

**Bilineal (bilineage) leukemia
are they well defined within WHO 2008
classification?
what can we learn from these uncommon
cases?**

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„Strange leukemias“

- WHO 2008: Mixed phenotype acute leukemia = umbrella category
- Bilineal AL subgroup of MPAL
 - BCR/ABL^{pos}, MLL rearranged category separate category
 - Bilineal leukemia can be defined by flow cytometry and/or morphology

WHO 2008 (M. Borowitz et al.)

1) when there are two or more distinct populations of leukaemic cells, one of which would meet immunophenotypic criteria for acute myeloid leukaemia (with the exception that this population need not comprise 20% of all nucleated cells);

Weir et al. (*Leukemia*, 2007), Gerr et al. (*British journal of Haematology*, 2010) = preference in classification by flow cytometry

Czechia incidence

(central review of immunophenotyping and morphology)

- Evaluation period 1996 – 02/2011

identified **3** cases out of **1065** primary leukemia cases
incidence 0.28%

UPN1: B/myeloid AL: cALL (57%) (partial CD10neg) with aberrant expression of CD117, CD13, CD66c, CD38 heterogenous and myelomonocytic population (18%)

UPN2: T/myeloid AL: prae T ALL (55%) with aberrant expression of CD117 and AML (39%) with aberrant expression of CD7

UPN3: B/myeloid AL: cALL (68%) with weak CD19 expression aberrant expression of CD13, CD66c and CD2 and myelomonocytic population (22%)

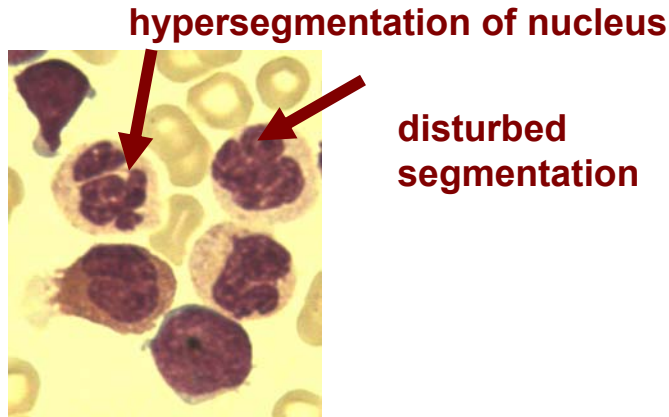
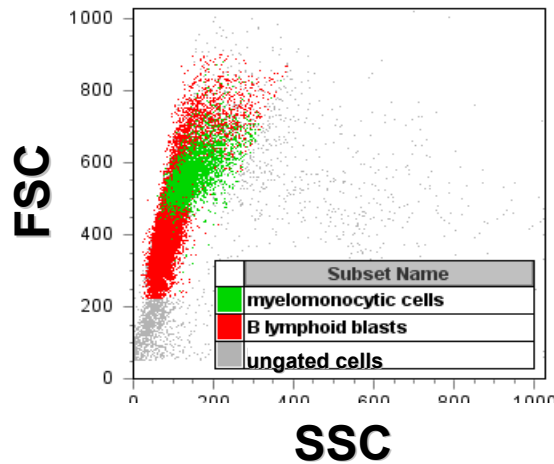
UPN1

diagnosis: cALL partly CD10neg, CD34++, aberrant CD13, CD117, immunologically: 18% myelomonocytic cells (CD14+CD66c+CD19neg), morphologically: granulocytic dysplasia present (18.8%)

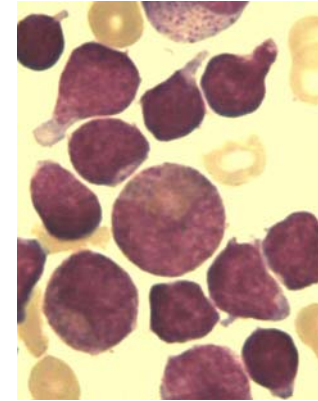
days 5/8: myelomonocytic blasts increased, prednisone poor response

