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Case SH2017-0256
Session 5: Pre-Malignant Clonal Hematopoietic Proliferations

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THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

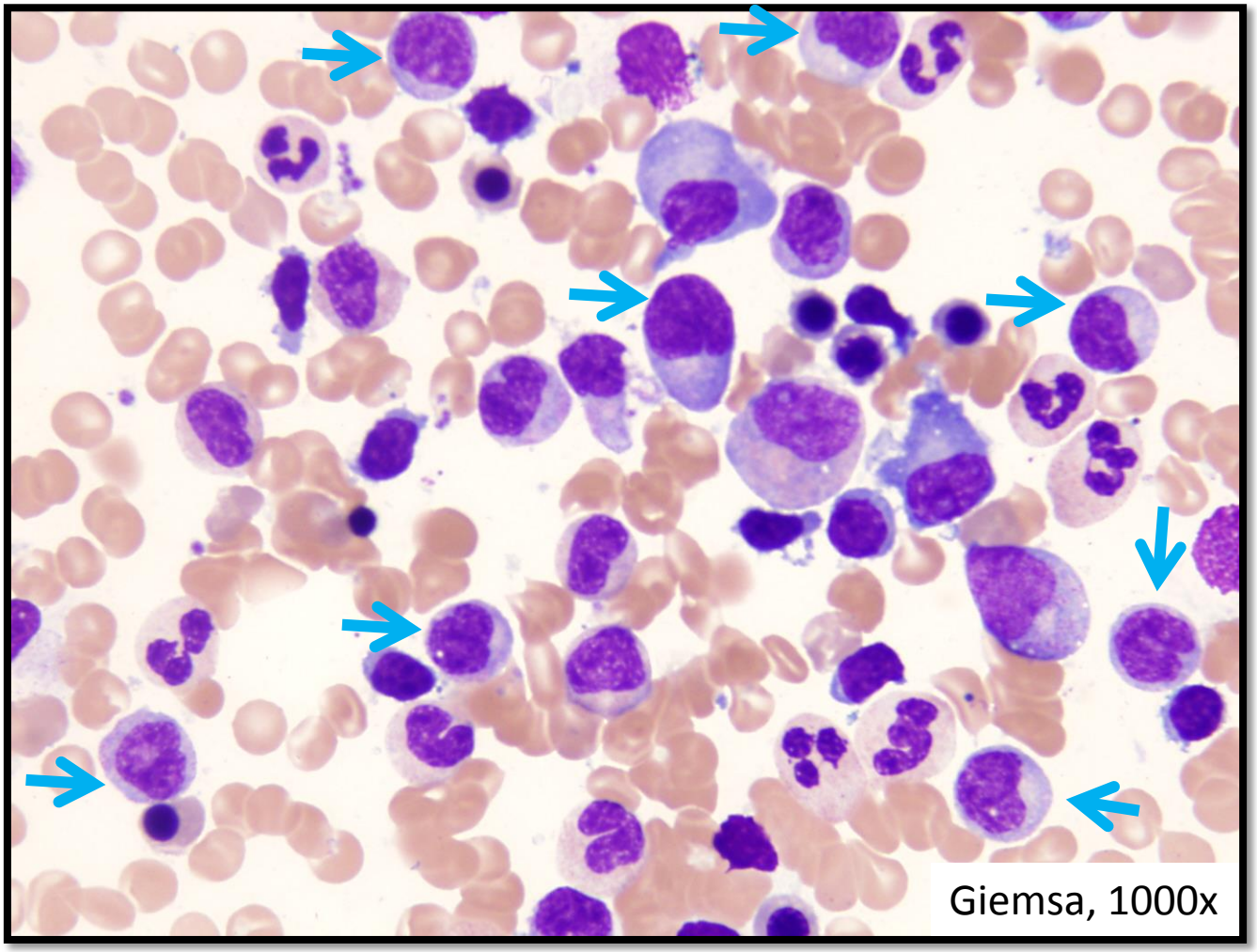
Clinical History

- 74 y/o man
- Untreated chronic myelomonocytic leukemia (CMML) diagnosed 7 years earlier
- Presented for follow-up
  - No specific symptoms
  - No hepatosplenomegaly

