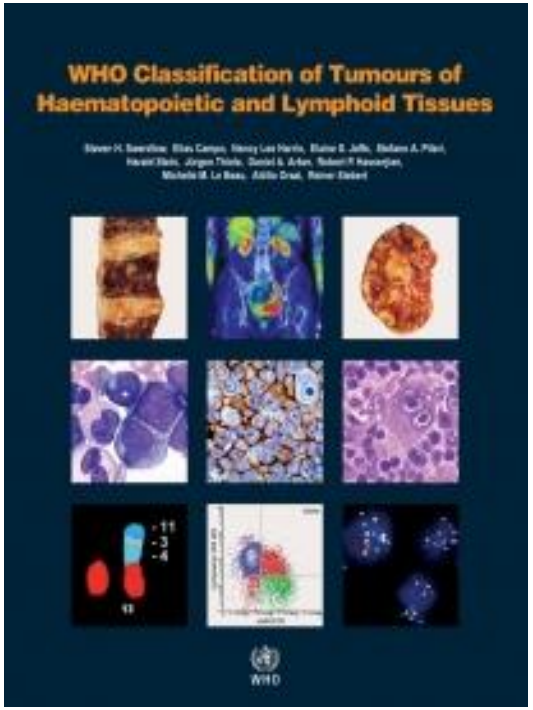
Gray-zone myeloid neoplasms: diagnosing cases overlapping different disease categories

Attilio Orazi, MD, FRCPath. (Engl.)
Professor and Chair, Department of Pathology
Paul L Foster School of Medicine, Texas Tech University Health Science Center, El Paso, TX -- USA

Neoplastic Diseases for the Practitioner. Texas Tech University Health Science Center, El Paso, TX -- June 14, 2019

Working with the WHO classification

- The classification recognizes entities which fit well into specific “diagnostic boxes”
- Our current approach allows classifying with a good degree of reproducibility the vast majority of cases encountered in daily practice
- However, rare cases “have not read the book”



Precise Classification: Clinical Relevance

Different group attribution may trigger:

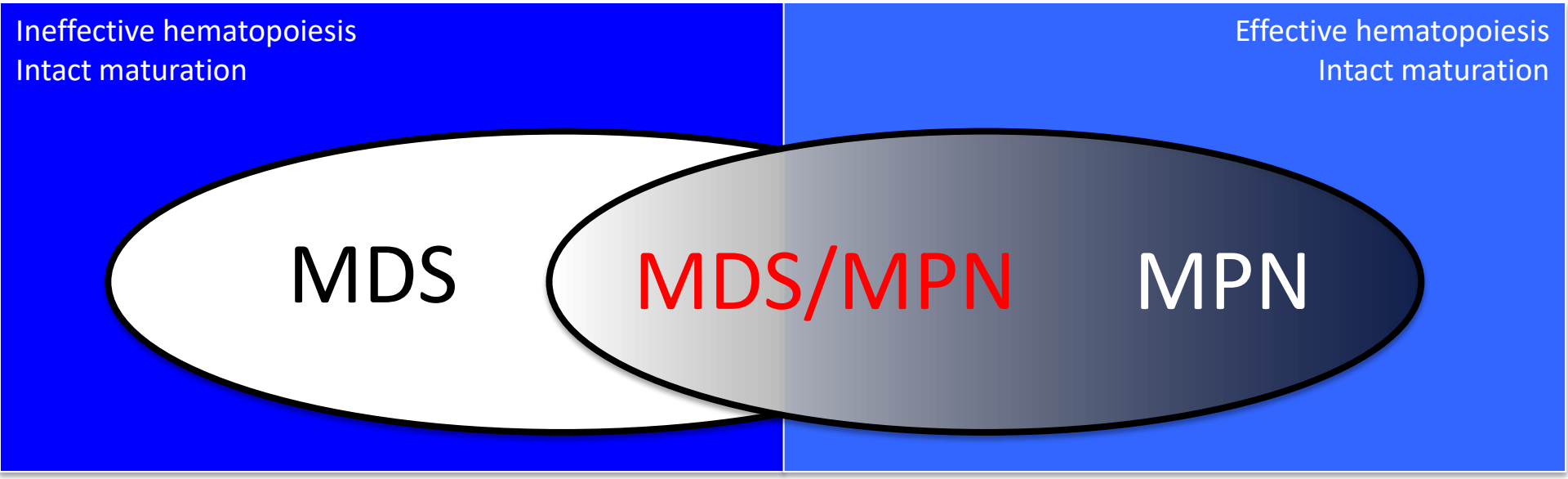
- Disease specific reflex testing
- Different follow-up intervals
- Disease specific interventions
  - JAK1/2 inhibition or Peg-IFN vs hypomethylation
  - Clinical trial enrollment
  - HSCT (different type of conditioning, timing)

Gray Zone Cases

The color of truth is gray

-André Gide

- Cases of myeloid neoplasm which seem to be falling between different diagnostic categories
- In some, confounding factors may play a role or they may be truly unclassifiable overlaps because of "discordant" clinicopathologic / genetic findings
- We will focus on chronic myeloid neoplasms, specifically:
  - Myelodysplastic Syndromes (MDS)
  - Myelodysplastic/myeloproliferative Neoplasms (MDS/MPN)
  - Myeloproliferative Neoplasms (MPN)



- ***Cytopenias***
- ***Dysplastic morphology***

- MDS with single lineage dysplasia
- MDS with ring sideroblasts and single lineage or multilineage dysplasia
- MDS with multilineage dysplasia
- MDS with excess blasts-1
- MDS with excess blasts-2
- MDS, unclassifiable
- MDS with isolated del(5q)

- ***Overlap features***

- Chronic myelomonocytic leukemia
- Atypical CML, *BCR-ABL1* negative
- MDS/MPN with ring sideroblasts and thrombocytosis
- MDS/MPN, unclassifiable

- ***Elevated counts***
- ***Non-dysplastic morphology***

- Chronic Neutrophilic Leukemia
- Polycythemia Vera
- Essential Thrombocythemia
- Primary Myelofibrosis
- Chronic Eosinophilic Leukemia, NOS
- MPN, unclassifiable

Courtesy of Robert Hasserjian, MD Mass Gen Hospital, Harvard University

Gray Zone: MDS vs. MDS/MPN

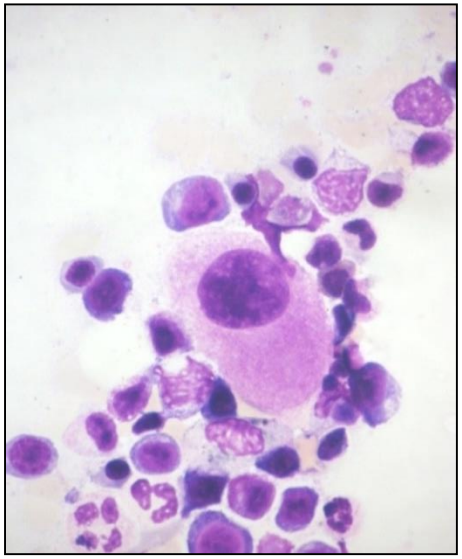
Abbreviations: MDS: Myelodysplastic Syndrome; MPN: Myeloproliferative Neoplasm

