Case 0148

Acute myeloid leukemia with myelodysplasia-related changes and cryptic t(8;16)(p11;p13); KAT6A/CREBBP

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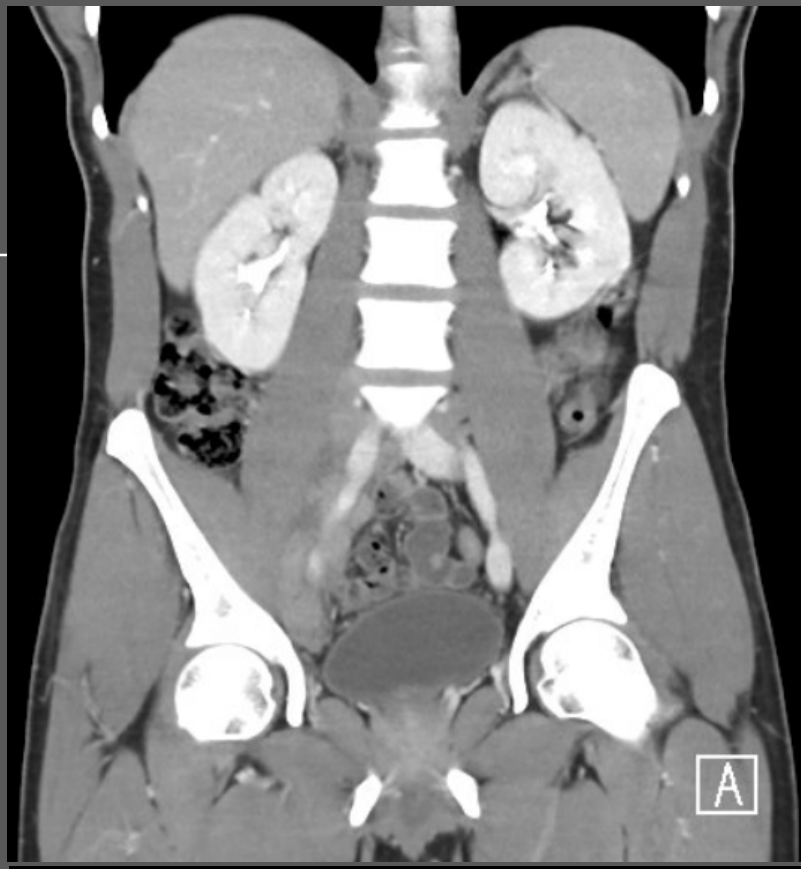
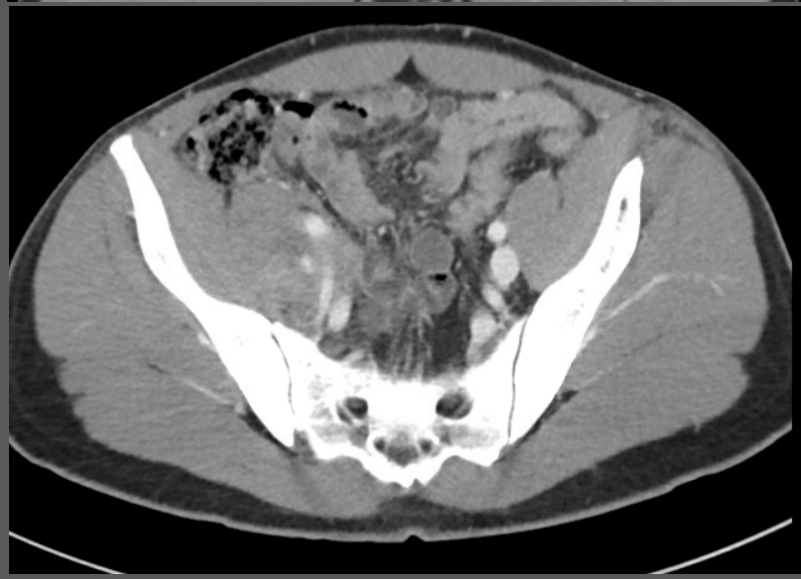
Clinical presentation

- 24 year-old male with one month history of right-sided low back pain and right leg swelling
- Past and social history:
  - Non-smoker; social alcohol consumption
  - No significant medical or surgical history
- Review of systems:
  - Weight loss (40 lbs over two months, unintentional)
  - Generalized fatigue, dyspnea on exertion and chills
- Laboratory findings:
  - Hb 12.9 g/dl (13.5- 16 g/dl), Hct 38.4 (37- 47%), WBC count 3.2 x 10^9/L (3.5- 11 x 10^9/L), rare circulating blasts (0.8%) and platelet count 157 x 10^9/L (150- 400 x 10^9/L)
  - Serum LDH 739 IU/L (100- 220 IU/L)
  - D-dimer 696 ng/ml (0- 230 ng/ml)

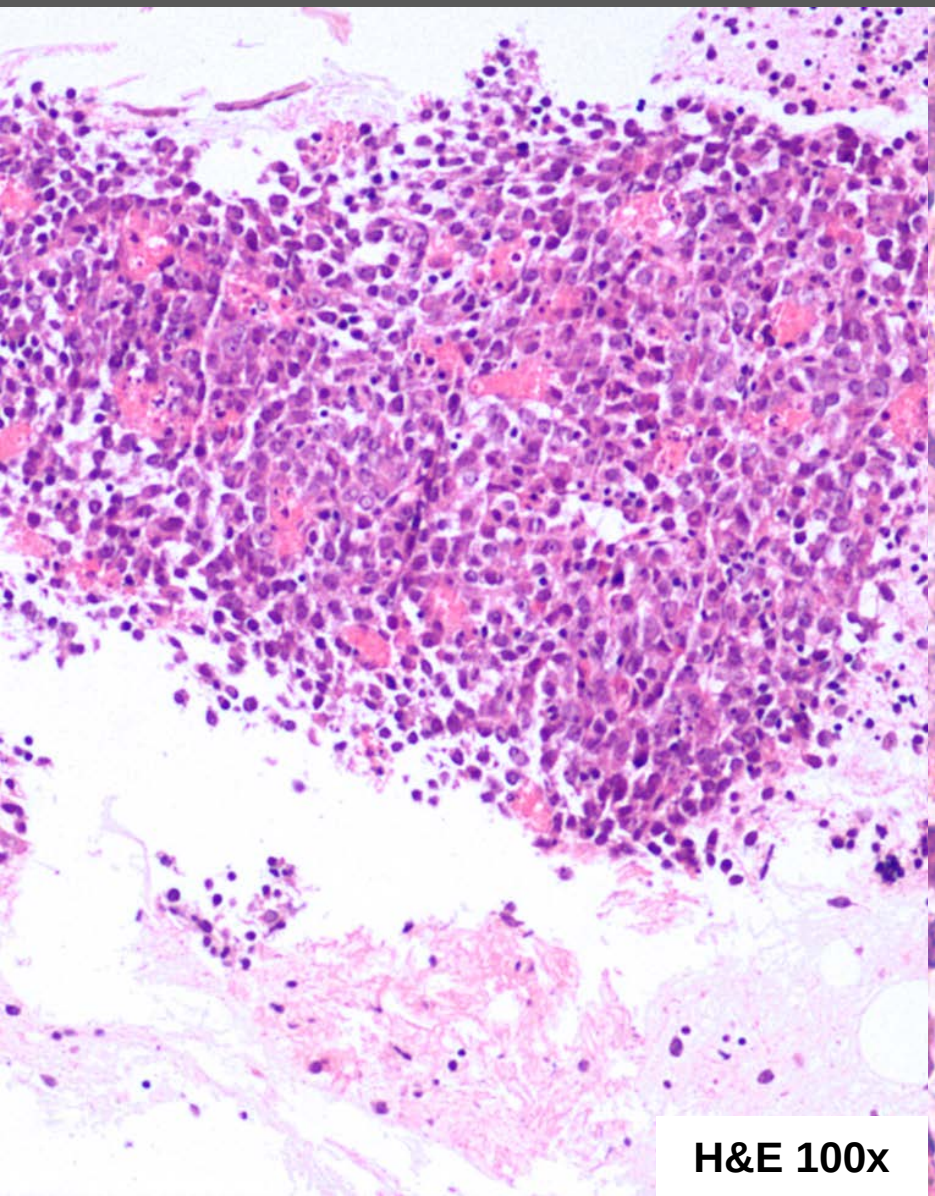
Radiology

- Right Lower Extremity U/S:
  - No deep venous thrombosis
  - Diminished respiratory phasicity within right common femoral vein
- Abdomen and pelvis CAT:
  - Bulky retroperitoneal and inguinal adenopathy
  - Ill-defined soft tissue thickening of right psoas muscle with areas of hypoattenuation
  - Compression of right external iliac vein
  - Enlargement of paraspinal soft tissues at T11
- Testicular U/S:
  - No testicular lesions

