Acute Myeloid Leukemia with *JAK2* V617F Mutation

Case 0057

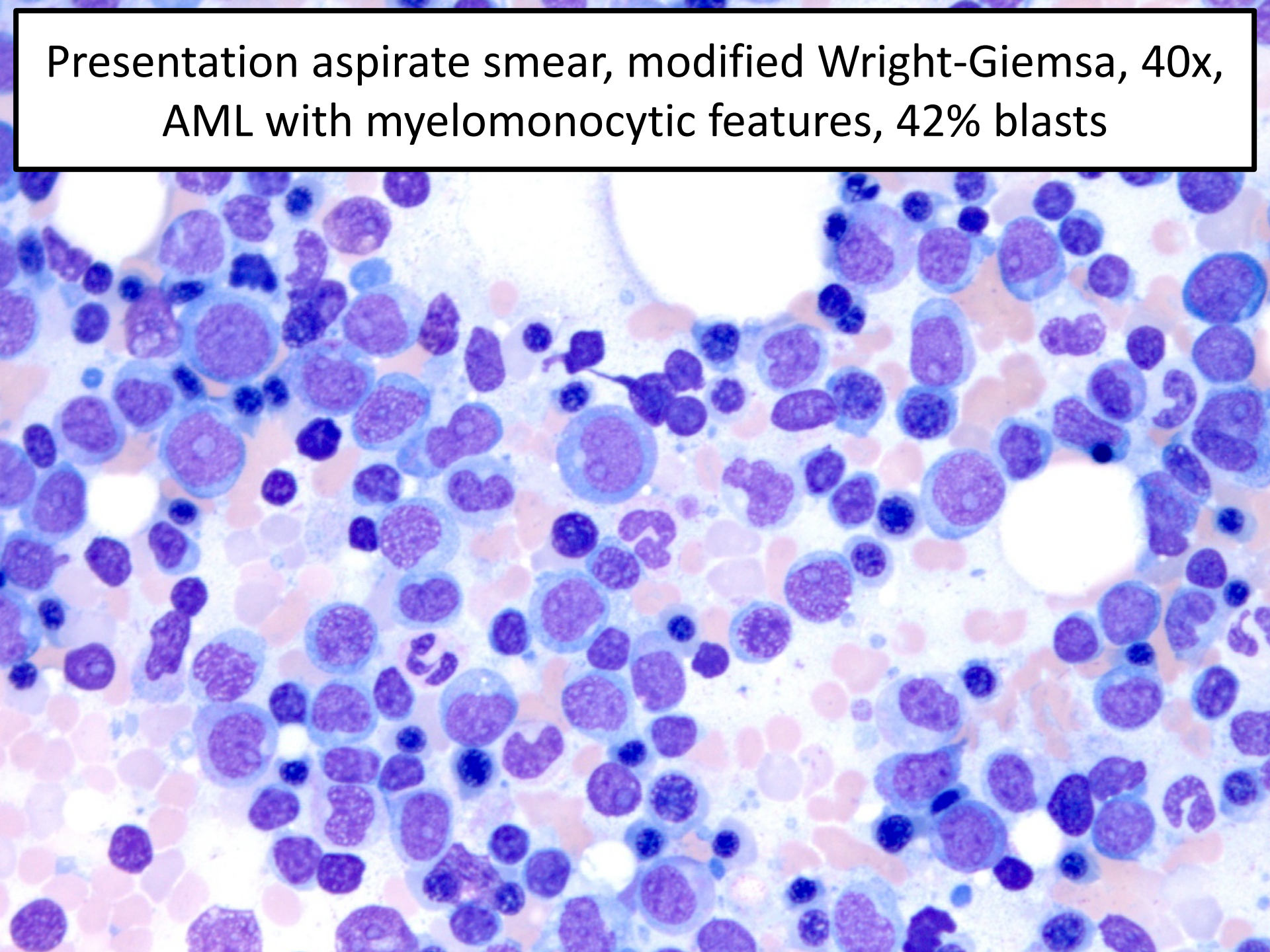
Jason Aynardi, MD; Rashmi Manur, MD; Jennifer Morrissette, PhD; Adam Bagg, MD

