Pediatric B-ALL with iAMP21

Society for Hematopathology/European Association for Haematopathology Symposium and Workshop 2017

Case number SH2017-0366

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Presentation

- 6 year old girl presented to the Emergency Department with several weeks of aches and fatigue, as well as recent onset sore throat and fever
- Physical exam showed pallor, fever, tachycardia, and tachypnea
- Rapid strep test was positive
- CBC showed leukocytosis, anemia, and thrombocytopenia

CBC

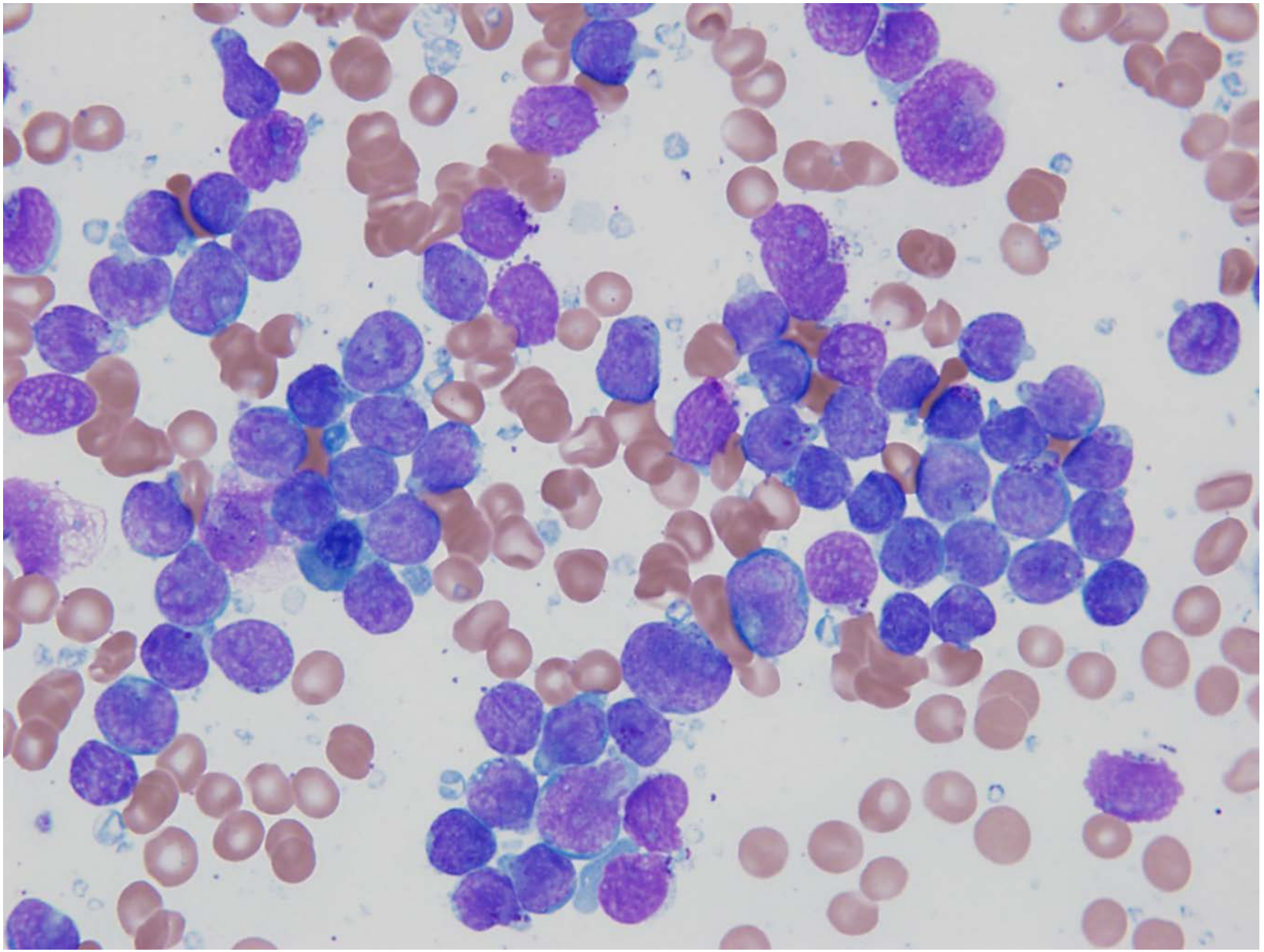
WBC: 17.4 K cells/uL

- 79% blasts

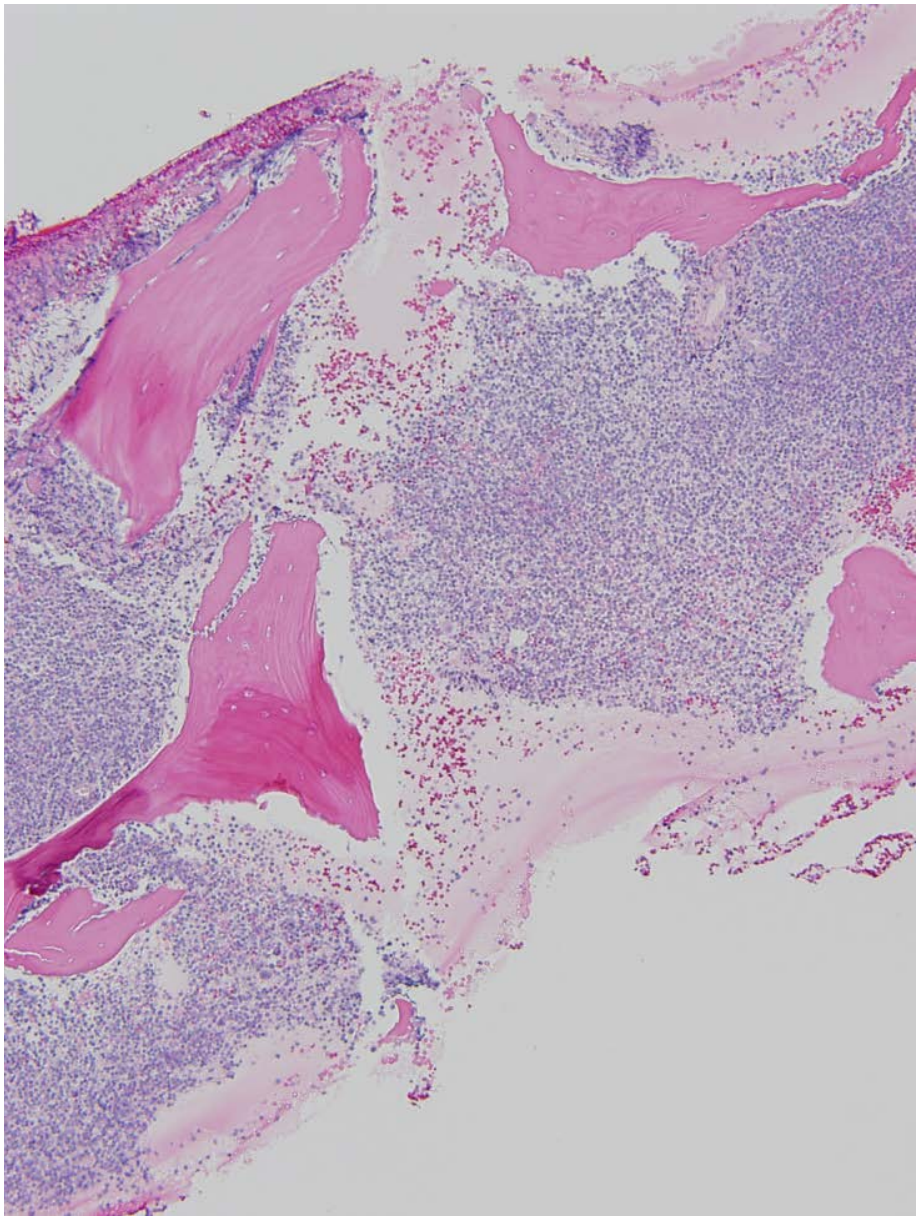
Platelets: 19 K cells/uL