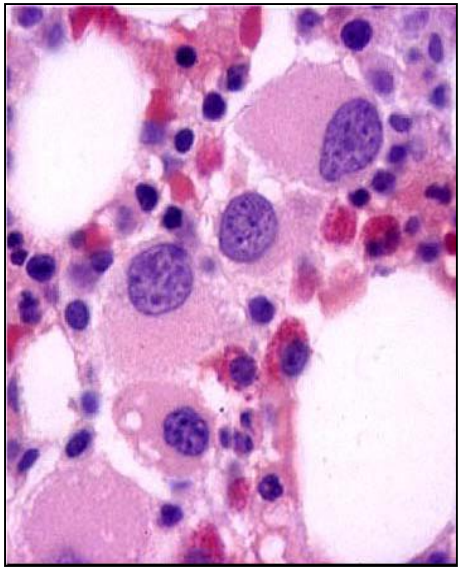
Gray zones in MDS with isolated del(5q)

- **MDS with isolated del(5q) and *JAK2* V617F mutation**
- **MDS with isolated del(5q) and *SF3B1* (ring sideroblasts)**

MDS with isolated del(5q)

- MDS del(5q) may have one additional cytogenetic abnormality [excluding -7, del(7q)]
- Macrocytic anemia, normal or high plts.; no incr. blasts in blood or bone marrow
- Marrow is normocellular to mildly hypercellular with typical nonlobated megakaryocytes
- RPS14 haploinsufficiency (microarray based gene expression profiling)
- Lenalidomide: median survival of 146 months
- TP53 mutations are prognostically relevant
- **The impact of other types of mutations is not well understood**





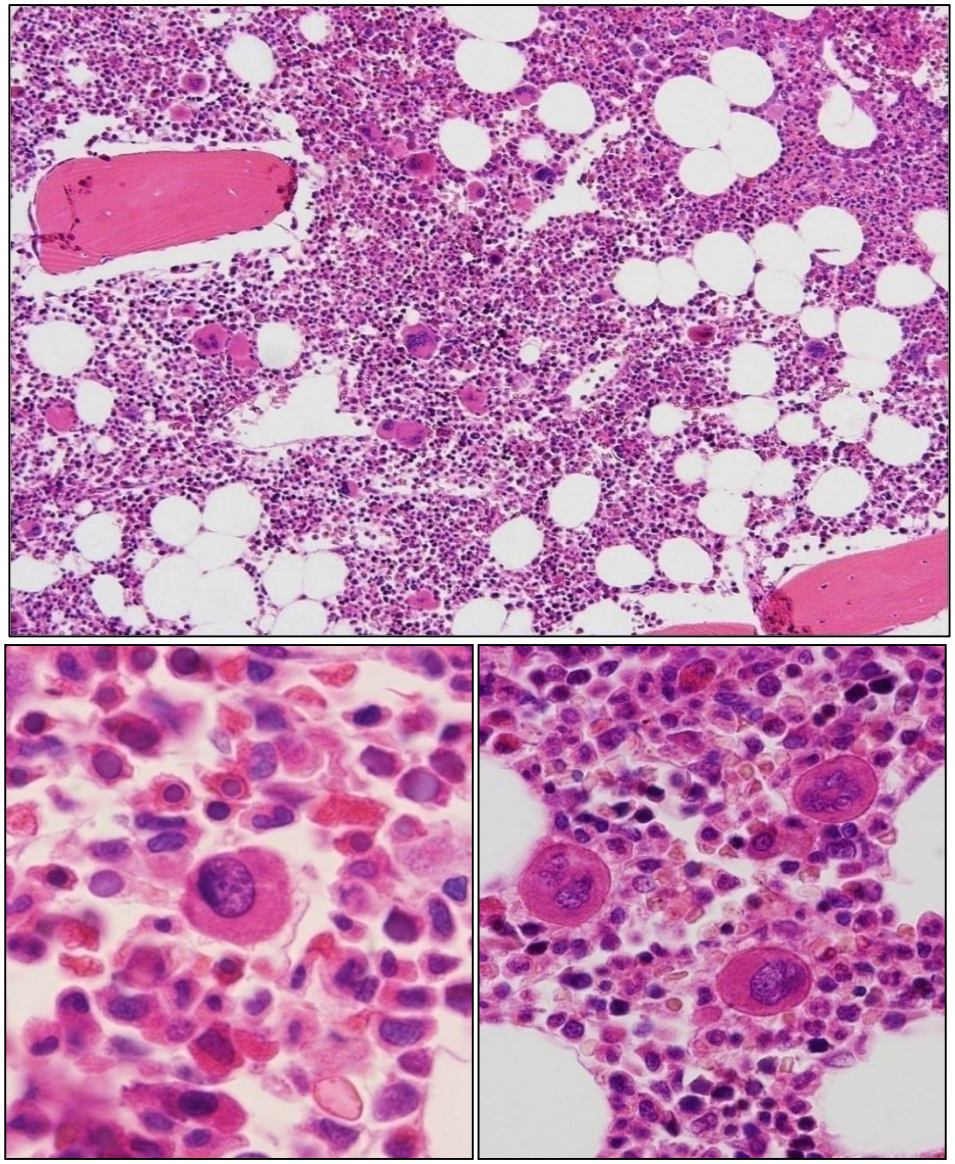
MDS 5q- with JAK2 mutation

- Rare: 10% cases
- A trend towards **higher platelet count**
- **Higher WBC**
- No difference in median HB 9.0 vs 8.7 g/dL (p=0.272)

Ingram et al: *Leukemia* 2006; 20:1319

Other studies:

- Patnaik MM Leukemia 2010
- Meggendorfer M et al. Haematologica 2017



MDS with isolated del(5q) and *JAK2* V617F mutation

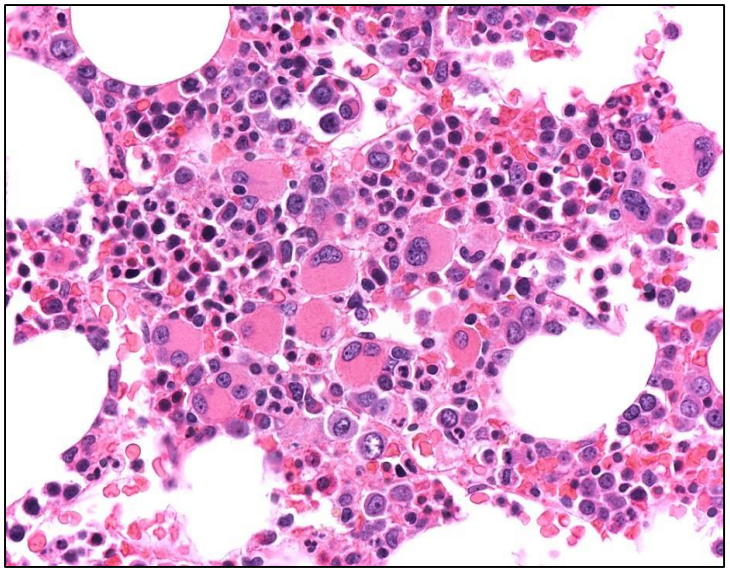
Our Ongoing Study

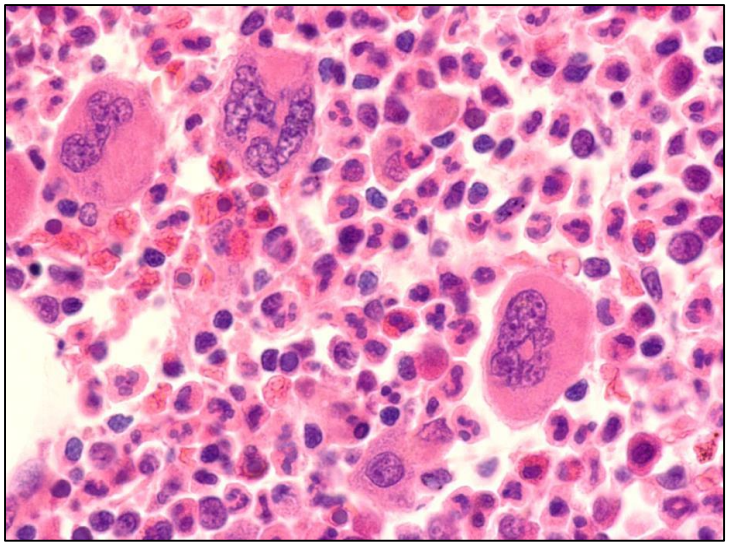
Dr. Valentina Sangiorgio, Visiting Fellow Univ. Milano, Italy