University of Pennsylvania

Clinical History

- 62-year-old man with persistent leukopenia following a diagnosis of “infectious mononucleosis”
- No history of a myeloproliferative neoplasm
- CBC two months prior to AML diagnosis:
  - WBC 4.2 k/µL, Hgb 11.6 g/dL, Plt 260 k/µL
- CBC at time of AML diagnosis:
  - WBC 2.7 k/µL, Hgb 11.7 g/dL, Plt 152 k/µL

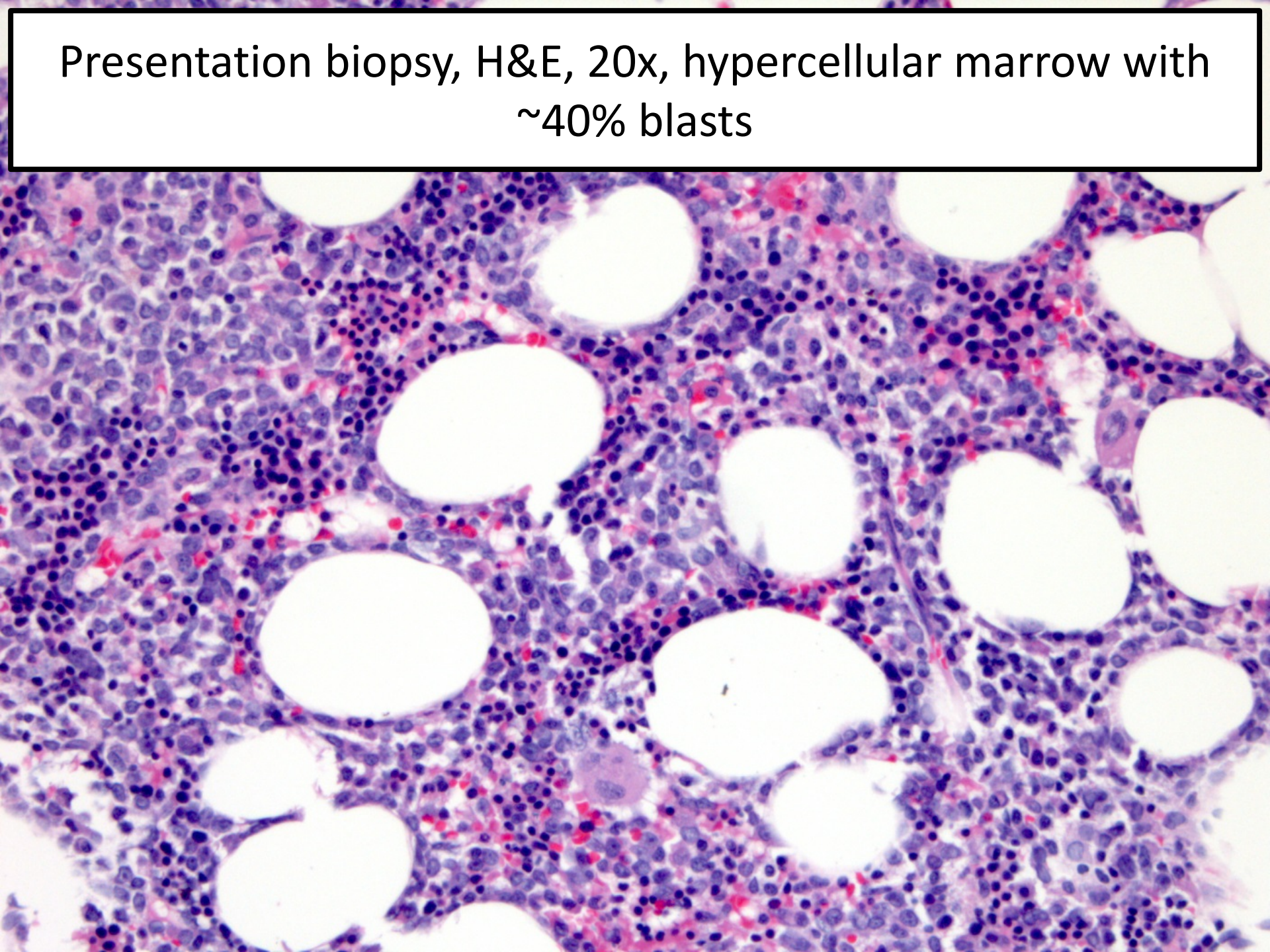
Presentation aspirate smear, modified Wright-Giemsa, 40x, AML with myelomonocytic features, 42% blasts



