AML with t(8;16) shows unique clinical, morphological and cytogenetic features

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INTRODUCTION

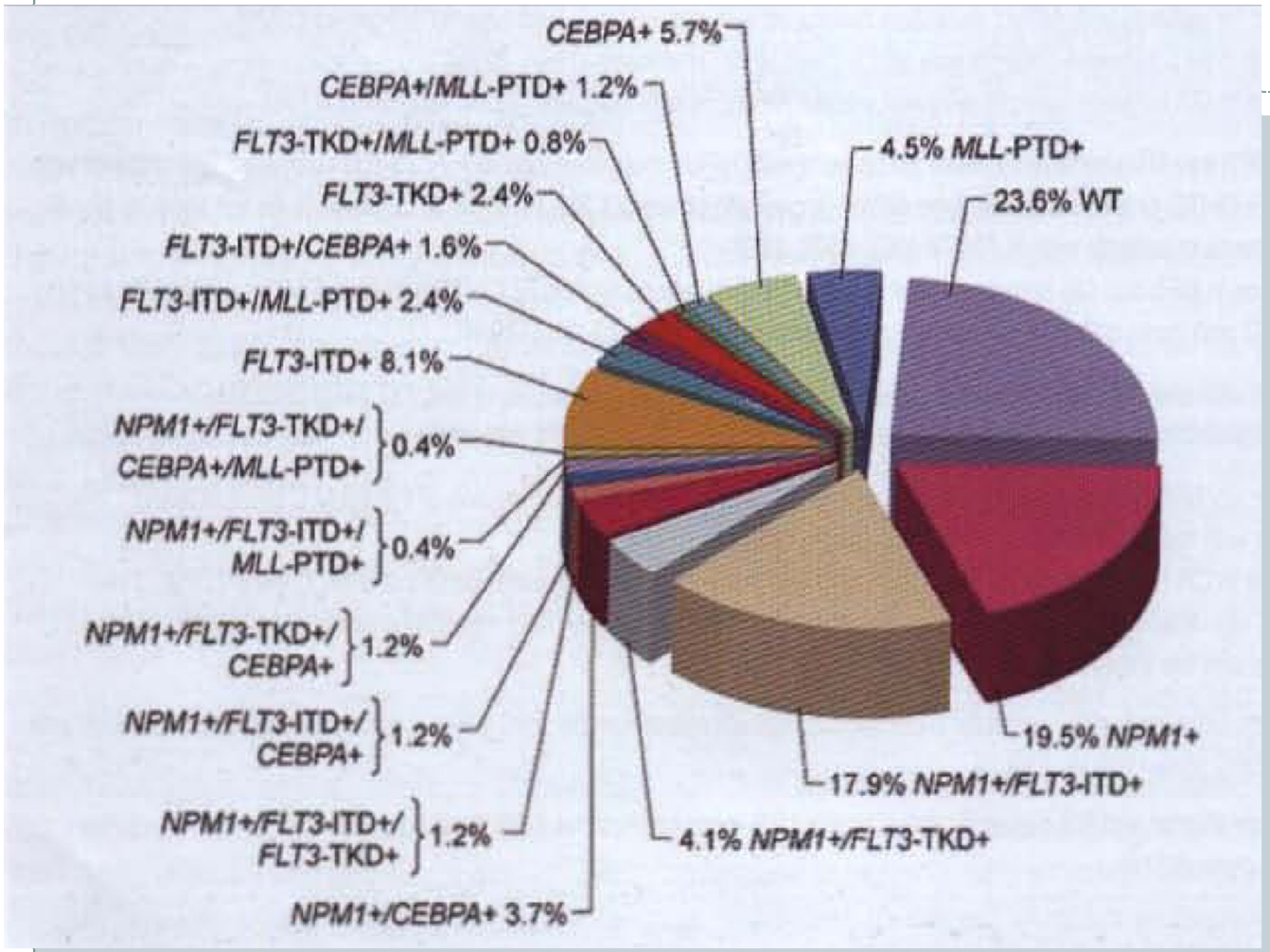
- t(8;16) (p11.2;p13.3) is a recurrent, myeloid-specific cytogenetic abnormality detectable on routine cytogenetic karyotypic analysis.
- Rare (0.7% of AML) but comprises 6.5% of AML of the M4/M5 FAB subtype.
- Initially described in **pediatric** leukemias and is the second most common recurrent cytogenetic abnormality in rare cases of **congenital** leukemia.
- Aggressive and often **therapy-related** with frequent resistance to standard chemotherapy, similar to AML with MLL rearrangements (though, outcome may even be inferior).

Acute Myeloid Leukaemia and Related Precursor Neoplasms (WHO)

- **Acute myeloid leukaemia with recurrent genetic abnormalities**
- Acute myeloid leukaemia with myelodysplasia-related changes
- Therapy-related myeloid neoplasms
- **Acute myeloid leukaemia, not otherwise specified**
- Myeloid sarcoma
- Myeloid proliferations related to Down syndrome
- Blastic plasmacytoid dendritic cell neoplasm

AML with balanced translocations/inversions (WHO 2008 classification)

- Acute myeloid leukaemia with t(8;21)(q22;q22); RUNX1·RUNX1T1
- Acute myeloid leukaemia with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB·MYH11
- Acute promyelocytic leukemia with t(15;17)(q22;q12); PML-RARA
- Acute myeloid leukaemIa with t(9;11)(p22;q23); MLLT3·MLL
- Acute myeloid leukaemia with t(6;9)(p23;q34); DEK-NUP214
- Acute myeloid leukaemia with inv(3)(q21q26.2) or t(3;3)(q2/;q26.2); RPN/·EVI1
- Acute myeloid leukaemia (megakaryoblastic) with t(1;22)(p13;q13); RBMI15-MKL1



Pie chart based on 246 patients analyzed for the presence of mutations in the NPM1 and CEBPA genes, FLT3-ITD, FLT3-TKD and MLL-PTD. Each sector indicates the percentage of patients harboring one or more of the aforementioned mutations. WT indicates patients with only wild-type alleles of the genes testing. From Mrozek et al* and adapted from Dohne et al**

*Mrózek K et al. Bloomfield CD. Blood. 2007 Jan 15;109(2):431-48. Epub 2006 Sep 7. Review.
Mutant nucleophosmin (NPM1) predicts favorable prognosis in younger adults with acute myeloid leukemia and normal cytogenetics: interaction with other gene mutations.
**Döhner K et al, Blood. 2005 Dec 1;106(12):3740-6.

