Case 0094

NUP214-ABL1 Fusion:

A Novel Discovery in Acute Myelomonocytic Leukemia

MUSC
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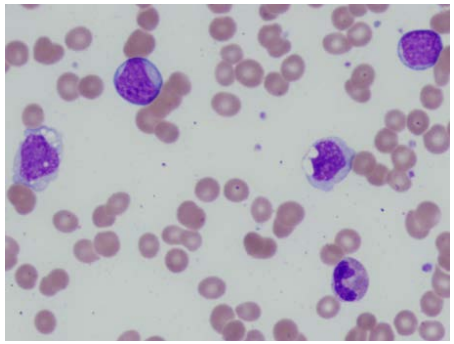
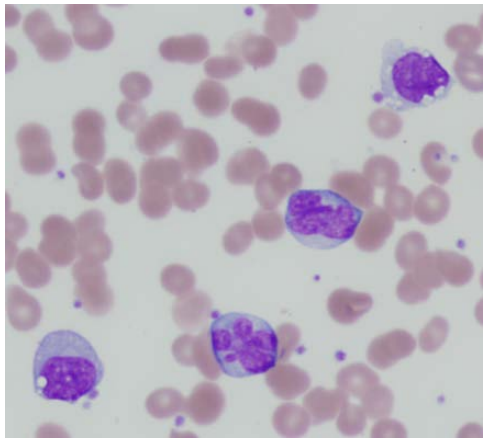
Case Report - 64 year old Caucasian Male

Past Medical History → Osteoarthritis
Family History → Negative for bleeding/platelet disorders, AML or MDS

Presented to an outside hospital with 1 month history:

- Progressive dizziness
- Fatigue
- Insomnia





Further work-up revealed:

- Anemia
- Leukopenia
- Pain/tenderness over area of spleen

Managed with 1 unit of pRBCs and transferred to MUSC for work up:

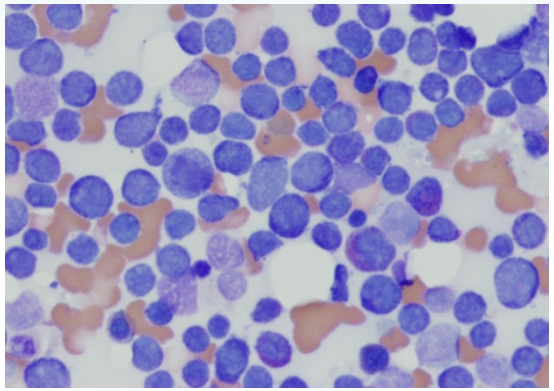
- Suspicious for acute leukemia

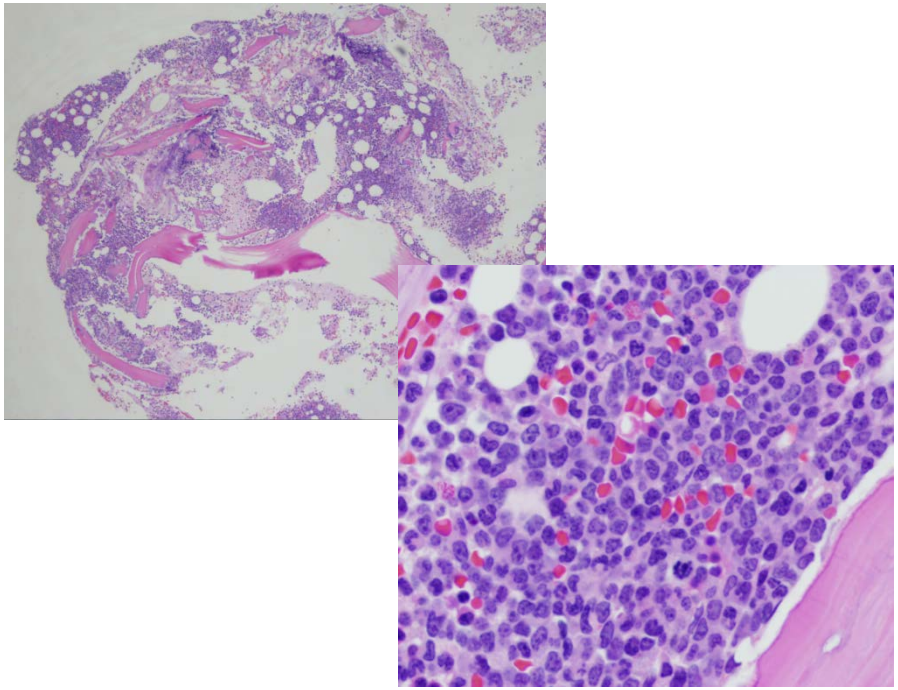
Bone Marrow Biopsy performed at MUSC revealed…

