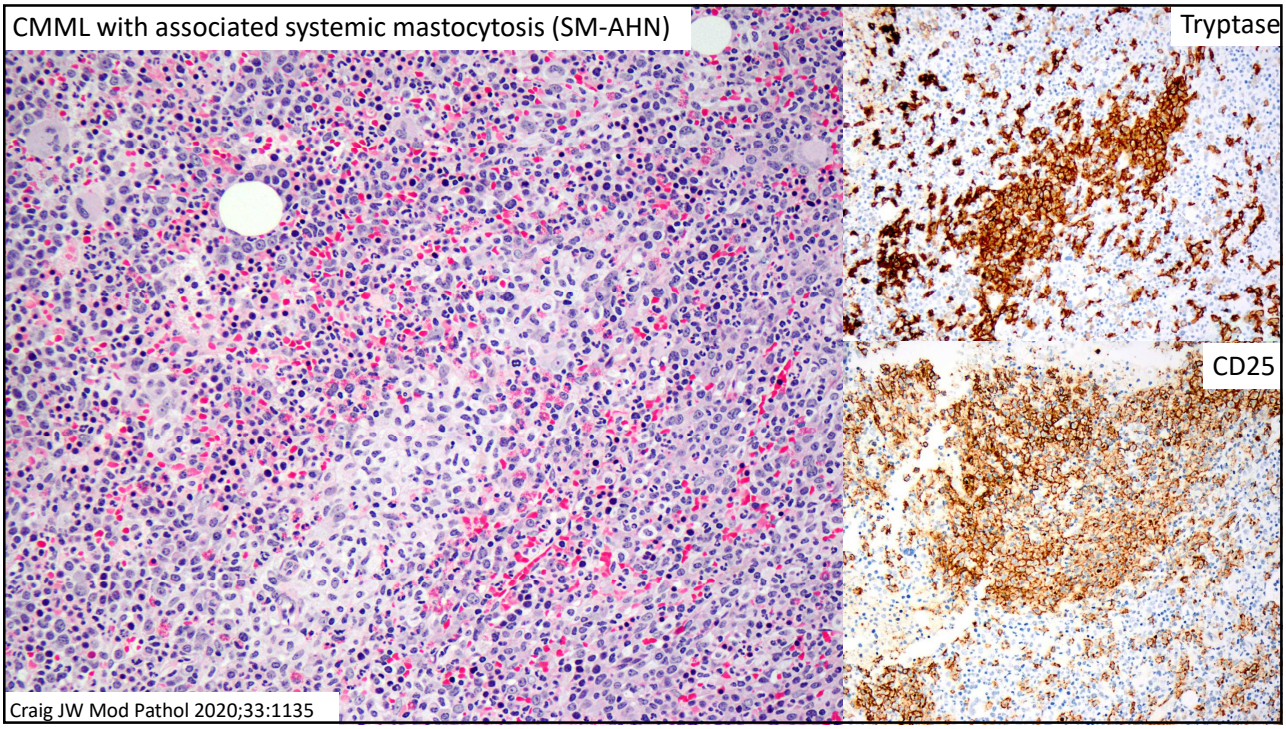
CD163

Other diagnostic issues with CMML

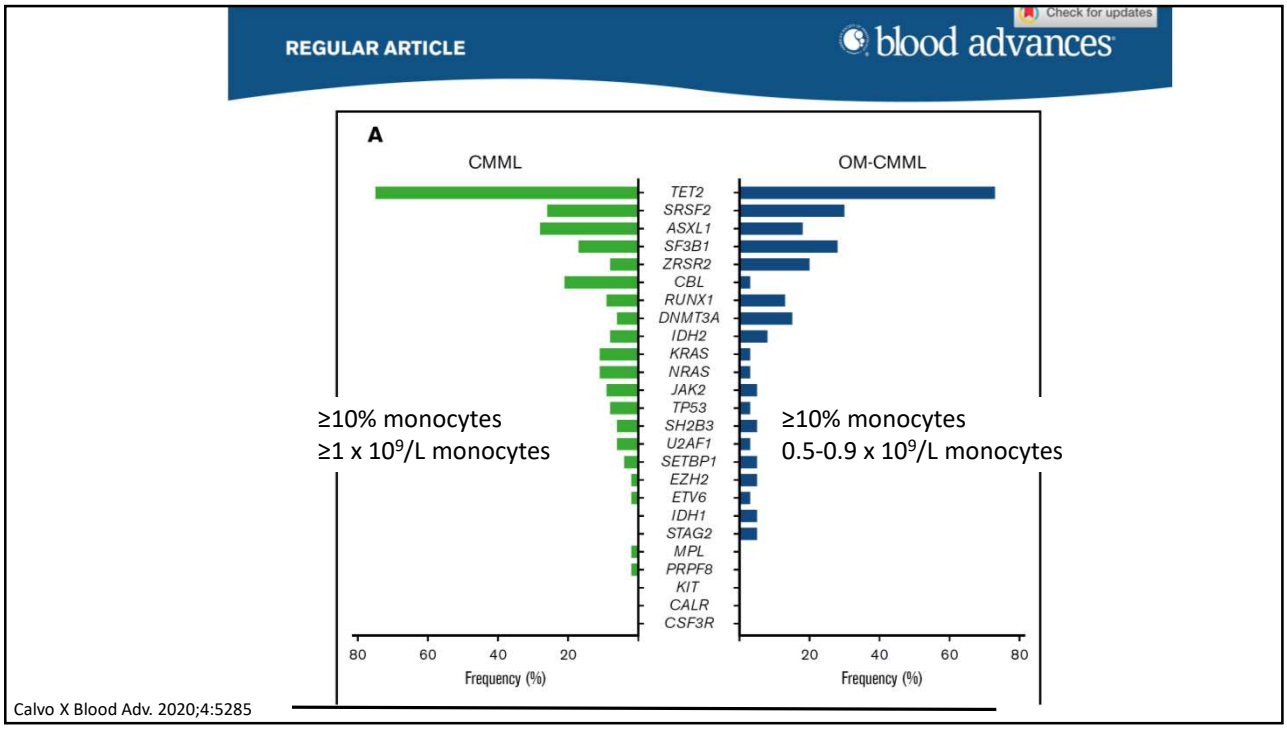
- Always check the monocyte count before diagnosing MDS!
  - Marrow monocytes often are NOT increased in CMML—definition is based on peripheral blood monocytes
  - Dysplasia in CMML can be subtle or even absent
- "Oligomonocytic" CMML is increasingly being recognized
  - Cytopenic patients with ≥10% blood monocytes and absolute monocyte count of 0.5 – 0.9 x 10^9/L
    - These patients have similar mutation profiles and clinical behavior to 'conventional CMML'
- Keep an eye out for other myeloid cell proliferations that may accompany CMML in the bone marrow
  - Systemic mastocytosis (may be subtle—have a low threshold for tryptase staining!)
    - Detection of a *KIT* mutation by NGS can be a clue and 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)