Aspirate differential count

- 42% blasts
- 2% promyelocytes
- 10% myelocytes/metamyelocytes
- 5% bands/neutrophils
- 40% nucleated red blood cells
- 1% plasma cells

Presentation biopsy, H&E, 20x, hypercellular marrow with ~40% blasts



Megakaryocyte morphology

- Megakaryocytes are decreased with no evidence of MPN-like atypia

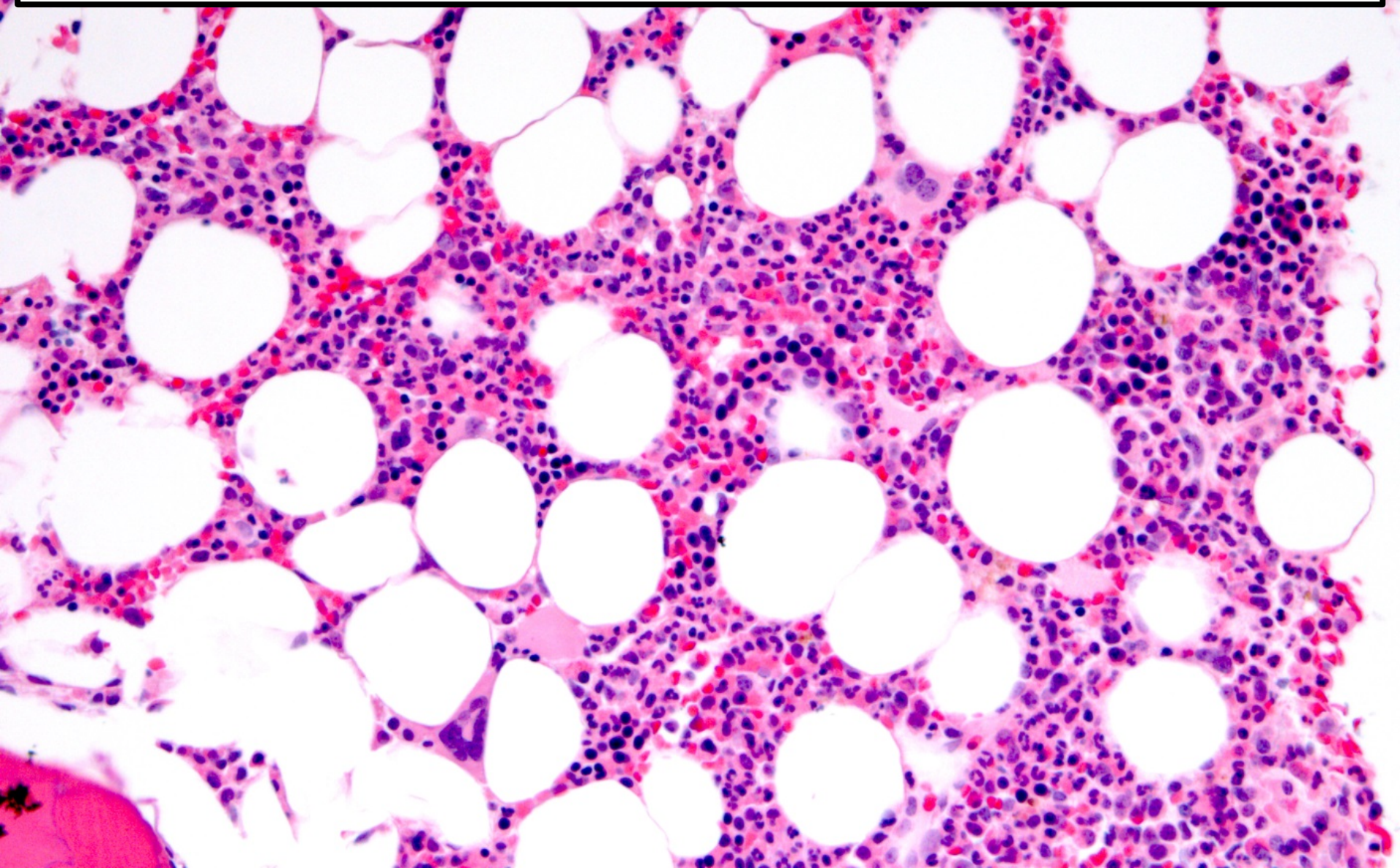
Additional studies

- Flow cytometry: blasts dominantly positive for CD33, CD34, CD64, CD117, HLA-DR and MPO
- Immunohistochemistry: not performed
- Cytogenetics: 46,XY[20]

Molecular genetics at presentation

Gene	DNA change	Protein change	Allele frequency
ASXL1	c.2122C>T (nonsense)	p.Q708X	40%
IDH2	c.419G>A (missense)	p.R140Q	41%
JAK2	c.1849G>T (missense)	p.V617F	34%

Post-therapy biopsy, H&E, 20x, trilineage hematopoiesis, no evidence of acute leukemia or myeloproliferative neoplasm