- 47 cases of MDS with isolated del(5q) between 2001 and 2018, classified according to WHO (Revised 4th edition)
- **6 cases (12.7%)** were ***JAK2* V617F positive**.
- Pts. at diagnosis showed:
  - ✓ **Mild leukocytosis** (80% of cases; mean WBC 12.8x10^9/L)
  - ✓ **Relatively high Hb levels** (mean Hb 12.1 g/dL)
  - ✓ **Thrombocytosis** (mean platelets count 466x10^9/L)
- **Splenomegaly: 50%** of patients had diagnosis had splenomegaly (mean spleen size 14.6 cm)
- **LDH** available in 3/6 pts: mean value 490 (normal <250 U/l)

Microscopic Findings

- Hypercellular BM
- Megakaryopoiesis increased
- Heterogeneous megakaryocytes:
  - Small forms with hypolobated or nonlobated nuclei
  - Large megakaryocytes with hyperlobulated nuclei





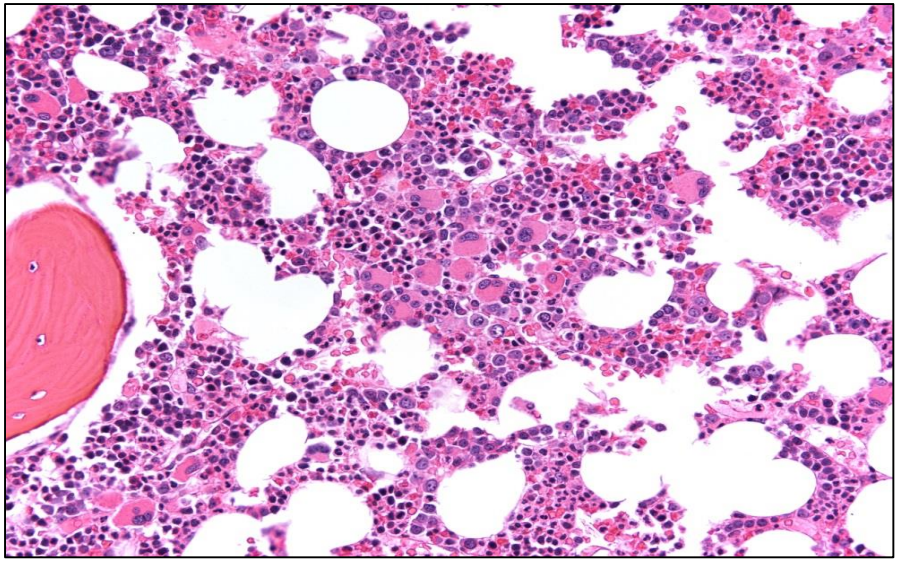
Preliminary Results

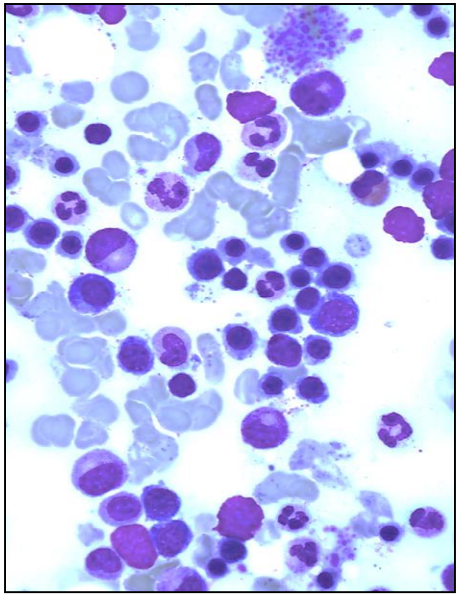
- **MDS del(5q) plus JAK2 mutation** has a clinical picture and BM morphology MDS/MPL-like
- Prognosis: although we did see evidence of progression (incr. blasts and fibrosis) in three of our pts., the small databases and short follow up did not allow to get statistical confirmation
- Currently del(5q) trumps mutations in this MDS sybtype
  - Should these cases be re-classified as MDS/MPN?

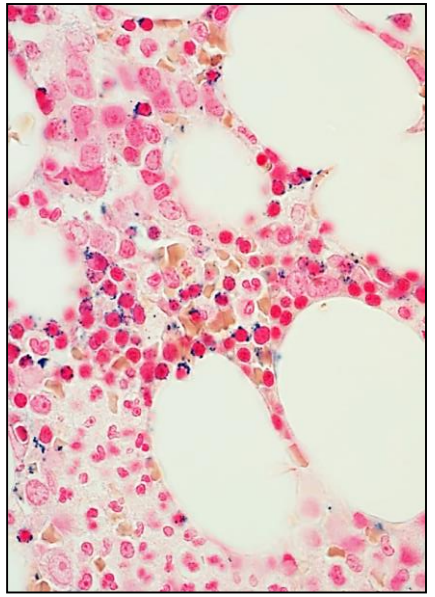
MDS with isolated del(5q) plus *SF3B1*

SF3B1 mutation in MDS with 5q-

- Rare <5-10% cases
- Correlation with RS has nbot be examined
- It is unclear whether the presence of *SF3B1* mutation affects the prognosis of MDS 5q-







Preliminary Results

Dr. Valentina Sangiorgio, Visiting Fellow Univ. Milano, Italy

- 8/20 cases of MDS with isolated del(5q) tested by NGS **had SF3B1 mutations** (all with ring sideroblasts at MDS-RS frequency of ≥15%)
  - 6/8 mutated cases **had other concurrent mutations** (TET2, DNMT3A, RUNX1, P53, ETV6)
- **Unclear differences in morphology or prognosis** Seems to validate WHO position to ignore the *SF3B1* and/or RS in a case of MDS with isolated 5q

