Therapy-related MDS/AML with *KMT2A (MLL)* Rearrangement Following Therapy for APL
Case 0328

Kenneth N. Holder, Leslie J. Greebon, Gopalrao Velagaleti, Hongxin Fan, Russell A. Higgins
Initial Case: Clinical Presentation

- 44 year old woman presented with a 12 day history of fatigue, epistaxis, gum bleeding, vaginal bleeding.
- CBC: WBC: 1.8 x10^3/μL, Hemoglobin: 6.3 g/dL, Hematocrit 17.9%, Platelets: 21 x10^3/μL
- Clinical concern for DIC.
Initial Case: Peripheral Blood and Bone Marrow Morphology
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Initial Case Ancillary Studies:
Flow Cytometry and Molecular Tests

91% of cells expressed CD13, CD33, CD117, and MPO, and lacked HLA-DR, CD34, B-cell and T-cell antigens

RT-PCR gel for *PML-RARA* with R6 and D4 primers for exon 3 or 6 of *PML* and exon 2 or 3 of *RARA*

- Patient sample
- Positive control
Initial Case Ancillary Studies: FISH and Cytogenetic Analysis

FISH: 91% of cells positive for t(15;17) PML-RARA

Chromosome Analysis:
46,XX, t(15;17)(q24;q21)[19]/ 46,XX[1]
Initial Case: Diagnosis and Treatment

• Acute Promyelocytic Leukemia with t(15;17) PML-RARA

• All-trans retinoic acid (ATRA) started on day of presentation.

• Induction chemotherapy with Idarubicin/ATRA

• Two consolidations with Idarubicin/ATRA.

• One consolidation with Mitoxantrone/ATRA.

• Maintenance: three courses of ATRA; four courses methotrexate & 6-mercaptopurine.

• Patient had good response and was in complete remission up to 15 months post induction.
Follow-up Case: Clinical Presentation

• 15 months after induction for APL, the patient returned with new complaint of one week history of headache and difficulty chewing due to violaceous gingival swelling.
  – Peripheral blood RT-PCR and FISH were negative for *PML-RARA* as recently as 3-4 weeks prior.

• CBC: WBC: 53.0 x10^3/μL, Hemoglobin: 6.8 g/dL, Hematocrit 20.2%, Platelets: 9 x10^3/μL
Follow-up Case: Peripheral Blood Morphology
Follow-up Case: Differential Diagnosis

- Relapsed APL now with change to microgranular morphology
- Therapy-related MDS/AML
Follow-up Case: Bone Marrow Morphology
Follow-up Case: Flow Cytometry

Bone Marrow Aspirate Flow: neoplastic cells expressed variable CD13, CD14, CD15, CD11c, and positive for CD33, HLA-DR, and dim CD4, and were negative for CD34, CD117, B-cell, and T-cell antigens.
Follow-up Case: Cytochemical Stains

Bone Marrow Aspirate
Non-specific esterase: strongly positive staining which was inhibited by fluoride.

Bone Marrow Aspirate
Myeloperoxidase: negative in neoplastic cells.
Follow-up Case: Molecular Analysis

Negative RT-PCR for \textit{PML-RARA}

RT-PCR gel for \textit{PML-RARA} with R6 and D4 primers for exon 3 or 6 of \textit{PML} and exon 2 or 3 of \textit{RARA}

Negative result with sensitivity as low as 1 in 10,000 cells
Follow-up Case: FISH KMT2A (MLL) Break-Apart Probe

Marrow FISH: demonstrating MLL gene rearrangement in 91.5% of cells
Follow-up Case: Cytogenetic Analysis

Marrow Karyotype: 46;XX, t(9;11)(p22;q23)[20]
Follow-up Case: Diagnosis and Treatment

• Therapy-related MDS/AML with $KMT2A$ ($MLL$) rearrangement [$t(9;11)(p22;q23)$].

• Simultaneous and integrated evaluation by multiple modalities including molecular/cytogenetic studies confirmed t-MDS/AML and not recurrence of the patient’s prior APL.

• Patient was treated for t-MDS/AML but remission was not achieved.

• She succumbed to complications of disease ~4 months after diagnosis of t-MDS/AML.
Discussion

• Development of t-MDS/AML after treatment of APL is a rare (1%) but serious complication.
  – 42 cases of t-AML reported after Tx for APL.
  – 7 of which showed $KMT2A$ ($MLL$) rearrangement with 1 prior report of t(9;11).

• Treatment with ATRA + chemotherapy vs ATRA + arsenic trioxide (ATO).
  – Literature suggests at least non-inferiority for ATRA + ATO in low to intermediate-risk and possibly in high-risk.
  – Less prolonged cytopenias, mucositis, and/or infection with ATRA + ATO.
  – Increased liver toxicity and QT prolongation with ATRA + ATO.
Thank You