Initial - Bone Marrow Biopsy

Aspirate:

- Hypercellular
- Predominantly immature cells with minimal evidence of terminal differentiation
- Blasts comprise 85% of cellularity





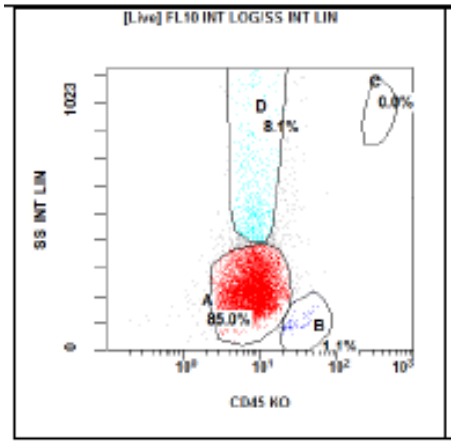
Bone Marrow:

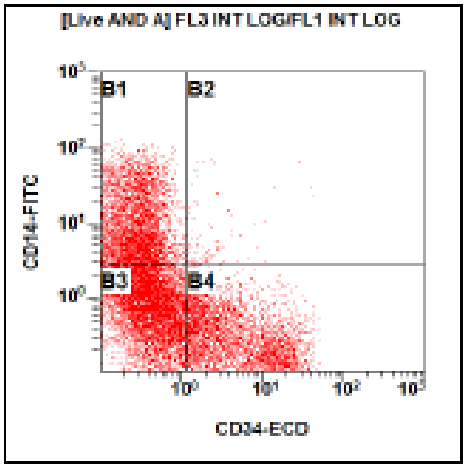
- 50% cellularity
- Myeloid series consists mostly of immature cells with minimal evidence of terminal differentiation

Initial - Flow Cytometry

Blasts comprise 88% of non-erythroid marrow elements, expressing:

- CD34 (subset)
- HLA-DR
- CD33
- CD13
- CD14 (variable)
- CD64
- CD38
- CD4
- CD25 (dim)
- CD123
- cMPO (dim)





Consistent with monocytoid differentiation

Pertinent negatives:

CD117, CD16, CD56, CD19, CD20, sKap, sLamb, CD10, CD23, CD2, CD3, CD5, CD7, CD8, CD57, cTDT, cCD79a, cCD3, cCD22

Initial - Additional Findings

Microarray:

- Single abnormal clone in 90% of cells with focal deletions of 11p including the WT1 gene, 21q including focal deletion of exons 3-8 of the RUNX1 gene, and a nested gain of exons 2-10 of the KMT2A gene

FISH:

- Inv(16) - Normal

FLT3 Status:

- Positive for FLT3-ITD mutation

Cytogenetics:

- 46,XY[20] - Normal male karyotype

Summary of Mutations:

- FLT3-ITD
- WT1 (deletion)
- RUNX1 (focal deletion)
- KMT2A (nested gain)

Initial - Clinical Management

DIAGNOSIS: Acute Myelomonocytic Leukemia

Initiated 7+3 induction chemotherapy:

- Bone marrow biopsy for day 14 post induction monitoring showed refractory disease