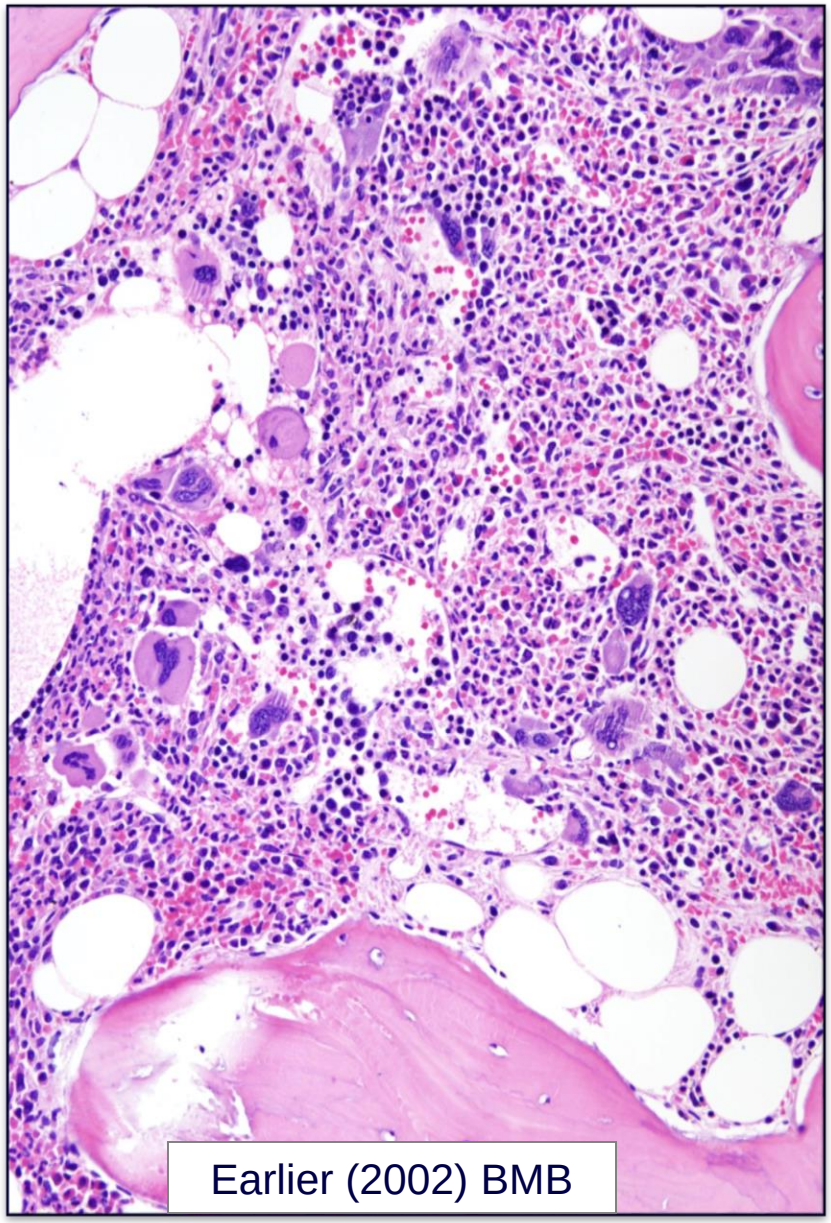
Gray zone: MPN vs. MDS-MDS

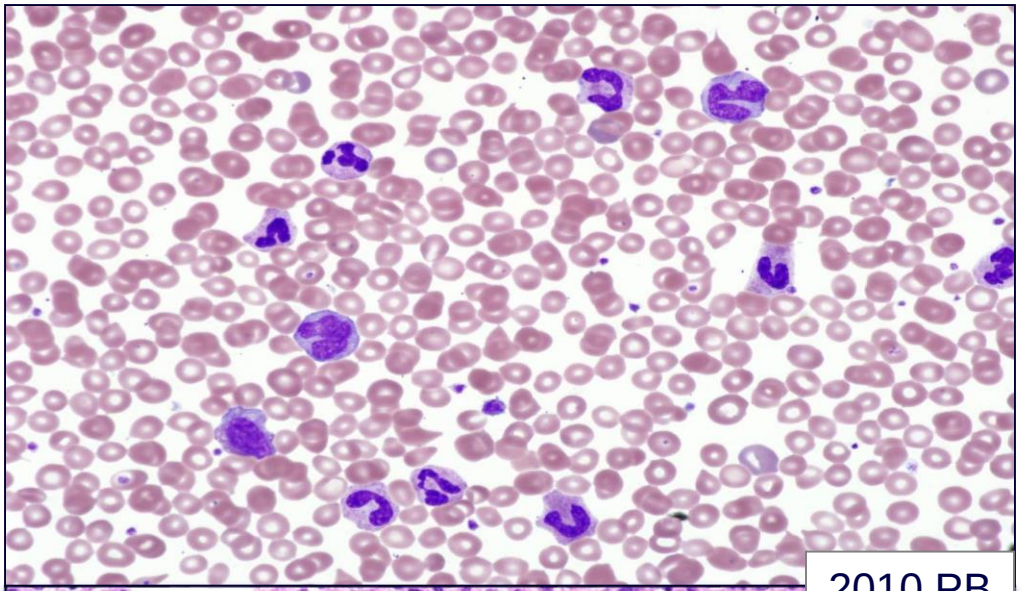
Primary Myelofibrosis with Monocytosis

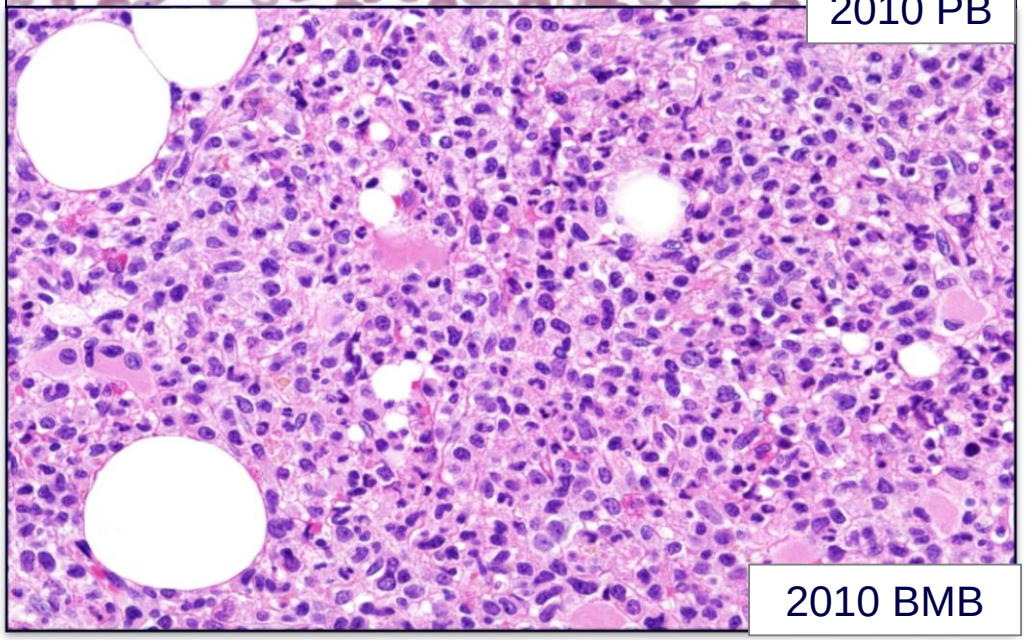
vs.

Chronic Myelomonocytic Leukemia (CMML)

Primary Myelofibrosis with Monocytosis







Boiocchi L. et al. *Mod Pathol*. 2013;26:204-12

Diagnostic criteria for CMML (Update 2016)

- Persistent PB monocytosis $\geq 1\times10^9$/L and $\geq$ 10% of the WBC
- **Not meeting WHO criteria for** *BCR-ABL1* pos. CML, **PMF,** PV or ET [a]
- No rearrangement of *PDGFRA, PDGFRB, FGFR1*, or *PCM1-JAK2*
- Fewer than 20% blasts (include promonocytes) in the PB and BM
- Dysplasia in $\geq$ myeloid lineages. If myelodysplasia is absent, the diagnosis of CMML may still be made if the other requirements are met, and an acquired cytogenetic or molecular genetic abnormality [b] is detected, --*or*-- - the monocytosis persisted for at least 3 mos. and all other causes of monocytosis have been excluded

[a]Cases of MPN can be associated with monocytosis or they can develop it during the course of the disease. These cases may simulate CMML. A previous documented history of MPN excludes CMML, while the presence of MPN features in the BM and/or of MPN-associated mutations (*JAK2, CALR* or *MPL*) tend to support MPN with monocytosis rather than CMML. [b]The presence of mutations in genes often associated with CMML (e.g. *TET2, SRSF2, ASXL1, SETBP1*) in the proper clinical contest can be used to support a diagnosis. It should be noted however, that some of the mutations can be age related or be present in subclones. Caution would have to be used in the interpretation.