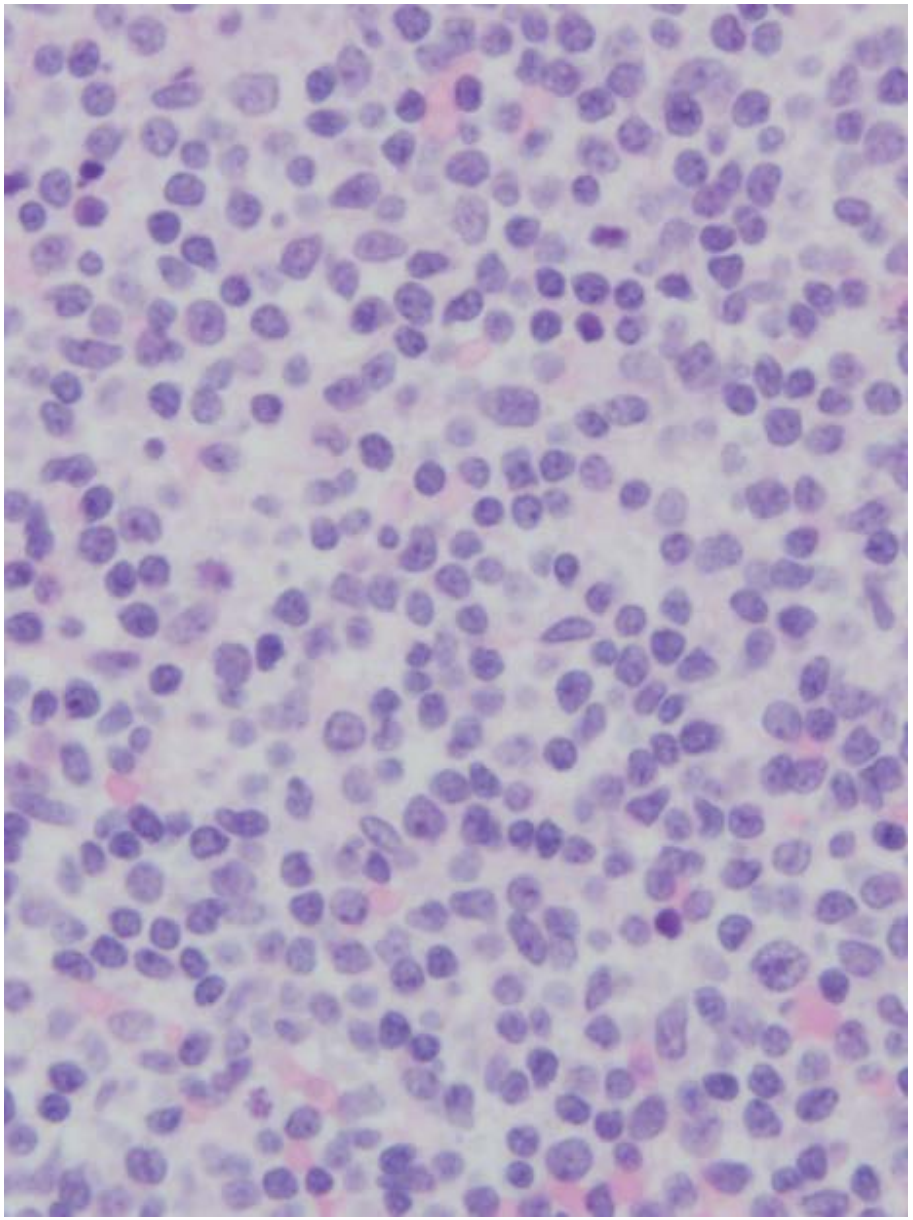
Hemoglobin: 4.1 g/dL

Bone marrow aspirate smear

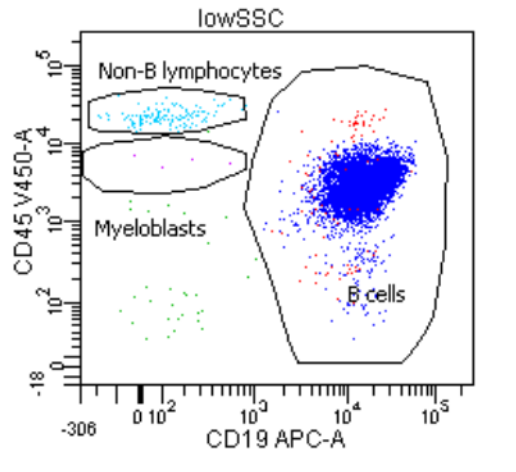


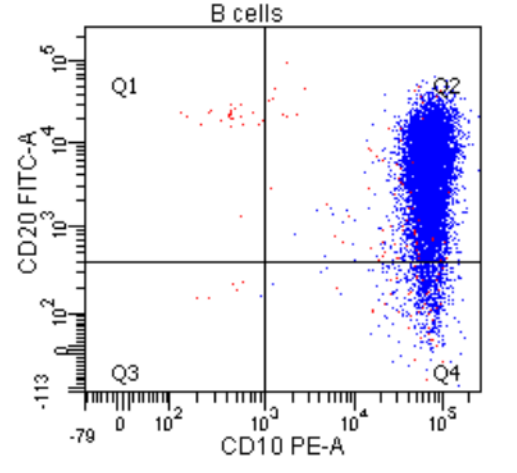
Core biopsy

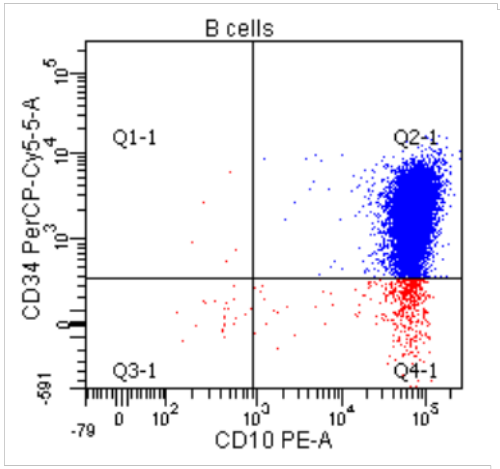


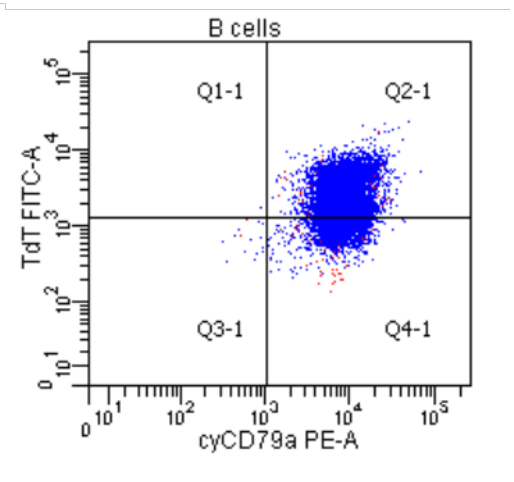


Bone marrow: flow cytometry



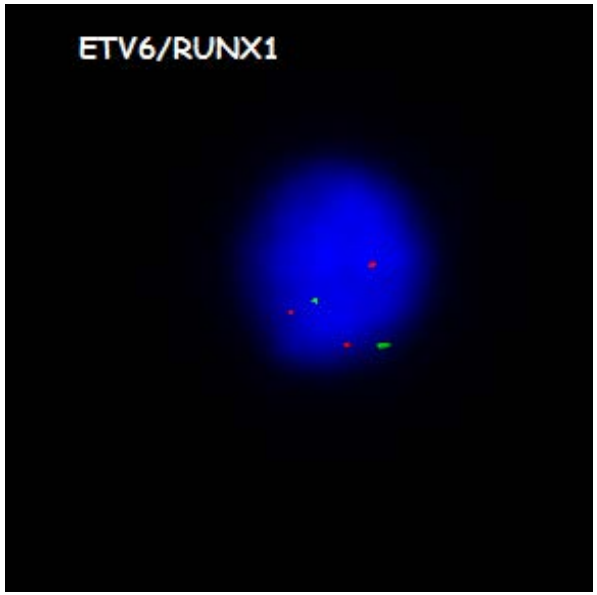