day 8: morphology consistent with AML diagnosis

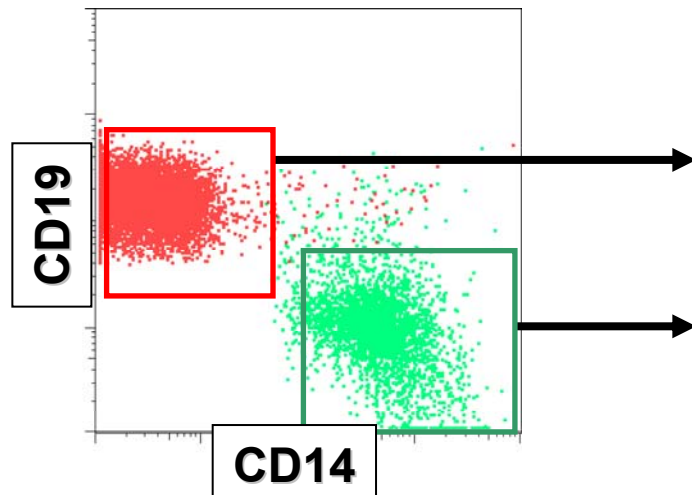
FLT3/ITD, MLL deletion



lymphoblasts



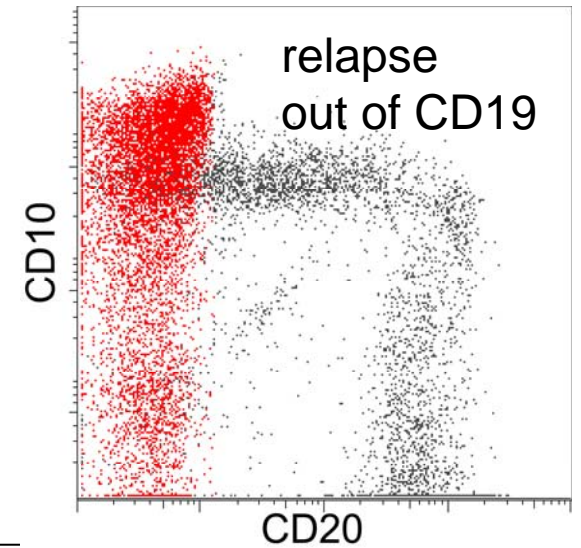
ARE THE POPULATIONS CLONALLY RELATED, ARE THE MYELOID CELLS REAL BLASTS?