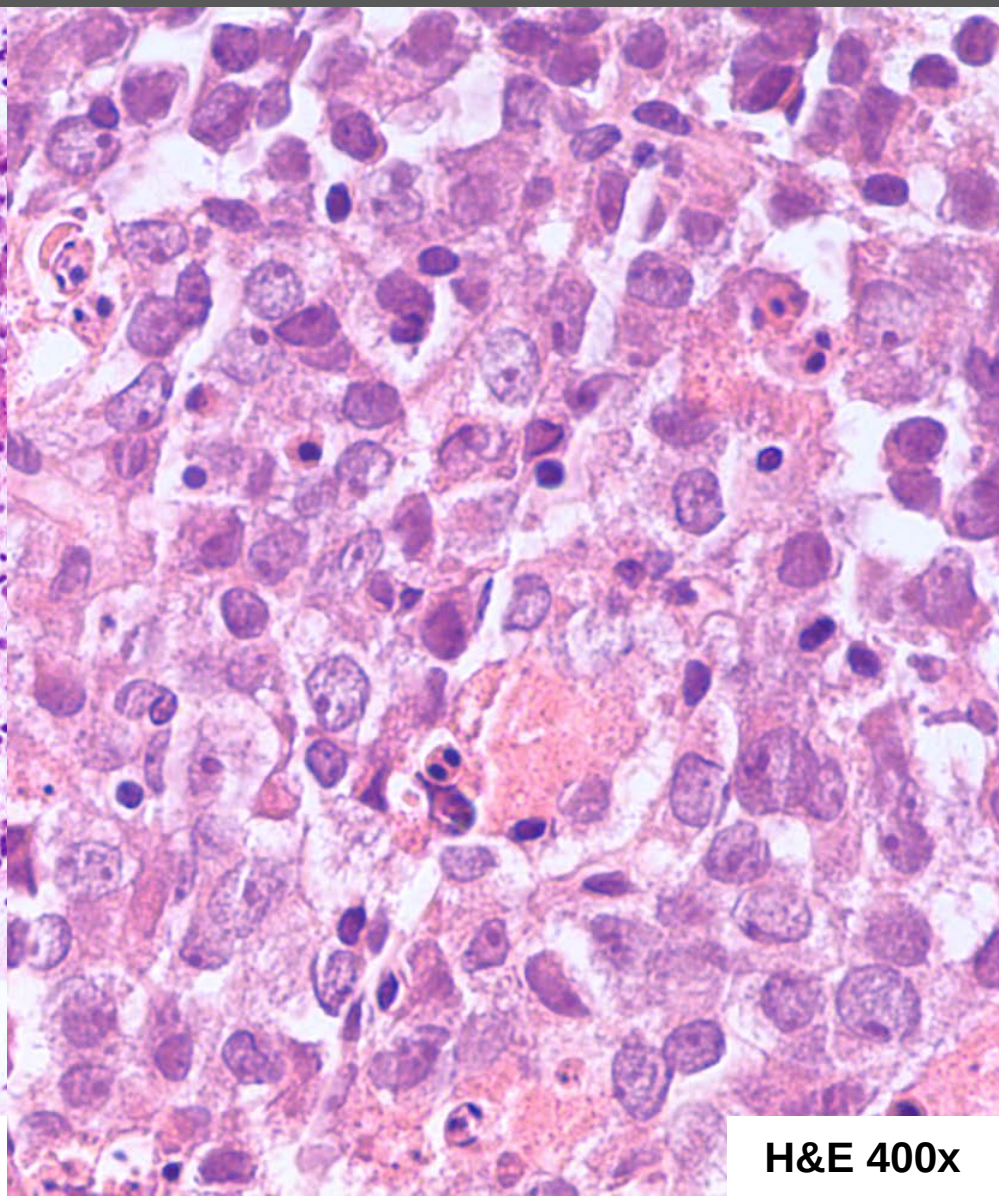




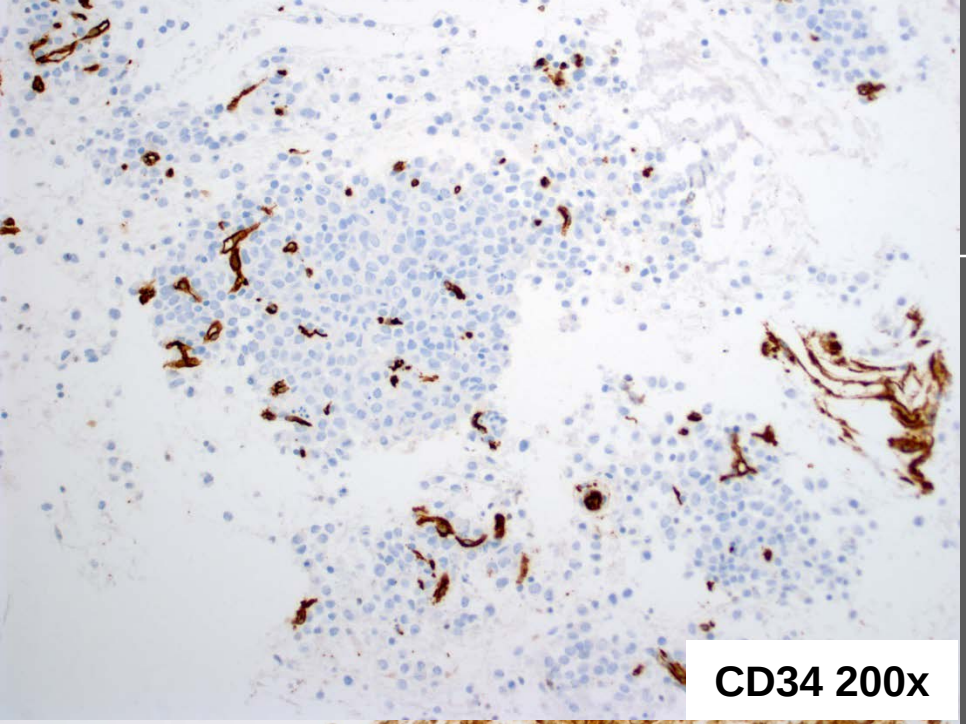
Right inguinal lymph node biopsy



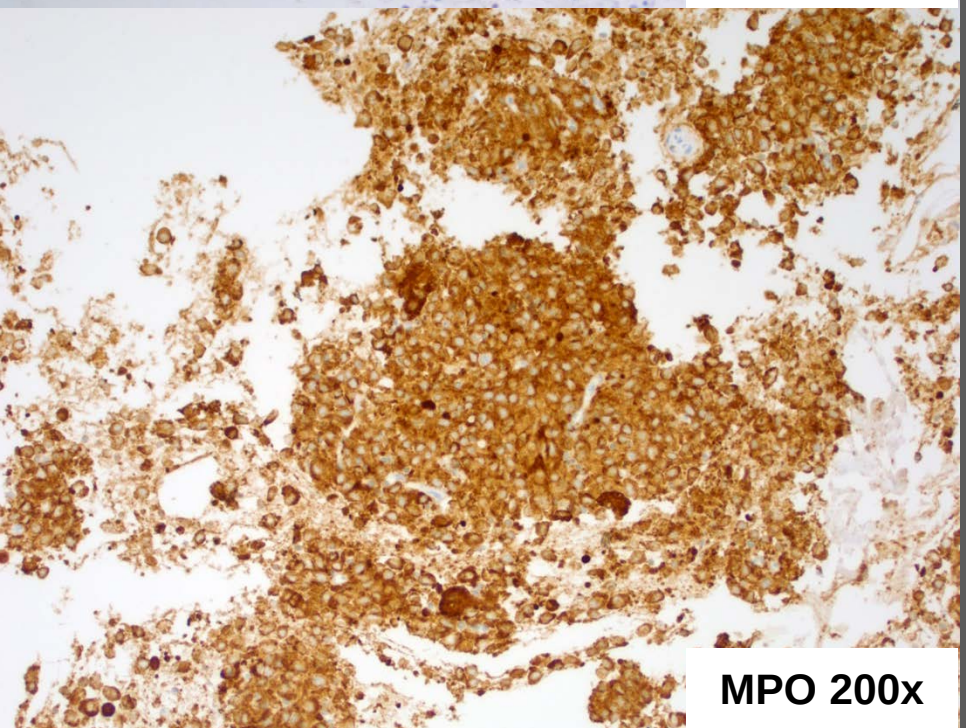
H&E 100x



H&E 400x



CD34 200x



MPO 200x

Immunophenotype

- Positive markers