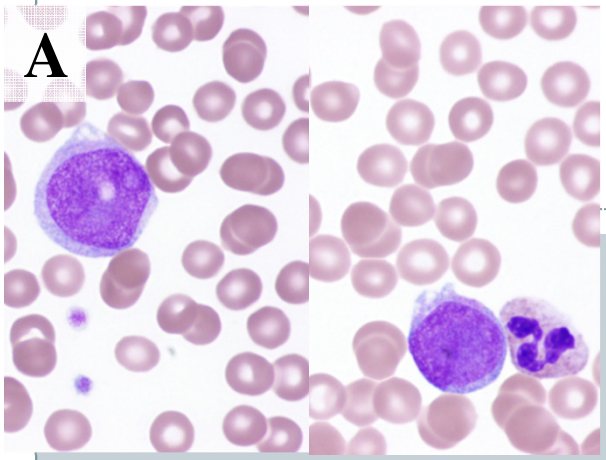
AML with t (8;16)

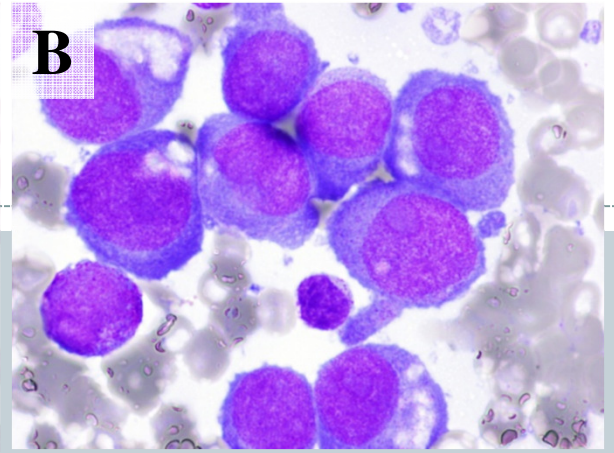
- Initially reported as a malignant histiocytosis (Schouten et al), AML with t(8;16) commonly shows blast hemophagocytosis, DIC, and extramedullary infiltration
- Often a **monocytoid** leukemia but difficult to classify based on unusual cytochemical staining (parallel MPO/NSE positivity in blasts).
- Thought to be an initiating event in leukemogenesis and fuses MYST3 (8p11), which encodes for a histone acetyltransferase, to CREBBP (16p13), which encodes for a transcriptional co-activator and acetyltransferase, generating a novel fusion protein that **inhibits RUNX1 regulated transcription**, leading to differentiation block.
- **Variant translocations** related to t(8;16) include t(10;16)(q22;p13), t(8;22)(p11;q13), inv(8)(p11q13), t(8;20)(p11;q13) and show similar features, including blast erythrophagocytosis.
- Although >100 cases of t(8;16) have been reported, **infants and children are underrepresented** in recent studies

TABLE 1. Patient Characteristics/CHW,DenverCH

	Age	Sex	WBC	Sites	Subtype	Immunophenotype‡	Karyotype	DIC , Hemophago-cytosis	Outcome
1	5y	F	18,600/ul	Bone marrow, peripheral blood	De novo FAB M5a	CD34-, CD117-, MPO+, NSE+ CD4+, CD56+, TdT-, CD163-	46,XX,der(7)t(6;7)(q15;q31),**t(8;16)(p11.2;p13.3)**[14]/46,XY[6]	Minimal blast hemophagocytosis	Alive, 19 months s/p transplant
2	8y	F		Bone marrow, peripheral blood	Therapy-related FAB M5b	CD34-, CD117?, MPO-, NSE+ CD2+, CD19+, TdT-	46,XX,t(5;10)(p15.3;q24),del(7)(q31),**t(8;16)(p11.2;p13)**,inv(17)(p13q23)[16]/ 46,XX, t(1;15)(q21;q24),t(5;10)(p15.3;q24),t(6;7)(q27;p15),t**(8;16)(p11.2;p13)**,t(13;17) (q14;p13)[1]/ 46,XY[3]	None	DOD, <1 year following diagnosis
3	1m	M	381,000/ ul	Peripheral blood, skin, CSF	De novo FAB M4	CD34-, CD117-, MPO+, NSE+ CD56(dim+), TdT(dim+)	46,XY,**t(8;16)(p11.2;p13.3)** [inc2]/46,XY[2]	DIC	Alive, 19 months s/p reinduction and URD cord blood transplant
4	14y	F	171,000/ ul	Peripheral blood, bone marrow	De novo FAB M4	CD34-, CD56+, CD15+, CD4+	**t(8;16)(p11.2;p13.3)** nuc ish(5'KAT6A, 3' KAT6A)x2 (5'KAT6A sep 3' KAT6Ax1)[25/100]	DIC hemophagocytosis	DOD, 2 months after bone marrow transplant
5*	20m	M		Skin	Therapy-related	No flow	**t(8;16)(p11.2;p13.3)** by FISH	Hemophagocytosis	Alive 1 year after bone marrow transplant

*Early therapy-related myeloid sarcoma and deletion of 9q22.32 to q31.1. Brickler MM, Basel DG, **Gheorghe G**, Margolis DM, Kelly ME, Ehrhardt MJ. Pediatr Blood Cancer. 2014 Sep;61(9)