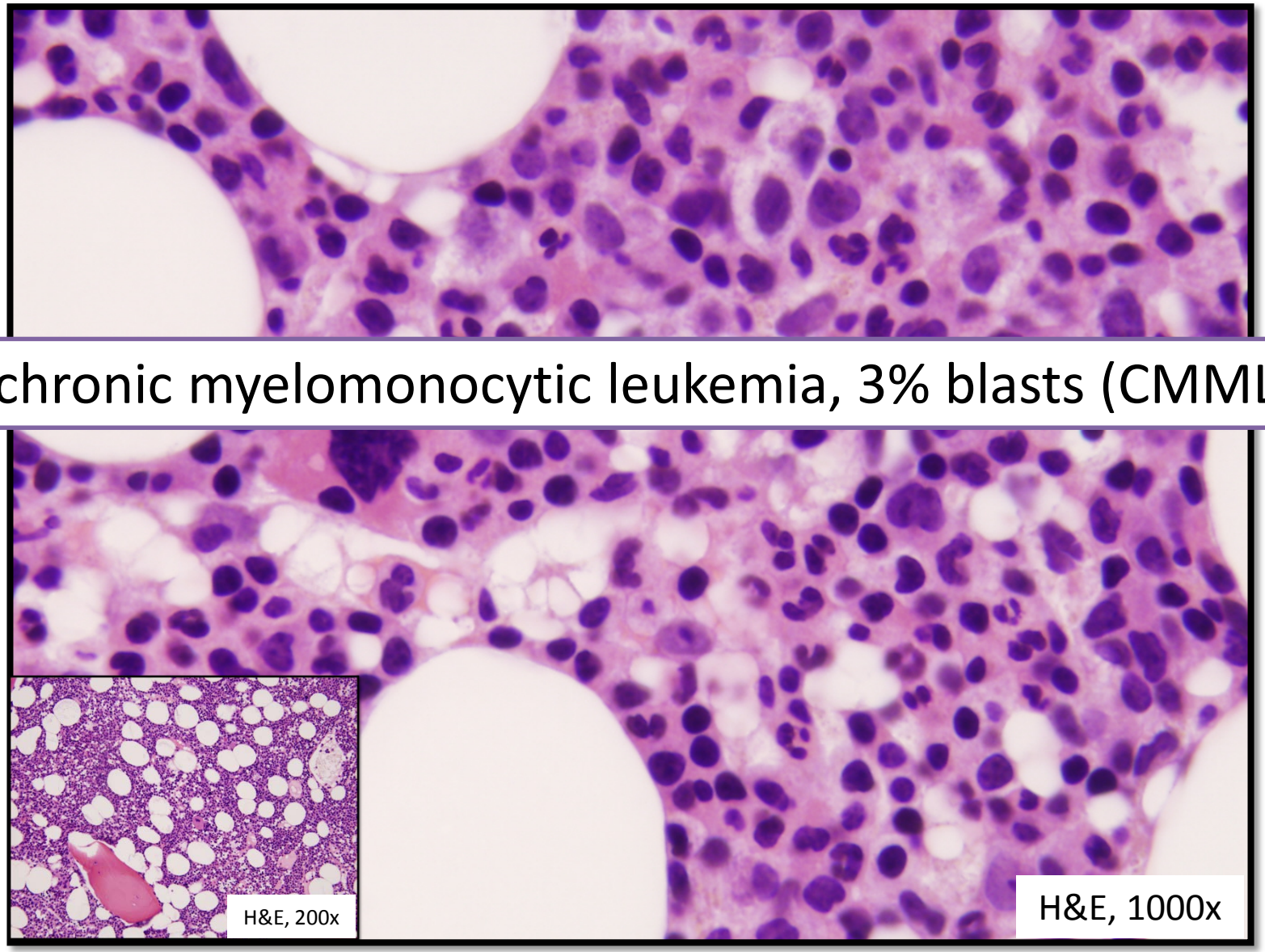
Laboratory Data

- WBC 8.5 x 10^9/L
  - Monocyte % 37.0 % (2.0-7.0)
  - Mono Abs 3.15 10^9/L (.08-0.70)
- Hgb 12.7 g/dL
- Plt 162 x 10^9/L
- LDH 516 IU/L (< 618)