  CD45, MPO, Lysozyme, CD4, CD99, c-MYC, BCL-6

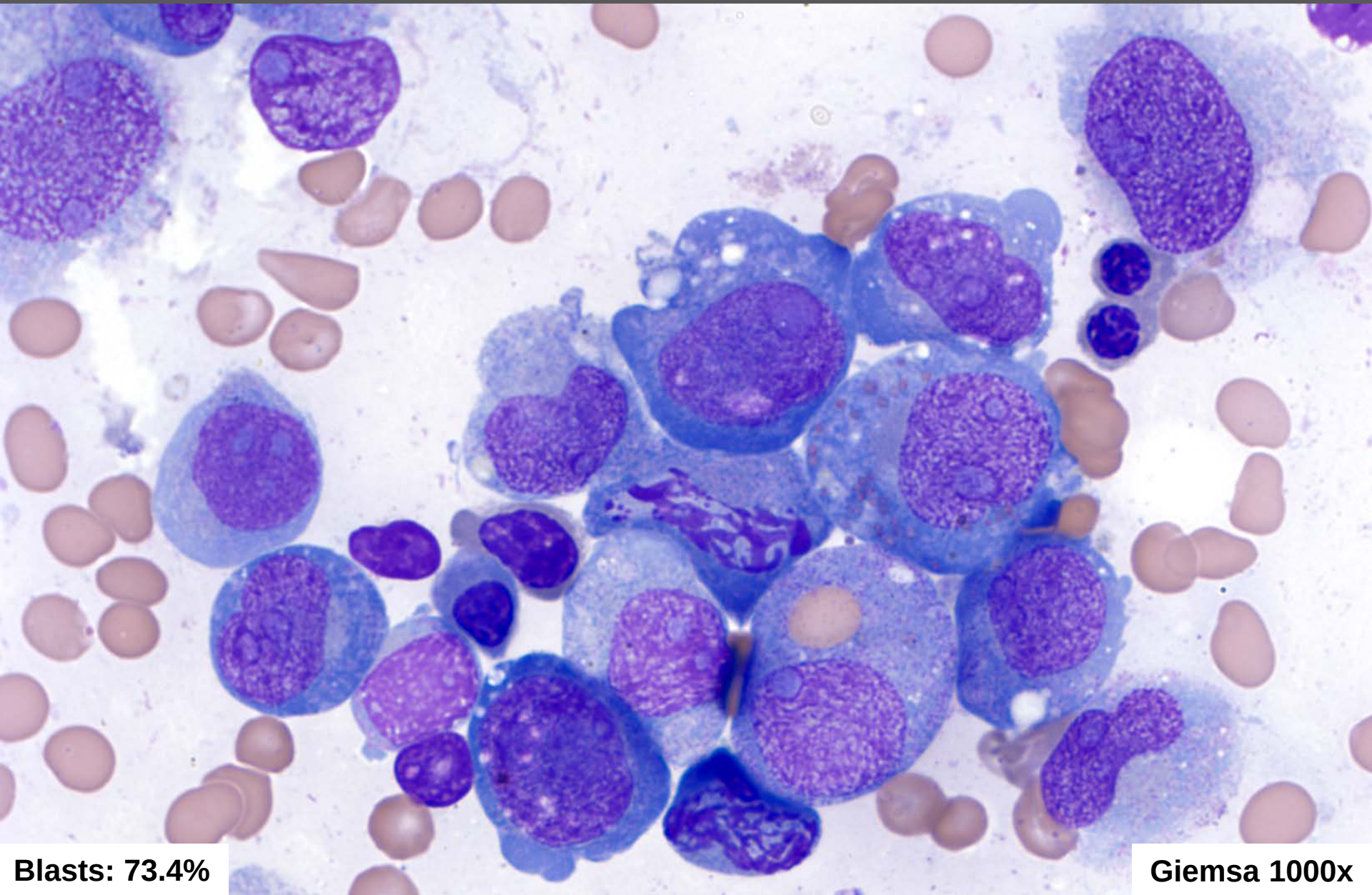
- Negative markers

  CD34, TdT, CD20, CD79a, Pax-5, CD138, MUM-1, CD10, BCL-2, CD5, and CD30

Final diagnosis

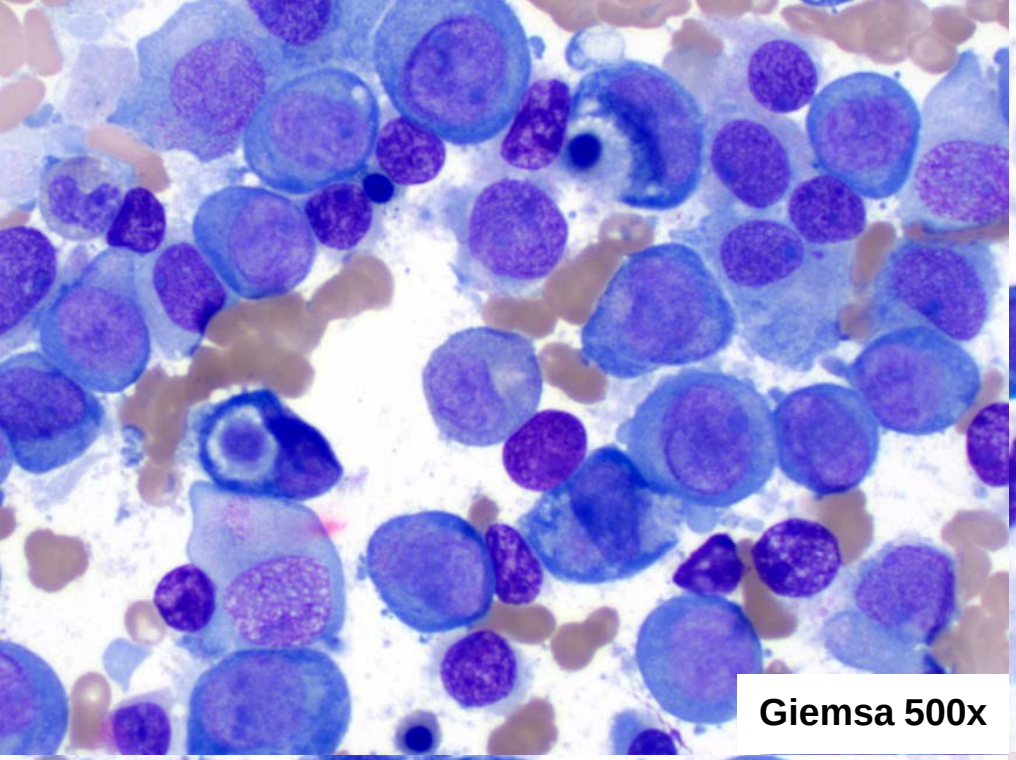
Myeloid neoplasm, consistent with myeloid sarcoma