Adapted from Orazi A et al. WHO 2016 update

MODERN PATHOLOGY (2017), 1–13

Myeloid neoplasms with features intermediate between primary myelofibrosis and chronic myelomonocytic leukemia

Jennifer Chapman[1], Julia T Geyer[2], Mahsa Khanlari[1], Adrienne Moul[1], Carmen Casas[3], Scot T Connor[3], Yao-Shan Fan[3], Justin M Watts[4], Ronan T Swords[4], Francisco Vega[1] and Attilio Orazi[2]

[1]Division of Hematopathology, Department of Pathology, University of Miami/Sylvester Comprehensive Cancer Center, Miami, FL, USA; [2]Division of Immunopathology, Department of Pathology and Laboratory Medicine, Weill Cornell Medicine, New York, NY, USA; [3]Division of Cytogenetics, Department of Pathology, University of Miami/Sylvester Comprehensive Cancer Center, Miami, FL, USA and [4]Division of Hematology and Oncology, Department of Medicine, University of Miami/Sylvester Comprehensive Cancer Center, Miami, FL, USA

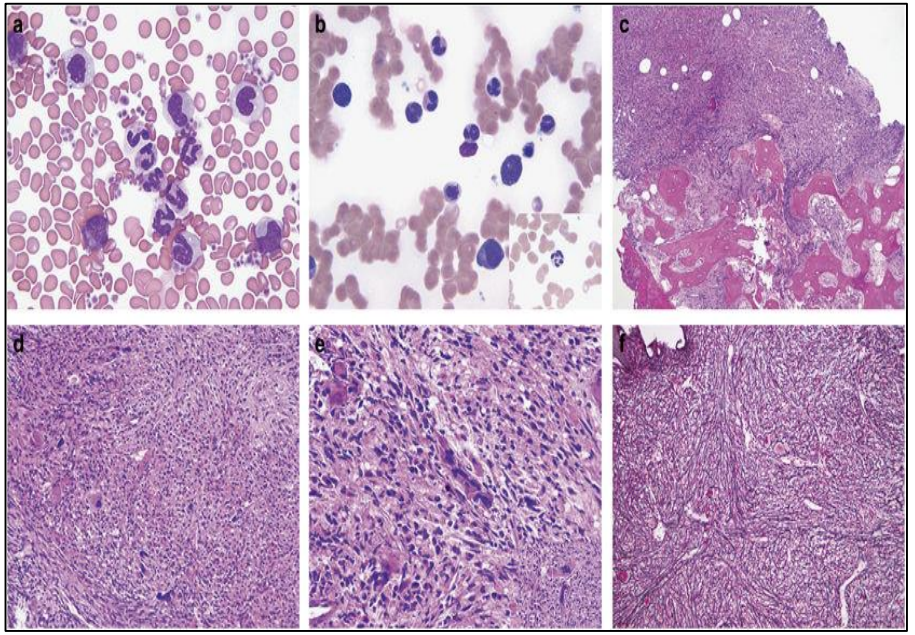
Monocytosis can develop during disease course in primary myelofibrosis simulating that seen in chronic myelomonocytic leukemia, and should not lead to disease reclassification. In contrast, at presentation, rare cases have clinical, morphologic, and molecular genetic features truly intermediate between primary myelofibrosis and chronic myelomonocytic leukemia. The taxonomy and natural history of these diseases are unclear. We identified cases which either: (1) fulfilled the 2008 World Health Organization criteria for primary myelofibrosis but had absolute monocytosis and, when available, chronic myelomonocytic leukemia-related mutations (*ASXL1*, *SRSF2*, *TET2*) or (2) fulfilled criteria of chronic myelomonocytic leukemia but had megakaryocytic proliferation and atypia, marrow fibrosis, and myeloproliferative-type driver mutations (*JAK2*, *MPL*, *CALR*). Patients with established primary myelofibrosis who developed monocytosis and those with chronic myelomonocytic leukemia with marrow fibrosis were excluded. By combining the pathology databases of two large institutions, six eligible cases were identified. Patients were predominantly male and elderly with monocytosis at diagnosis (average 17.5%/2.3 × $10^3/\mu l$), organomegaly, primary myelofibrosis-like atypical megakaryocytes admixed with a variable number of chronic myelomonocytic leukemia-like hypolobated forms, variable myelodysplasia, marrow fibrosis and osteosclerosis. All had a normal karyotype and no myelodysplasia-associated cytogenetic abnormalities. Five of the patients in whom a more extensive molecular characterization was performed showed co-mutations involving *JAK2* or *MPL* and *ASXL1*, *SRSF2*, *TET2*, *NRAS*, and/or *KRAS*. Disease progression has occurred in all and two have died. Rare patients present with features that overlap between primary myelofibrosis and chronic myelomonocytic leukemia and are thus difficult to classify based on current World Health Organization criteria. Biologically, these cases likely represent primary myelofibrosis with monocytosis, dysplasia, and secondary (non-driver) mutations at presentation. Alternatively, they may represent a true gray zone of neoplasms. Their clinical behavior appears aggressive and innovative therapeutic approaches may be beneficial in this particular subset.

Modern Pathology advance online publication, 1 December 2017; doi:10.1038/modpathol.2017.148

MODERN PATHOLOGY
USCAP AN OFFICIAL JOURNAL OF THE UNITED STATES AND CANADIAN ACADEMY OF PATHOLOGY
Publishing innovative clinical and translational research in the pathology of human disease

Mod Pathol. 2018;31:429-441

Case 4



MPL(44%), *ASXL1*(43%), *SRSF2*(46%), *TET2*(48%), *TET2*(42%), *NRAS*(25%), a mutation of uncertain significance in *EZH2*(51%)

46,XY[20]. FISH for MDS-associated abnormalities negative

Gray zone: MPN vs. MDS-MDS

Chronic Neutrophilic Leukemia (CNL)