A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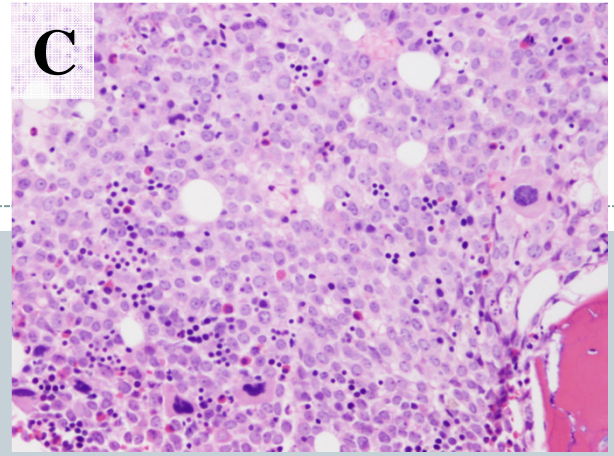
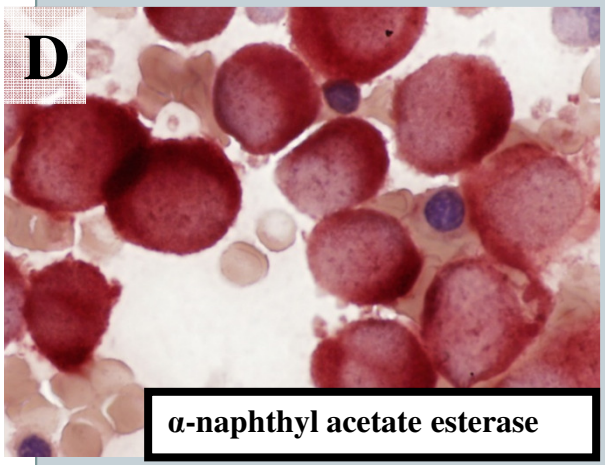
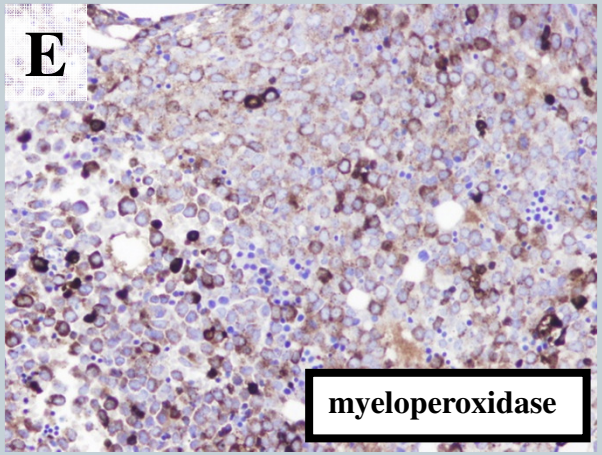
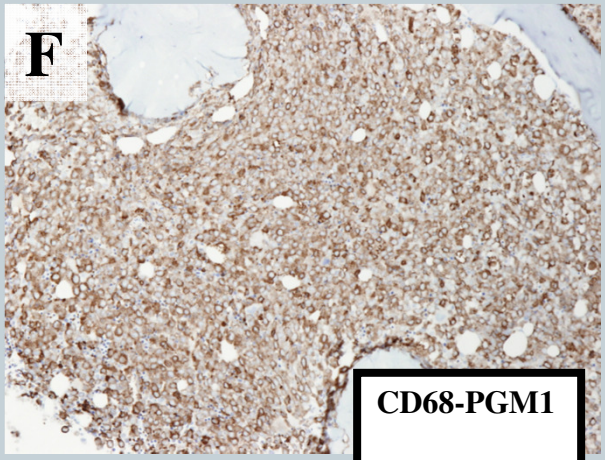
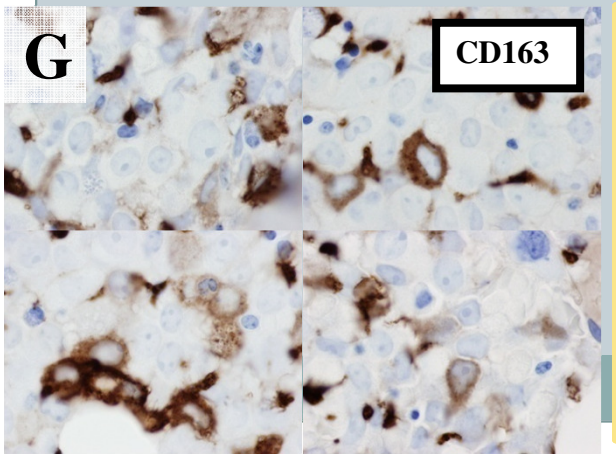
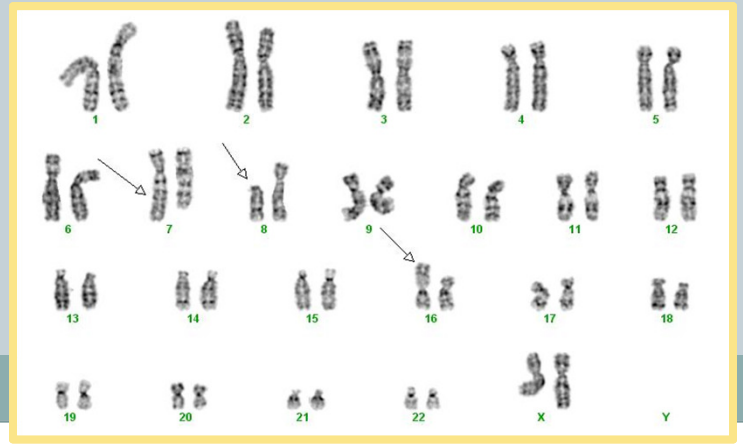