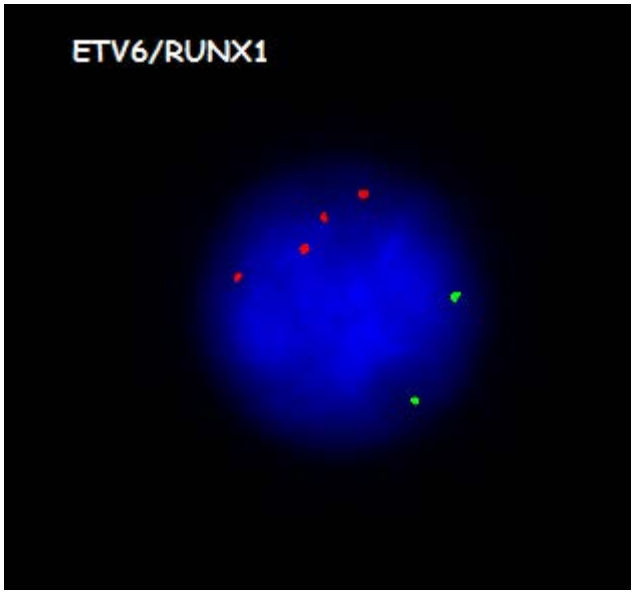


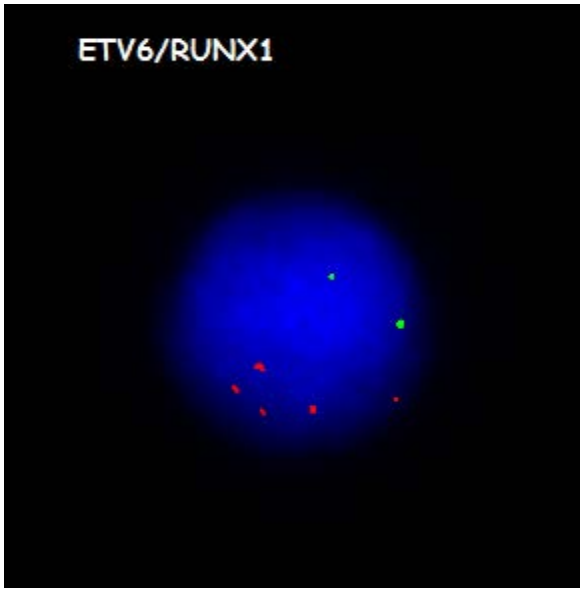


- ETV6/RUNX1 FISH
  - Negative for a ETV6/RUNX1 (TEL/AML1) rearrangement.
  - Three, four, and five copies of RUNX1 were observed in 17.5%, 48.5%, and 16.5% of cells, respectively:

nuc ish(ETV6x2,RUNX1x3)[35/200]/(ETV6x2,RUNX1x4)[97/200]/(ETV6x2,RUNX1x5)[33/200]