Bone marrow aspirate smears showing monocytosis, dysgranulopoiesis

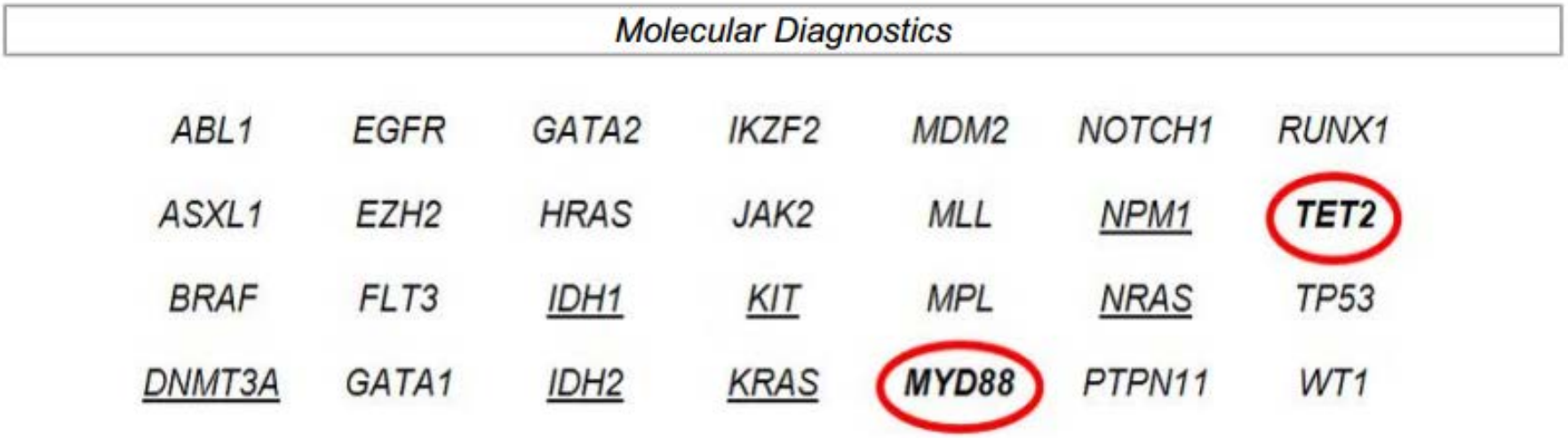


BM biopsy: hypercellular with myeloid hyperplasia and dysmegakaryopoiesis



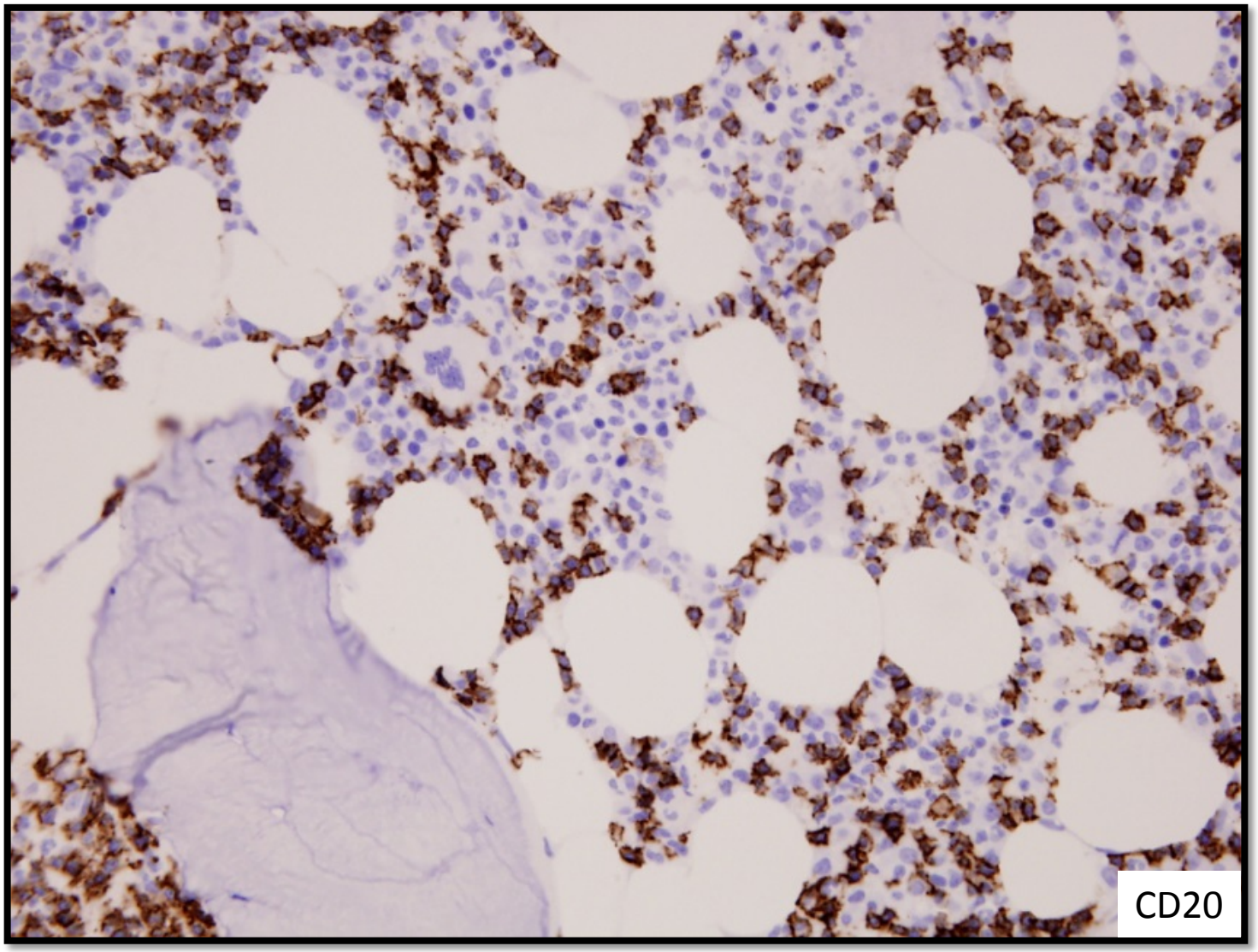
Dx: chronic myelomonocytic leukemia, 3% blasts (CMML-0)