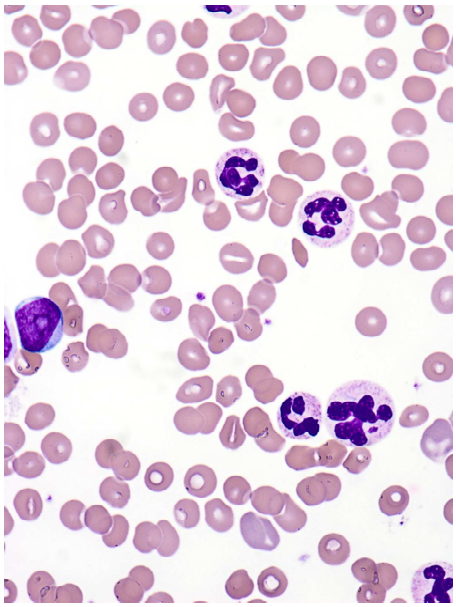
Craig JW Mod Pathol 2020;33:1135



Calvo X Blood Adv. 2020;4:5285

Atypical CML, *BCR-ABL1* negative

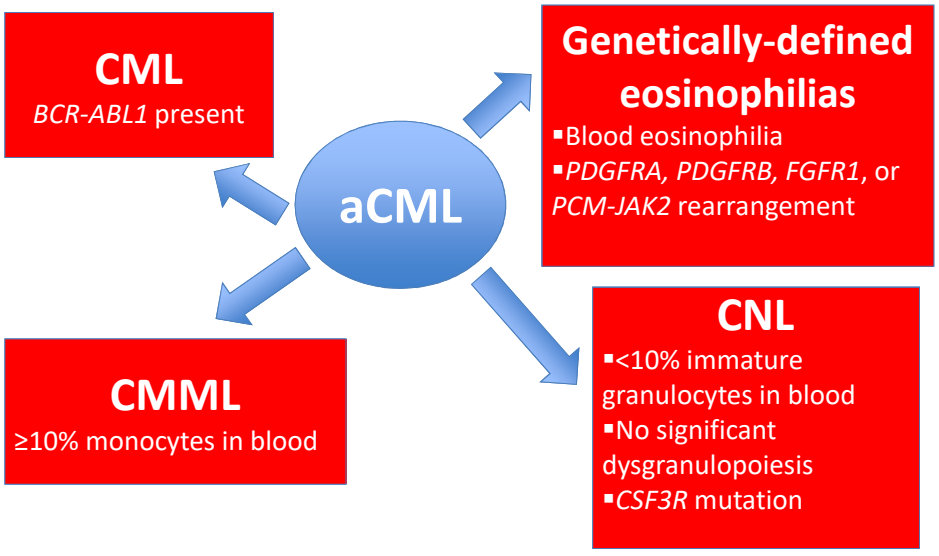
- MDS/MPN characterized by excess production of granulocytes
- Marked granulocytic dysplasia and left-shift in blood
- Can mimic CML in its presentation, but is a completely unrelated disease



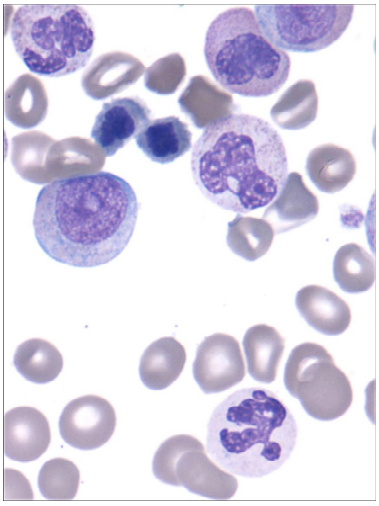
Atypical CML, *BCR-ABL1* negative WHO 2017 definition

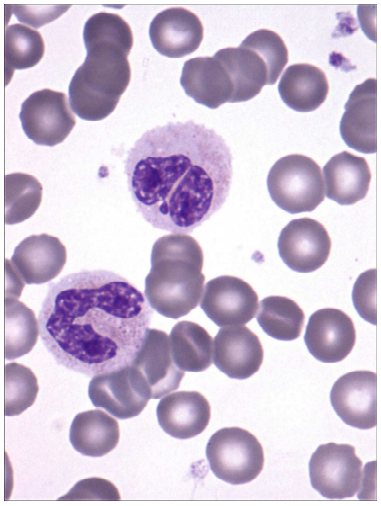
- Leukocytosis (WBC ≥13 x 10^9/L) with ≥10% immature granulocytic forms
- Prominent dysgranulopoiesis in blood and marrow
- Exclusion of common mimics
  - CML
  - Chronic neutrophilic leukemia (CNL)
  - CMML
  - Genetically-defined eosinophilic neoplasms

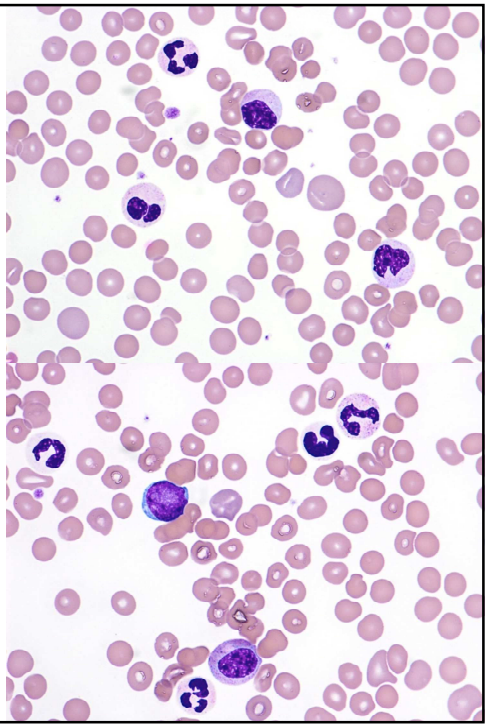
The differential diagnosis of atypical CML, *BCR-ABL1* negative