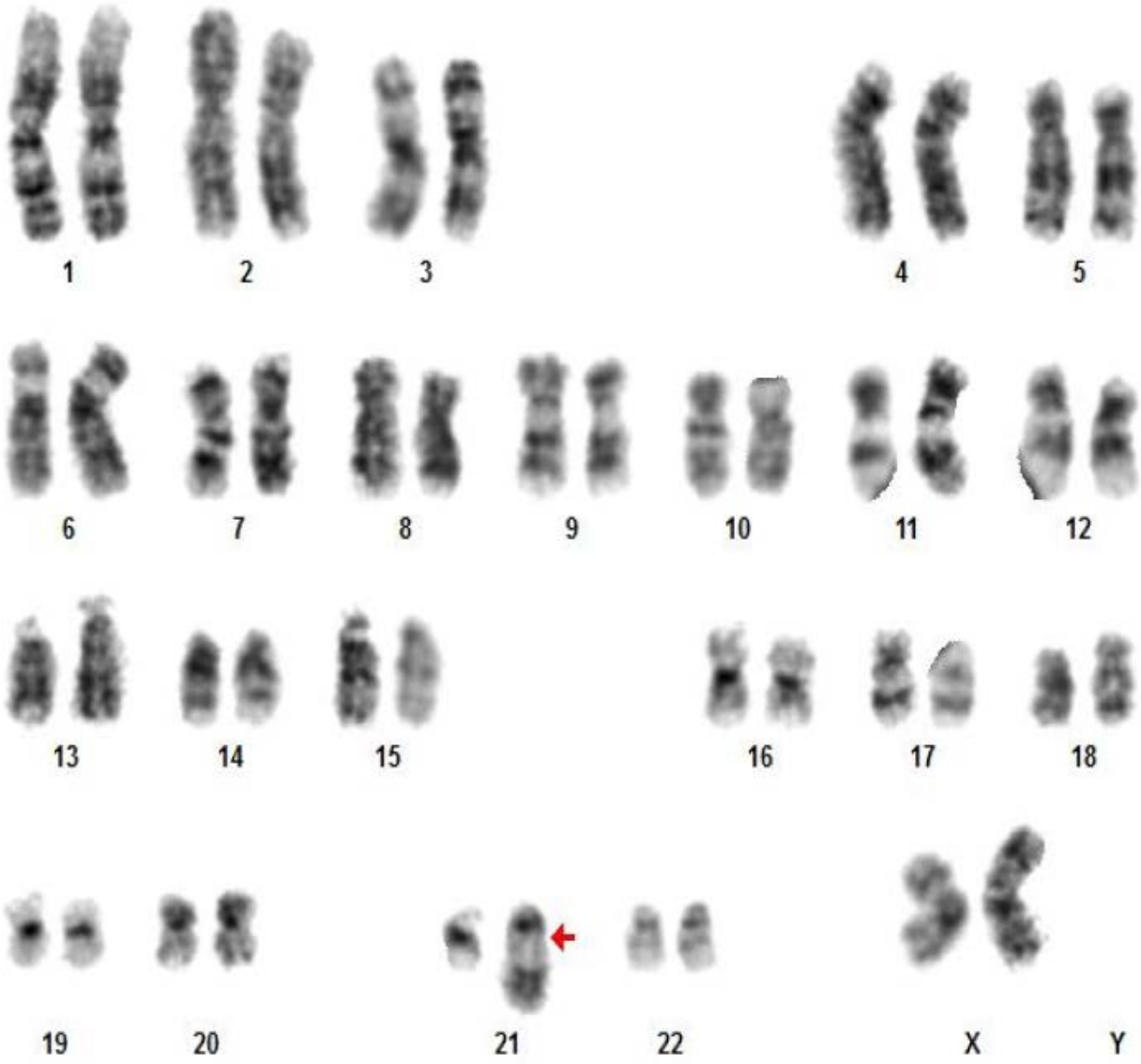






Additional results:
FISH for a rearrangement or loss/gain of KMT2A (MLL) and for a BCR/ABL1 rearrangement was negative.