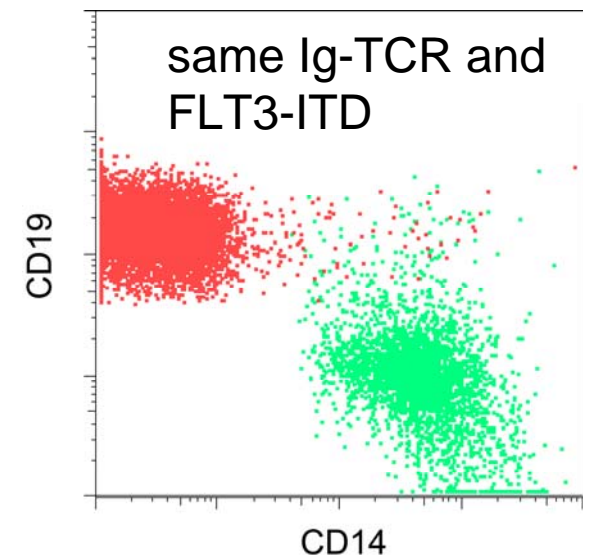
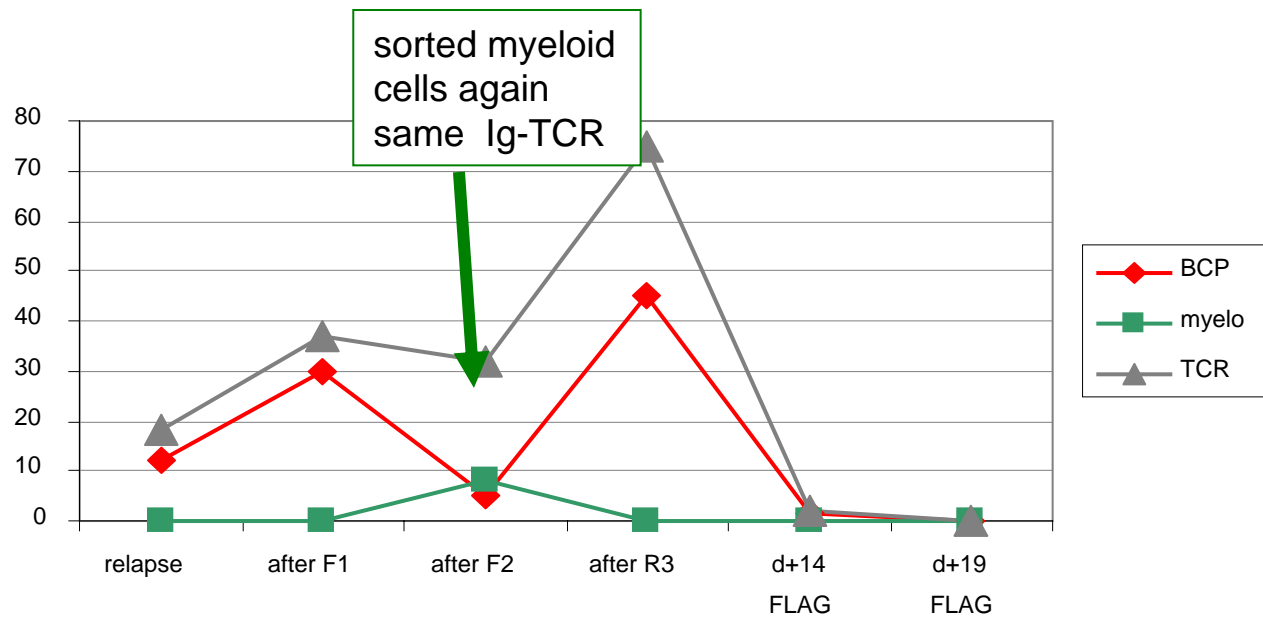
Surprisingly both populations containing same Ig-TCR rearrangements and FLT3-ITD

UPN1

Outcome after day 33: Interfant 99, SCT in CR1 ... relapsed predominantly as cALL (no clear myeloid clone present)



Treatment of relapse (ALL REZ BFM 2002) reappearance of myeloid clone after 2nd block