C


D
α-naphthyl acetate esterase

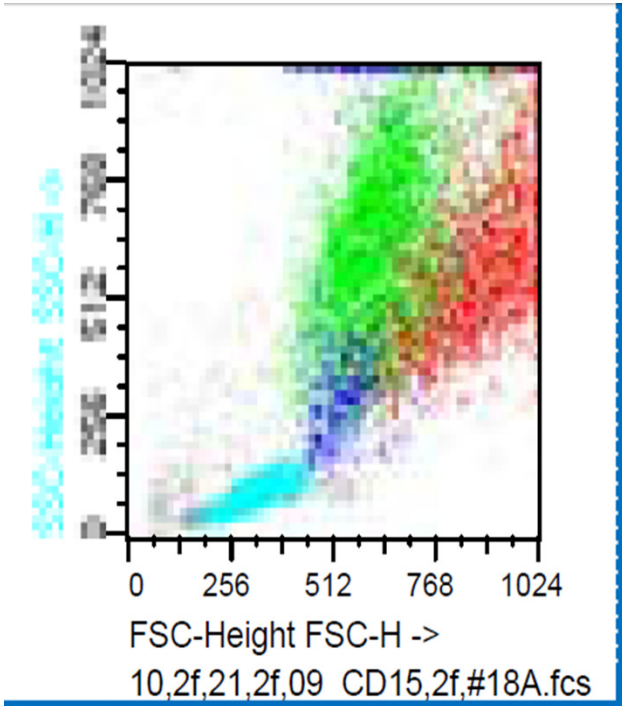

E
myeloperoxidase

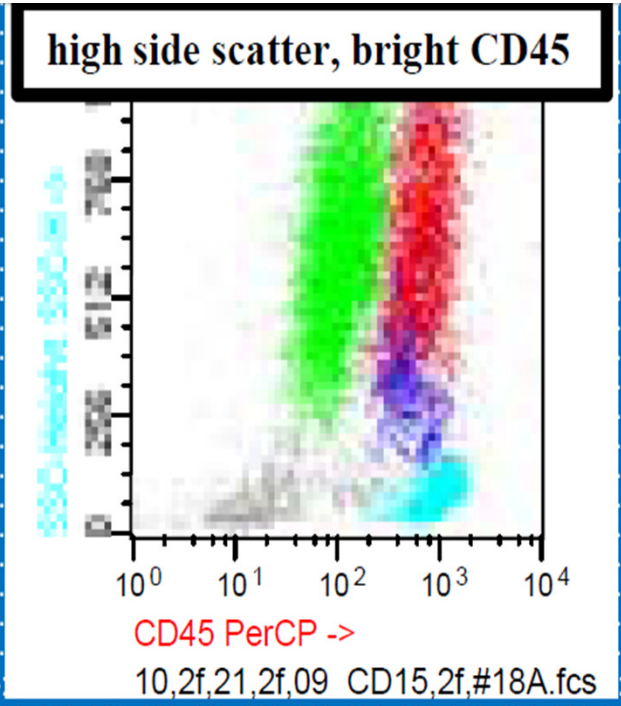

F
CD68-PGM1

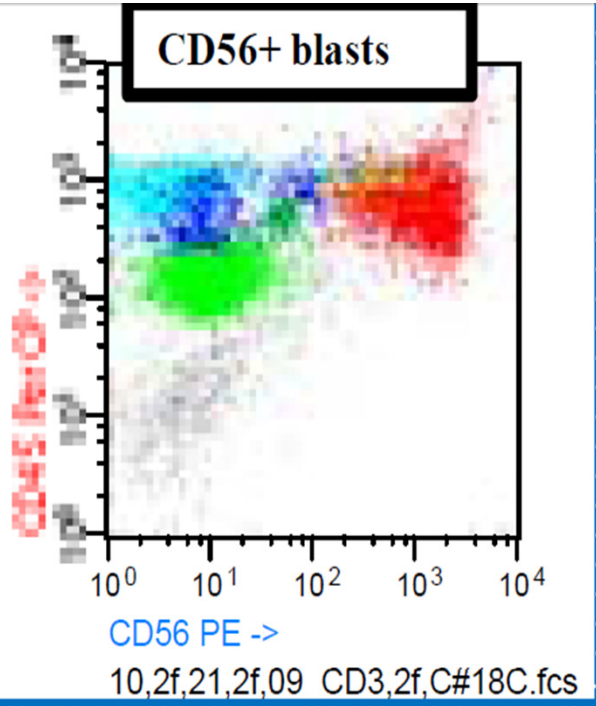

G
CD163

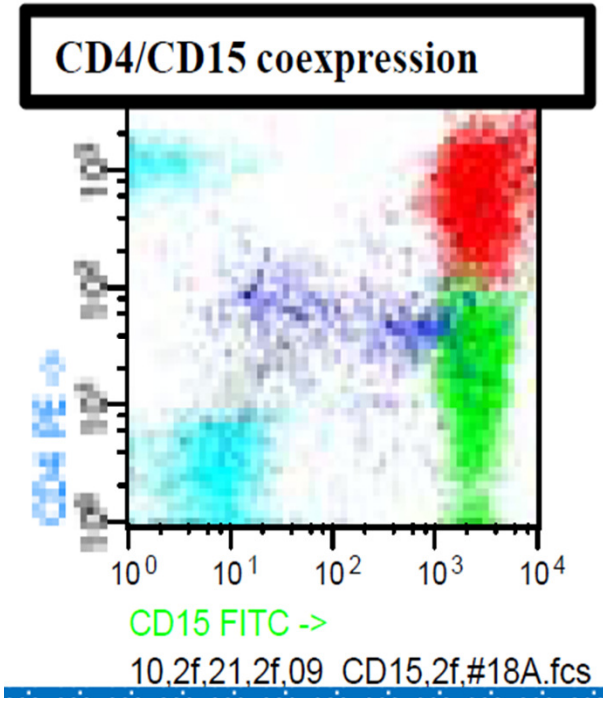


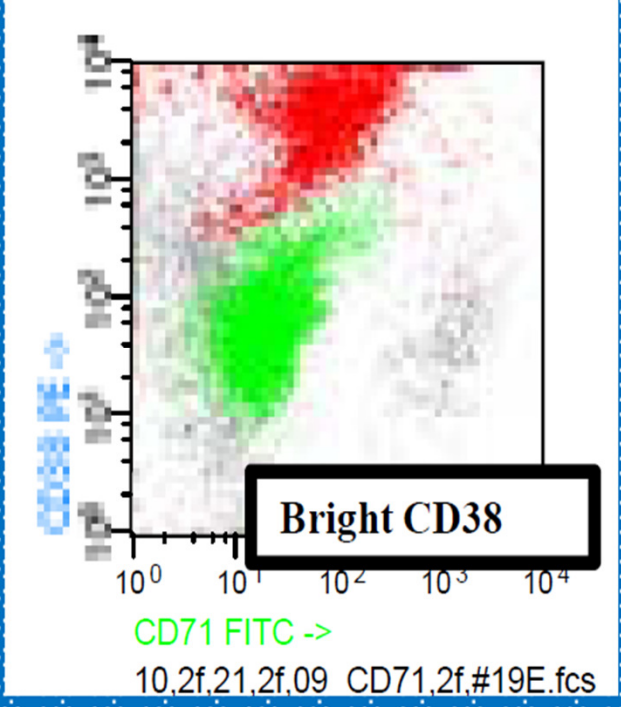