Karyotype:
46,XX,add(21)(q22)[13]/46,XX[7]



Targeted sequencing: Rapid Heme Panel (RHP)

- Amplicon-based next generation sequencing test
  - Brigham and Women's Hospital, Center for Advanced Molecular Diagnostics
  - Designed for fresh blood and bone marrow samples (EDTA)
- 730 exons in 95 genes
  - Hot spots in oncogenes
  - Whole genes for tumor suppressors
- Approximately 1000x coverage
- Report gives:
  - Sequence alterations with variant allele fraction
  - Copy number alterations based on read count analysis

RHP genes (targeted exons)

Targeted Gene/Exon List (genomic coordinates available upon request):

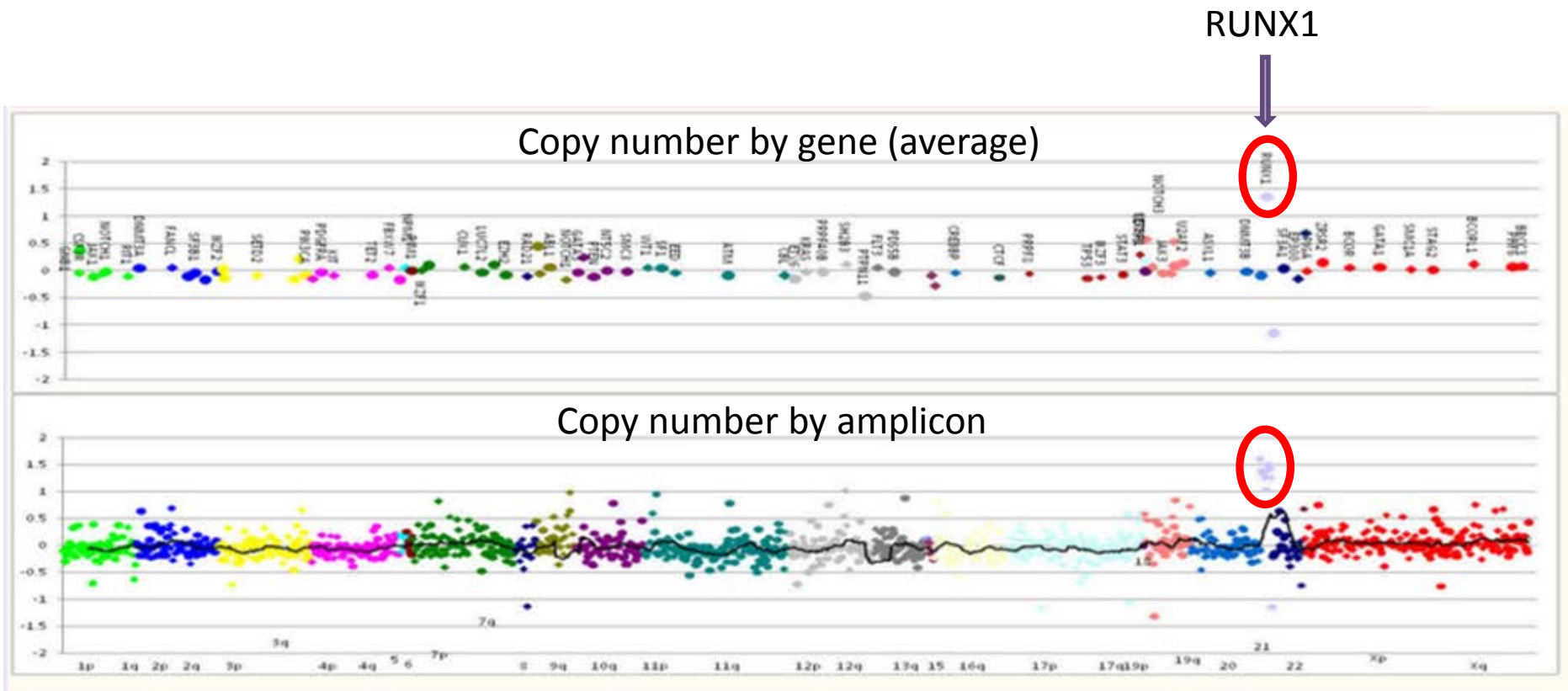
ABL1 e2-e10	ASXL1 e1-e13	ATM e2-e63	BCL11B e4
BCOR e2-e15	BCORL1 e1-e12	BRAF e15	BRCC3 e3-e11
CALR e9	CBL e7-e8	CBLB e9-e11	CD79B e5-e6
CEBPA e1	CNOT3 e1-e2	CREBBP e2-e21, e23-31	CRLF2 e6
CSF1R e22	CSF3R e14-e18	CTCF e3-e12	CTNNB1 e2-e4
CUX1 e1-e21	CXCR4 e2	DNMT3A e2-e23	DNMT3B e2-e23
EED e1-e12	EGFR e18-e21	EP300 e18-e27	ETV6 e1-e8
FANCL e1-e14	FBXW7 e8-e12	EZH2 e2-e8, e11-e20	FLT3 e14-e16, e20
GATA1 e2-e6	GATA2 e2-e6	GATA3 e4-e6	GNAS e8-e9
GNB1 e5-e6	IDH1 e4	IDH2 e4	IKZF1 e2-e8
IKZF2 e1-e8	IKZF3 e1-e8	IL7R e6	JAK1 e10-e25
JAK2 e12, e14	JAK3 e11-e24	KIT e8-9, e11, e17	KRAS e2-e5
LUC7L2 e3-e11	MAP2K1 e2-e3	MEF2B e3	MPL e10
MYD88 e5	NOTCH1 e24-e28	NOTCH1 e34	NOTCH2 e24-e28
NOTCH2 e34	NOTCH3 e25-e26	NOTCH3 e33	NPM1 e10-e11
NRAS e2-e5	PAX5 e3, e6-e7	NT5C2 e9, e11, e13, e15, e17	
PDS5B e3-e35	PHF6 e2-e10	PDGFRA e10-e21, e23	PIGA e2-e6
PIM1 e1-e6	PRPF40B e2-e26	PIK3CA e2, e10, e21	PRPF8 e2-e43
PTEN e1-e9	PTPN11 e1-e15	RAD21 e2-e14	RET e7
RIT1 e1-e6	RPL10 e5	RUNX1 e2-e9	SETBP1 e4
SF3B1 e12-e16	SF1 e1-e10, e13	SF3A1 e1-e2, e5-e16	SETD2 e1-e4, e6-e21
SH2B3 e2-e8	SMC1A e1-e25	SMC3 e2-e29	SRSF2 e1
STAG2 e3-e35	TET2 e3-e11	STAT3 e2-e17, e21-23	TLR2 e1
TP53 e2-e11	U2AF1 e2, e6	U2AF2 e1-e12	WHSC1 e17-e18
WT1 e1-e10	XPO1 e15-e16	ZRSR2 e1-e11	