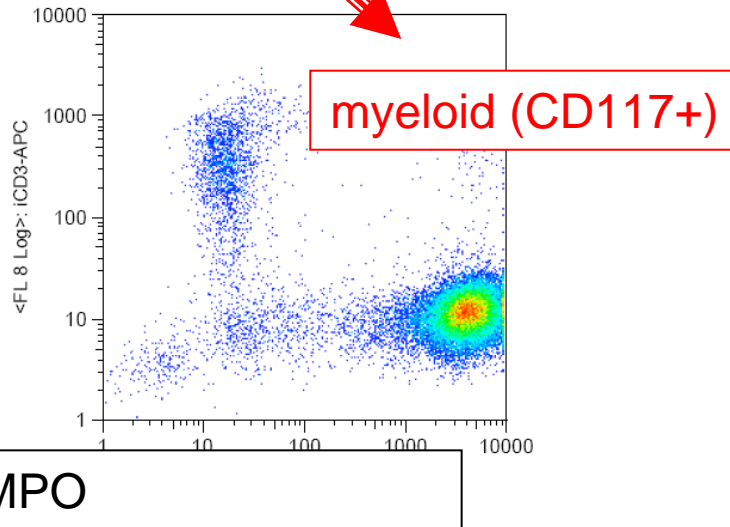
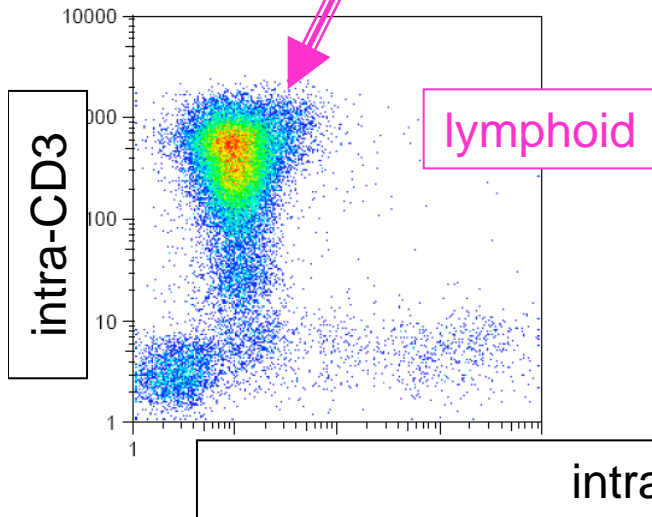
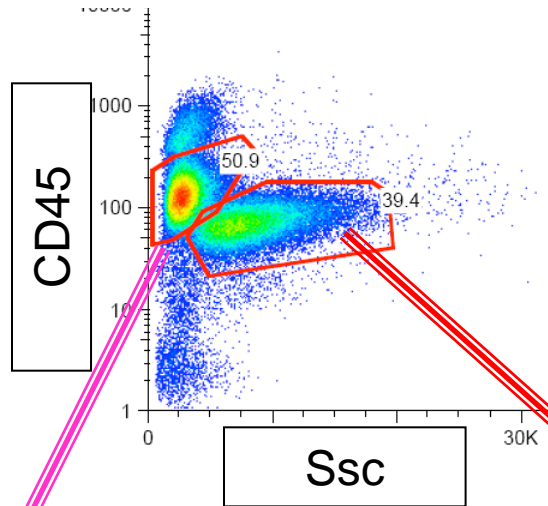
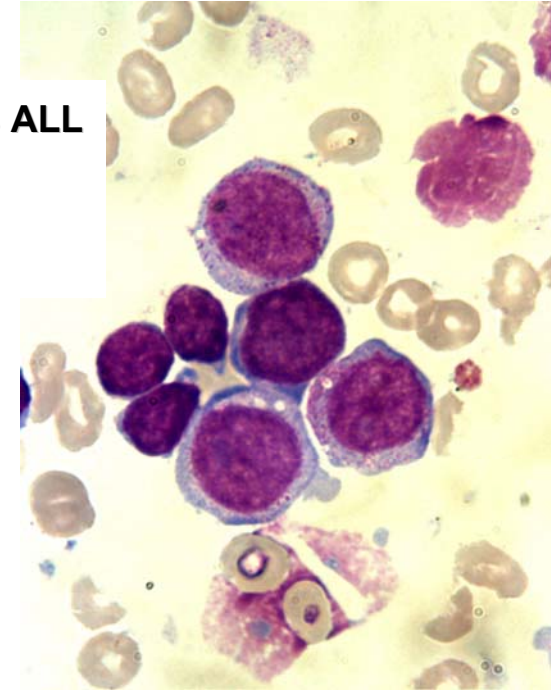
UPN2

diagnosis: 2 populations prae T (55%) and AML (39%), started treatment as ALL

day 8: both population responding to therapy AML (6%), prae T ALL (0.2%)