Case 1



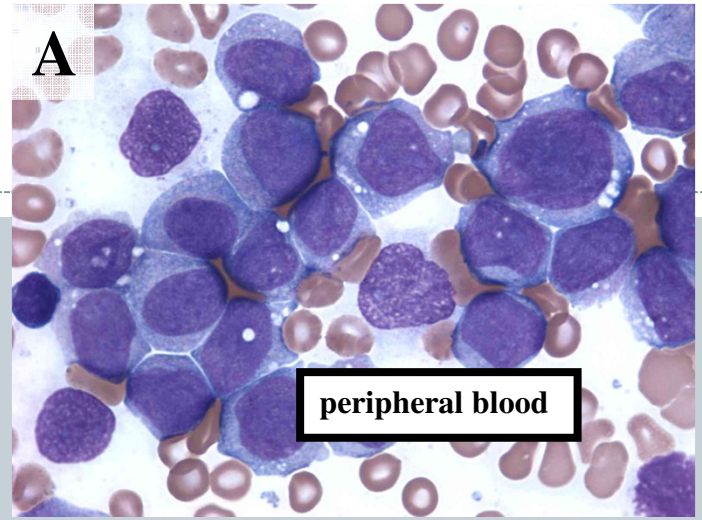


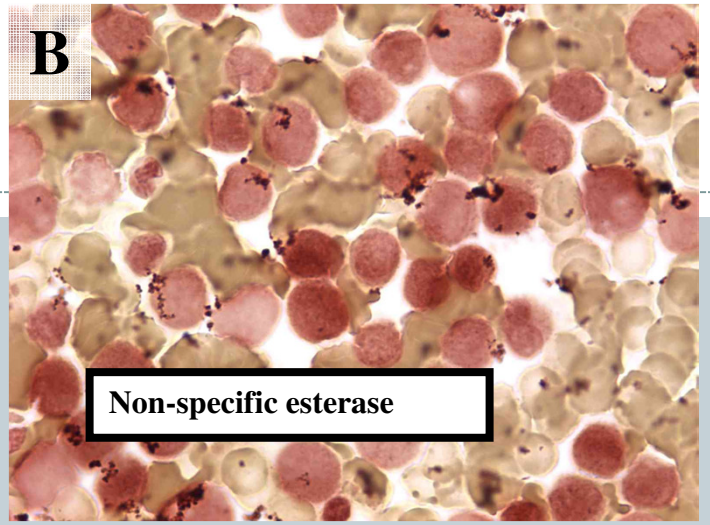






Red: Blasts
Green: Granulocytes
Blue: Monocytes
Cyan: Lymphocytes


A
peripheral blood

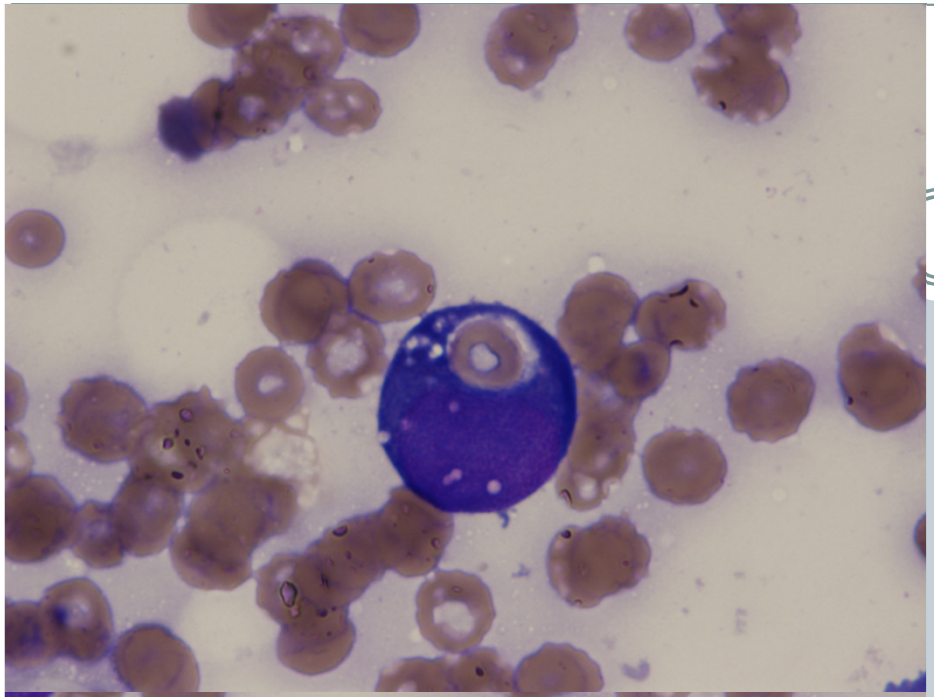

B
Non-specific esterase

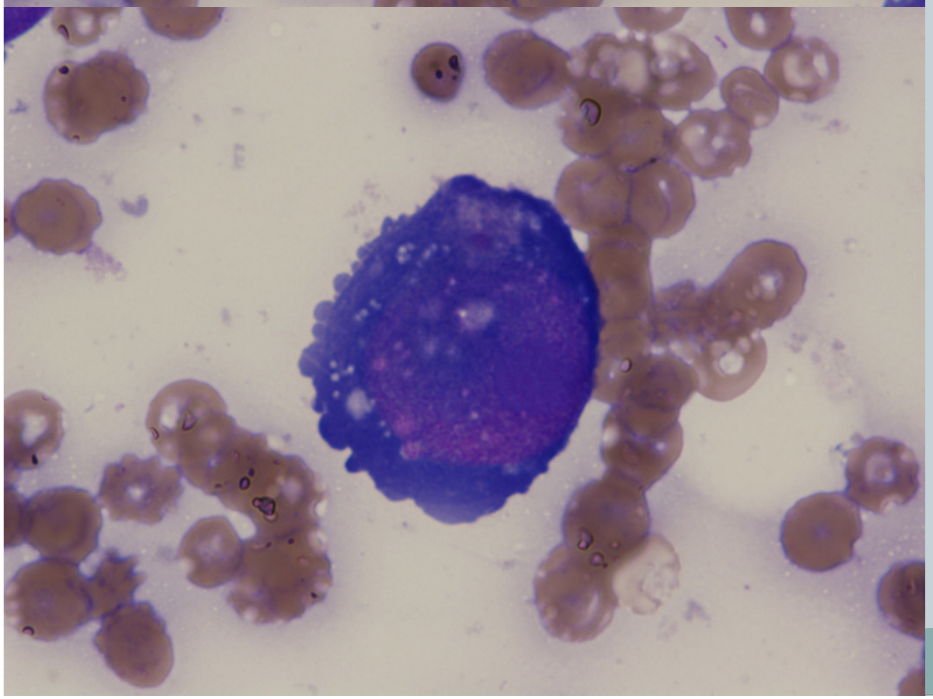