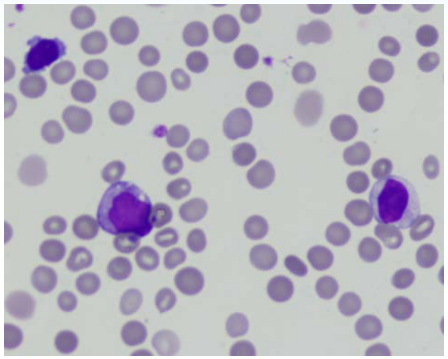
Enrolled in a clinical trial for FLT3 directed therapy with **Gilteritinib**

- CTO 102233 → ASP2215
- Tyrosine kinase inhibitor

2 - 3 months after presentation:

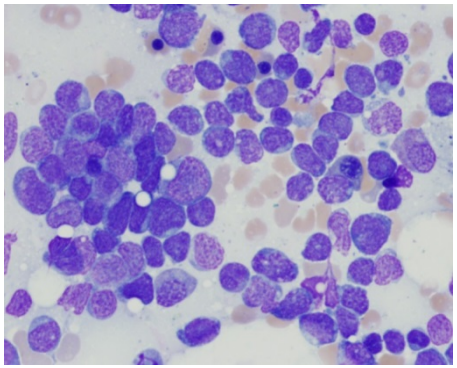
- Send out test for FLT3 came back as wild-type
- Stopped participation in clinical trial due to progressive disease seen on 3 month follow up biopsy
- Began salvage chemotherapy with FLAG-Ida

Follow-up - Smear & Bone Marrow Biopsy



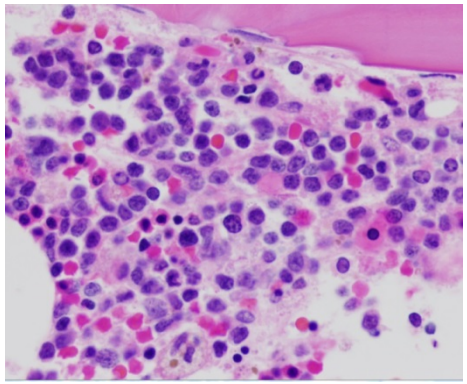
Peripheral Smear:

- Predominance of lymphocytes with circulating blasts



Aspirate:

- Predominantly blasts with rare hematopoietic cells
- Blasts comprise 75% of cellularity



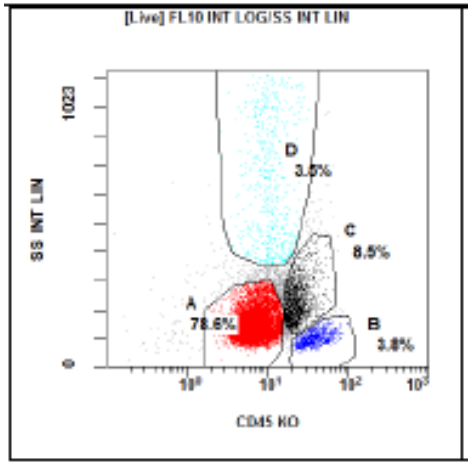
Bone Marrow:

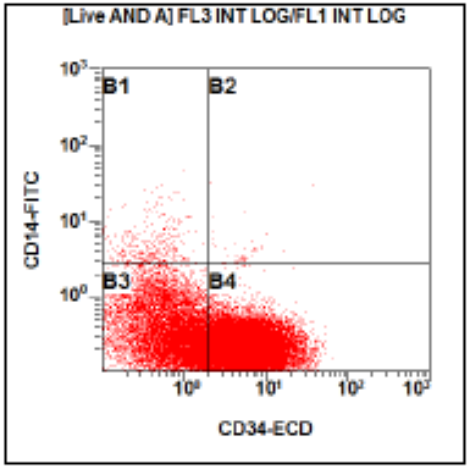
- 40% cellularity
- Increased blast population identified

Follow-up - Flow Cytometry

Blasts comprise 79% of non-erythroid marrow elements, expressing:

- CD34 (dim)
- CD117 (dim)
- HLA-DR
- CD33 (dim)
- CD13 (dim)



