Probable Early Myelodysplastic Syndrome

Case Number: SH2017-269

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Clinical History

- 67-year-old man
- PMHx:
  - Sweet's syndrome & knee pain 6 years ago (prednisone)
  - Progressed to polyarthritis (DMARDs)
  - Developed pulmonary histoplasmosis (prednisone)
  - Mild leukopenia for past 21 mths (MTX)
  - 6 mths ago developed acute pericarditis (colchicine)
- Mild microcytic anemia, neutropenia, & relative monocytosis→ BM bx to r/o T-LGL

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CBC

- Hgb 12.3 g/dL
- RBC 5.88 x 10^{12}/L
- **MCV 69.2 fL** ↓
- **RDW 18.4%** ↑
- **WBC 3.3 x 10^9/L** ↓
- PLT 172 x 10^9/L

WBC Differential (%)

- Neutrophils: 51→ **ANC 1.7 x 10^9/L**
- Lymphocytes: 24→ **ALC 0.8 x 10^9/L**
- Monocytes: **24**→ AMC 0.8 x 10^9/L
- Basophils 1

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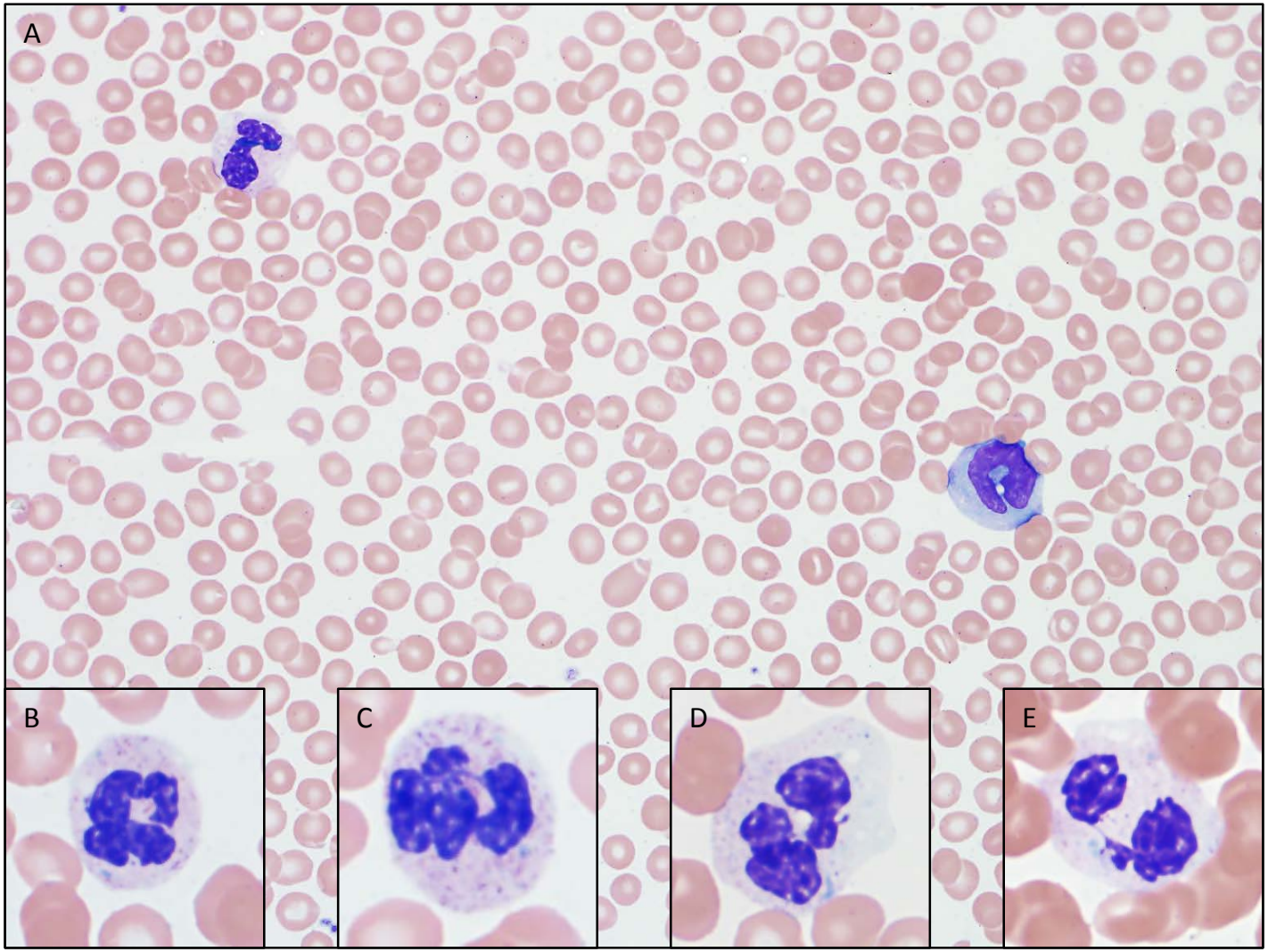
PB Smear



- Rather unremarkable PB smear (A)
- While the majority of the circulating neutrophils were cytologically normal (B & C), **occasional hypogranular (D) and Pseudo-Pelger-Hüet (E) neutrophils** were present