Right iliac crest bone marrow

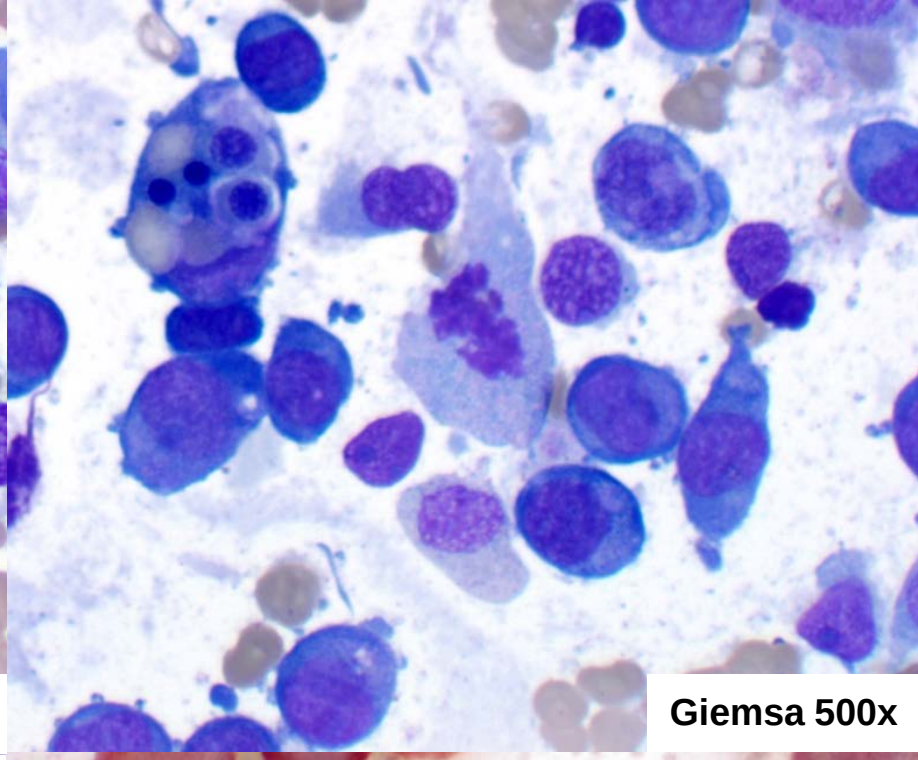


Blasts: 73.4%

Giemsa 1000x



Giemsa 500x



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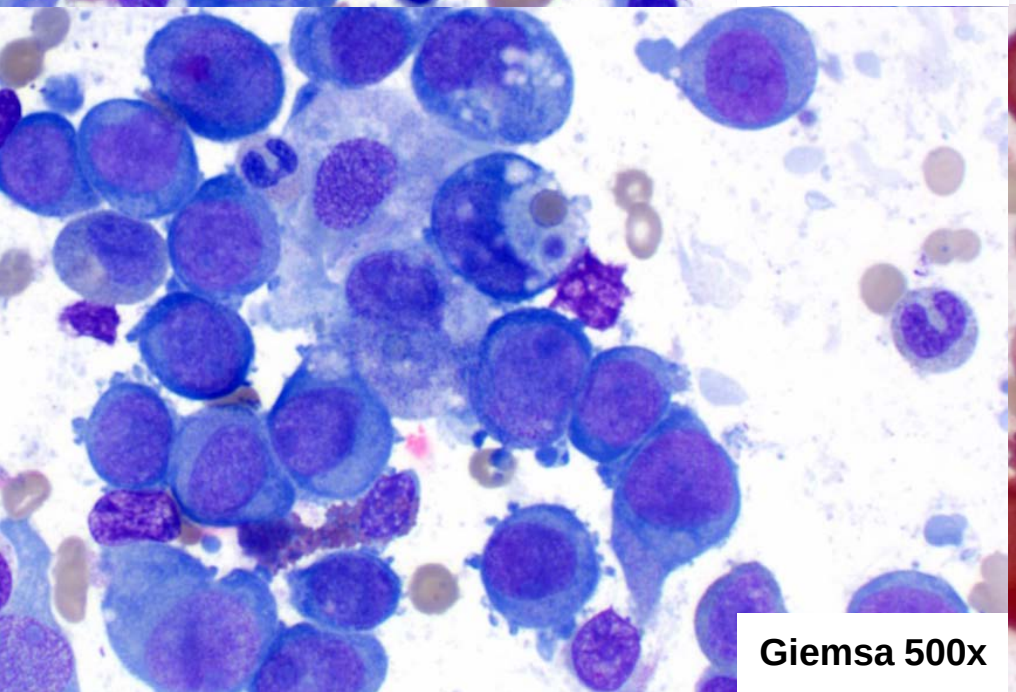
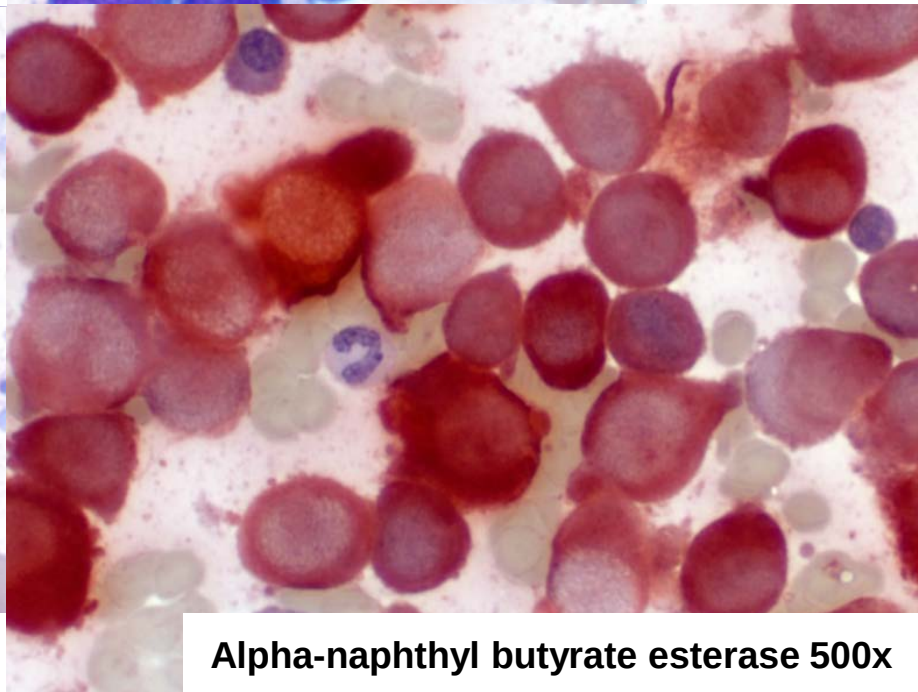
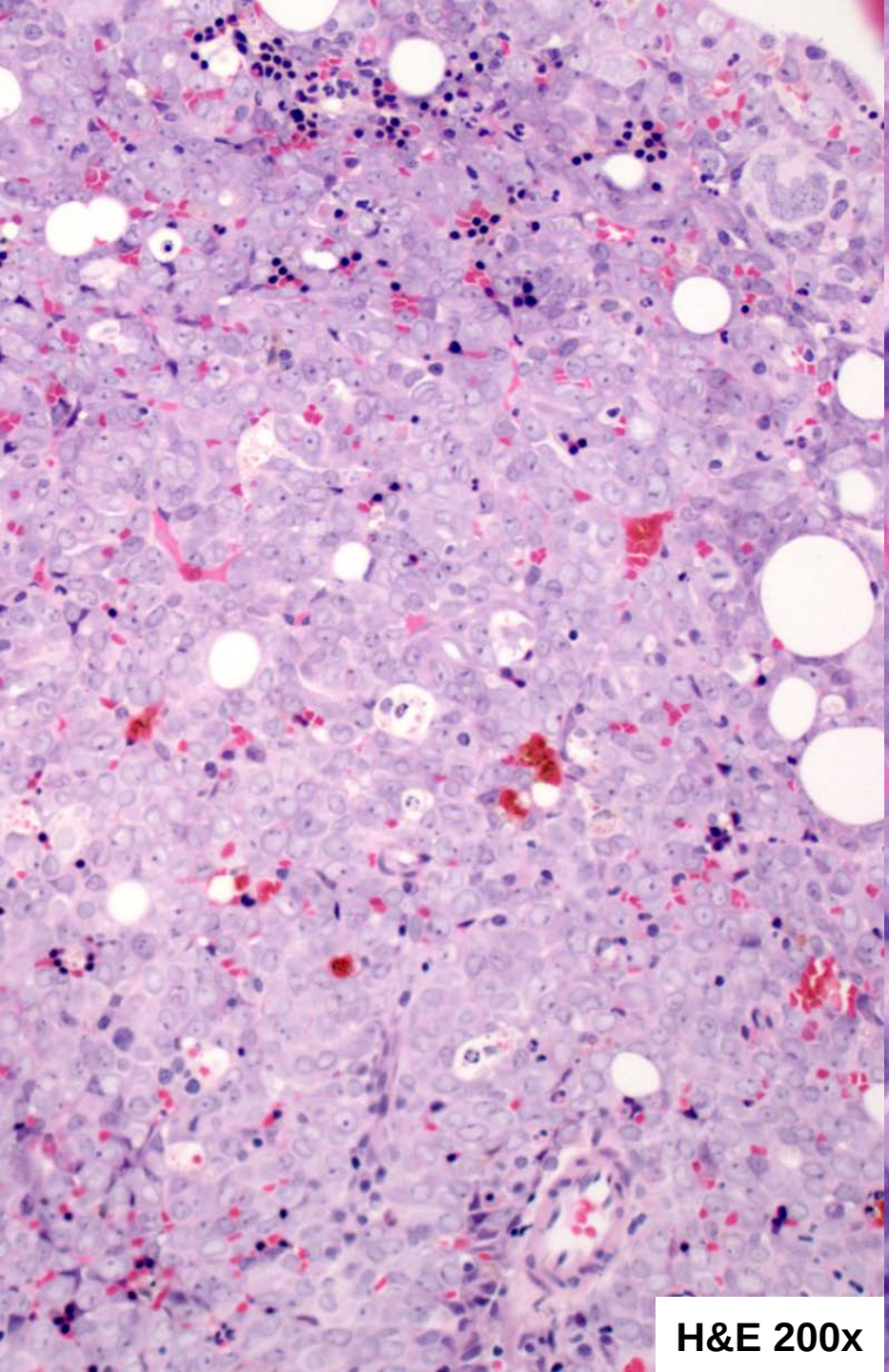
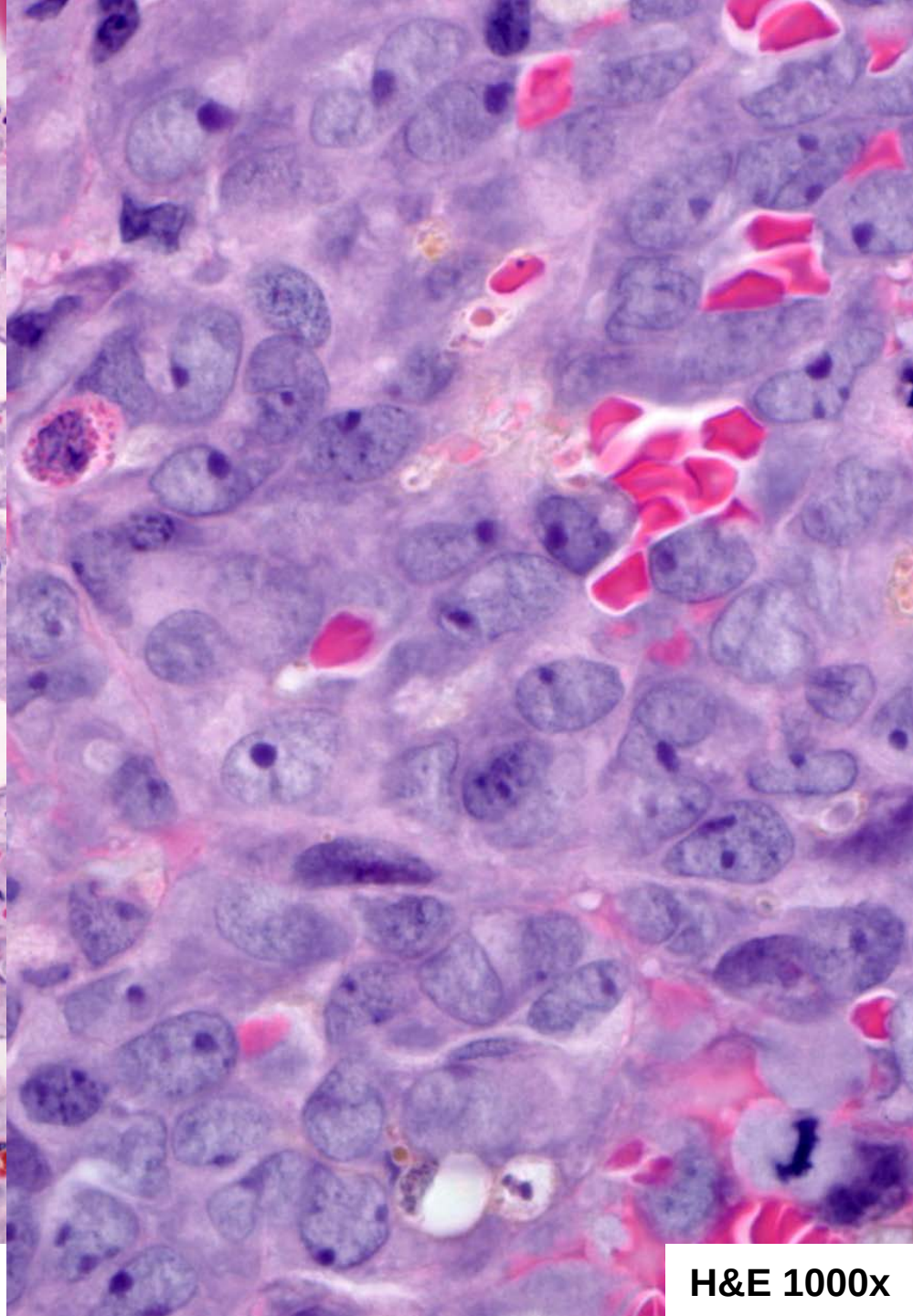


