NUP214-ABL1 Fusion:
A Novel Discovery in Acute Myelomonocytic Leukemia

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Case 0094
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%) 

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

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

Cytogenetics:
› 46,XY[20] - Normal male karyotype

Summary of Mutations:
• RUNX1 (focal deletion)
• KMT2A (nested gain)
• NUP214-ABL1 (fusion & amplification)
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)

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

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

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!

Changing What’s Possible | MUSC.edu
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 ➔ ???
References


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FINAL PANEL DIAGNOSIS:
Acute myeloid leukemia with mutated \textit{RUNX1} (with cryptic \textit{NUP214-ABL1})