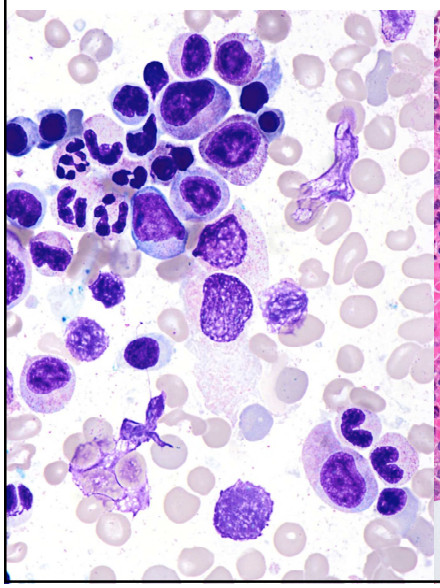
Atypical CML peripheral blood

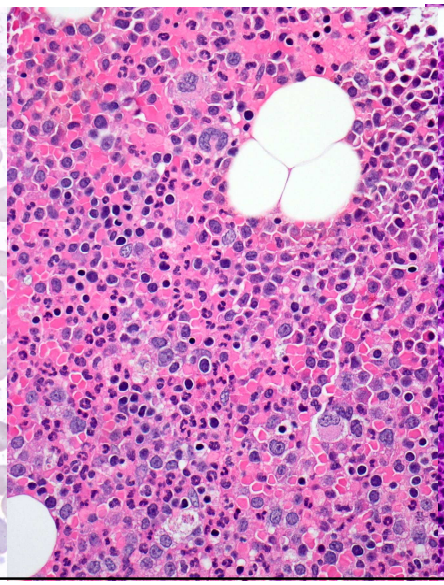


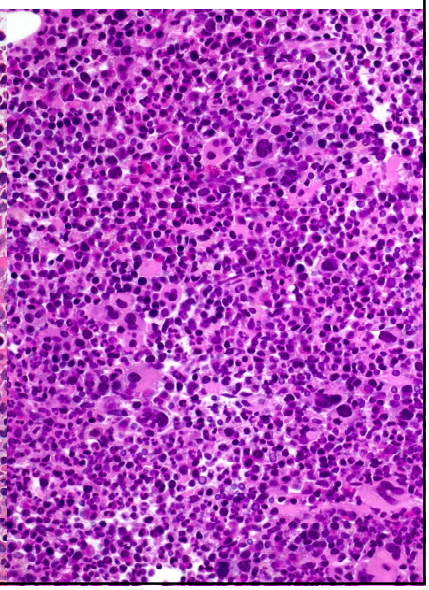




Atypical CML bone marrow



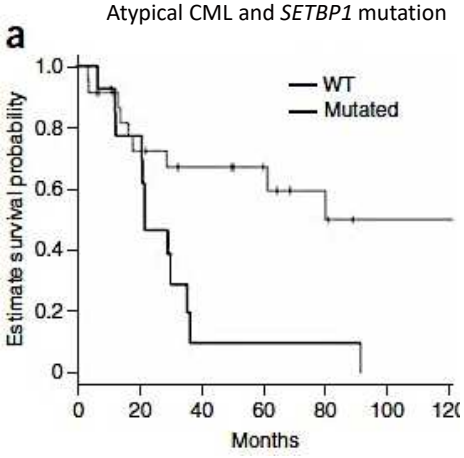




Clinical and genetic features support atypical CML as a distinct MDS/MPN entity

- Generally poorer prognosis than other MDS/MPN
  - Tyrosine kinase inhibitors are ineffective
- *SETBP1* or *ETNK1* mutations seen in 1/3 of cases, uncommon in other MDS/MPN entities
- *JAK2, CALR, MPL*, and *CSF3R* mutations are uncommon

Atypical CML and *SETBP1* mutation

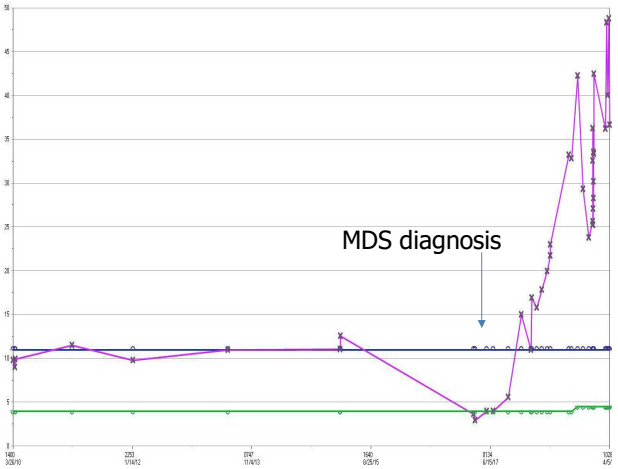


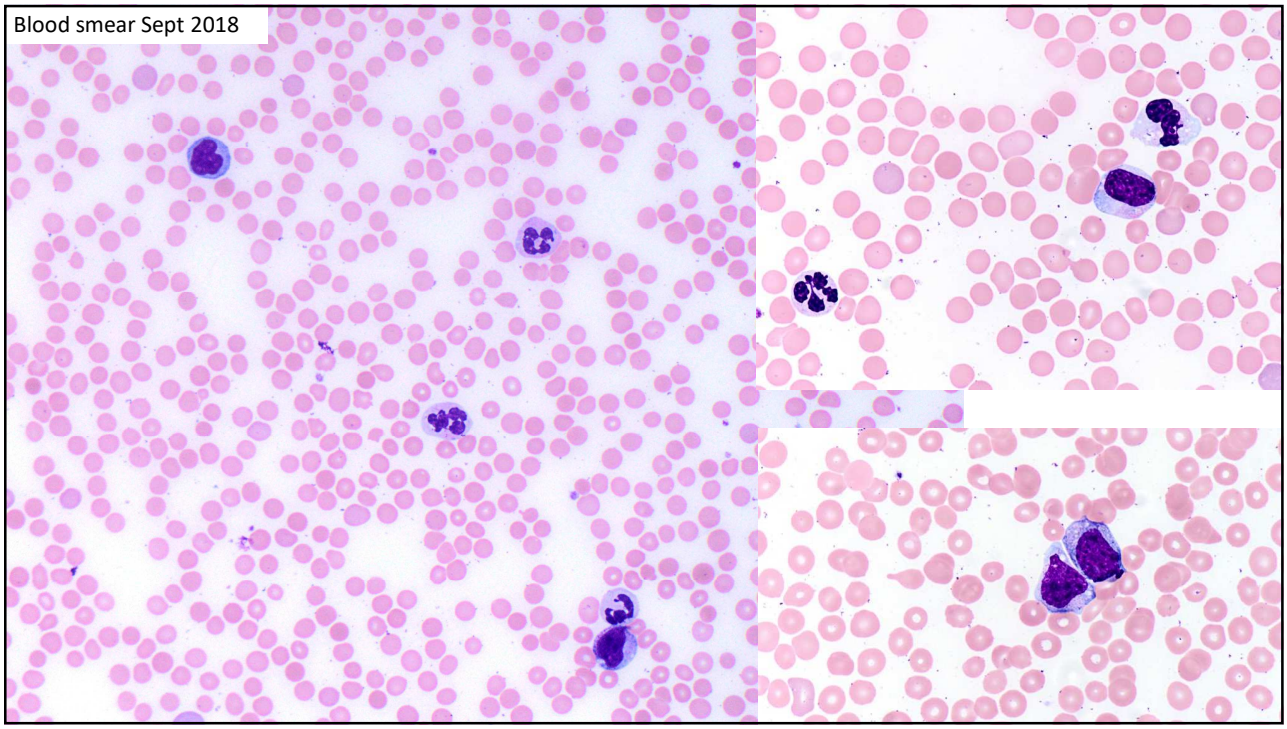
Piazza R et al. Nat Genet 2013;45:18, Wang SA et al. Blood 2014;123:2645, Gotlib J et al. Blood 2013;122:1707, Maxson JE et al. NEJM 2013;368:1781, Pardanani A et al. Leukemia 2013;27:1870