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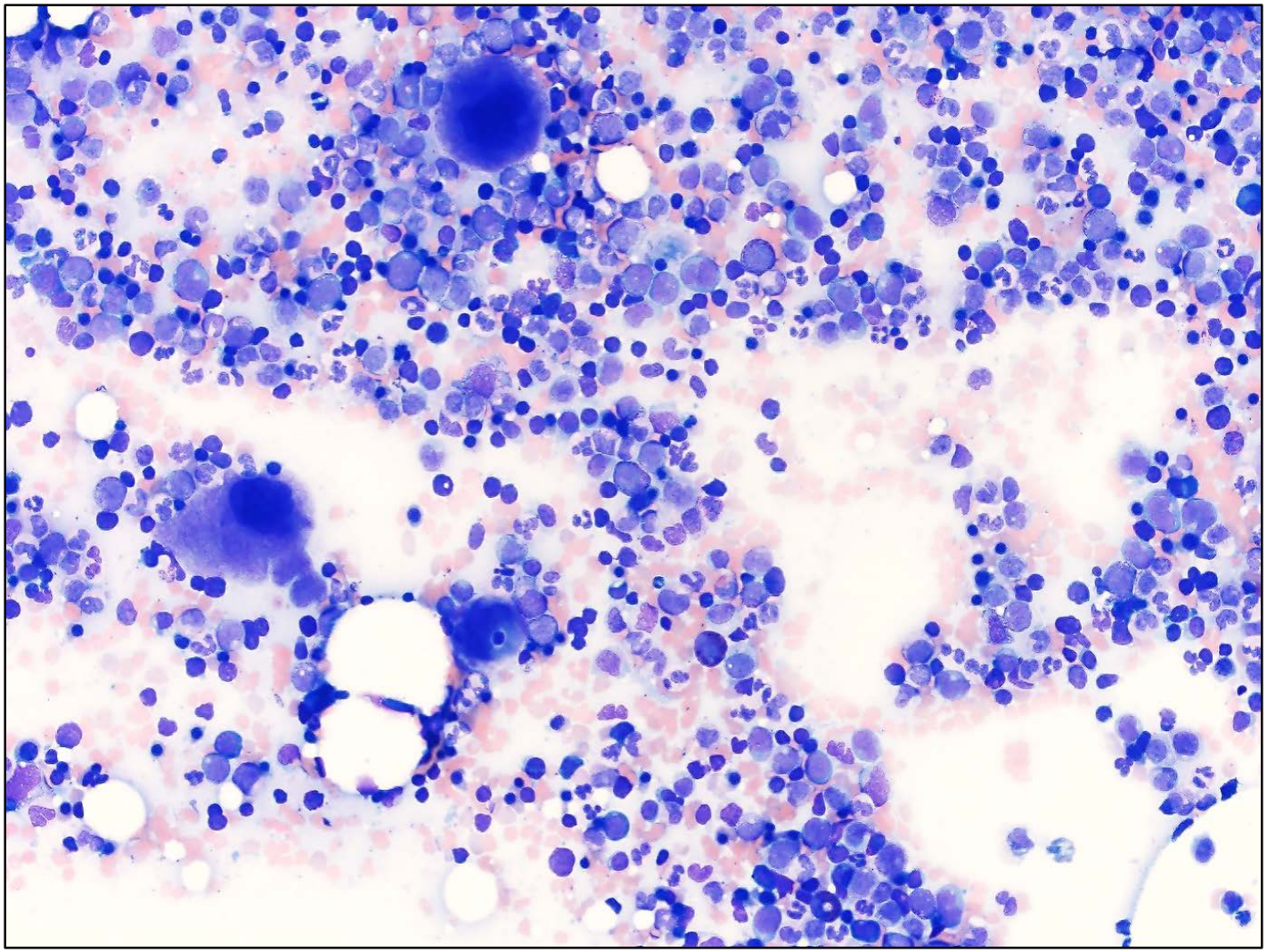
BM Aspirate



- Cellular with intact trilineage hematopoiesis

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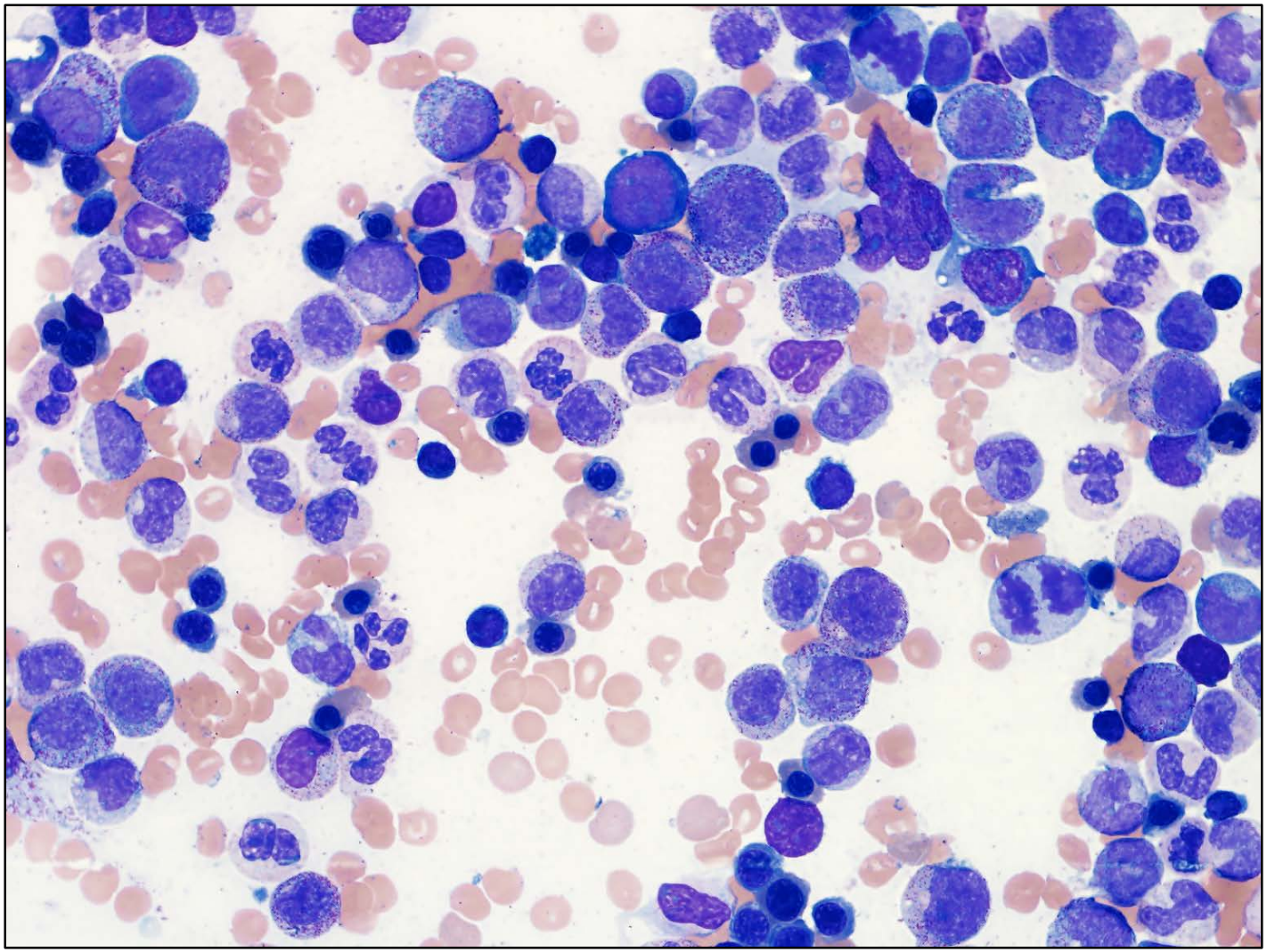
BM Aspirate Con't



- Unremarkable erythroid maturation
- Majority of the granulocytic maturation unremarkable
- No increase in blasts