Targeted gene panel results: sequence alterations

- PTPN11 NM_002834 c.179G>T p.G60V 19.2% of 569 reads
  - Known activating mutation

Targeted sequencing panel: read count analysis

High copy-number gain of RUNX1 and loss of U2AF1



B-ALL with intrachromosomal amplification of chromosome 21 (B-ALL with iAMP21)

- Reported as a distinct cytogenetic subtype of B-ALL in 2003
- Included as a provisional subtype of B-ALL in 2016 WHO classification
- Approximately 2% of pediatric B-ALL
- Patients tend to be older with low presenting white blood cells counts

Robinson et al., Blood, 2007; Arber et al., Blood, 2016

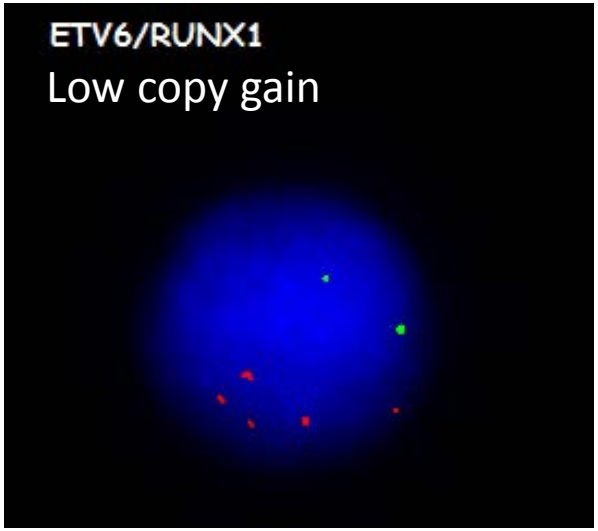
B-ALL with iAMP21: biology

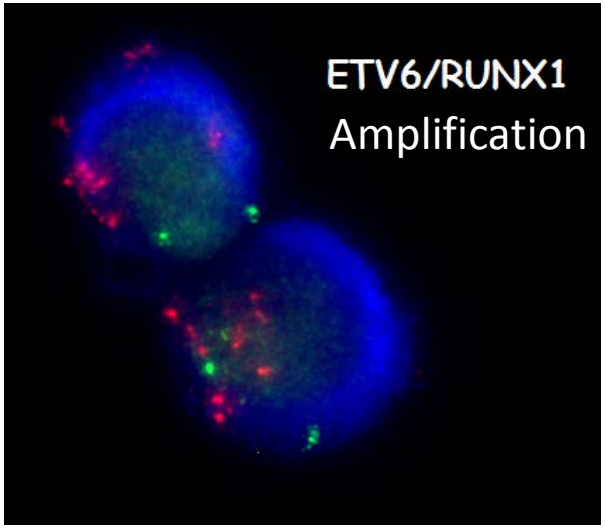
- Characterized by multiple copies of RUNX1
  - Usually these copies are on chromosome 21
  - May also be on a marker chromosome
- iAMP21 is usually the primary genetic abnormality
  - Majority of cases are near-diploid
    - iAMP21 is sole change in ~20%
    - Whole chromosome or arm-level numeric abnormalities are relatively common, including +X in ~20%
    - Very rare cases reported with concurrent high hyperdiploidy, ETV6-RUNX1, or BCR-ABL1
  - Abnormal chromosome 21 seems to arise through multiple breakage-fusion bridge cycles and chromothripsis
    - Increased risk of B-ALL with iAMP21 in patients with the germline Robertsonian translocation rob(15;21) or a germline ring chromosome 21 r(21)