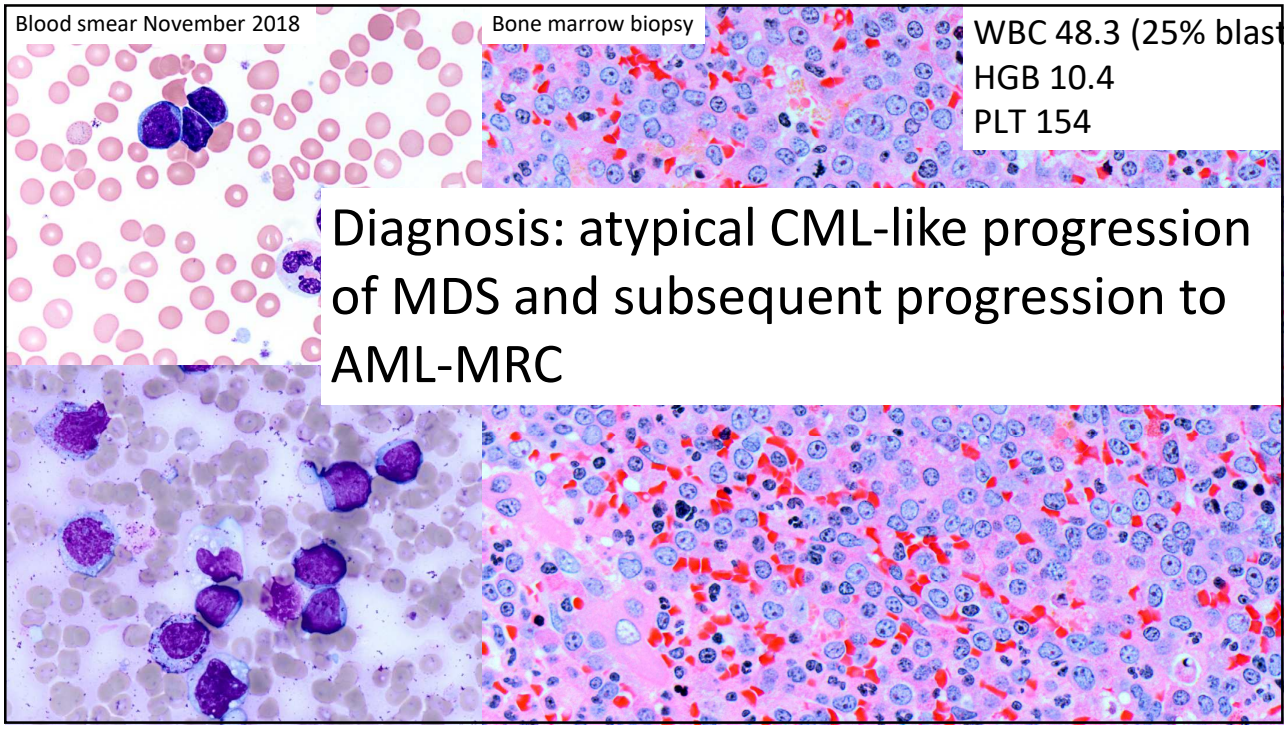
MDS/MPN-like progression of MDS

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

Graph of WBC over time

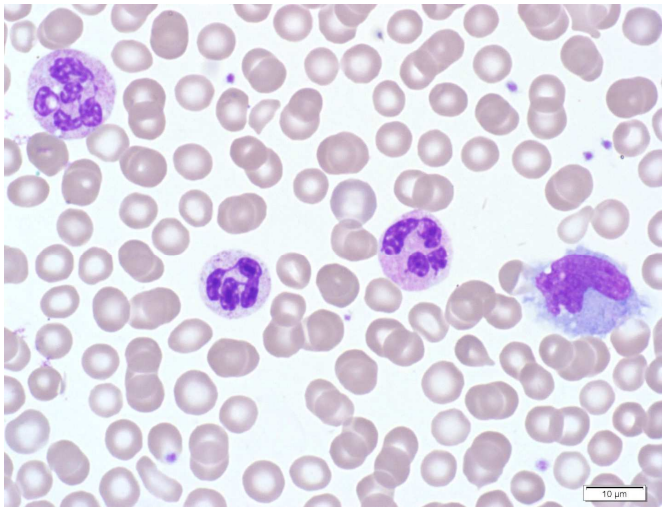



Blood smear Sept 2018


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

Juvenile myelomonocytic leukemia

- Rare MDS/MPN affecting infants and young children
- Proliferation of granulocytes and monocytes
- RAS pathway mutations are common
- Often occur in the setting of genetic predisposition
  - Noonan syndrome or neurofibromatosis



Juvenile myelomonocytic leukemia diagnostic algorithm

Mandatory features

- Blood monocyte count 1 x 10^9/L
- Blood and marrow blasts <20%
- Splenomegaly
- No *BCR-ABL1* rearrangement

RAS pathway genes, mutated in 85% of JMML patients: *PTPN11*, *KRAS*, *NRAS*, *CBL*, *NF1*

OR

At least one genetic feature

- Somatic mutation in *PTPN11, KRAS* or *NRAS*
- Clinical diagnosis of N1 or germline *NF1* mutation
- Germline *CBL* mutation and loss of heterozygosity of CBL
- Monosomy 7 or other chromosomal abnormality