BM: next generation sequencing

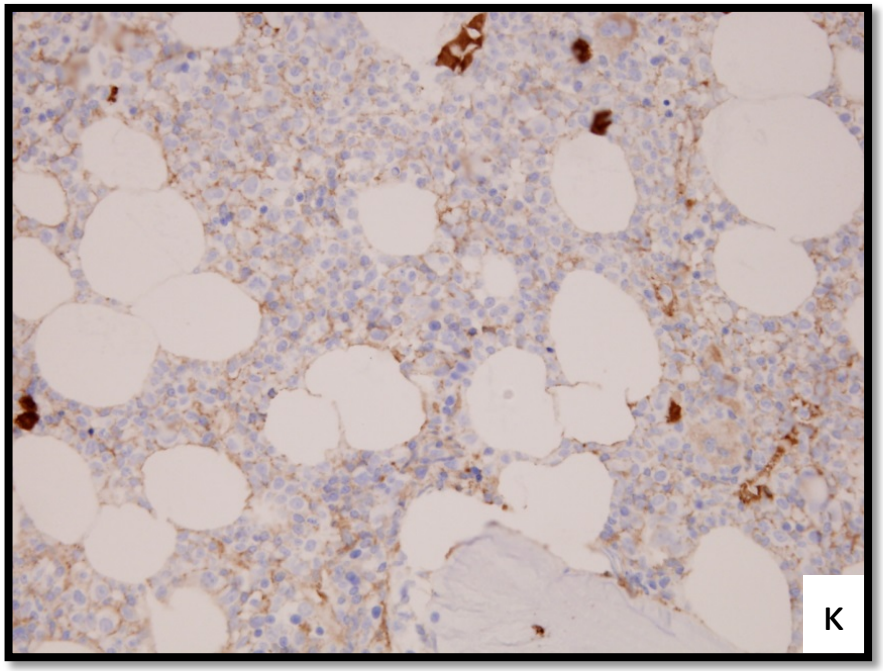


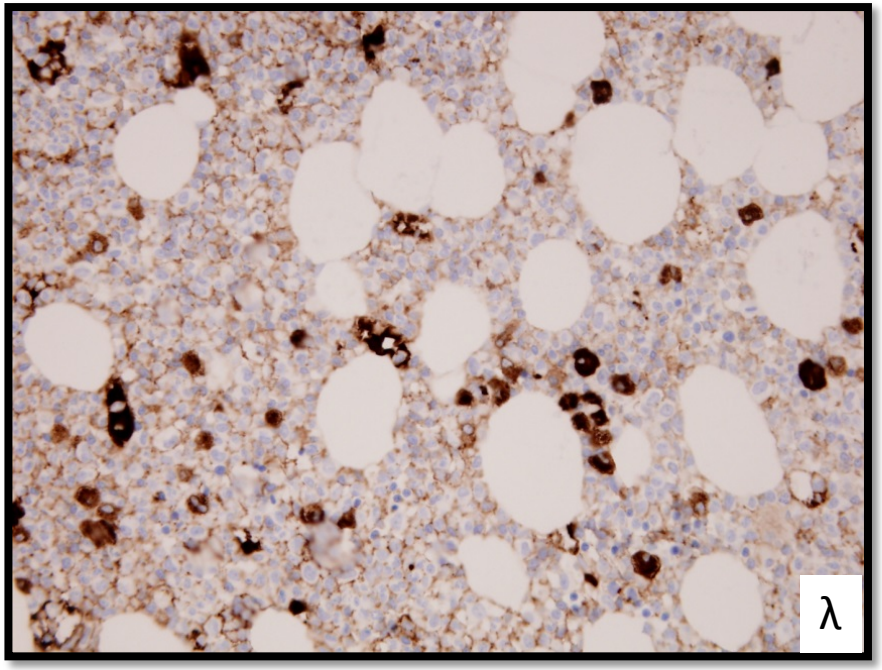
Variant designation	Gene	HGNC mutation designation	chromosome	Variant allele fraction
Likely pathogenic	*TET2*	c.2504_2505del p.S835*	chr4	0.41
Likely pathogenic	*TET2*	c.4502_4505del p.Q1501fs	chr4	0.18
Likely pathogenic	*TET2*	c.1699_1703del p.L567fs	chr4	0.06
Likely pathogenic	*TET2*	c.3535dupA p.R1179fs	chr4	0.03
Pathogenic	***MYD88***	**c.794T>C p.L265P**	**chr3**	**0.02**