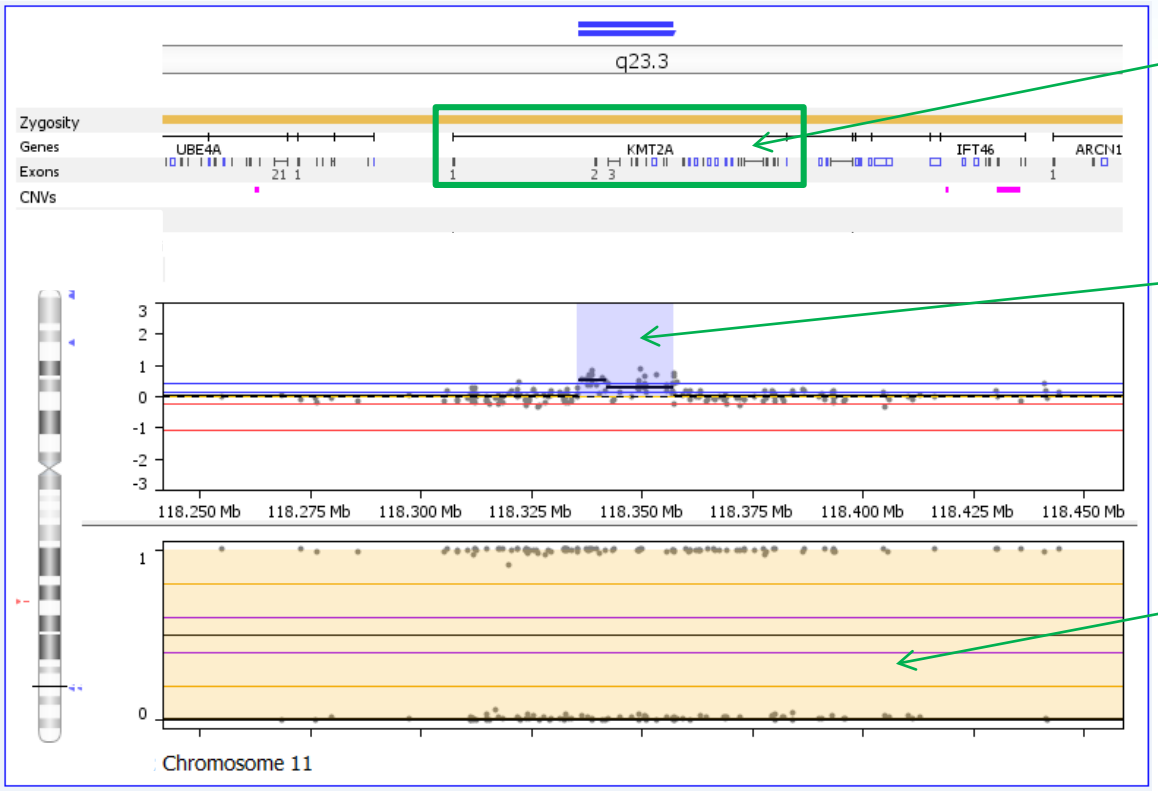


Indicates myeloid lineage

Pertinent negatives*:
CD56, CD14, CD16, CD64

*A limited panel was used to look for minimal residual disease

Follow-up - Microarray: Major clone (~80%)