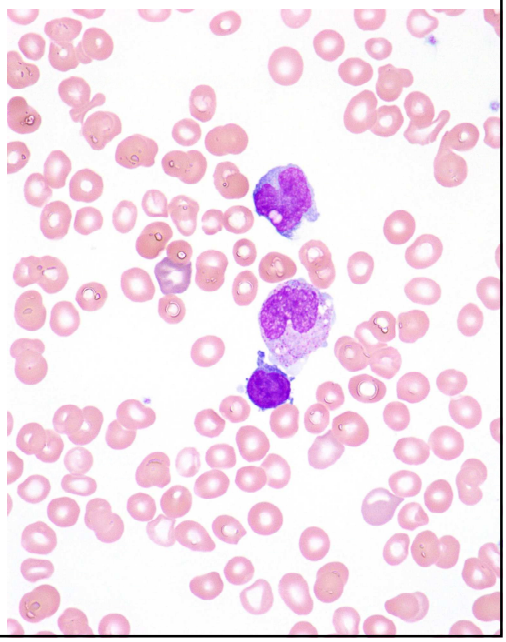
At least two other features

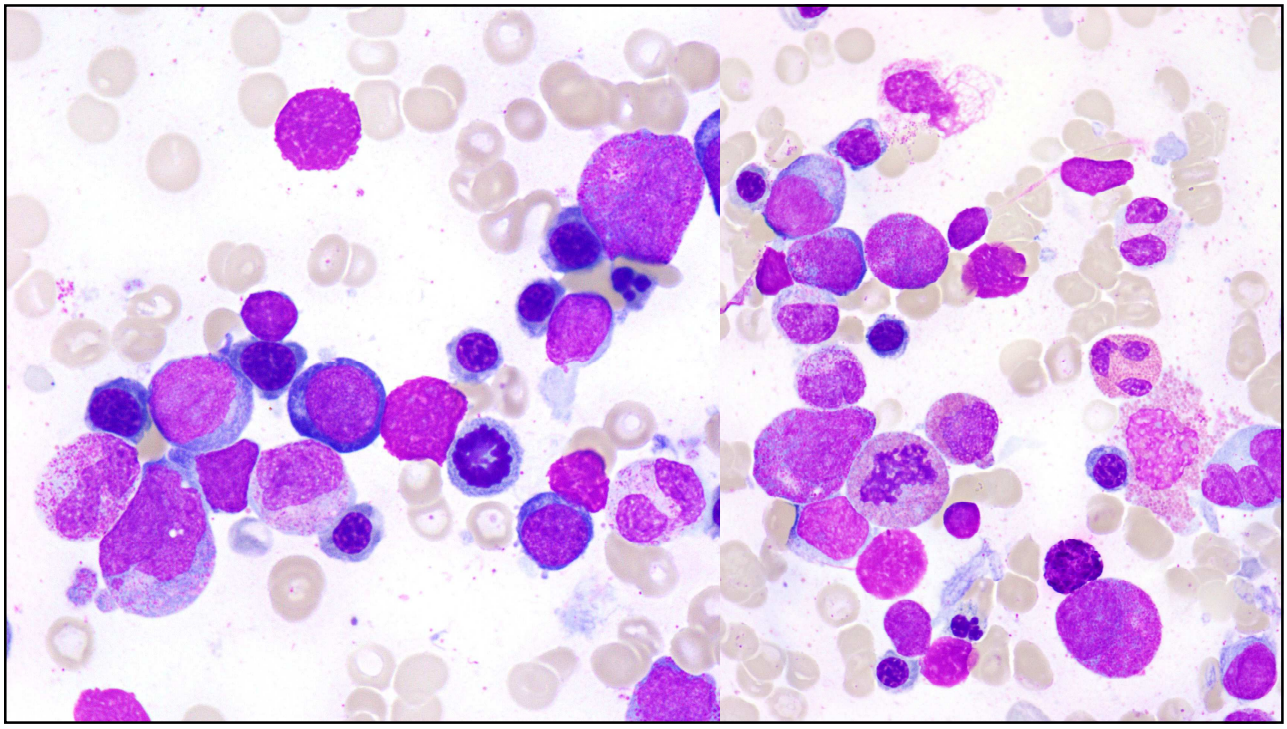
- Increased hemoglobin F for age
- Myeloid or erythroid precursors in blood
- GM-CSF hypersensitivity of bone marrow cells in vitro
- Hyperphosphorylation of STAT5

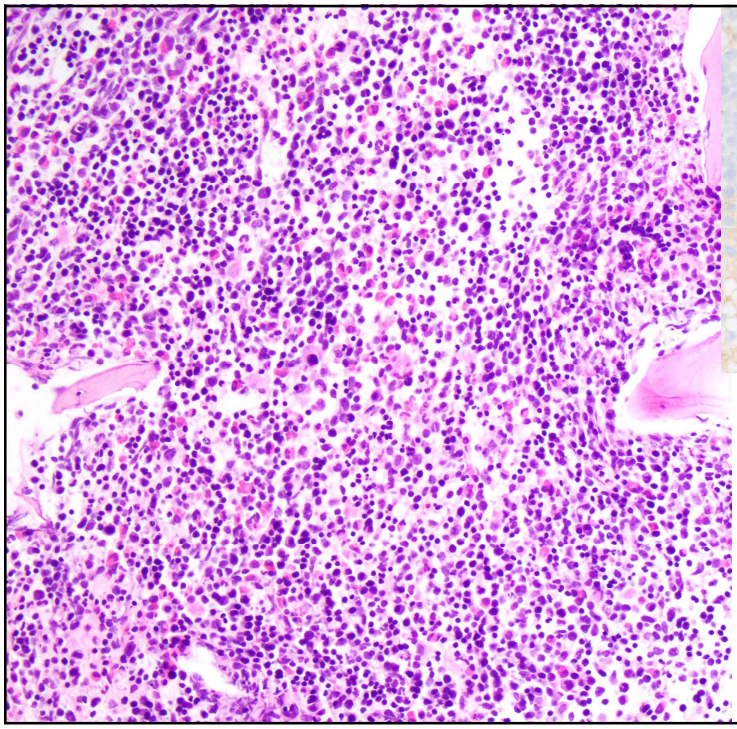
Courtesy of Olga Weinberg, UTSW Medical Center