BM biopsy: interstitial B-cell infiltrate

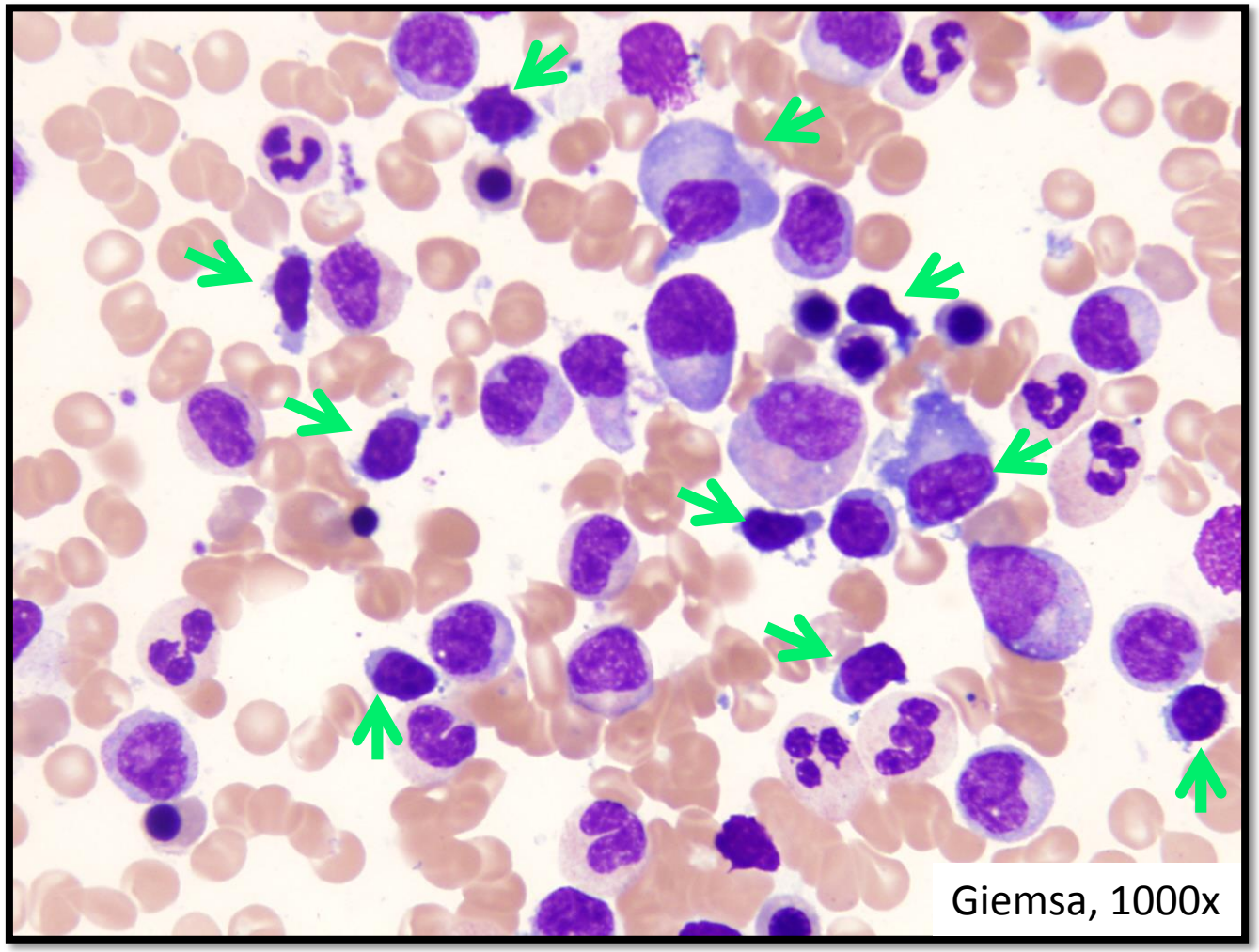


BM biopsy: monotypic (Ig λ) plasma cells





BM aspirate smear: retrospectoscopic view



Lymphocytes: 13%; plasma cells 2%

Additional studies recommended

- The patient returned 6 months after his last visit
  - **IgM** **442 mg/dL (35-242)**
  - IgA 183 mg/dL (85-499)
  - IgG 1134 mg/dL (600-1616)