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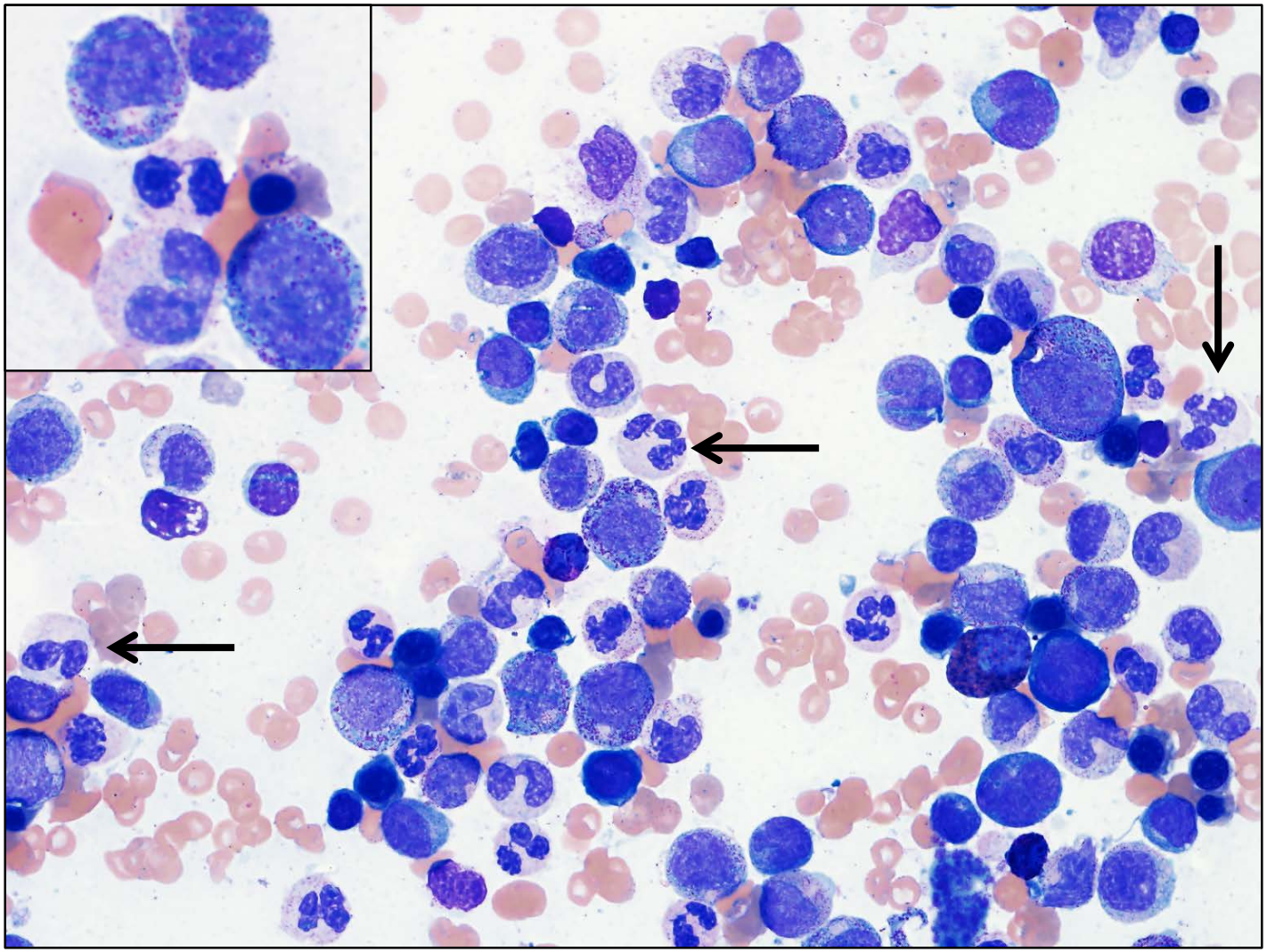
BM Aspirate Con't



- However, there were occasional areas with **subtle hypogranular neutrophils (arrows) and a rare Pseudo-Pelger-Hüet form** was identified (insert)

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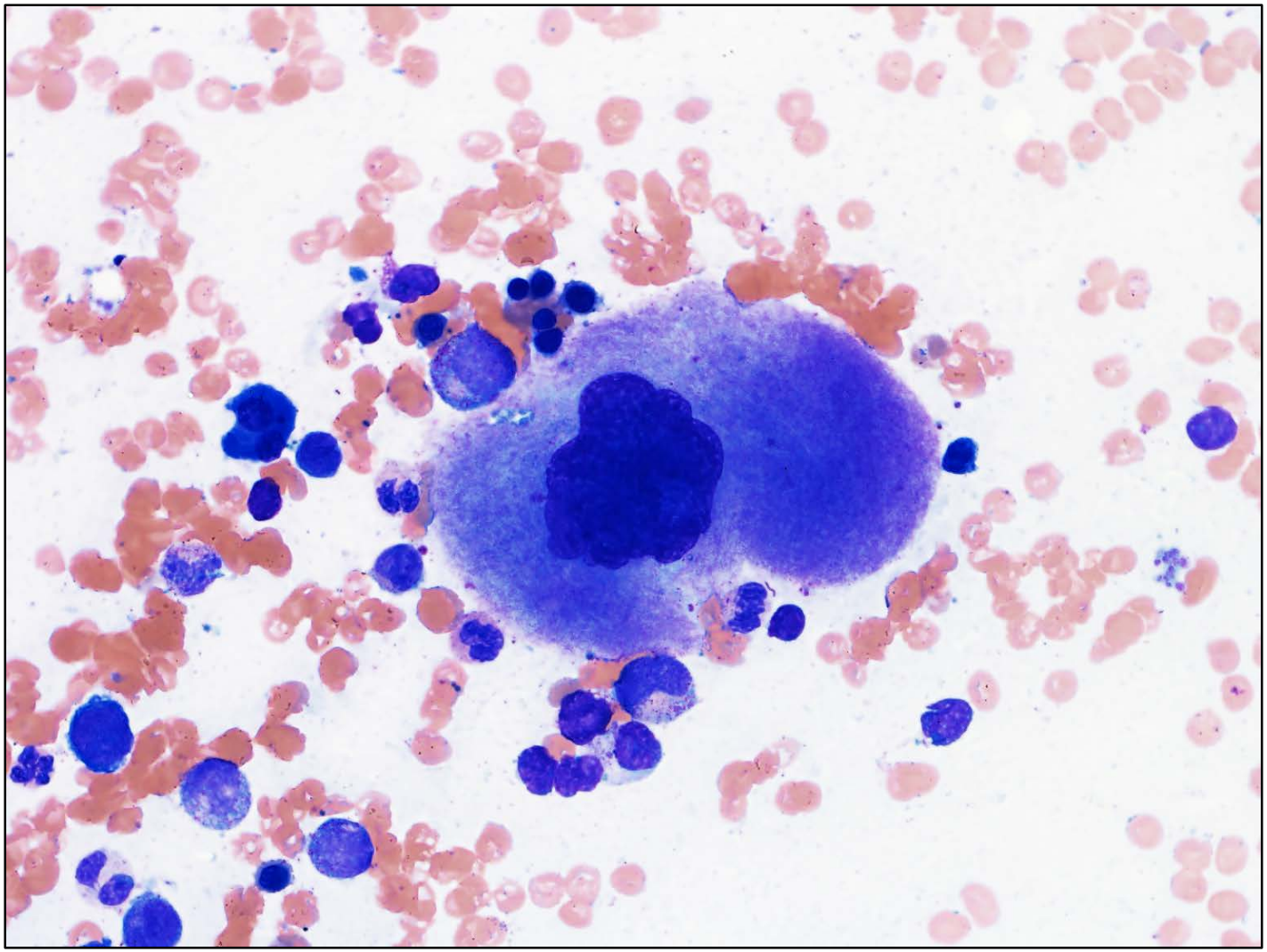
BM Aspirate Con’t