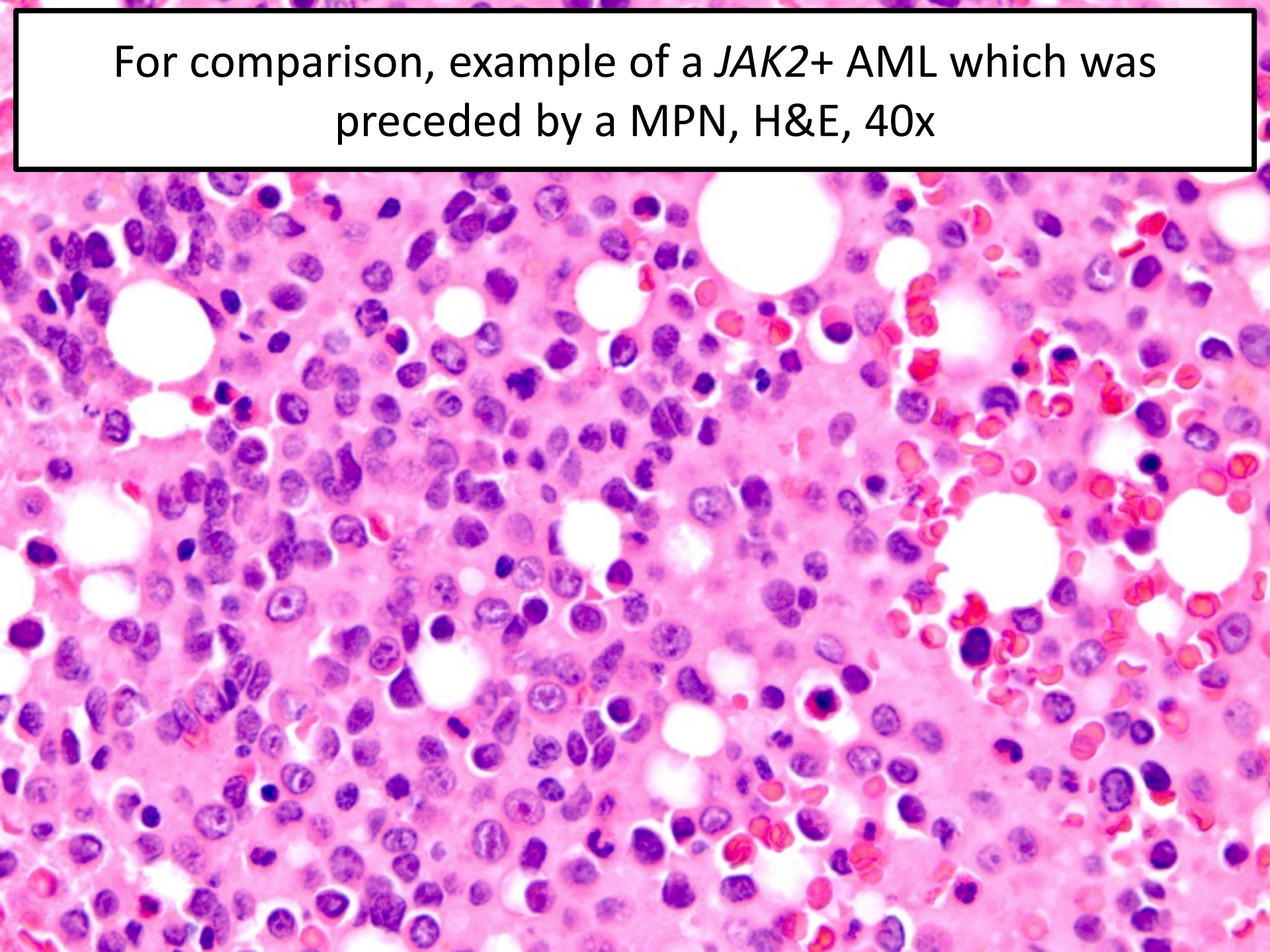


Molecular genetics at second relapse

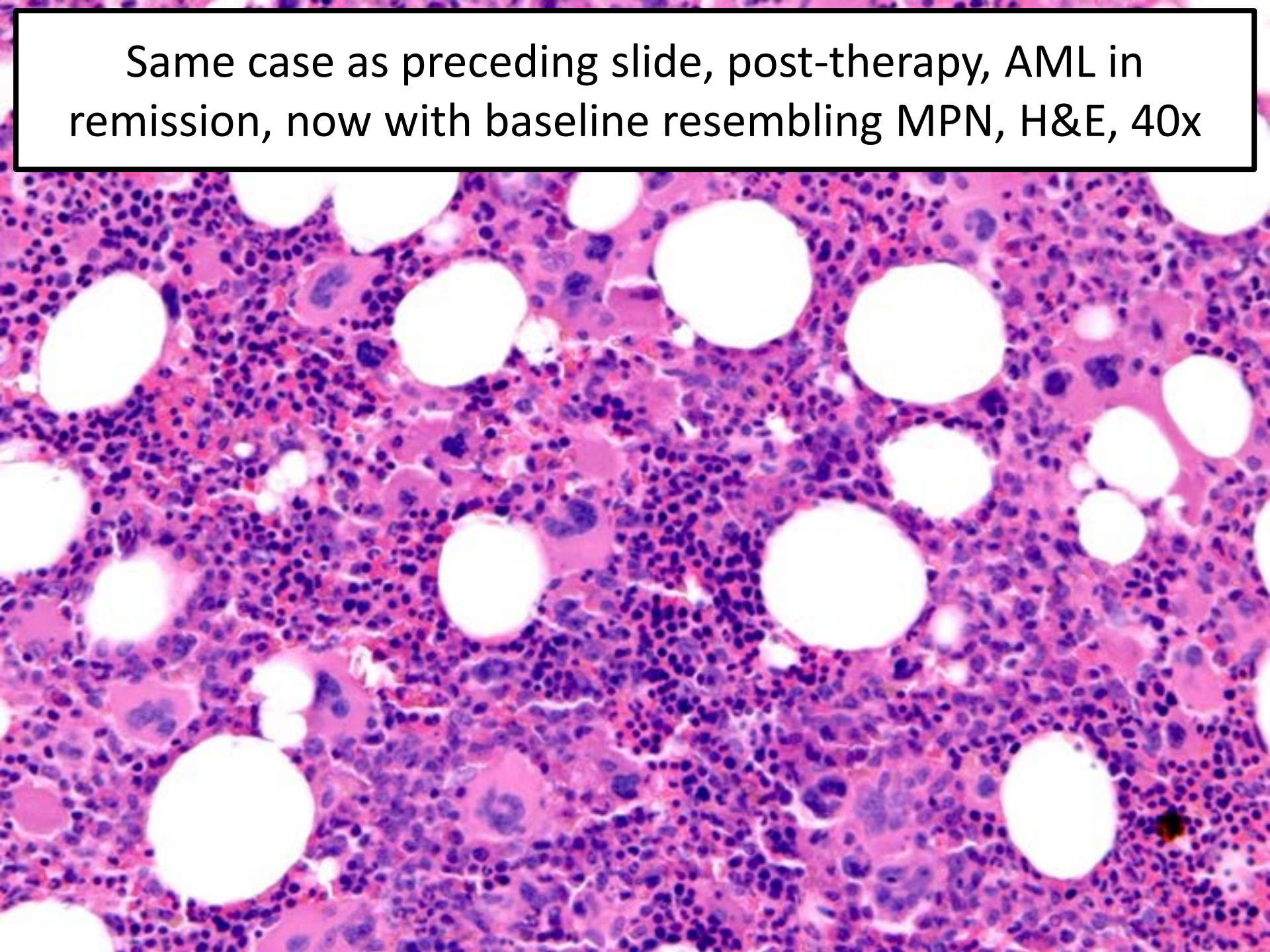
	DNA change	Protein change	Allele frequency
ASXL1	c.2122C>T (nonsense)	p.Q708X	23%
IDH2	c.419G>A (missense)	p.R140Q	24%
JAK2	Not detected	N/A	N/A