C
myeloperoxidase

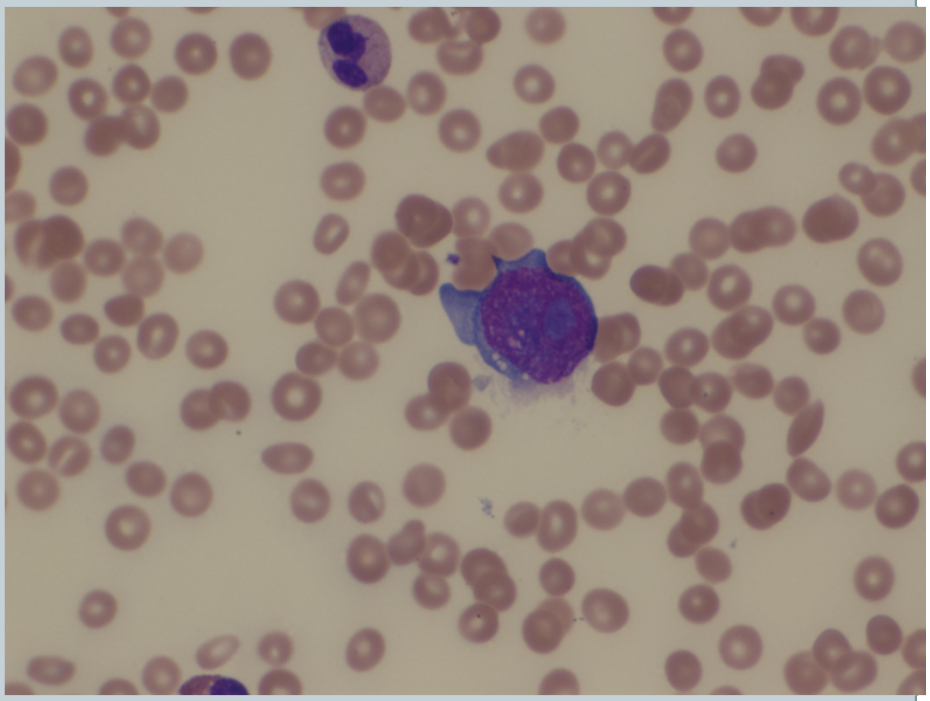
Case 3

14 yo with ho leukemia

- 14 yo with respiratory failure, cytopenia
- History of leukemia with t (8;16), 2 months s/p transplant
- Transfusion reaction (Trali) vs relapsed leukemia
- DIC: fulminant course