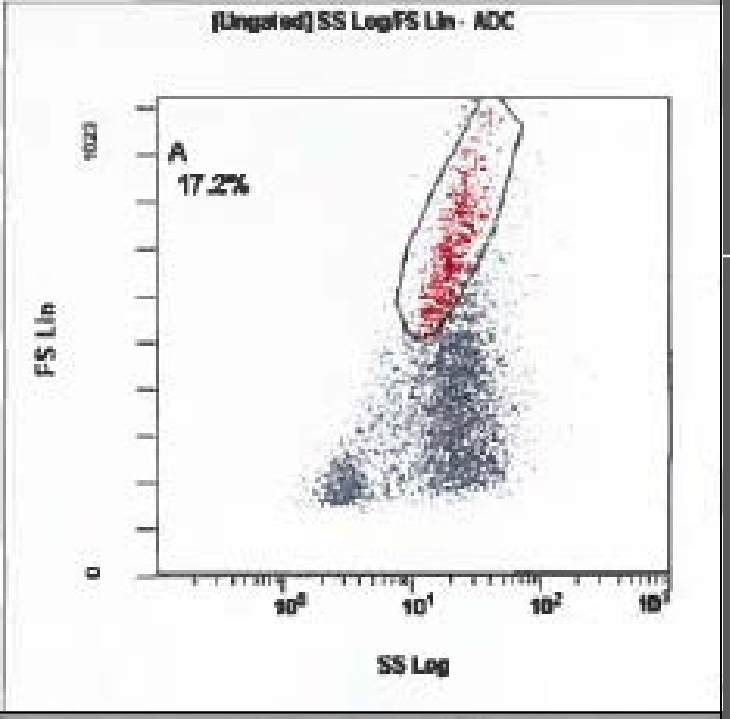
Giemsa 500x

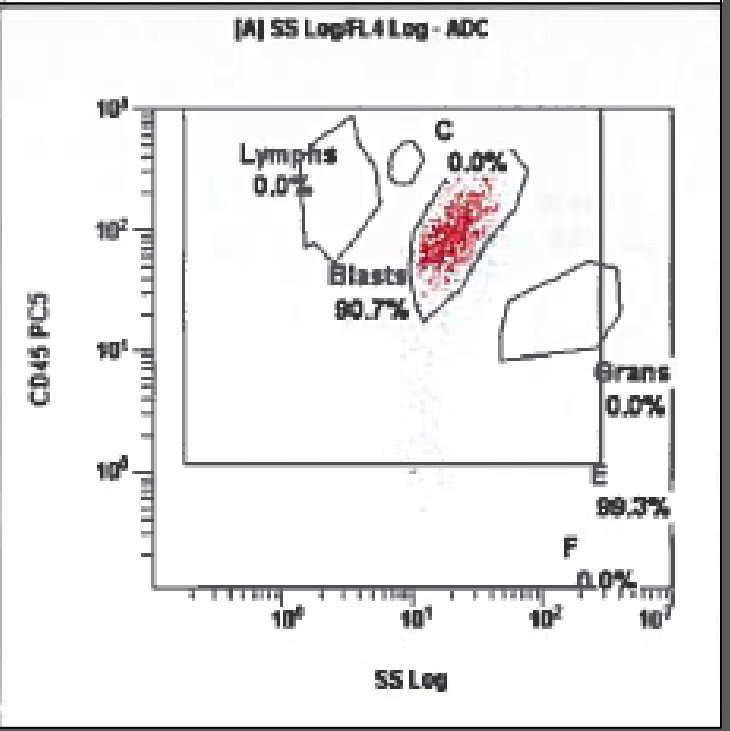


Alpha-naphthyl butyrate esterase 500x


H&E 200x


H&E 1000x





Flow cytometry

CD45 bright blasts (46% of all white blood cells) with unusually high side scatter

Immunophenotype

- Flow cytometry:
  - Positive for CD13, CD33, CD14, CD15, CD36, CD64, CD56, CD71, CD4, CD9 and HLA-DR
  - Negative for CD34, CD2, CD3, CD7, CD19, CD10, CD22, CD235a, CD11b, CD61, CD41 and CD24
- Immunohistochemistry:
  - Positive for CD68 and MPO
- Cytochemistry:
  - Positive for alpha-naphthyl butyrate esterase

Molecular and cytogenetic analyses

- Karyotype
  - 46,XY,add(1)(q21),t(6;13)(p23;?q32),del(7)(q22q32),del(8)(p11),del(9)(p13p22),der(16)t(1;16)(q21;p13.3)[6]/47,idem,+mar[6]/46,XY[8]
- Molecular
  - *FLT3* ITD and TKD mutation – not detected
  - *CEBPA* mutation – not detected
  - *NPM* mutation, cell based – not detected
- FISH
  - nuc ish (*CBFB*x2)[200]
  - nuc ish (*MLL*x2)[200]

Final diagnosis

Acute myeloid leukemia with myelodysplasia-related changes

- Monocytic differentiation
  - CD34 negative blasts with monocytic markers (CD4, CD14, CD64 and CD68)
  - Extramedullary involvement

Unique features

- Prominent erythrophagocytosis
- Strong alpha-naphthyl butyrate esterase positivity *and* myeloperoxidase positivity
- High side scatter and bright CD45 by flow cytometry
- Evidence of disseminated intravascular coagulation

AML with t(8;16)(p11;p13)

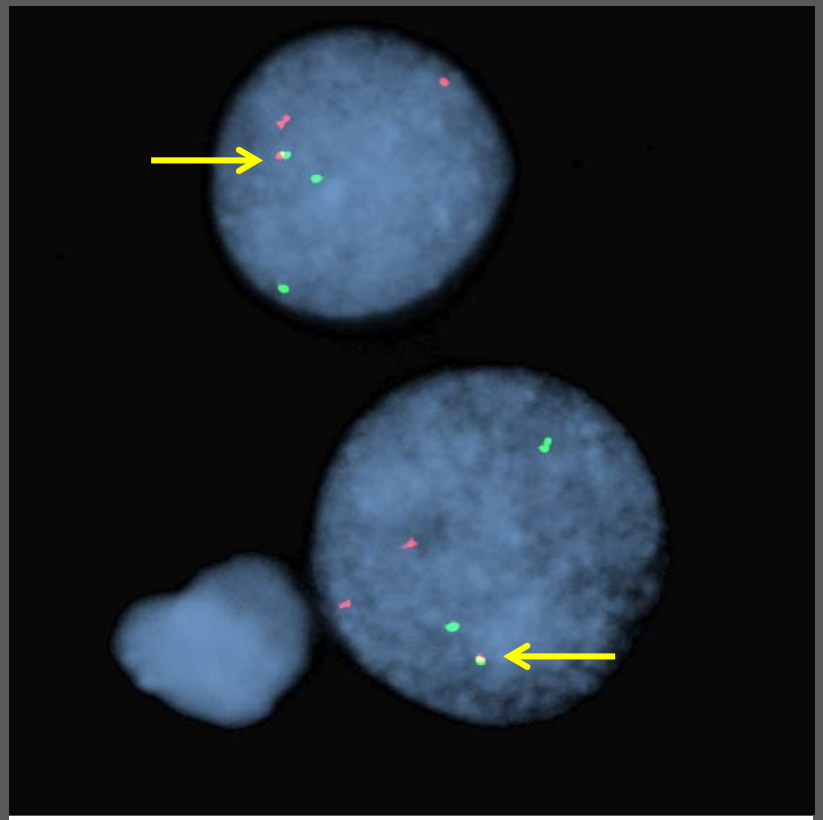
First described in 1983 in an infant with AML associated hemophagocytosis

- *KAT6A* (*MYST3* or *MOZ*) on 8p11
  - Monocytic leukemia zinc finger protein (histone acetyltransferase- activates AML1 transcription factor complex)
- *CREBBP* (*CBP*) on 16p13
  - Binds cAMP response element-binding protein (CREB) (nuclear transcriptional coactivator with intrinsic histone acetyltransferase activity)
- Fusion transcript of unknown significance
  - Many variants (*KAT6A* exon 15 or 16 to *CREBBP* exon 2-8; both in and out of frame)

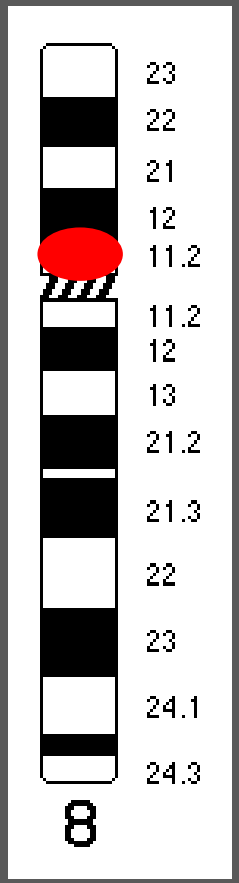
Karyotype

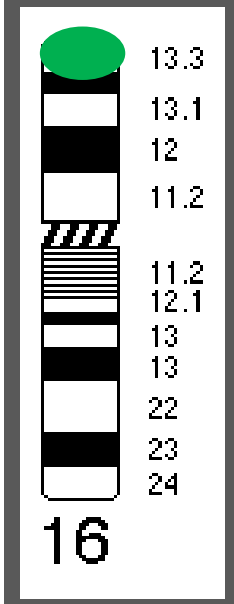
- 46,XY,add(1)(q21),t(6;13)(p23;?q32),del(7)(q22q32),del(8)(p11),del(9)(p13p22),der(16)t(1;16)(q21;p13.3)[6]/47,idem,+mar[6]/46,XY[8]