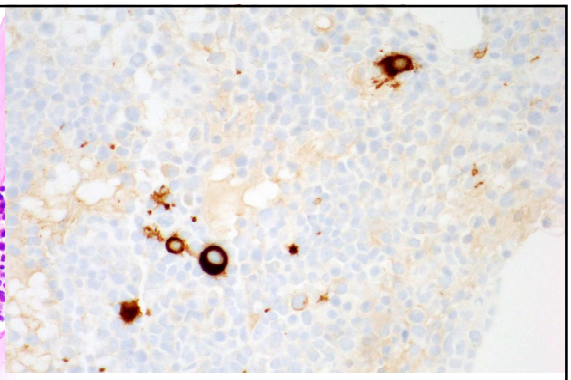
Juvenile myelomonocytic leukemia

- 2 year-old presented with hepatosplenomegaly
- WBC 7.0 x 10^9/L (21% monocytes)
- HGB 7.3 g/dL
- PLT 52 x 10^9/L









- 45, XY, -7 [14]/45,sl, del(12)(p12p13)[6]
- *BCR-ABL1* negative
- Flow cytometry: 20% monocytic cells in marrow

Juvenile myelomonocytic leukemia diagnostic algorithm

RAS pathway genes, mutated in 85% of JMML patients
- *PTPN11*
- *KRAS*
- *NRAS*
- *CBL*
- *NF1*

Mandatory features
- Blood monocyte count 1 x 10^9/L √
- Blood and marrow blasts <20% √
- Splenomegaly √
- No *BCR-ABL1* rearrangement √

OR

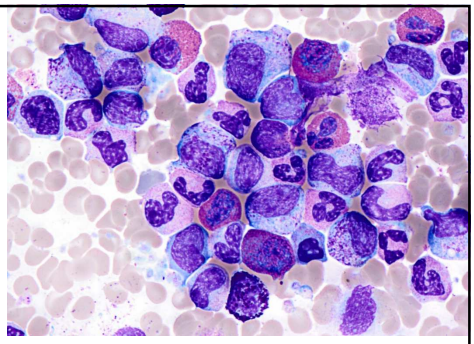
At least one genetic feature
- Somatic mutation in *PTPN11, KRAS* or *NRAS*
- Clinical diagnosis of NF1 or germline *NF1* mutation
- Germline *CBL* mutation and loss of heterozygosity of CBL
- Monosomy 7 or other chromosomal abnormality √

At least two other features
- Increased hemoglobin F for age
- Myeloid or erythroid precursors in blood
- GM-CSF hypersensitivity of bone marrow cells in vitro
- Hyperphosphorylation of STAT5

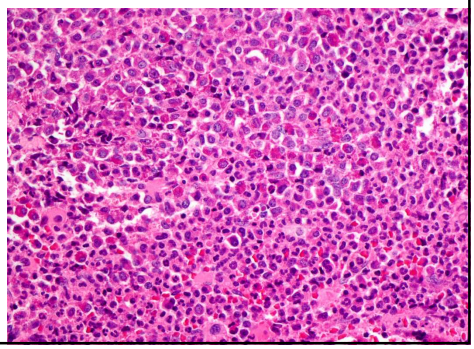
Courtesy of Olga Weinberg, Boston Children's Hospital

JMML differential diagnosis

- Leukemoid reaction
  - Children may develop marked leukocytosis in response to infections or other stresses
- CML
  - Can occur in children, but very rare in children <3 years old
- Transient myeloproliferative disorder in Down syndrome or Noonan syndrome

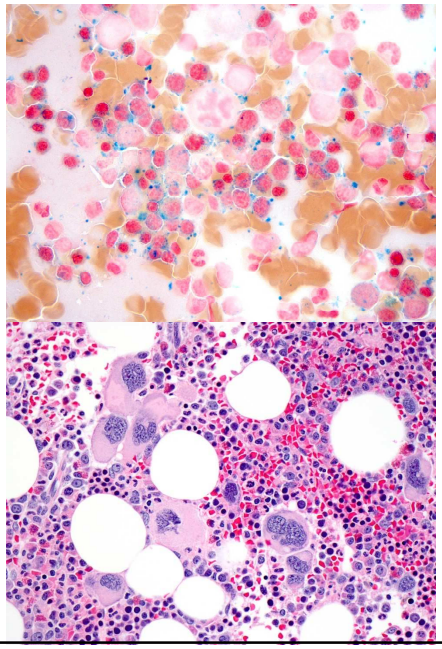


CML, *BCR-ABL1+* in a 13 year-old



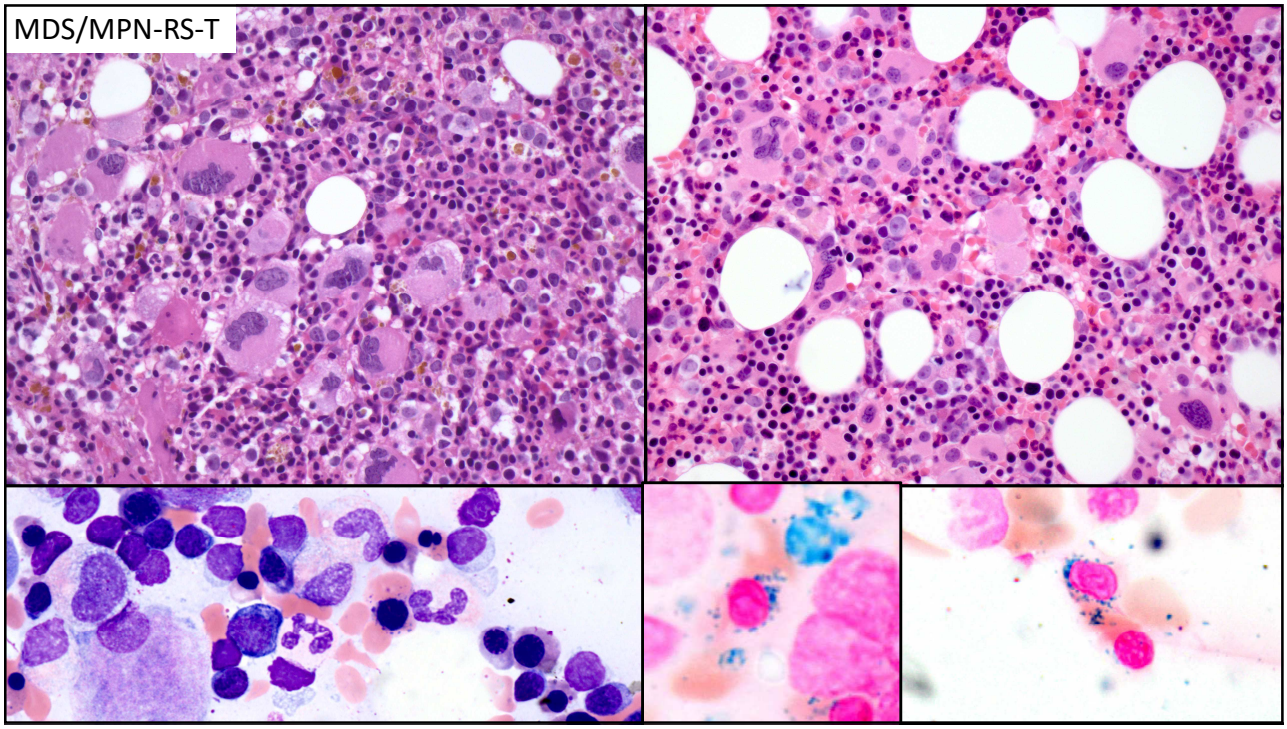
MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)