- Occasional hyperchromatic megakaryocyte

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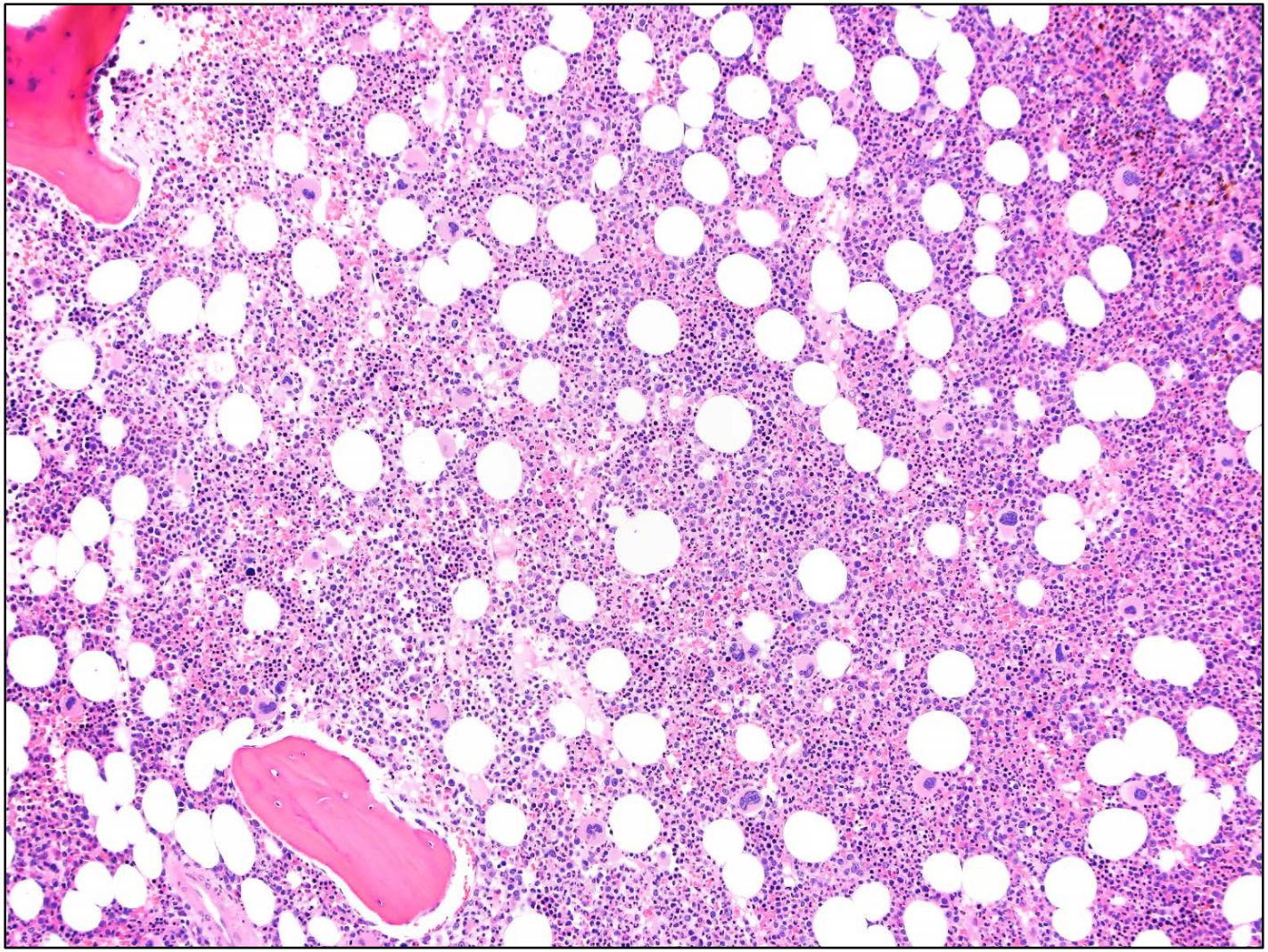
BM Biopsy