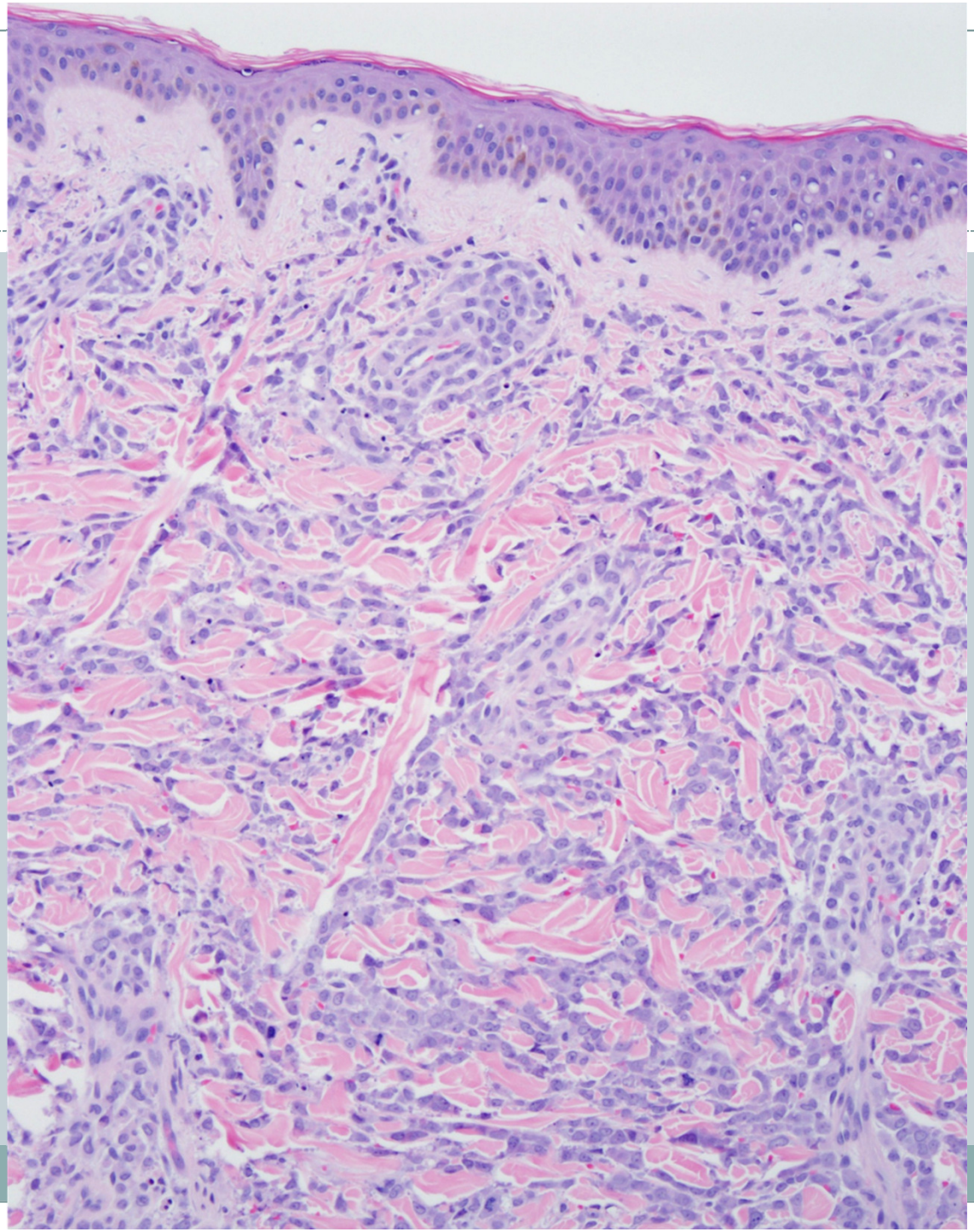


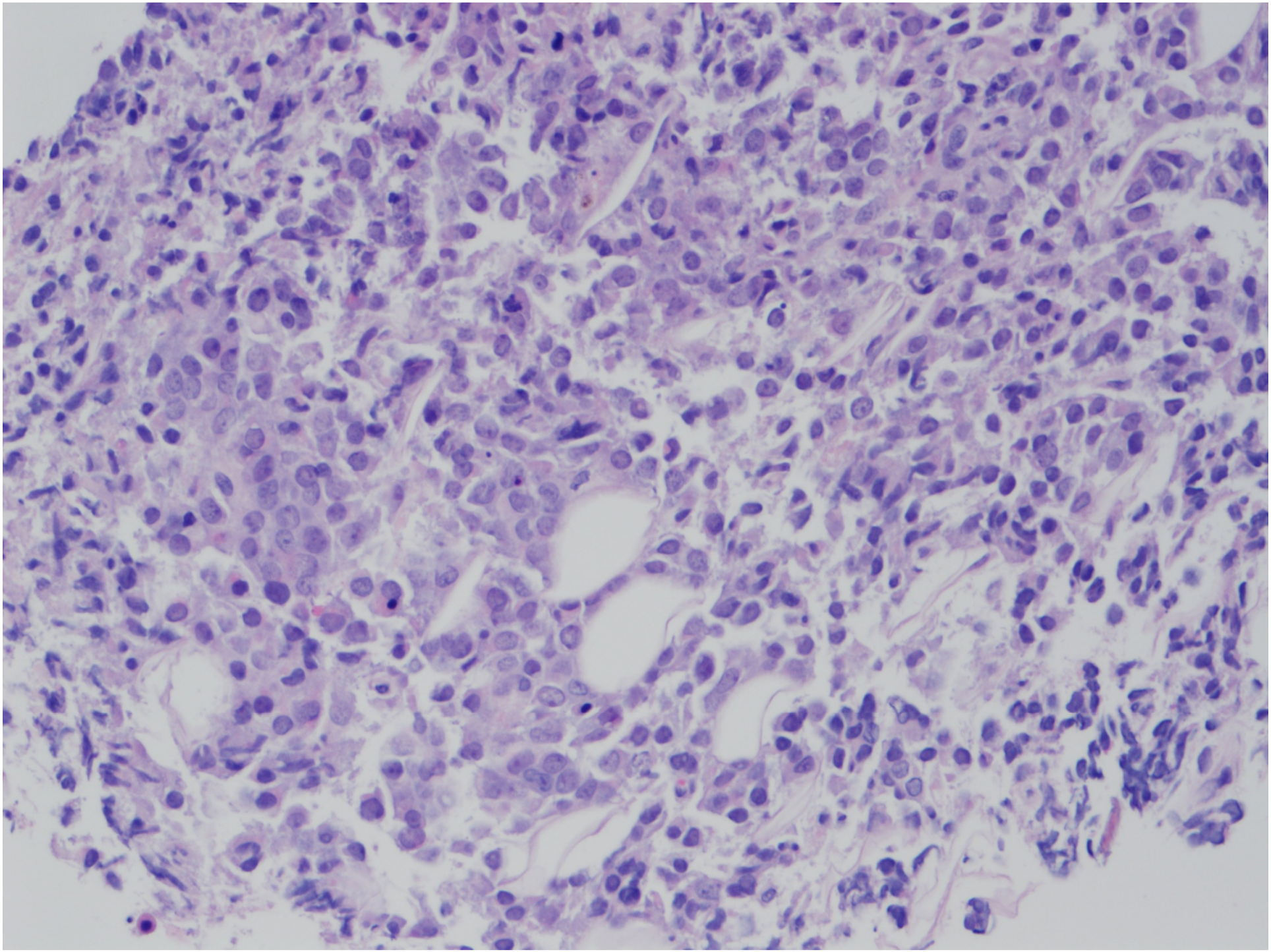


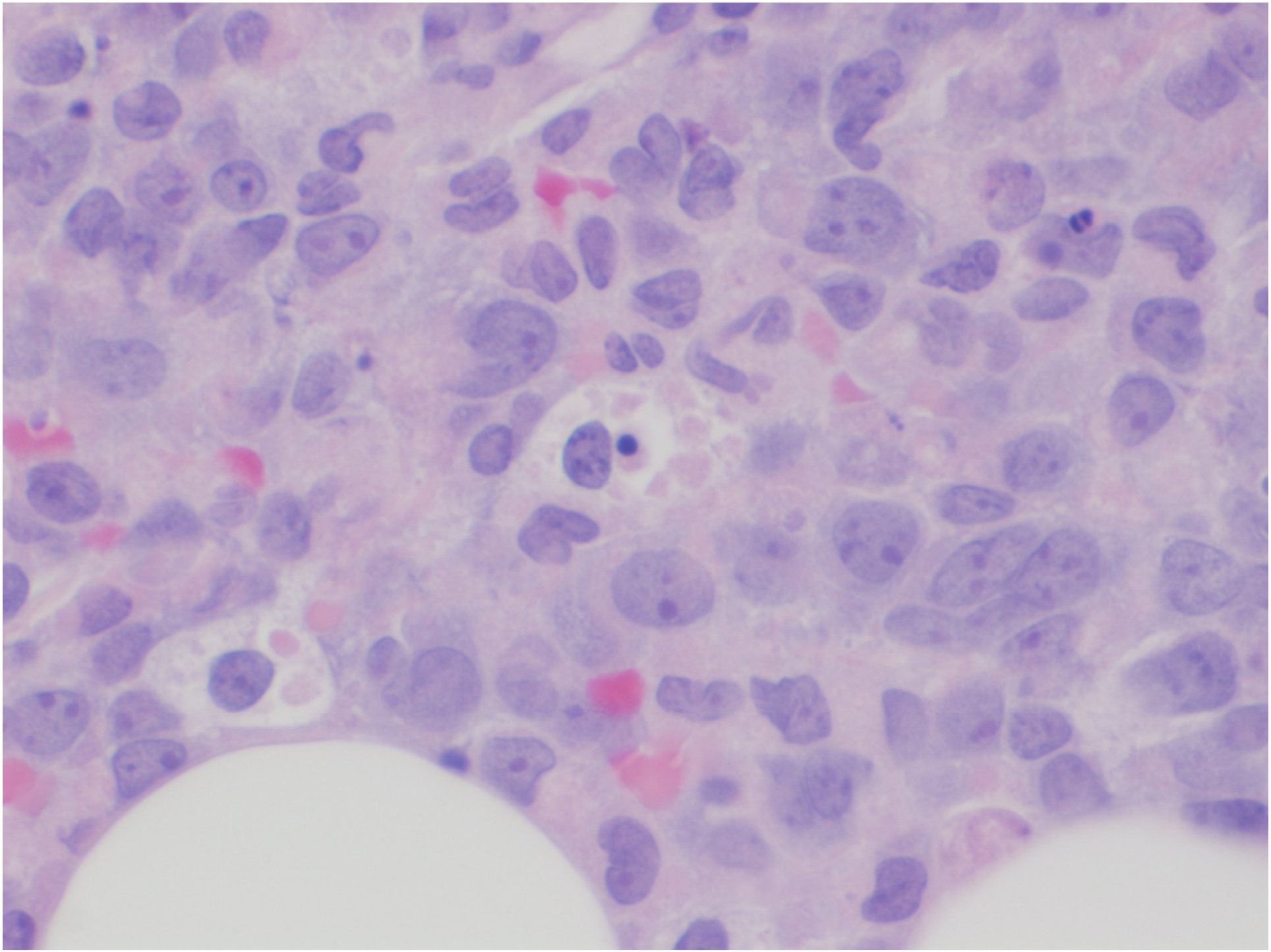


20 mo ho neuroblastoma..

- 20 month old male with 5 week history of growing papules on posterior scalp
  - Non-tender, Firm
- History of stage 4 neuroblastoma
  - Diagnosed at 13 months of age
  - Received 8 cycles chemotherapy Cyclophosphamide, Etoposide, Carboplatin, Doxorubicin







Extramedullary AML

- **Myeloid sarcoma**
- positive for CD68-KP1, CD43, CD33, Lysozyme, Myeloperoxidase (MPO), CD45

- Also known as:
  - Extramedullary acute myeloid leukemia (AML).
  - Chloroma
- A t(8:16) translocation was present in tumor cells analyzed by FISH
  - Fuses MOZ (monocytic leukemia zinc finger) to CREB-binding protein
  - Found in *de novo* and therapy-related AML

Myeloid Sarcoma

- Tumors of myeloid origin occurring at extramedullary locations
- Typically occur in the setting of overt bone marrow involvement
- Treatment is chemotherapy
  - Local recurrence or frank leukemia typically develops within several months without treatment

Discussion

- Neuroblastoma can have cutaneous metastases
- Pathology confirmed isolated cutaneous myeloid sarcoma, occurring on therapy
- Our patient remains in remission ~1y post-HCT

Discussion

- Acute myeloid leukemia with t(8;16)(p11.2;p13.3) is **not yet a distinct entity** in the WHO 2008 Classification
- An **aggressive** course is typical, but evidence for disseminated intravascular coagulation and hemophagocytosis must be sought
- **Pediatric AML with t(8;16) is underrepresented in recent literature** but shows similar features to adult cases
- Diagnostic pearls include:
- Monocytic/monoblastic differentiation with cytoplasmic vacuolization2,3
- MPO/NSE dual positivity – how to classify?
- CD34-/CD117- blasts that often show CD56 and may rarely have dim TdT expression
- The 8p11 fusion gene, MYST3 (MOZ), is involved in both de novo and therapy-related cases1,2 and may be crucial in the understanding of leukemogenesis, which could provide therapeutic targets