FISH for KAT6A/CREBBP



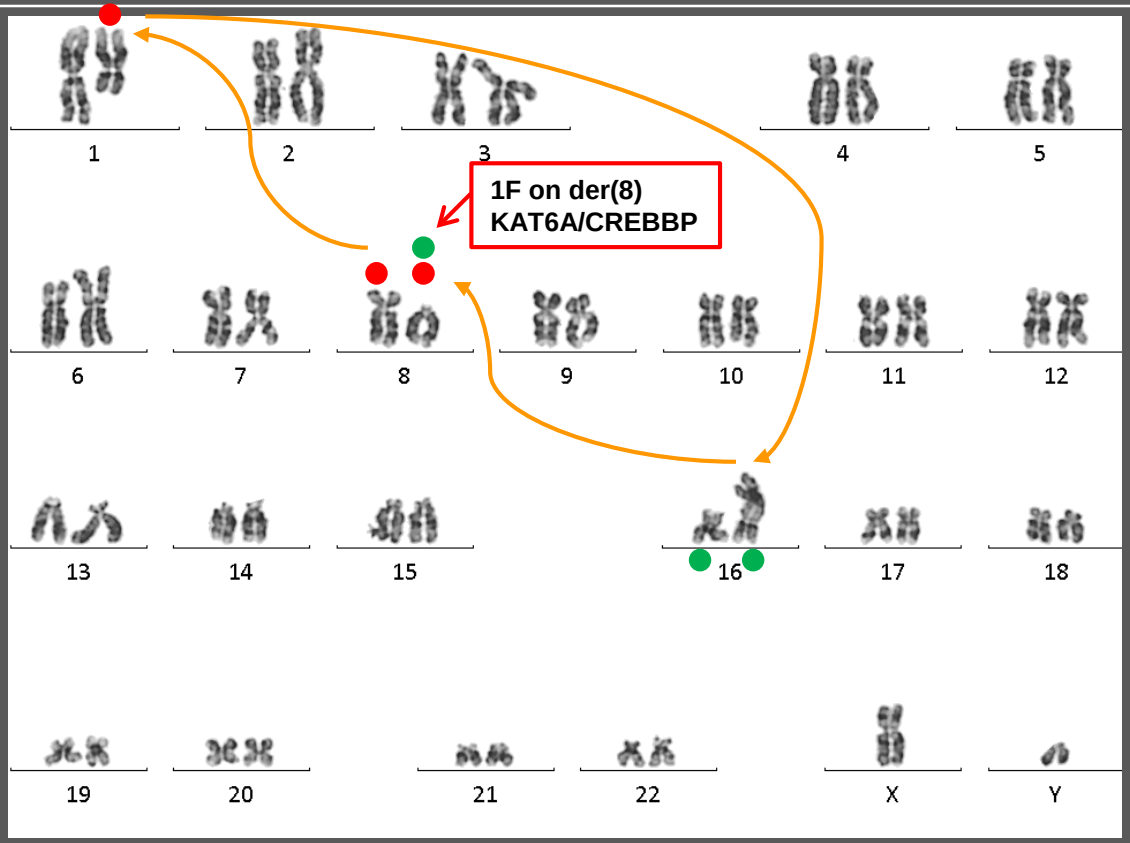
KAT6A[8p11.2](R)/CREBBP[16p13.3](G)





KAT6A/CREBBP fusion in 77.8% of nuclei evaluated

Amended karyotype



46,XY,**t(1;16;8)(q21;p13;p11),**t(6;13)(p23;?q32),del(7)(q22q32),del(9)(p13p22)[6]/47,idem,+mar[6] /46,XY[8]

Three way translocation resulted in 1q material on 16p; 16p material (CREBBP) on 8p (KAT6A) with resultant KAT6A/CREBBP fusion; and 8p material (KAT6A) on 1q

Revised final diagnosis

Acute myeloid leukemia with myelodysplasia-related changes and cryptic t(8;16)(p11;p13); *KAT6A/CREBBP*

Despite distinct phenotypic findings, t(8;16)(p11;p13); KAT6A/CREBBP is not recognized as a recurrent genetic abnormality for the purposes of AML classification

- Frequent association with complex karyotype and/or prior therapy
- Reported marked difference in outcome of pediatric versus adult cases
- Other translocation partners also associated with similar phenotypic abnormalities
- Distinct gene expression (close to MLL-rearranged AML) and microRNA profile

AML with t(8;16)(p11;p13)

Series	Total cases	t-AML cases	Pediatric cases
Gervais 2008	29	22	
Haferlach 2009	13	7	0
Boyd 2009	3	3	
Brown 2012	13	2	5
	23	0	1
Diab 2013	18	6	2
Coenen 2013	62	1	62
Gupta 2014	1	1	
Blieden 2014	1	0	
Chakroborty 2014	1	1	
Andrade 2016	5	0	5 (all <24 mo)
Hanada 2016	1	0	1
Barrett 2017	1	0	1
Hoshino 2017	1	0	
Totals	172	43 (25%)	77 (45%)

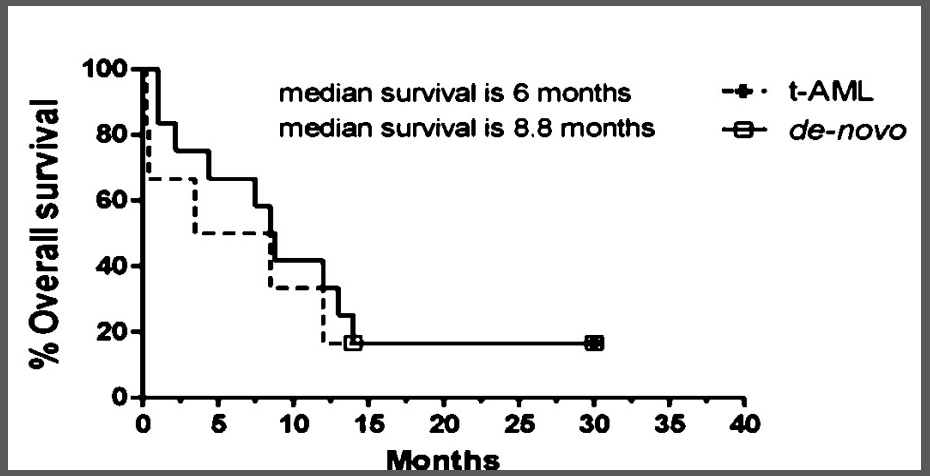
- At least 172 reported cases
- 0.2- 0.4% of AML; 1.6% of t-AML
- Female predominance (64%)
- Median age at diagnosis
  - Adults: 63 yrs (19- 92 yrs)
  - Pediatric: 1.2 yrs (>50% younger than 2 yrs; 30% in first month)
- Monocytic differentiation (93%)
- Parallel MPO and NSE positivity (96%)
- Erythrophagocytosis (70%)
- Disseminated Intravascular Coagulation (40%)
- Extramedullary involvement (54%)
  - Leukemia cutis - more in adults
  - Granulocytic sarcoma - more in pediatric
  - CNS involvement - more in pediatric

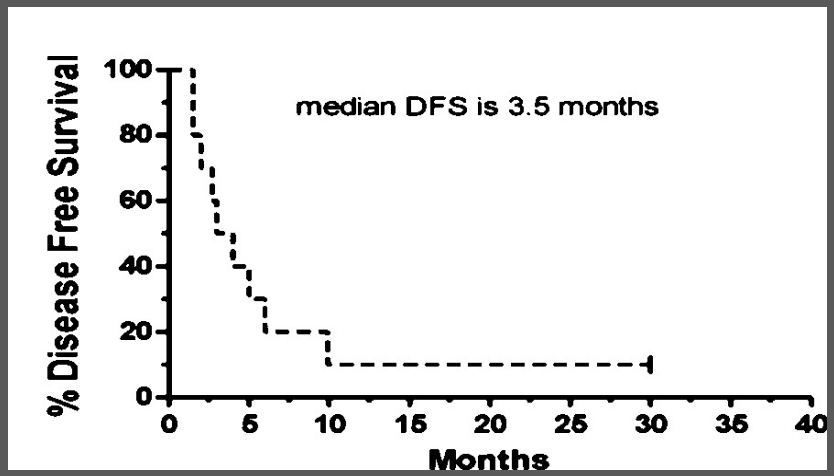
Cytogenetic aberrations

	Total	Isolated t(8;16)	Additional karyotypic aberrations		
			Single	Complex	Unspecified
All cases	169	99 (59%)	29 (17%)	23 (13%)	18 (11%)
Pediatric	74	50 (68%)	15 (20%)	9 (12%)	
t-AML	35	15 (43%)	13 (37%)	7 (20%)	
***de novo* adult**	39	23 (59%)	2 (5%)	5 (13%)	9 (23%)

- 59% of all cases and 43% of t-AML cases have t(8;16)(p11;p13) as isolated cytogenetic abnormality at initial presentation
- 20% of t-AML cases and *at least* 13% of adult *de novo* cases presented with complex karyotype
- Additional abnormalities are more likely in t-AML and adults
- Cytogenetic complexity does not correlate with morphological features or clinical presentation