- MDS/MPN characterized by overexuberant production of platelets and ineffective production of red cells
- Anemia due to the presence of ring sideroblasts
- Previous name 'refractory anemia with ring sideroblasts and marked thrombocytosis (RARS-T)'



MDS/MPN-RS-T WHO 2017 definition

- Anemia with erythroid lineage dysplasia
  - May or may not have granulocytic or megakaryocytic dysplasia
- ≥15% ring sideroblasts
- 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
- *SF3B1* and *JAK2* co-mutations are common, but are not currently required for the diagnosis



MDS/MPN-RS-T: a posterchild for the MDS/MPN family

MPN-like features

- **Clinical**
  - **Thrombocytosis**
  - **Need for cytoreduction**
- **Morphologic**
  - **Large megakaryocytes with bulbous nuclei**
- **Genetic**
  - ***JAK2* mutation (50-60%)**
  - **Infrequent *CALR/MPL* mutation**

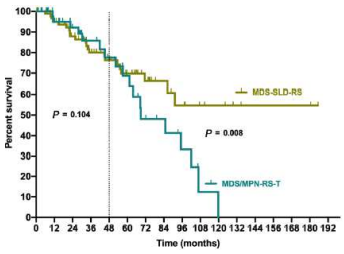
MDS-like features

- **Clinical**
  - **Macrocytic anemia**
  - **Transfusion requirement**
- **Morphologic**
  - **Erythroid dysplasia**
  - **Ring sideroblasts**
- **Genetic**
  - ***SF3B1* mutation (80-90%)**

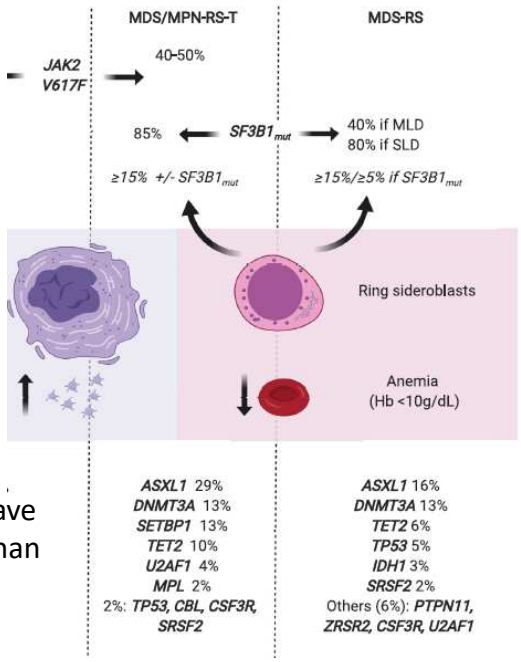
Wang SA Leukemia 2006;20:1641, Malcovati L Blood 2011;118:6239, Broseus Haematologica 2012;97:1036, Lu CM Leukemia & Lymphoma 2011;52:2405, Jeromin S Haematologica 2013;98:e15, Schmitt-Graeff A Haematolgica 2008;93:34, Szpurka H Blood 2006;108:2173, Jeromin S Haematologica 2015

MDS/MPN-RS-T in comparison to MDS-RS

- Both have frequent *SF3B1* mutation
- Both have erythroid dysplasia and ring sideroblasts (by definition)
- Usually *JAK2* or (rarely) *MPL* or *CALR* in MDS/MPN-RS-T
- MPN-like megakaryocytes in MDS/MPN-RS-T



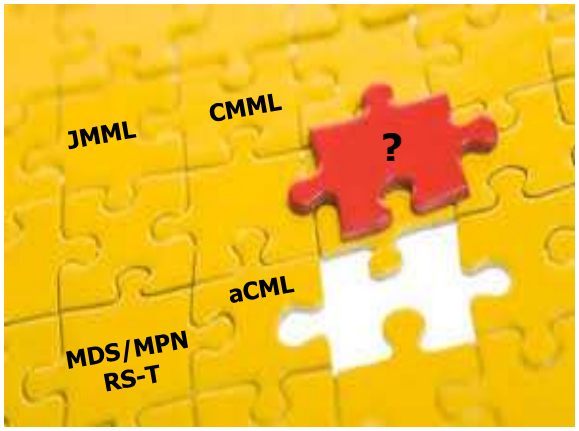
Both MDS-RS and MDS/MPN-RS-T have worse prognosis than essential thrombocythemia



Adapted from Montalban-Bravo G et al. Best Pract Res Clin Haematol 2020;33, Patnaik MM and Lasho TL, Hematology 2020 ASH Educational Program

MDS/MPN, unclassifiable

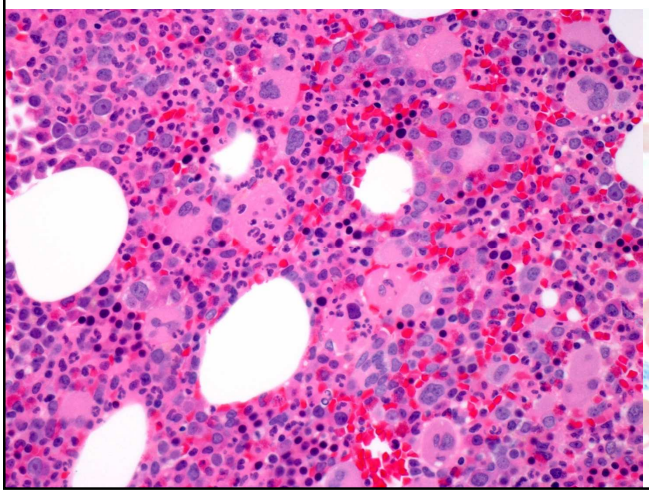
- MDS/MPN that cannot be placed into another category
- Usually due to:
  - Thrombocytosis + anemia and erythroid dysplasia, without ring sideroblasts
  - MDS/MPN with ring sideroblasts and thrombocytosis, but with excess blasts
  - Neutrophilia lacking granulocytic dysplasia, but with dysplasia in another lineage