- With further investigation, **AML with t(8;16)(p11.2;p13.3) may meet criteria to stand alone as a distinct diagnostic entity**

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Pediatric acute myeloid leukemia with t(8;16)(p11;p13), a distinct clinical and biological entity: a collaborative study by the International-Berlin-Frankfurt-Münster AML-study group

Eva A. Coenen, C. Michel Zwaan, Dirk Reinhardt, Christine J. Harrison, Oskar A. Haas, Valerie de Haas, Vladimir Mihál, Barbara De Moerloose, Marta Jeison, Jeffrey E. Rubnitz, Daisuke Tomizawa, Donna Johnston, Todd A. Alonzo, Henrik Hasle, Anne Auvrignon, Michael Dworzak, Andrea Pession, Vincent H. J. van der Velden, John Swansbury, Kit-fai Wong, Kiminori Terui, Sureyya Savasan, Mark Winstanley, Goda Vaitkeviciene, Martin Zimmermann, Rob Pieters and Marry M. van den Heuvel-Eibrink

Findings

- 62 pediatric patients from 18 countries (median age: 1.2 years), 2 therapy related
- 7 congenital cases showed spontaneous resolution but 4 relapsed eventually
- extramedullary disease: 66%
- CNS involvement: 15%
- DIC: 39%

Conclusion

- t(8;16)(p11.2;p13.3) or 8p11.2 *MYST3* rearrangements are recurrent cytogenetic abnormalities in acute myeloid leukemia and may best be **distinct in the WHO** classification
- An **aggressive** clinical course is typical (including DIC)
- **Pediatric** AML with t(8;16) is **underrepresented** but **may present as a congenital leukemia**
- **Spontaneous remissions common but clinical follow up very important**

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Acute myeloid leukaemia with 8p11 (MYST3) rearrangement: an integrated cytologic, cytogenetic and molecular study by the groupe francophone de cytogenetique hematologique

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The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes

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