  - Serum protein electrophoresis (SPEP)
    - In progress, results pending

Proposed Dx

Chronic myelomonocytic leukemia &

Lymphoplasmacytic lymphoma/
Waldenstrom macroglobulinemia

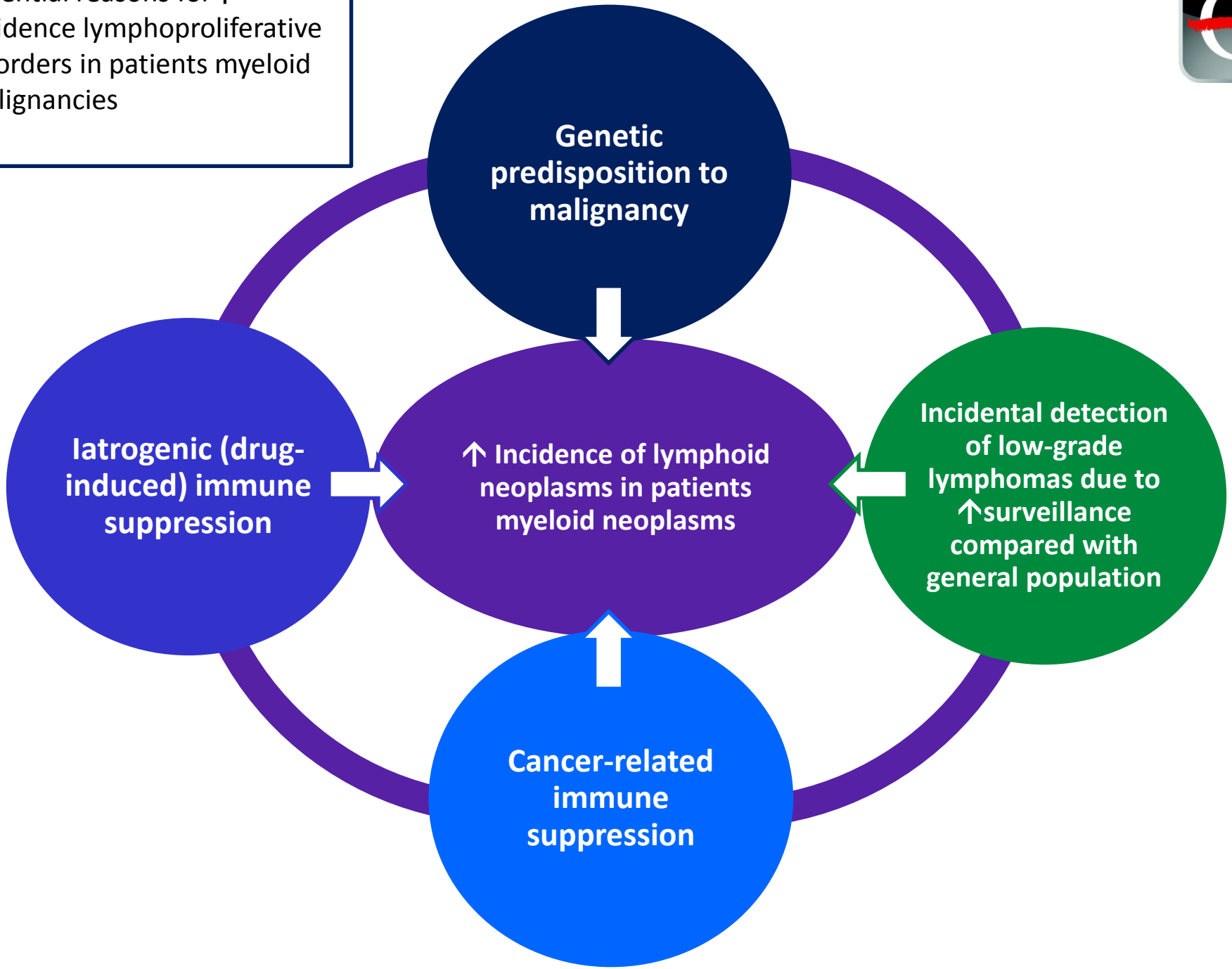
Discussion

Lymphoid neoplasms in patients with myeloid malignancies; co-incidence or linked?

- ↑ incidence of LPDs in patients with MPNs, particularly CML
  - Standardized incidence ratios (SIRs) for patients with MPN compared with the general population
    - CLL/SLL : 3.4 (95% CI 1.9-6.2)
    - Other NHL: 12.4 (95% CI: 4.7-33.6)
- Not as extensively studied in patients with AML/MDS
  - Possibly due to shorter survival and follow-up compared with CML

Vannucchi AM. *Cancer Epidemiol Biomarkers Prev*. 2009; 18(7): 2068.
Frederiksen H. *Blood*. 2011; 118(25): 6515
Susini MC. *Blood*. 2012; 119(16): 3861.
Frederiksen H. *Lancet Haematol*. 2015; 2(7): e289.
Miranda MB. *Leukemia*. 2016; 30(6): 1255.