Prognosis in adults

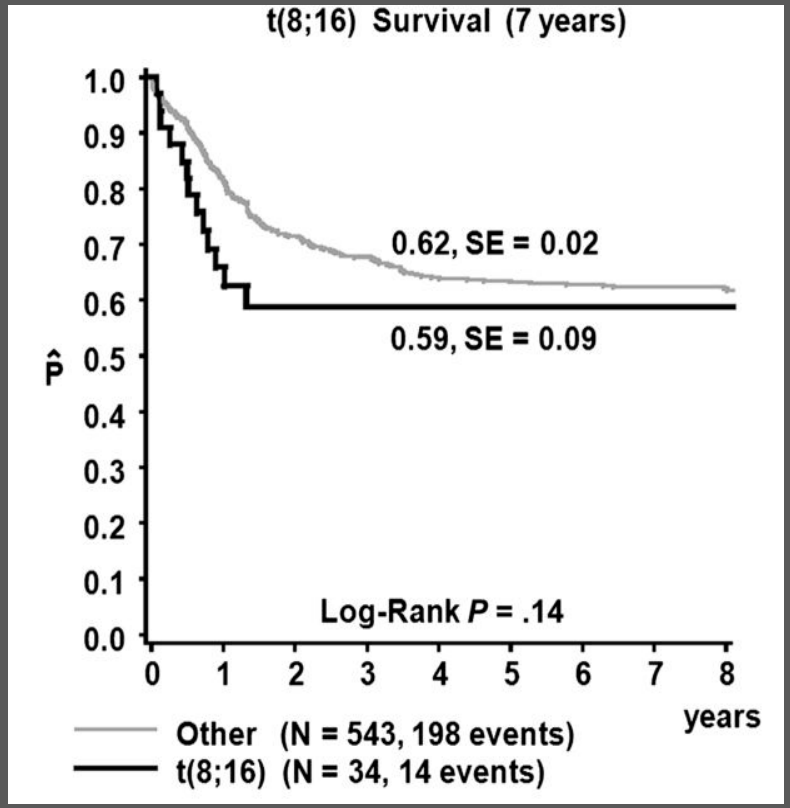




- Median overall survival - 4.7 to 8.8 months (t-AML- 6 months; not statistically significant)
- 50% mortality in first 10 months
- CR rate similar to other AMLs
- Short duration of remission; median DFS - 3.5 months
- Degree of cytogenetic complexity did not correlate with OS

Diab A. et. al. Leuk Res. 2013 Jan; 37(1): 32–36.

Prognosis in pediatric population



- 60% 5-year survival
  - Similar to other pediatric AML

Coenen et al. Blood 2013; 122: 2704-2713

Spontaneous Regression

- 12 reported pediatric (9 cases < 1 month; congenital) cases
  - t(8;16) the sole detected abnormality at initial presentation in all cases
  - EMD present in all cases (leukemia cutis in all except one)
  - Erythrophagocytosis and disseminated intravascular coagulopathy reported in one case each

- *Hoshino, et al 2017*: First reported adult case of spontaneous regression
  - t(8;16) the sole detected abnormality

Key points

- AML with t(8;16) has unique phenotypic attributes
  - Enables identification of cryptic translocations
- Increased incidence in perinatal and post-chemotherapy populations
- In majority of cases t(8;16) was only cytogenetic abnormality
  - Additional mutations more likely in older population or at recurrence
- t-AML and *de novo* cases exhibit similar phenotypic and prognostic features
  - Slight increased frequency of additional cytogenetic mutations in t-AML
- Available survival data reproducibly suggest adult cases behave poorly
  - Many potential confounders including age of studies, high initial mortality rate at presentation, etc.
- Spontaneous regression associated with absence of other cytogenetic abnormalities, DIC and erythrophagocytosis
  - Recently reported adult case suggests differences between adult and pediatric population may reflect therapeutic decisions not biology

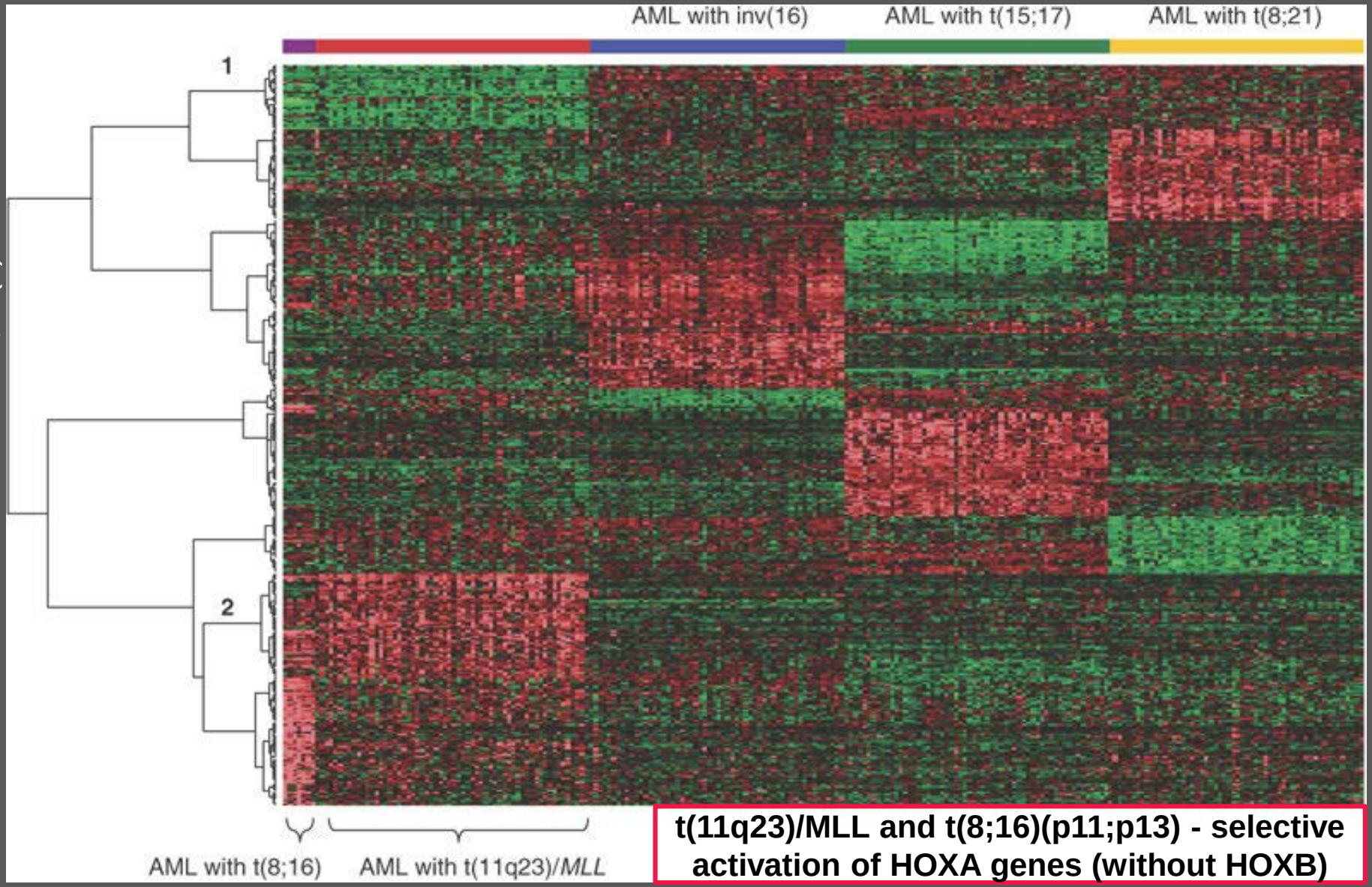
Clinical course

- Developed pulmonary embolism (started on rivaroxaban)
- Initiated on 7 + 3 chemotherapy
- Morphological and cytogenetic remission in Day 21 bone marrow
- Received mismatched related allogenic stem cell transplant
- Chronic GVHD of liver and GIT
- In remission 14 months after BMT

Final panel diagnosis

Acute myeloid leukemia with myelodysplasia-related changes [with t(1;16;8)(q21;p13;p11) KAT6A-CREBBP]

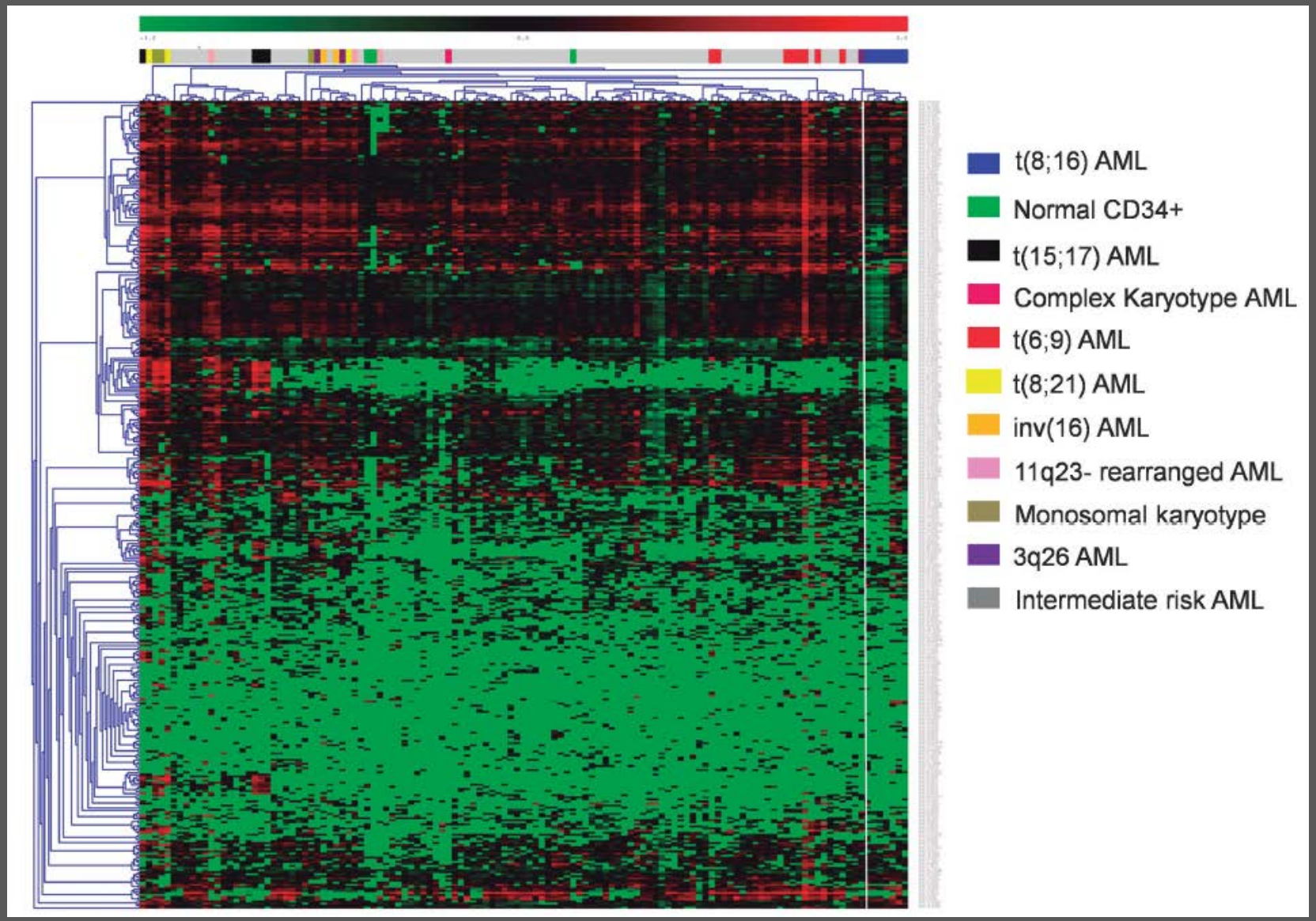
Distinct gene expression profile; close to MLL-rearranged AML