day 33: achieved CR

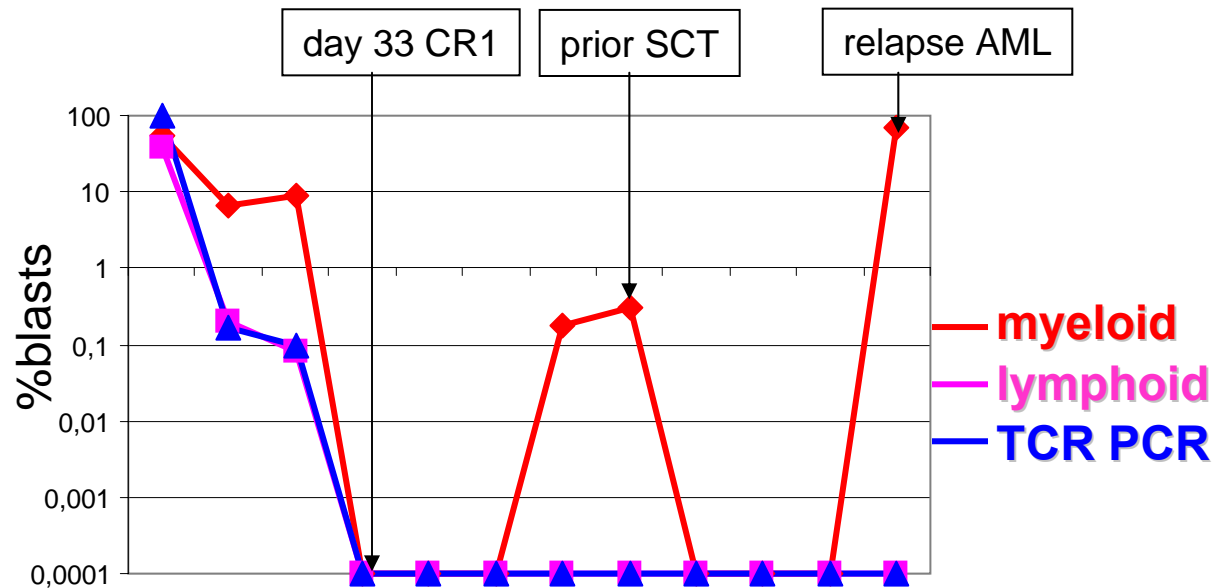
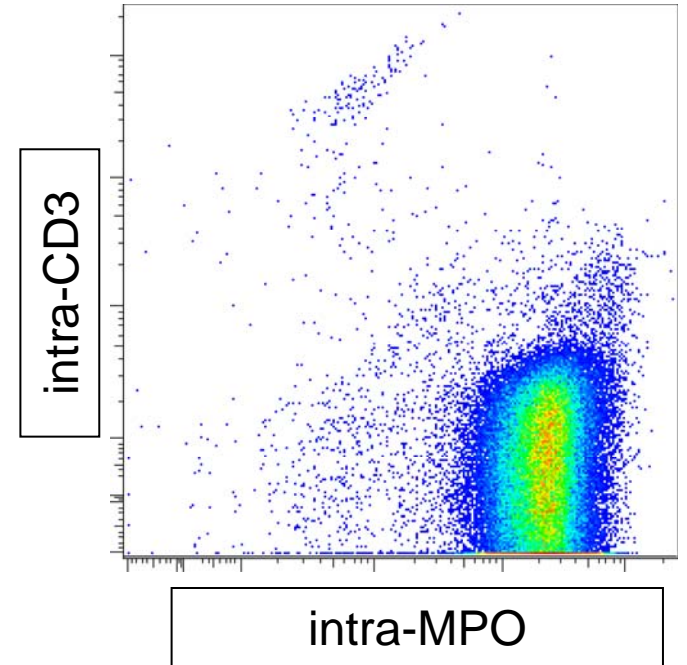
complex karyotype, highly suspectly MLL-AF10^{pos}



Sort performed at day 8 marrow: TCR clonality identified only in prae T ALL population

UPN2

Outcome after day 33: Interfant 2006
(ADE, MAE, MARMA), SCT in CR1 ...
relapsed 150 days after SCT
predominantly as AML (negative TCR
clonality)



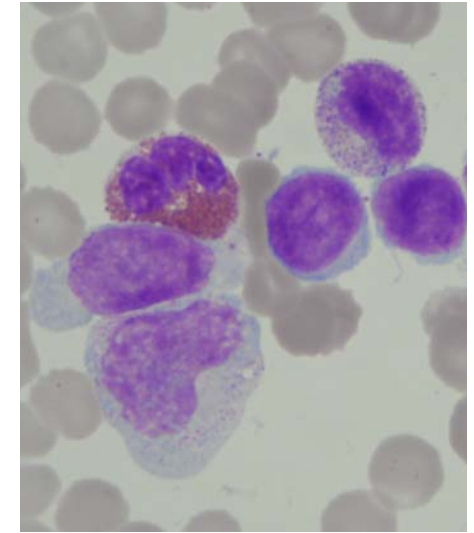
UPN3

diagnosis: 2 populations „cALL“ (69%) and myelomonocytic (22%), started treatment as ALL (+dasatinib due to CNS infiltration)