Potential reasons for↑ incidence lymphoproliferative disorders in patients myeloid malignancies



Ann Hematol (2014) 93:1605–1607
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LETTER TO THE EDITOR

IgG-lymphoplasmacytic lymphoma following polycythemia vera: JAK2 V617F and MYD88 L265P mutations separated in the same house

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Short Communication

Myelodysplastic syndrome with 5q deletion following IgM monoclonal gammopathy, showing gene mutation MYD88 L265P

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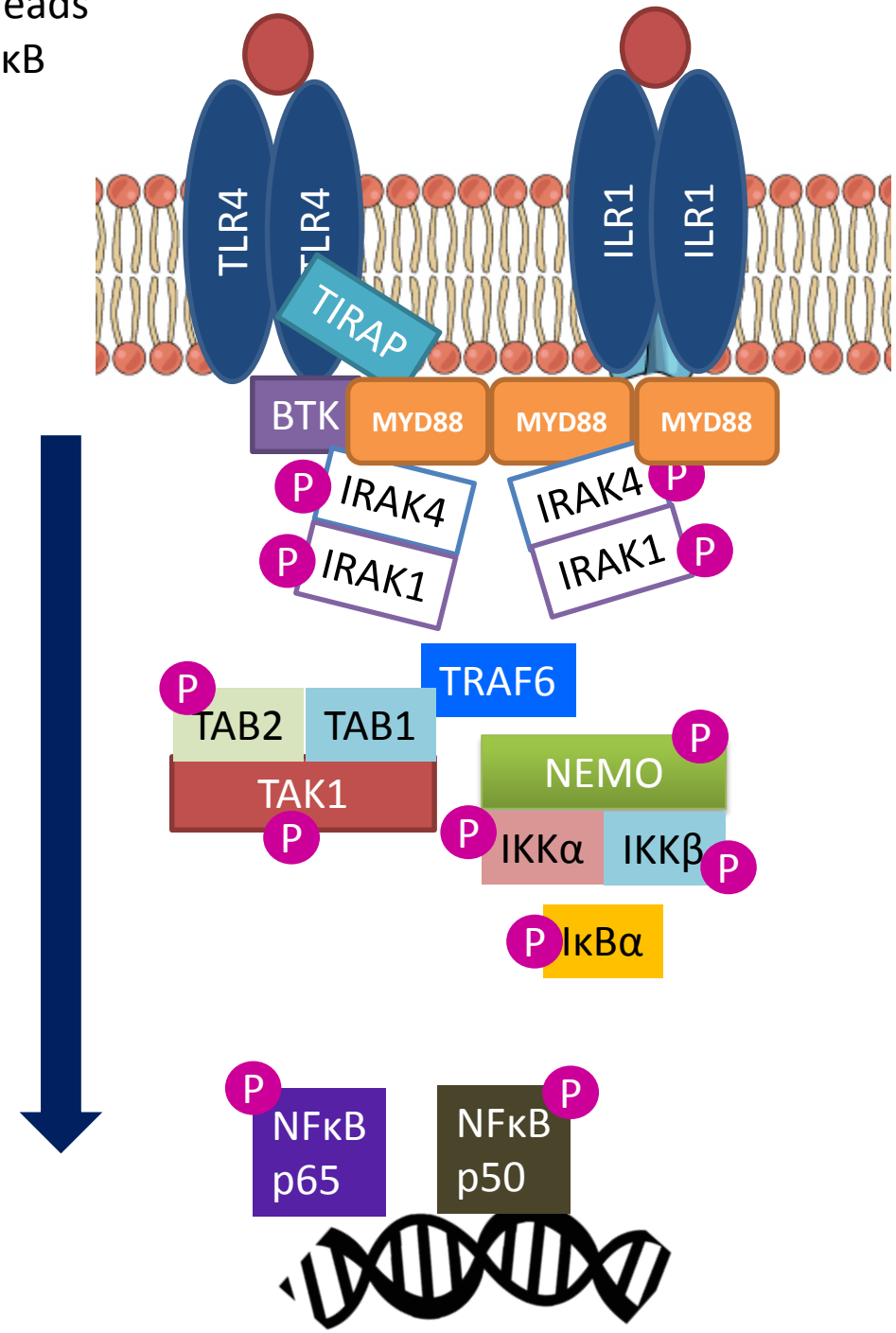
We identified 9 myeloid neoplasms with incidental *MYD88* p.L265P

Myeloid malignancy (n)	B-cell/plasma cell process	*MYD88* p.L265P VAF
AML (3)	CLL-type MBL	0.06
	IgM MGUS	0.03
	No additional work-up	0.01
MDS (2)	Increased interstitial CD20+ B-cells	0.04
	CLL-type MBL	0.01
CMML (2)	LPL/WM	0.02
	CLL-type MBL	0.01
ET (1)	Predominance of Igλ plasma cells	0.01
MDS/MPN-U (1)	CLL-type MBL	0.03

MYD88

- *MYD88* (myeloid differentiation primary response 88)
  - Maps to 3p22.2
  - Encodes for an adapter protein that acts as a signal transducer in the IL-1, IL-18 and Toll-like receptor signaling pathways, as part of the innate immune response.