*No sequencing data available during remission or at first relapse

For comparison, example of a *JAK2*+ AML which was preceded by a MPN, H&E, 40x



Same case as preceding slide, post-therapy, AML in remission, now with baseline resembling MPN, H&E, 40x



Significance of molecular genetic findings

- *JAK2* V617F mutation is seen in most *BCR-ABL1*-negative MPNs but only occurs rarely in *de novo* AML (~1%)
- The present case is also noteworthy for the loss of the *JAK2* mutation by the time of second relapse, despite the retention of the *ASXL1* and *IDH2* mutations
  - Suggests *JAK2* is not a driver mutation
- This case of *de novo JAK2* V617F positive AML prompted us to perform a study on additional cases

Multi-institutional study

- Initially, at Penn we identified and studied 21 cases of *JAK2* V617F+ AML in an attempt to identify features that distinguish *de novo* AML (n=11) from those that reflect transformation of an antecedent MPN (n=10)
- Eventually, the study was expanded to include cases from MGH, Cornell, and Cleveland Clinic, with a total of 15 AML-DN cases and 30 AML-MPN (data on next slide)
- Our findings indicate that *de novo* AML with *JAK2* V617F mutation represents a biological entity distinct from AML cases preceded by an MPN
- Interestingly, the loss of *JAK2* V617F seen following treatment in the present case was also observed in 5 other patients from the larger study (while it was retained in 3)

JAK2+ AML case series: transformed (AML-MPN) versus *de novo* (AML-DN)

	AML-MPN (n=30)	AML-DN (n=15)	p-value (not noted, if >0.05)
Clinical			
Splenomegaly	53%	20%	0.02
Hematologic			
PB blasts at time of AML diagnosis (mean)	39%	29%	-
MPN-like megakaryocytic atypia post-therapy	76%	0%	<0.01
Molecular			
JAK2 V617F allele frequency	50%	32%	0.04
Exclusive mutations	*ETV6* (n=3), *NRAS* (n=2)	*CEBPA* (n=2), *TET2* (n=3)	-
Cytogenetic			
Complex karyotype	57%	13%	<0.01
Outcome			
Survival from time of AML diagnosis (mean, months)	9.9	11.3	-
Overall survival (% deceased)	73%	40%	0.05

Final panel diagnosis

- Acute myeloid leukemia, not otherwise specified (acute myelomonocytic leukemia, with *JAK2* mutation)

Acknowledgements

- Heesun Rogers and Eric Hsi (Cleveland Clinic)
- Elizabeth Margolskee and Attilio Orazi (Cornell)
- Robert Hasserjian (Massachusetts General)
- Rashmi Manur (Pennsylvania Hospital)
- Paul Hess, Seble Chekol, Jennifer Morrissette, Daria Babushok, Elizabeth Hexner, and Adam Bagg (Hospital of the University of Pennsylvania)