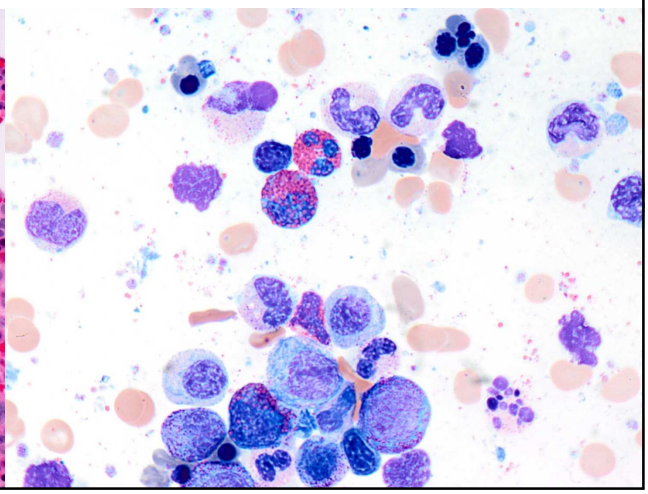


Typical example of MDS/MPN-U

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

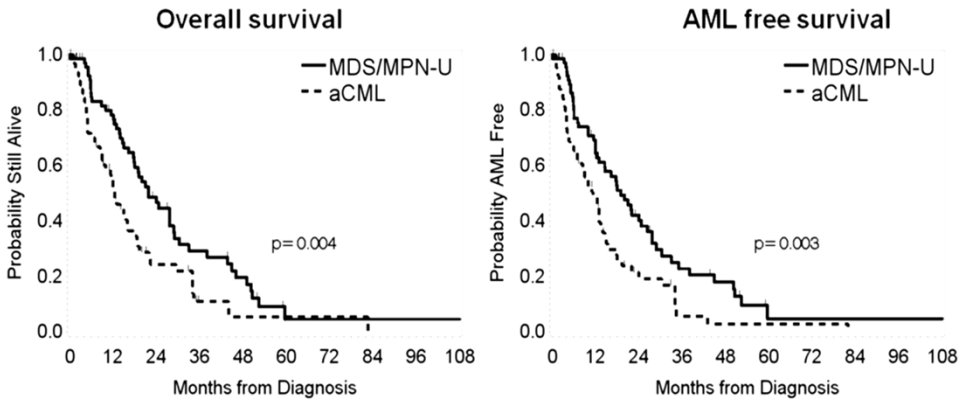
Normal karyotype
SETBP1, CSF3R, GATA2, ASXL1 mutations





MDS/MPN-U has more favorable prognosis than atypical CML

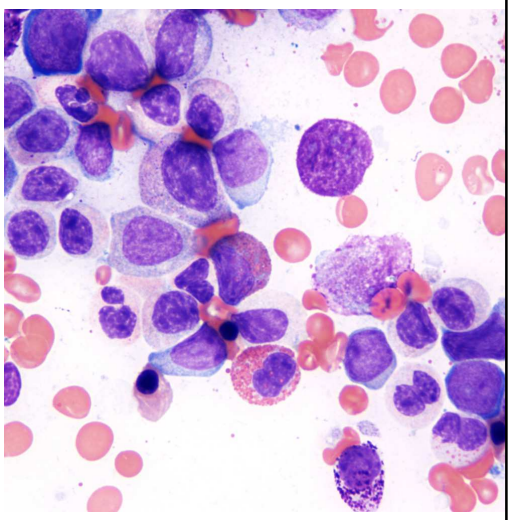
Figure 3



Wang SA et al. Blood. 2014; 123:2645

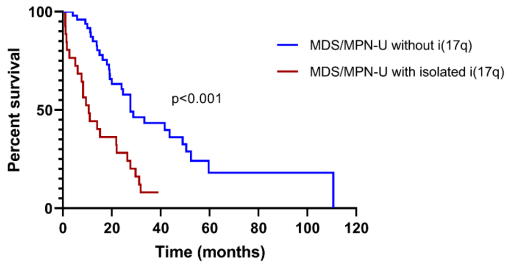
Isochromosome 17(q) in myeloid neoplasms

- Anemia, thrombocytopenia, leukocytosis
- Dysgranulopoiesis with neutrophil hypolobation or unilobation
- Rare *JAK2* mutation, no *TP53* mutation
- Many cases fall into atypical CML or MDS/MPN-U category



Kanagal-Shamanna R Cancer 2012;118:2879, Sanchez-Castro J Leuk Res 2013;37:769, Kanagal-Shamanna R Mod Pathol 2022;35:470.

MDS/MPN-U with i(17q) has worse OS than other MDS/MPN-U



Proposed new provisional MDS/MPN-U entity in 2022 ICC

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

Slide courtesy of Dr Attilio Orazi

MDS/MPN entities (WHO 2017)

	CMML	aCML	JMML	MDS/MPN-RS-T	MDS/MPN-U
Dysplasia	Any lineage	Granulocytic	Any lineage	Erythroids (ring sideroblasts)	Any lineage
Cytopenia	Any or none	Any or none	Any or none	Anemia	Any or none
Cytosis	Monocytes ≥1 x 10^9/L	WBC ≥13 x 10^9/L	Monocytes ≥1 x 10^9/L	Platelets ≥450 x 10^9/L	Platelets ≥450 x 10^9/L or WBC ≥13 x 10^9/L
Median OS	31 months	12 months	12 months	88-120 months	22 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%	**Monosomy 7 25%** **PTPN11 35%** NRAS/KRAS 25% CBL* 15% NF1* 10% **Germline*	***SF3B1* 85%** ***JAK2* 60%** *TET2* 25% *DNMT3A* 15% *MPL* 10% *ASXL1* 10%	*TET2* 30% *RUNX1* 15% *SETBP1* 10% *NRAS* 10% *CBL* 10% *EZH2* 10% *JAK2* 20%
Prognostic factors	Karyotype *ASXL1* mutation Blasts ≥10%	Karyotype Higher WBC Increased blasts	Mutation profile Thrombocytopenia Age >2 years	*SF3B1* mutation *JAK2* mutation	Karyotype

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.

Summary and take-home messages

- The MDS/MPN group encompasses diseases with morphologic dysplasia and one or more increased peripheral counts
- Detailed genetic characterization has identified correlations of mutation patterns with disease biology and prognosis in both MDS/MPN categories
- Diagnostic challenges include distinction from ‘pure’ MDS and MPN entities (including previously diagnosed cases with progression mimicking an MDS/MPN) as well as reactive monocytosis and leukocytosis