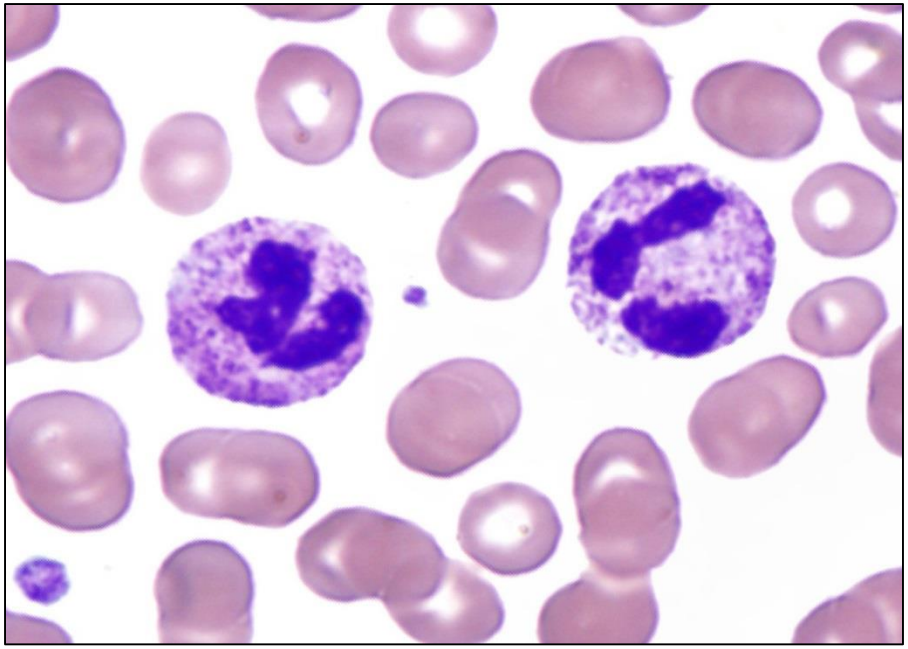
vs

Atypical Chronic Myeloid Leukemia *BCR-ABL1* neg. (aCML)

CNL vs. aCML

CNL

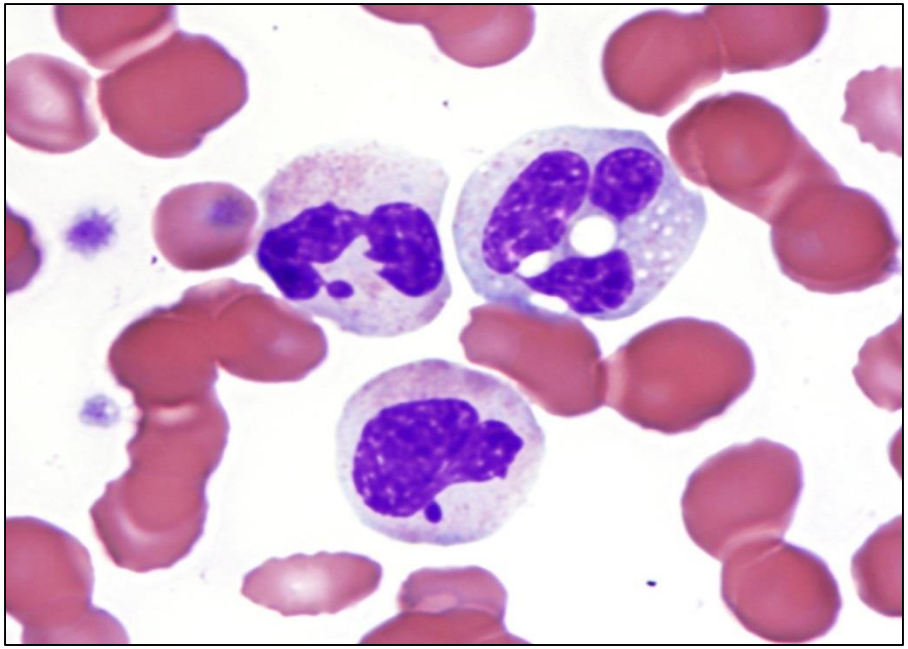
- Neutrophilia with no significant dysplasia (toxic granulations)



***CSF3R* (90%)**
additional *SETBP1* +/- (50%)
ASXL1
SF3B1 (rare; raises MDS/MPN overlap)

aCML

Neutrophilia with immature myeloid cells and dysplasia



***SETBP1* (15-32%)**
ETNK1 (9%); in one third of these, coexists with *SETBP1*
CSF3R (0 to <10%)

Practical suggestions

- When **diagnostically relevant cytogenetic abnormalities and mutations** are found together in a given case, the WHO stipulates that **cytogenetics trumps mutations**
- An in-depth review of the clinical history is always helpful
  - Please note that overlapping morphologic features can be caused by prior therapy
  - Co-morbidity, e.g. infections or cytokines may produce a MDS/MPN picture in a pt. with MDS
- Do not forget that some mutations although not “name changers” have a clear prognostic value and should be discussed in the diagnostic report
- Simply because a case cannot be fully classified (put in a specific box) do not overlook important “clinical triggers” e.g. the presence of an actionable genetic abnormality

Case (Dr. Gaur' patient)

Jan 2015

- **HB 6.9 g/dl**
- **MCV 94.4 fl**
- RBC 2.34 x10^6 /ml
- WBC 4.5 x10^9 /L
  - (N 50%; Myelo 1%, Meta 2%; Band 5%; Mono 2%; Lymp 40%)
- **PLT 547 x10^9 /L**

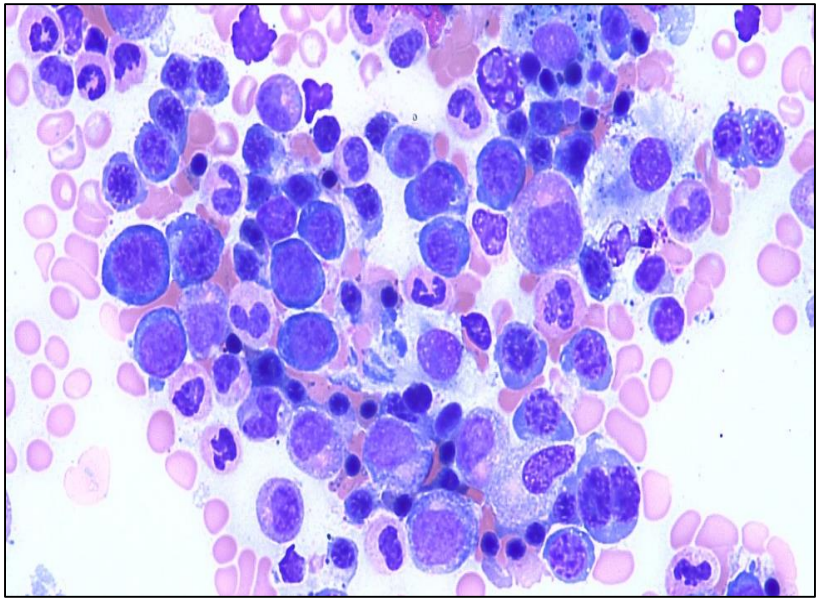
September 2015

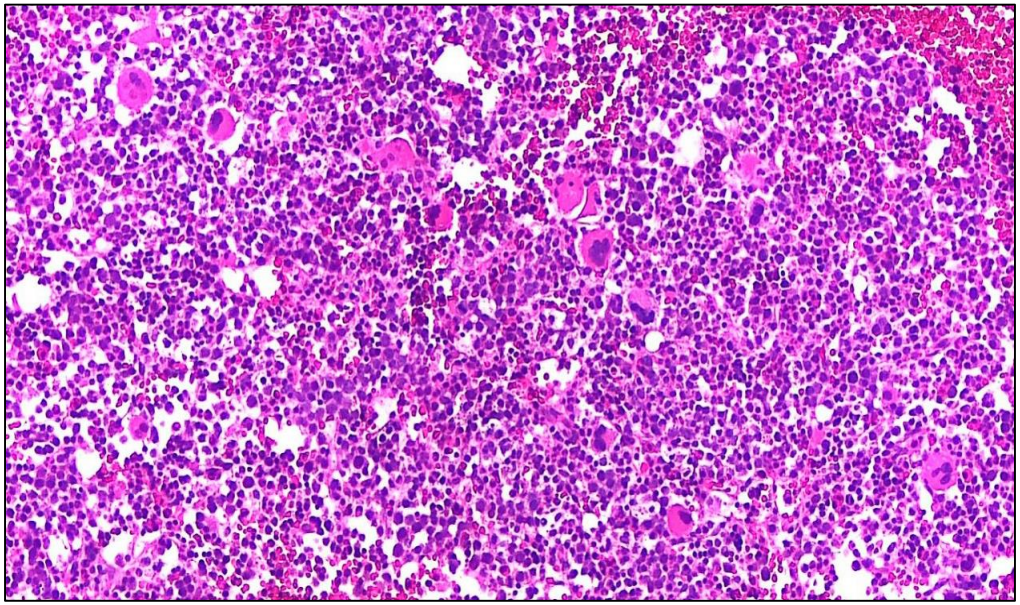
- **HB 8.4 g/dl**
- **MCV 91.8 fl**
- RBC 2.81 x10^6 /ml
- WBC 2.4 x10^9 /L
  - (N 38%; Eos 1%; Mono 1%, Lymp 60%)
- **PLT 378 x10^9 /L**