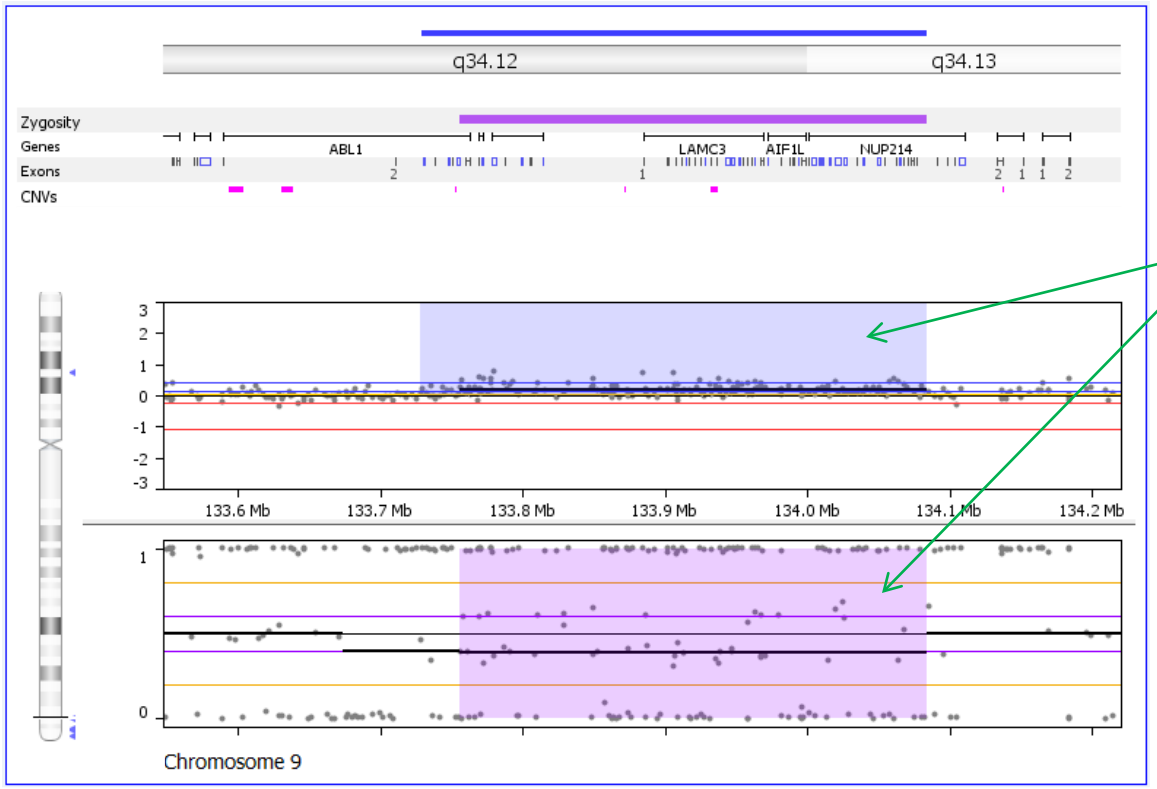
KMT2A gene

Duplication of exons 2-10

Loss of heterozygosity

This abnormal clone showed focal deletion of exons 3-8 of the RUNX1 gene and loss of heterozygosity of 11q with nested gain of exons 2-10 of the KMT2A gene

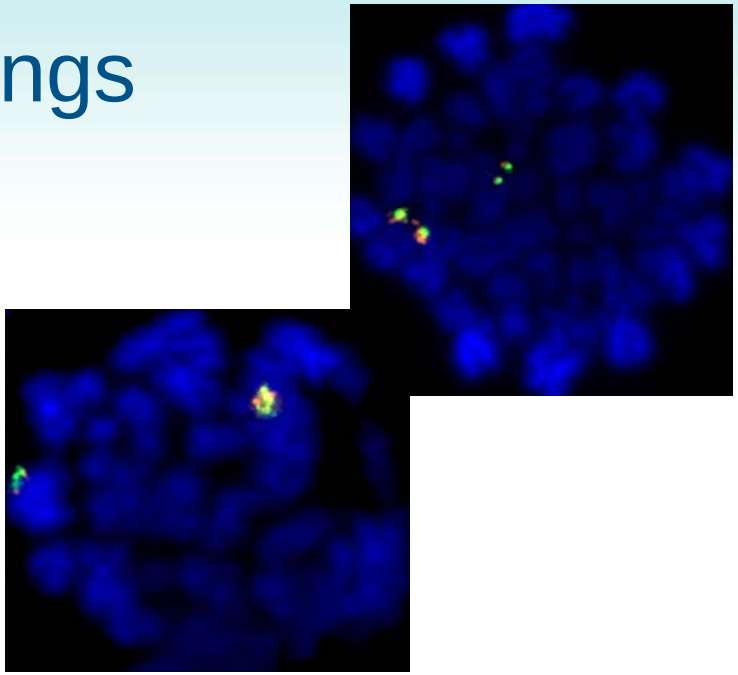
Follow-up - Microarray: Subclone



Duplication at breakpoint of exon 2 on ABL1 gene to exon 33 of NUP214 gene

A subclone showed a gain of 9q, consistent with a NUP214-ABL1 fusion

Follow-up - Additional findings



FISH:

› A break-apart probe for the NUP214 gene revealed apparent abnormal signal patterns consistent with gains of part of the ABL1 and NUP214 genes

FLT3 status:

› FLT3 wild type

Summary of Mutations:

- RUNX1(focal deletion)
- KMT2A (nested gain)
- NUP214-ABL1 (fusion & amplification)

Cytogenetics:

› 46,XY[20] - Normal male karyotype

Follow-up - Clinical management

FLAG-Ida salvage chemotherapy initiated

- Addition of **Sorafenib**
  - Multitargeted tyrosine kinase inhibitor
    - Currently used for HCC, RCC, differentiated thyroid cancer
  - Off-label, nonprotocol treatment for FLT3+ AML
    - Wanted to treat/suppress initial clone that was FLT3+

Bone marrow biopsy results post FLAG-Ida:

- No evidence of acute leukemia

Underwent allogenic matched unrelated donor hematopoietic stem cell transplant (Allo MUD HSCT)

Update - Status Post Transplant

Post-transplant complications:

- GVHD of Skin – biopsy proven grade 2
  - Received tacrolimus & methotrexate → resolved

Recent 6 month post-transplant Bone Marrow Biopsy:

- No morphologic or flow cytometric evidence of AML

1 year after initial presentation:

- Still receiving **sorafenib** daily
  - Plan to continue therapy for 1 - 2 years

Evolution of Disease

Initial Disease: *(single abnormal clone)*
- FLT3 → ITD mutation
- WT1 → Deletion
- RUNX1 → Deletion of exons 3-8
- KMT2A → Nested gain of exons 2-10 (PTD)

Refractory to 7+3 induction chemotherapy

Enrolls in clinical trial with Gilteritinib

2 - 3 months later

FLT3 testing came back as *wild type*

Due to progressive disease, patient pulled from clinical trial

Progression of Disease: *(two abnormal clones)*
- RUNX1 → Deletion of exons 3-8
- KMT2A → Nested gain of exons 2-10 (PTD)
- 11q → Loss of heterozygosity
- NUP214-ABL1 → Gain/amplification with fusion

1½ months later

Initiated FLAG-Ida salvage chemotherapy

Additional round of FLAG-Ida salvage chemotherapy with addition of Sorafenib

Remission achieved, Allo MUD HSCT performed

6 months later

No residual disease!

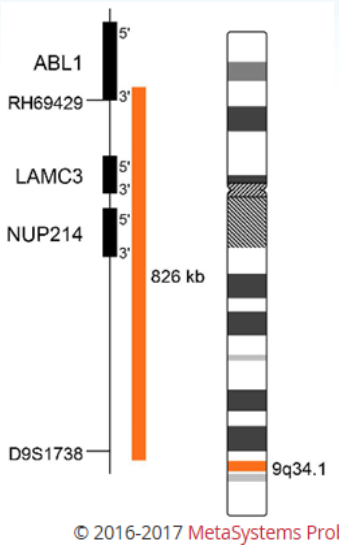
Clinical significance - NUP214-ABL1 fusion

NUP214 (nucleoporin 214):

- Nucleocytoplasmic transporter, band 9q34.13

ABL1:

- Tyrosine kinase, band 9q34.12



Previously reported in Acute Lymphoblastic Leukemias:

Comprise ~6% of T-ALLs

- Poor prognosis: usually a late event, associated with early relapse

Few cases of B-ALL

- Favorable prognosis: associated with a Ph-like form, sensitive to TKIs

Prognosis in AML → ???

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FINAL PANEL DIAGNOSIS:
Acute myeloid leukemia with mutated *RUNX1* (with cryptic *NUP214-ABL1*)