- Hypercellular bone marrow biopsy

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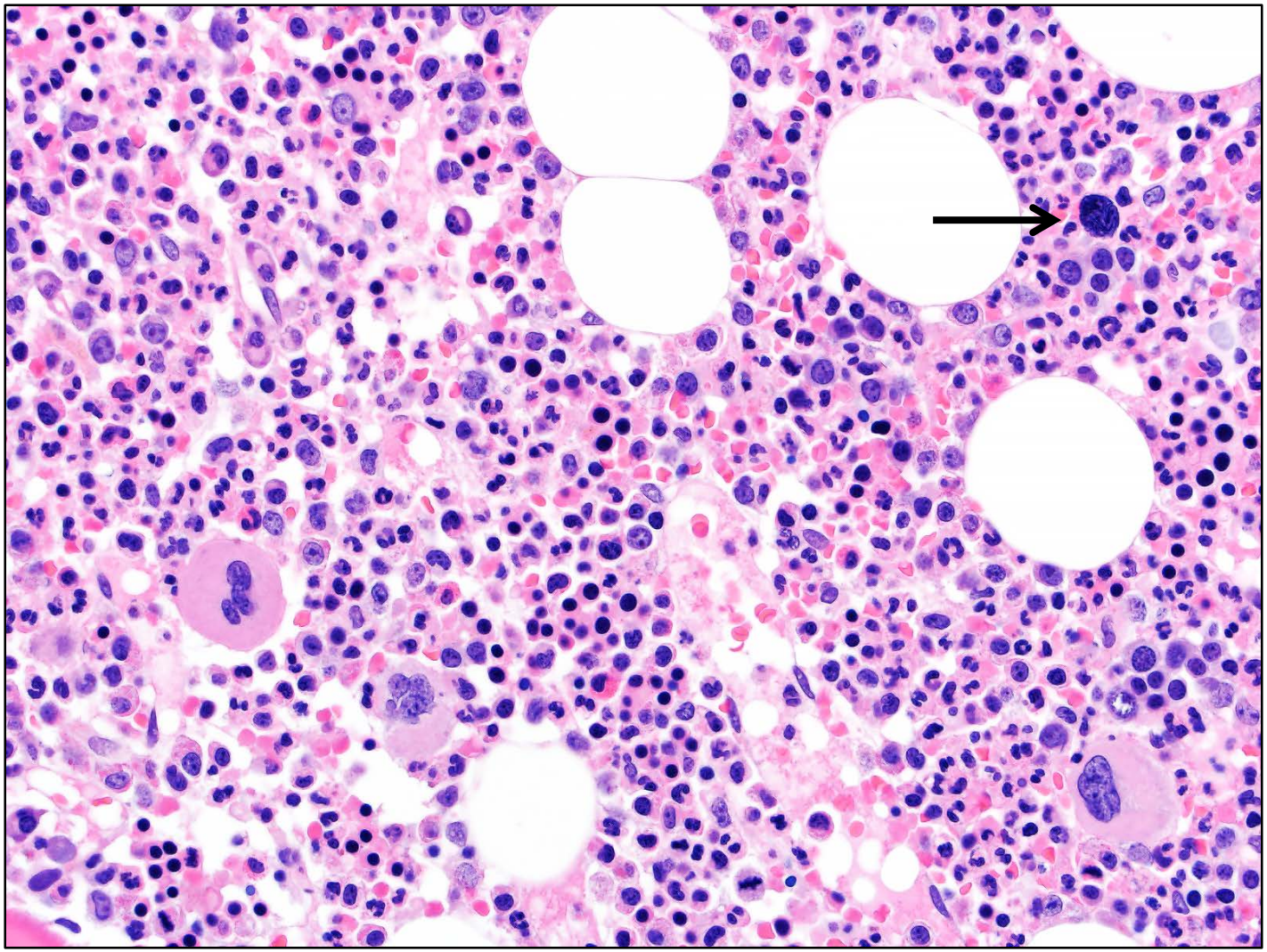
BM Biopsy Con't



- Panhyperplasia
- Aside from scattered hyperchromatic, bare megakaryocyte nuclei (arrow), trilineage hematopoiesis was morphologically unremarkable

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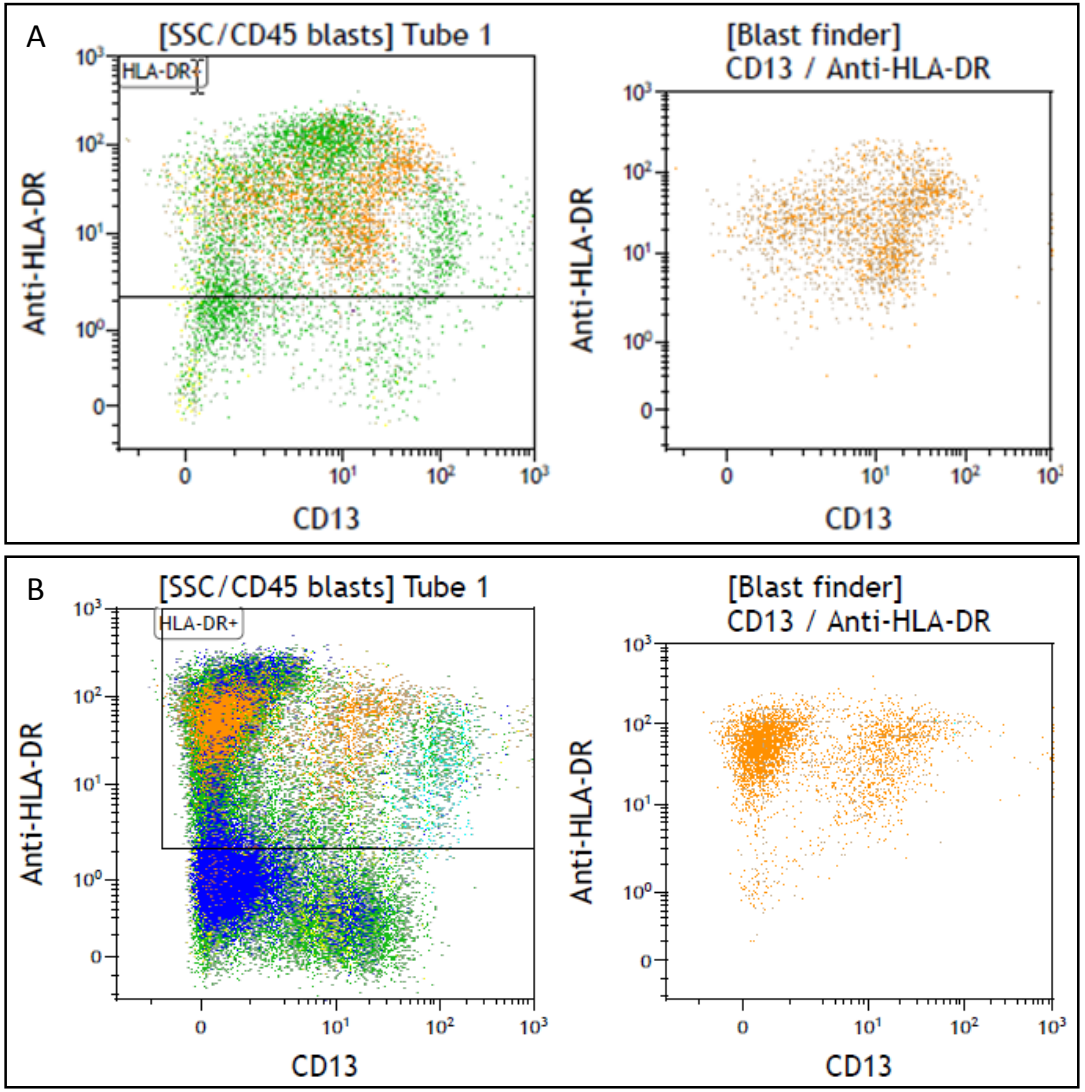
Flow Cytometry

- Top panel (A) of histograms represents normal HLA-DR/CD13 pattern of expression on blasts (orange population) for reference
- Bottom panel (B) of histograms reveals **abnormal HLA-DR/CD13 pattern of expression on blasts** (orange population) from the patient