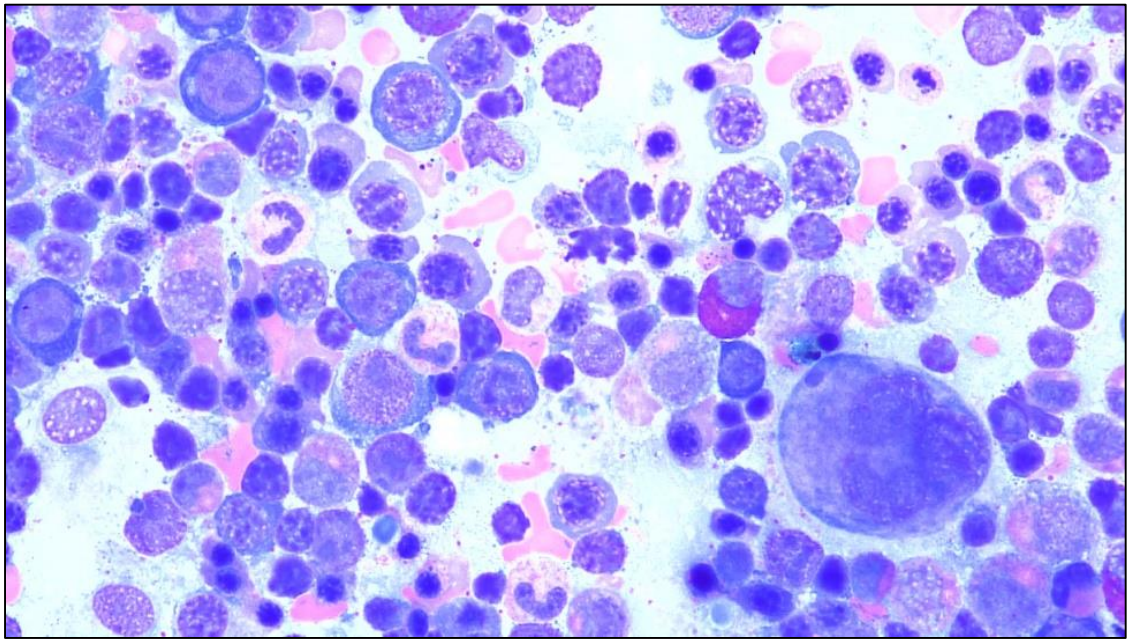
Normal karyotype at the two time points

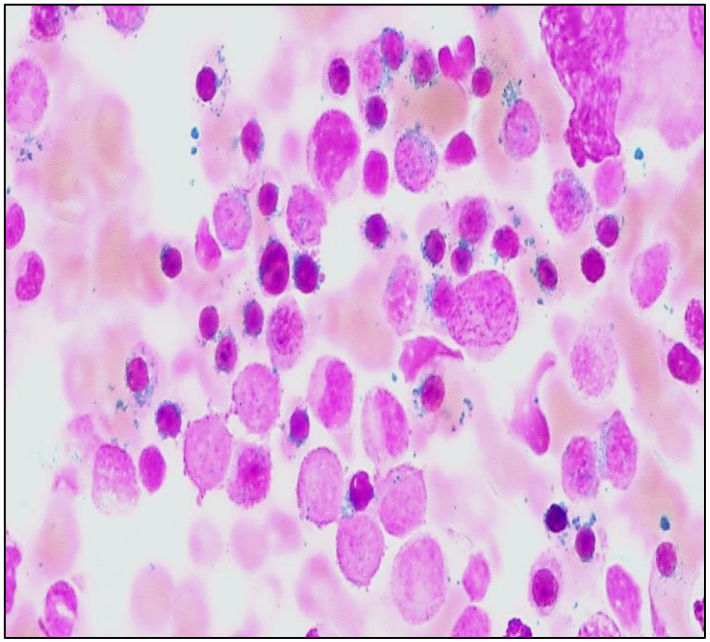
Presence of SF3B1 mutation detected in 09/15,

Marrow examination Jan 2015







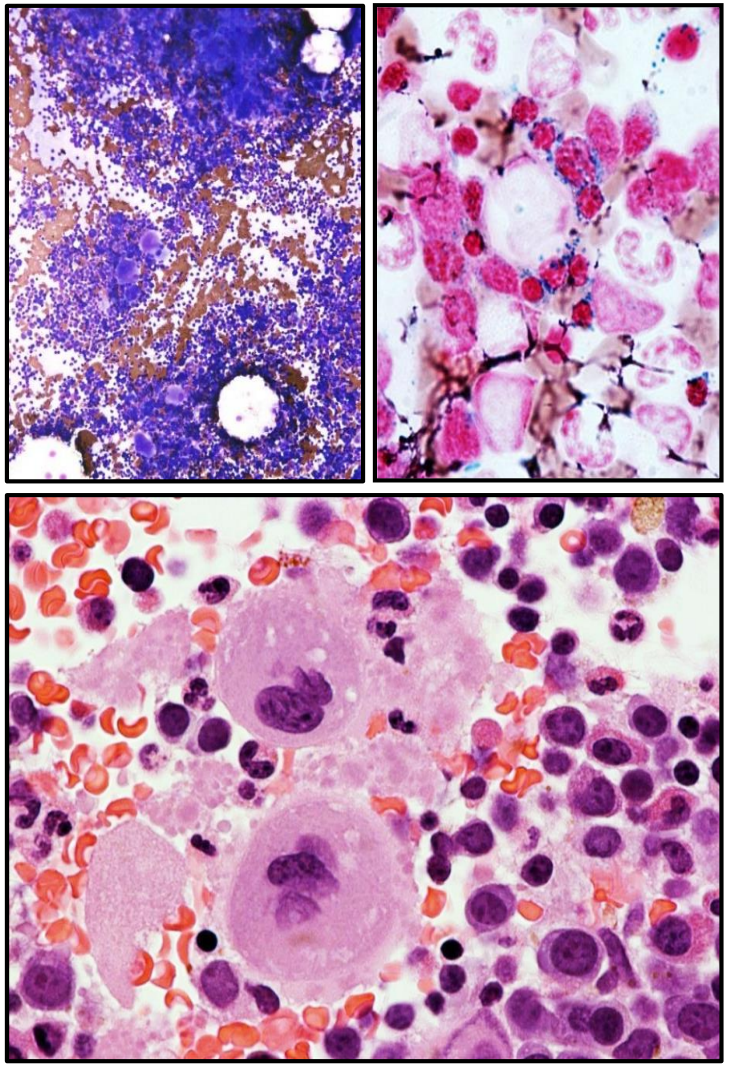


Diagnosis

- Marrow (01/15):
  - Myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)