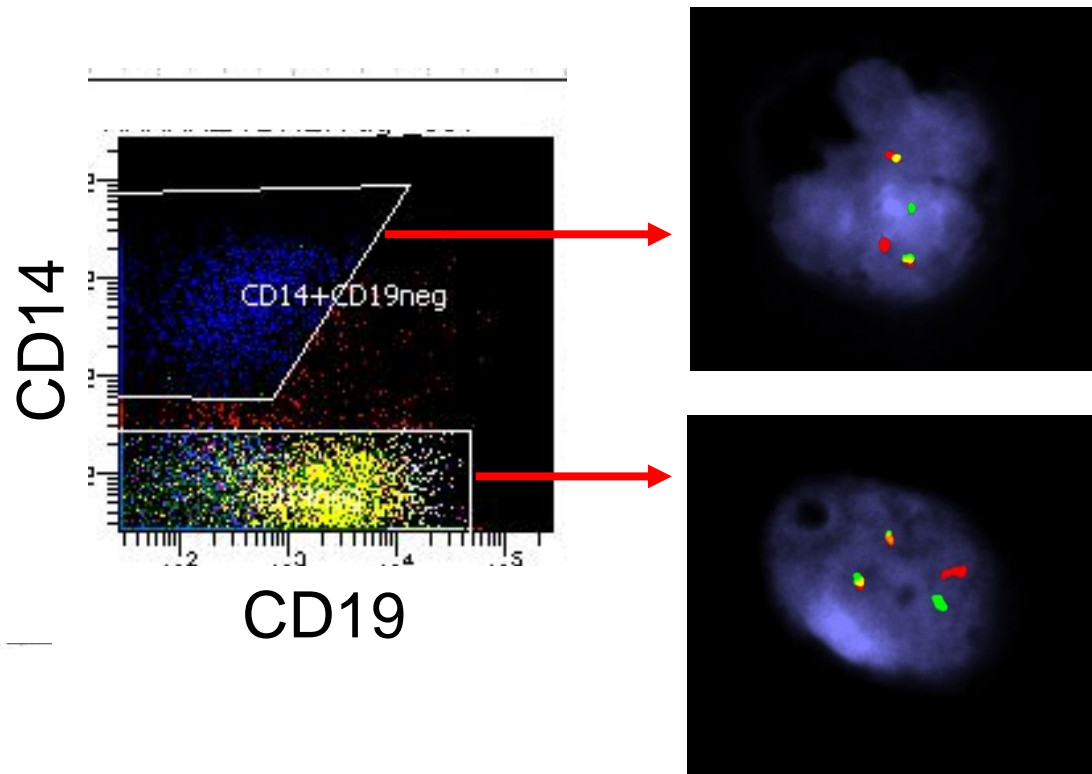
day 8: prednisone good response

day 33: achieved CR

BCR/ABL^{pos}, IKZF1 gene alteration (deletion of exons 2 and 3)



ARE THE POPULATIONS CLONALLY RELATED, ARE THE CELLS REAL BLASTS?



Both populations:
BCR-ABL^{pos}
(confirmed by FISH)
and same Ig-TCR
clonality

Vysis LSI BCR/ABL ES Dual Color Translocation Probe

Summary slide

	age (yrs)	WBC (x10 ⁹ /L)	phenotype	Ig-TCR clonality	cytogenetics	SCT	outcome
UPN1	1.9	190	cALL (57%) myeloid (18%)	both	FLT3/ITD del11q23	1 st CR	relapse died
UPN2	17	0.7	prae T (55%) AML (39%)	lymphoid	complex karyotype, susp. MLL-AF10	1 st CR	relapse died
UPN3	2	154	„cALL“ (69%) myeloid (22%)	both	BCR/ABL, IKZF1 deletion	1 st CR	molecular relapse successfully treated by ITKs

Conclusions

- **Although some bilineal leukemia do have two clearly separated populations = genetically these cells can be of one origin**
- **SHOULD WE CALL THEM BILINEAL?**
- **TAKE HOME MESSAGE: MRD based on Ig-TCR targets can monitor in some cases also the myeloid clone**
- **Flow cytometry preferred method but so far no identical criteria how exactly define bilineal AL**
- **Optimal treatment?**
- **MPAL BCR/ABL^{p0z}: treatment preferably in ALL protocol with inhibitor of tyrosine kinase**

Acknowledgement

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