MYD88 activation leads to increased NF-κB signaling



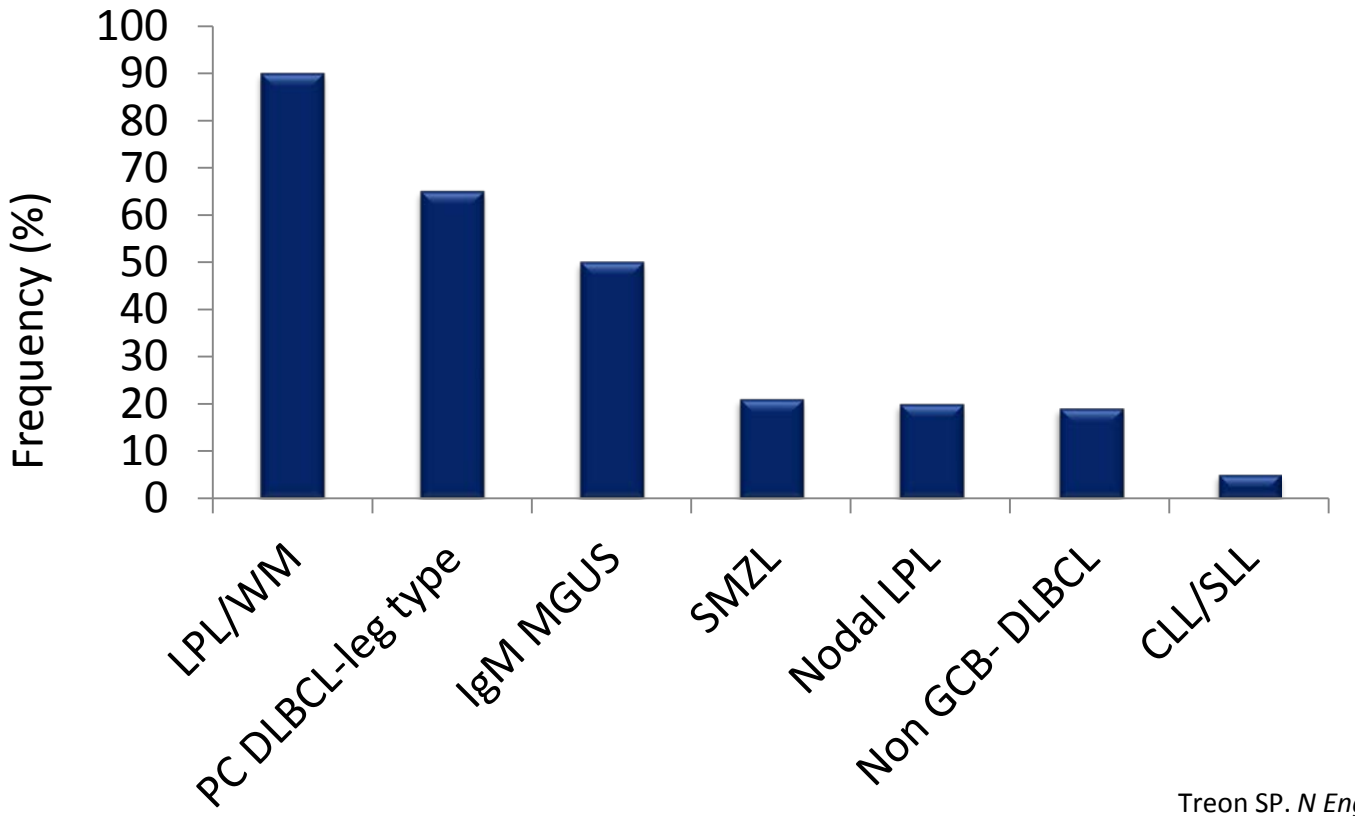
Treon SP. *N Engl J Med*. 2012; 367(9): 826.

MYD88 p.L265P

- *MYD88* p.L265P>> MYD88 gain of function
  - Toll–interleukin-1 receptor (TIR) domain of mutated MYD88 exhibits augmented oligomerization >> ↑ MYD88 signaling>> aberrant NFκB signaling
- While overexpression of wild-type MYD88 mRNA and protein is reported in MDS HSPC, *MYD88* is not mutated in myeloid malignancies.

Varney ME. *Exp Hematol*. 2015; 43(8): 587.

MYD88 p.L265P in B-cell neoplasms



Treon SP. *N Engl J Med*. 2012; 367(9): 826.
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Conclusions

- Patients with myeloid neoplasms may have concurrent or secondary lymphoid neoplasms
  - Low-grade LPDs may be obscured by the primary myeloid neoplasm
- Incidental molecular findings may provide a clue to occult pathology
- Identification of *MYD88* p.L265P should prompt additional work-up for assessment of a masked lymphoid neoplasm
  - IHC, flow cytometry
  - Serum Ig quantification
  - SPEP, IFE

Final Panel Diagnosis

- **Lymphoplasmacytic lymphoma in the setting of chronic myelomonocytic leukemia**

Thank You