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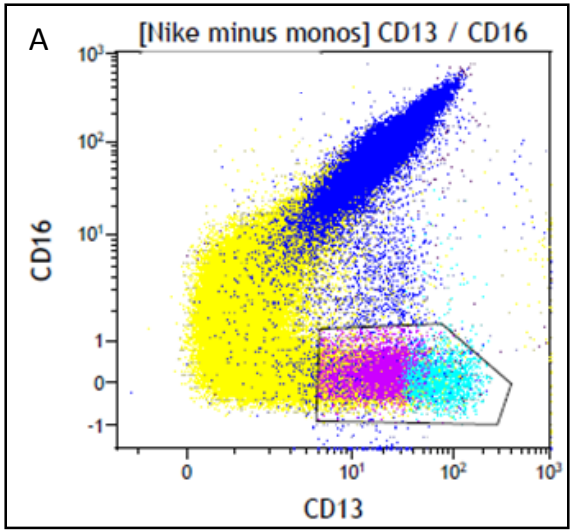
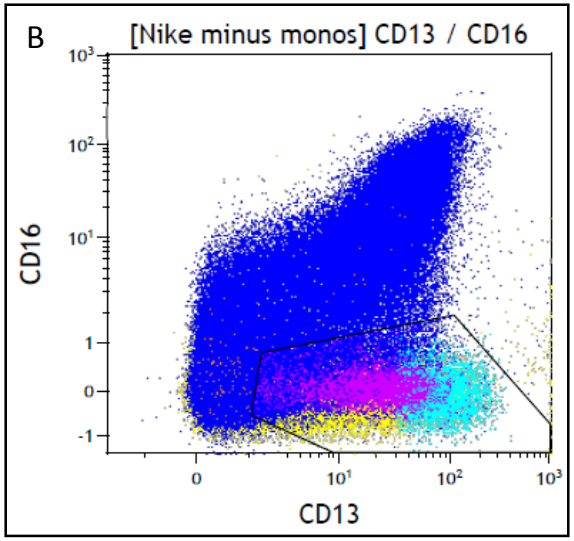
Flow Cytometry Con't

- Top histogram (A) represents normal CD13/CD16 pattern on maturing granulocytes for reference



- Bottom histogram (B) reveals an **equivocal CD13/CD16 pattern on maturing granulocytes** from the patient



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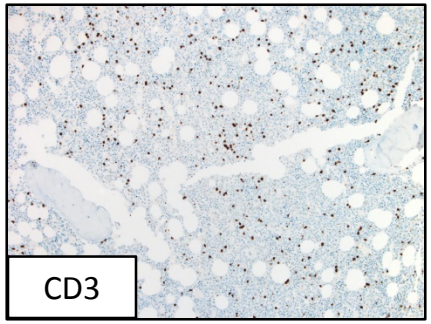
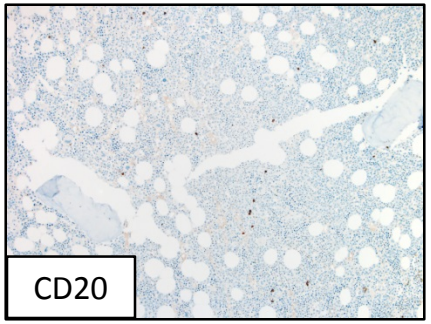
Special Studies

- Iron stain: Absent storage iron. No sideroblasts/ring sideroblasts.
- Butyrate esterase/chloroacetate esterase dual stain: No increase in monocytes. No dual esterase-positive cells.
- IHC: No abnormal infiltrates of CD3-positive T-cells (left) or CD20-positive B-cells (right)





- Conventional chromosome analysis: 46,XY[20]

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OncoHeme Next Generation Sequencing

- 4 pathogenic mutations:
  1. ***ASXL1***: c.1934dup; p.Gly646Trpfs*12 (**36%**)
  2. ***IDH1***: c.395G>A; p.Arg132His (**44%**)
  3. ***KRAS***: c.182A>G; p.Gln61Arg (**41%**)
  4. ***SRSF2***: c.284C>A; p.Pro95His (**44%**)

- Final diagnosis: Hypercellular bone marrow with panhyperplasia, slight granulocytic and megakaryocytic atypia, and no increase in blasts. No morphologic features that are diagnostic of a myeloid neoplasm are identified.

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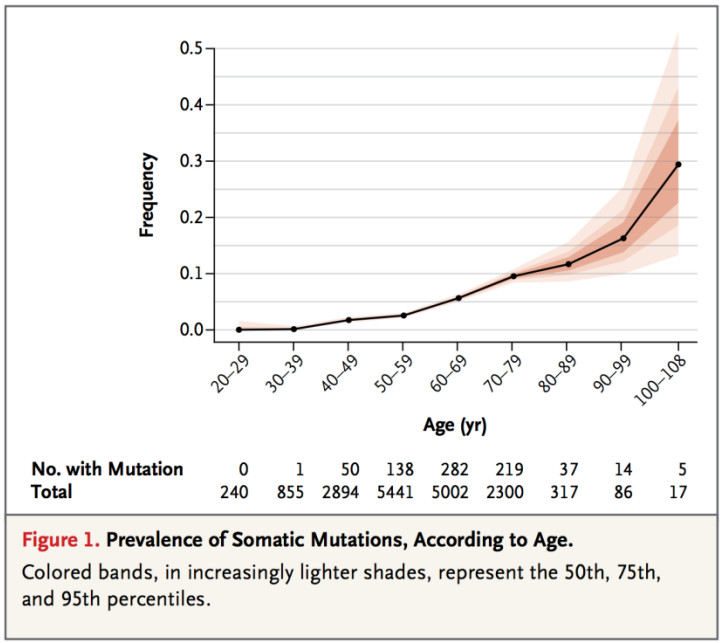
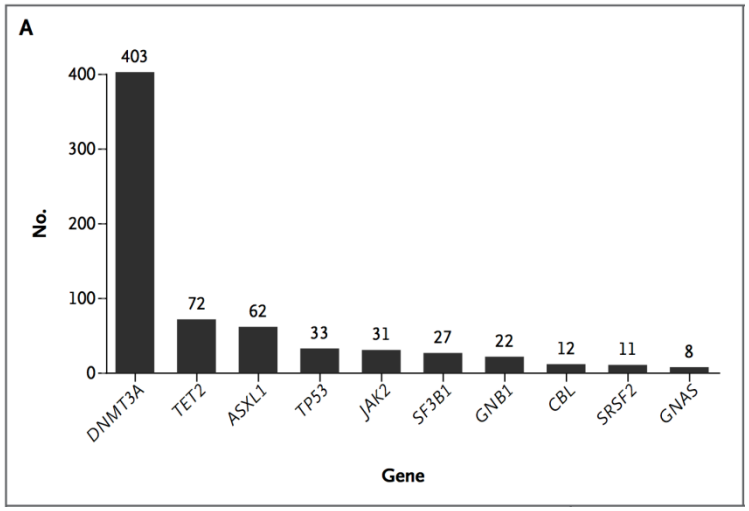
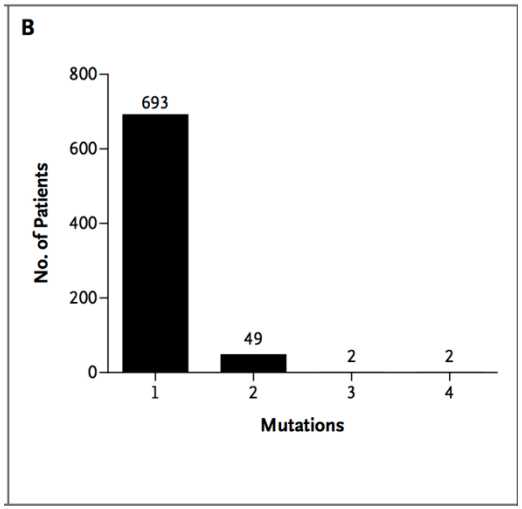
Jaiswal et al. Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med 2014;371:2488-98