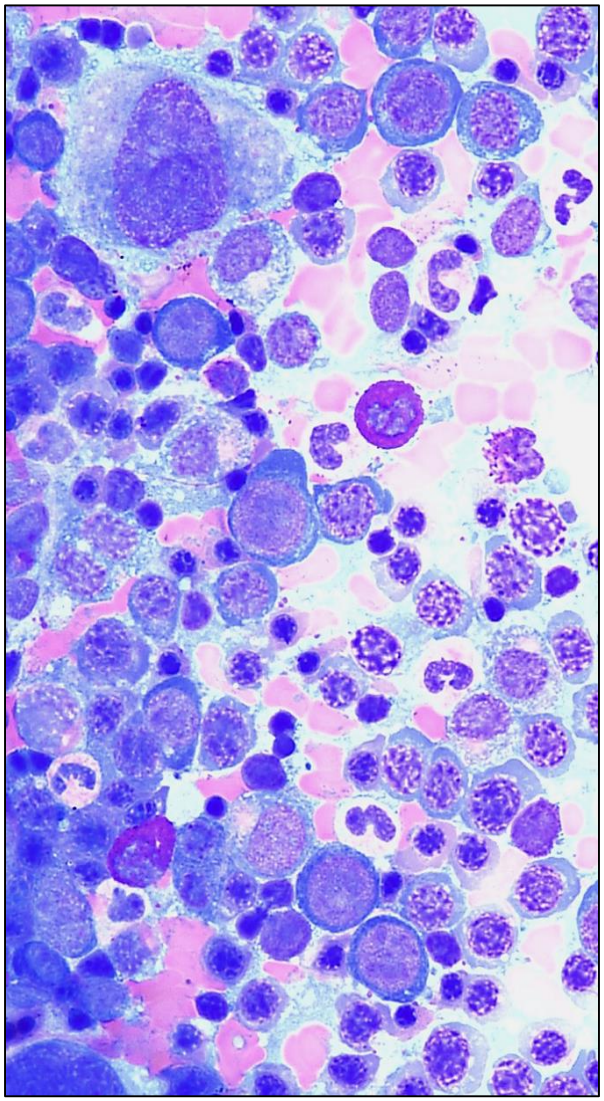
MDS/MPN-RS-T: The *Perfect* Overlap Syndrome

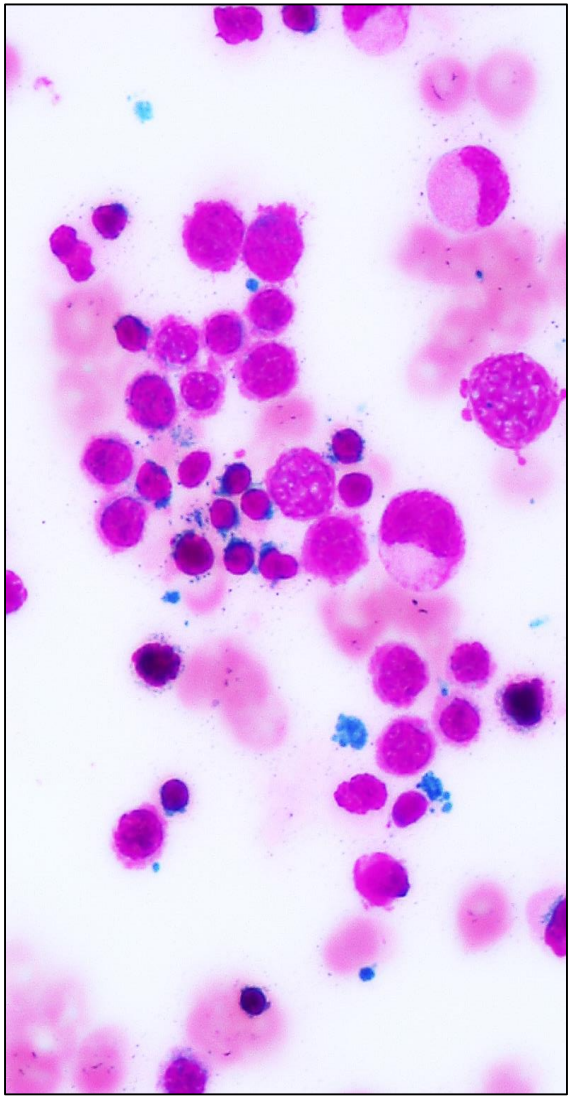
- Formerly known as refractory anemia with ring sideroblasts and thrombocytosis
- MDS/MPN hybrid features clinically, morphologically and molecularly
- May progress from MDS-RS
- ***SF3B1* mutation (80%)**
- ***JAK2* V617F pos. in up to 60%; *MPL W515K/L*, 5% (*CALR* rare)**
- Karyotype variable e.g., +8, del(20)(q11.2)

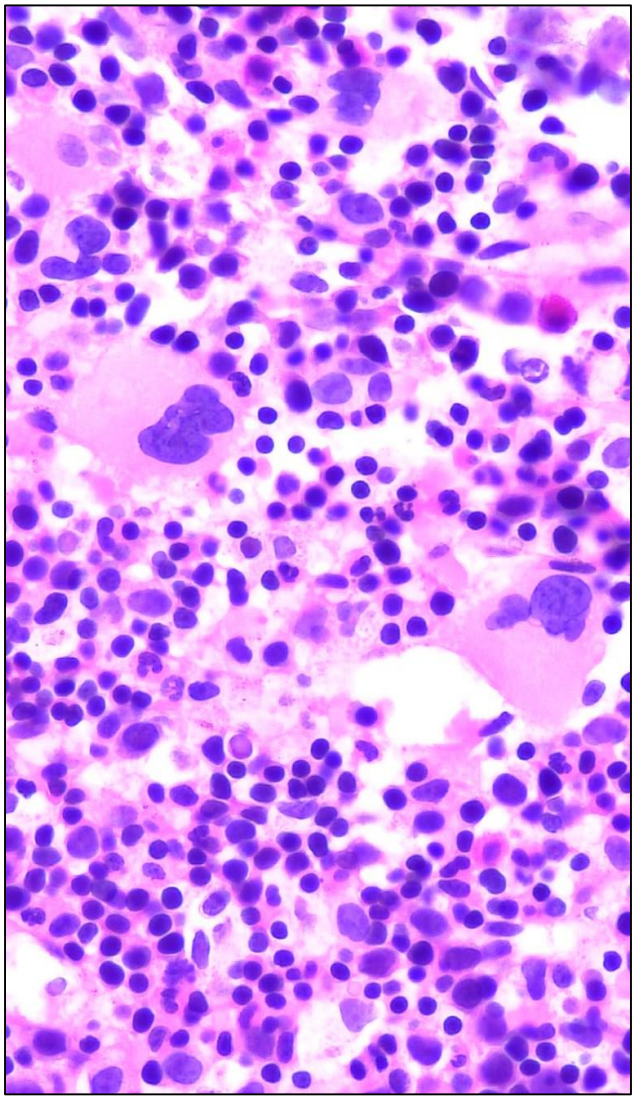


Orazi A et al. WHO Classification 2017. IARC Press Lyon, FR

Marrow Examination Sept 2015







Diagnosis

- Marrow (09/15):
  - Myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (in course of treatment)

Thank you!