Robinson et al., Genes, Chromosomes, and Cancer, 2007; Harrison et al., Leukemia, 2014

B-ALL with iAMP21: detection/diagnosis

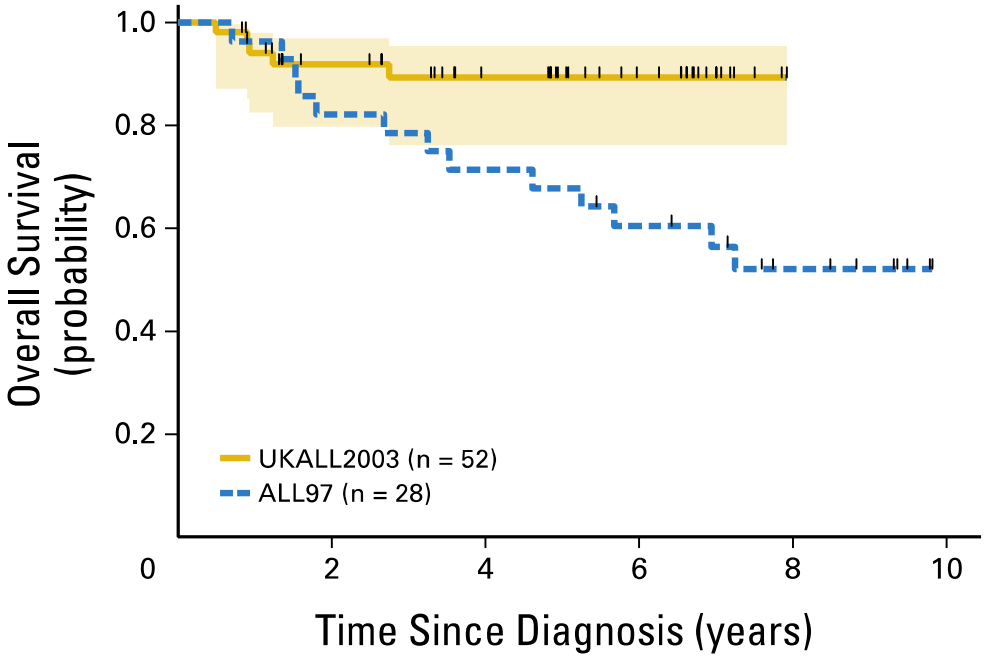
- FISH: can be detected using the same FISH assay used to detect ETV6-RUNX1 rearrangement
  - iAMP21 defined as:
    - 5 or more copies of RUNX1 in one nucleus by interphase FISH, or
    - 3 or more copies of RUNX1 on one chromosome by metaphase FISH
    - (Caution: additional copies of chromosome 21 are common in B-ALL, especially hyperdiploid B-ALL, usually 3-4 copies total)
- Karyotype: may be suspected with karyotype findings of add(21), dup(21), der(21), or loss of chromosome 21 associated with gain of a marker chromosome
- Other: may also be detected on sequencing panels with copy number analysis or on copy number arrays (as long as RUNX1 is well-covered)





B-ALL with iAMP21: prognosis

- Patients with iAMP21 treated with standard therapy show a high risk of relapse
- Treatment on high-risk arms with intensified therapy significantly reduces risk of relapse
  - Effect seen in multiple protocols
  - Most centers now intensify treatment for patients with iAMP21



Moorman et al., JCO, 2013

Summary

- B-ALL with iAMP21 is a new provisional category in the 2016 WHO categorization
- Approximately 2% of pediatric B-ALL
- Can be detected with FISH for ETV6-RUNX1
  - 5 or more copies of RUNX1 total, or 3 or more copies of RUNX1 on a single chromosome
- Associated with a worse prognosis when treated with standard-risk therapy
  - Treatment with high-risk therapy improves outcome

<u>Final panel diagnosis: B-ALL with iAMP21</u>

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