No. with Mutation	0	1	50	138	282	219	37	14	5
Total	240	855	2894	5441	5002	2300	317	86	17

Figure 1. Prevalence of Somatic Mutations, According to Age.
Colored bands, in increasingly lighter shades, represent the 50th, 75th, and 95th percentiles.





- Median VAF was 0.09

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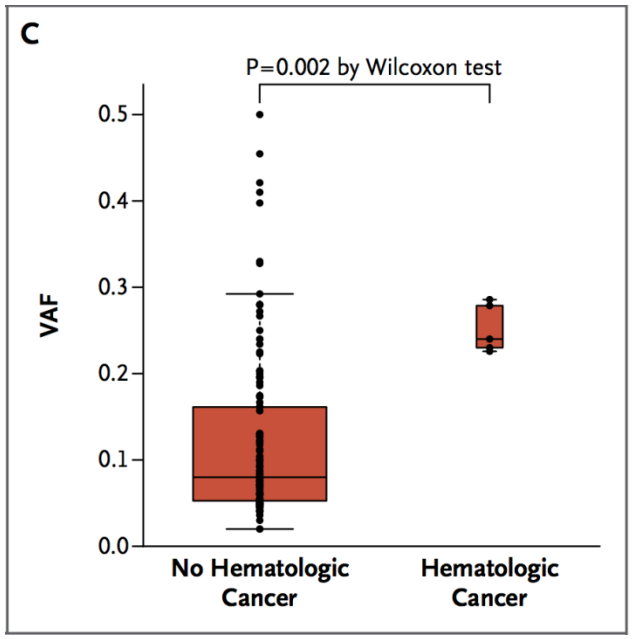
Jaiswal et al. Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med 2014;371:2488-98

	Risk of hematologic cancer
Detectable mutation	11.1x more common→ ~0.5%/yr
VAF ≥0.10	↑ by a factor of ~50→ ~1%/yr



Similar observations were made by Genovese et al. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. N Engl J Med 2014;371(26):2477-2487

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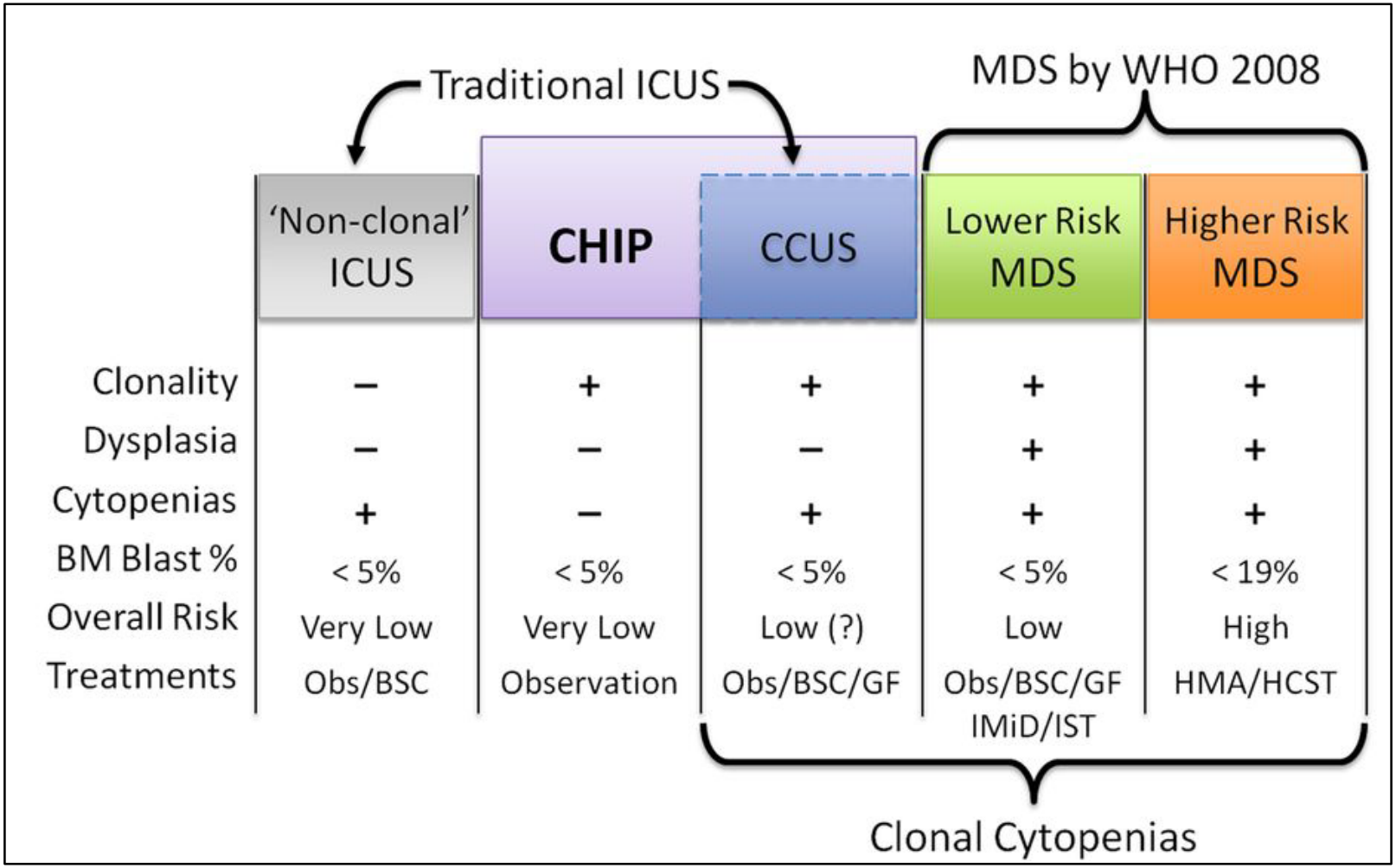
Steensma et al. Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. Blood 2015;126(1):9-16