Haferlach et. al., Leukemia. 2009;23(5):934-43

t(11q23)/MLL and t(8;16)(p11;p13) - selective activation of HOXA genes (without HOXB)

Distinct microRNA signature targeting RET proto-oncogene



Díaz-Beyá M. et. al. Leukemia. 2013 Mar;27(3):595-603.

Fusion partner promiscuity

- Fusion partners independently involved in AML-associated abnormalities:
  - *KAT6A* - t(8;19)(p11;q13), t(6;8)(q27;p11), t(8;22)(p11;q13) and inv(8)(p11q13)
  - *CREBBP* - t(10;16)(q22;p13) and t(11;16)(q23;p13)
- Erythrophagocytosis in AML seen in other scenarios
  - inv(8)(p11q13) – fusion partner for *KAT6A* is *NCOA2* (nuclear receptor coactivator 2, alias *TIF2*)
- Translocation not unique to leukemia, also reported in:
  - chordoma, breast papillomas, salivary adenoid cystic carcinoma, alveolar rhabdomyosarcoma & dysplastic nevi, mature T/NK cell neoplasm, CLL & Burkitt lymphoma

Acknowledgements

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  - Magdalena Czader
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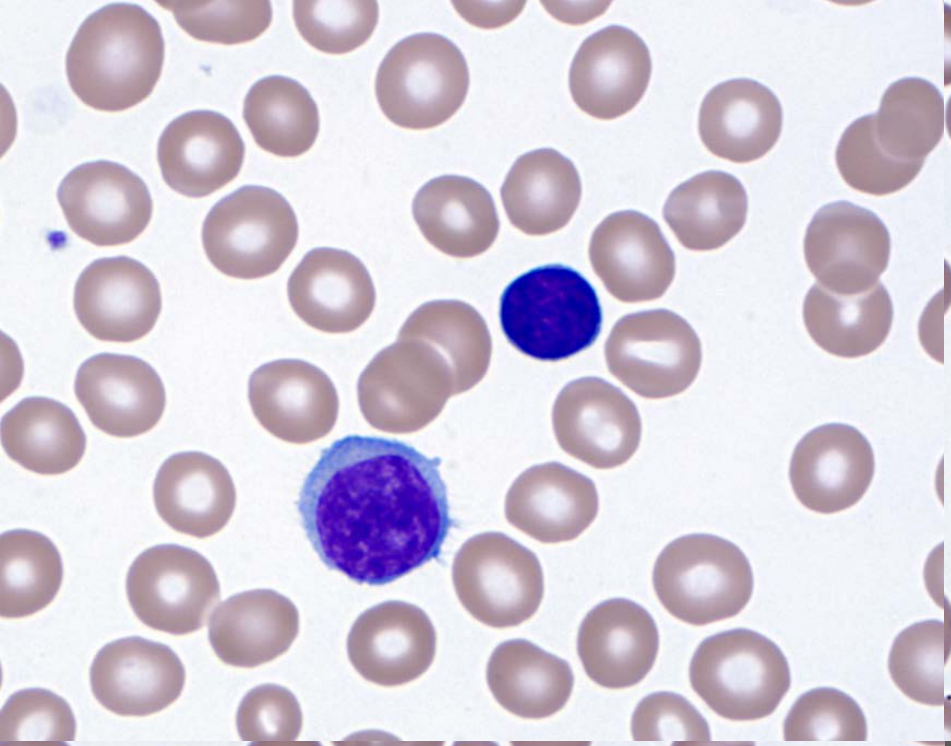

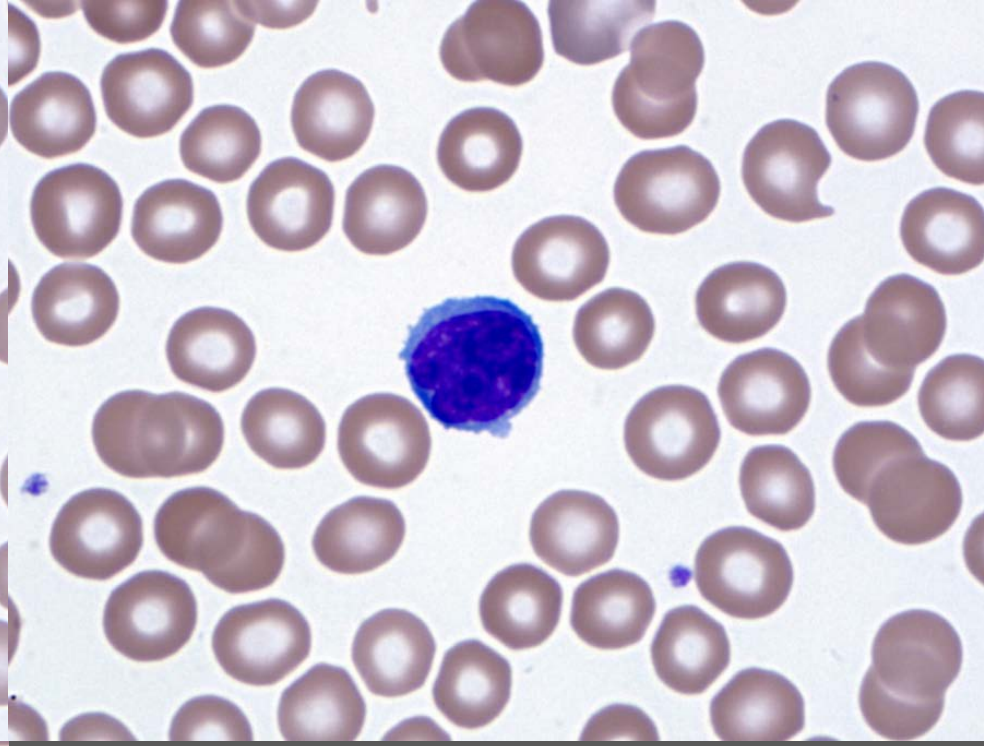

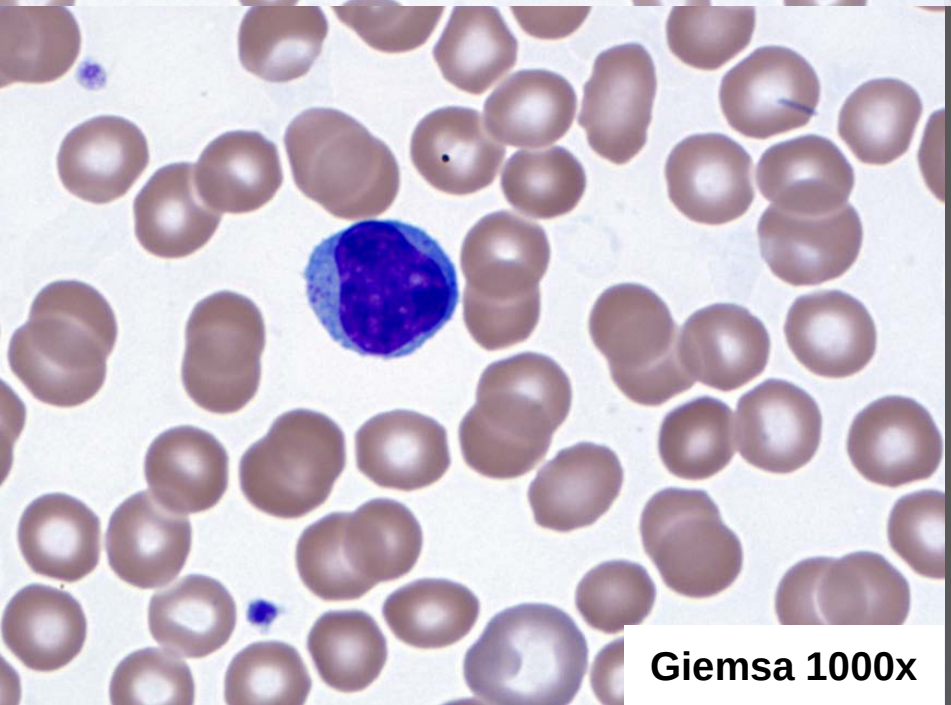

Giemsa 1000x

Circulating blasts- 0.8%