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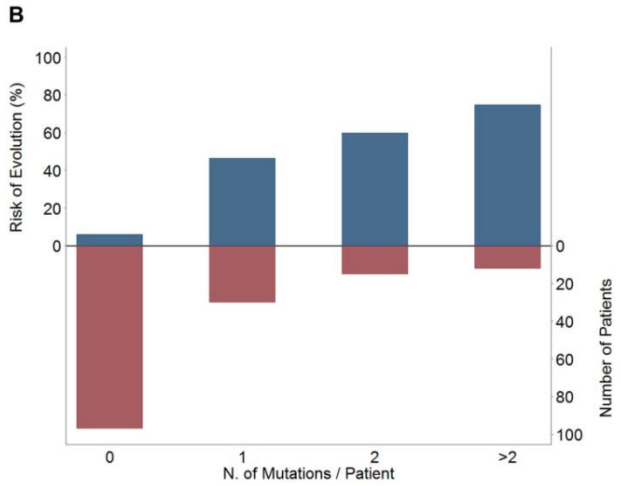
Malcovati et al. Clinical significance of somatic mutation in unexplained blood cytopenia. Blood 2017;129(25):3371-3378



- Mutations in **spliceosome genes** (*SF3B1*, *SRSF2*, *U2AF1*, & *ZRSR2*):
  - **Highest predictive value, irrespective of co-occurring mutations**
  - Detection of these mutations in patients with unexplained cytopenia should be considered highly predictive of myeloid neoplasm
- **Isolated** mutations in *DNMT3A*, *TET2*, & *ASXL1* had a lower predictive value

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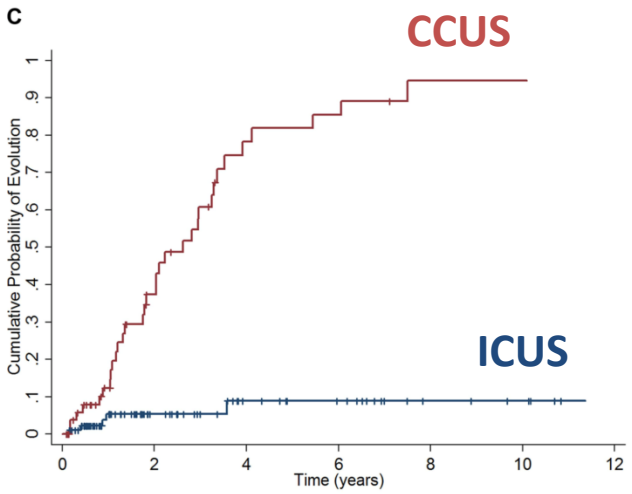
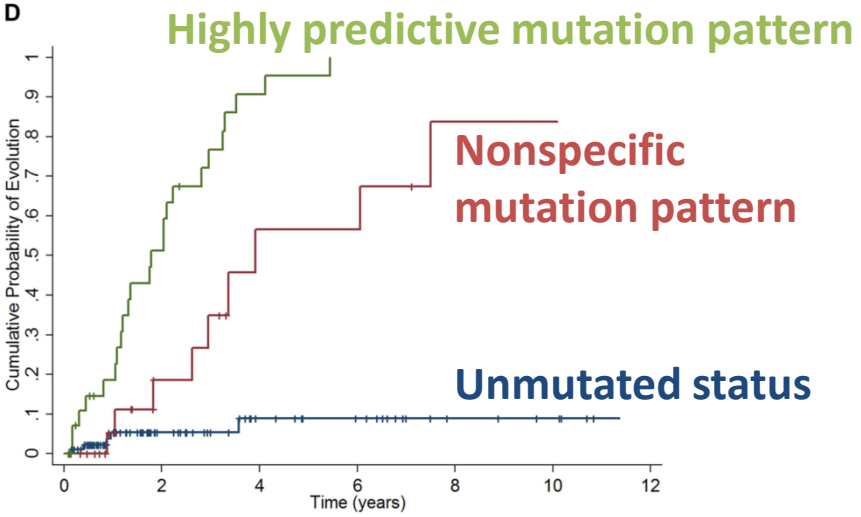
- **Clonal cytopenia had a 14x higher** probability of developing a myeloid neoplasm
- **95%** 5-yr cumulative probability of developing a myeloid neoplasm if **highly predictive mutation pattern**:
  1. Spliceosome gene mutations
  2. Mutations in *DNMT3A*, *TET2*, or *ASXL1* with comutations in *RUNX1*, *EZH2*, *CBL*, *BCOR*, *NRAS*, *CUX1*, *TP53*, or *IDH1/IDH2*





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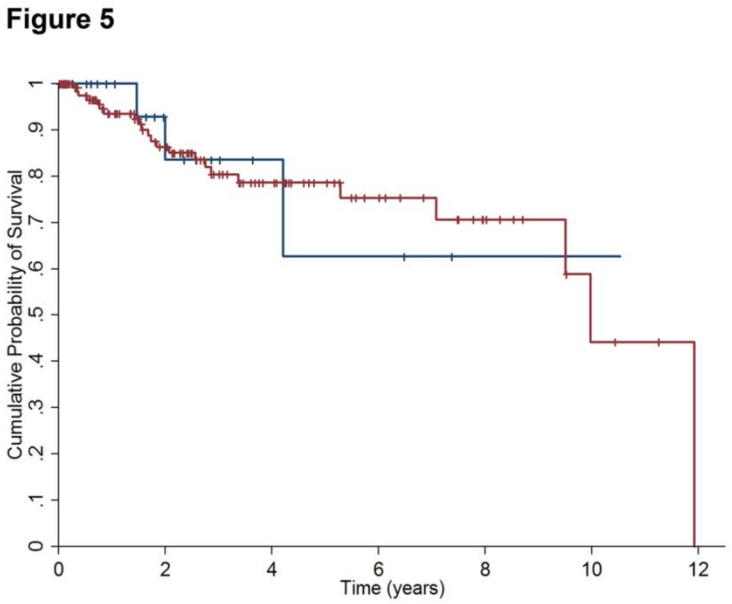
- No significant difference in overall survival & risk of disease progression when comparing:
  - **CCUS & highly specific mutation patterns (navy curve)**
  - **Myeloid neoplasm with myelodysplasia:**
    - **Without excess blasts (maroon curve)**
    - Similar mutation patterns



- Underlying genetic lesions may provide presumptive evidence of MDS even in the absence of definitive morphologic features

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Panel Diagnosis for Case Number: SH2017-269

- Clonal cytopenia of undetermined significance

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