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

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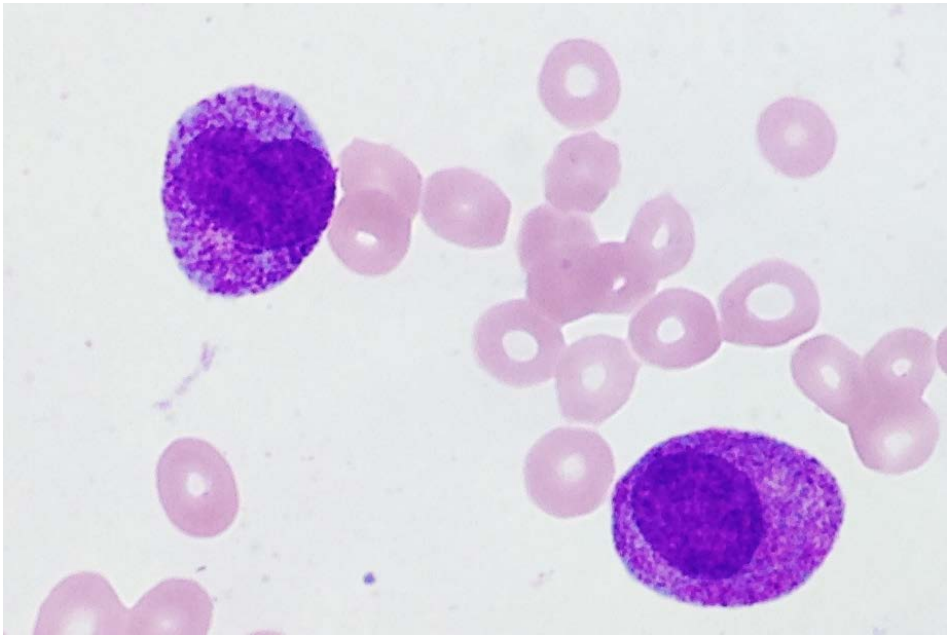
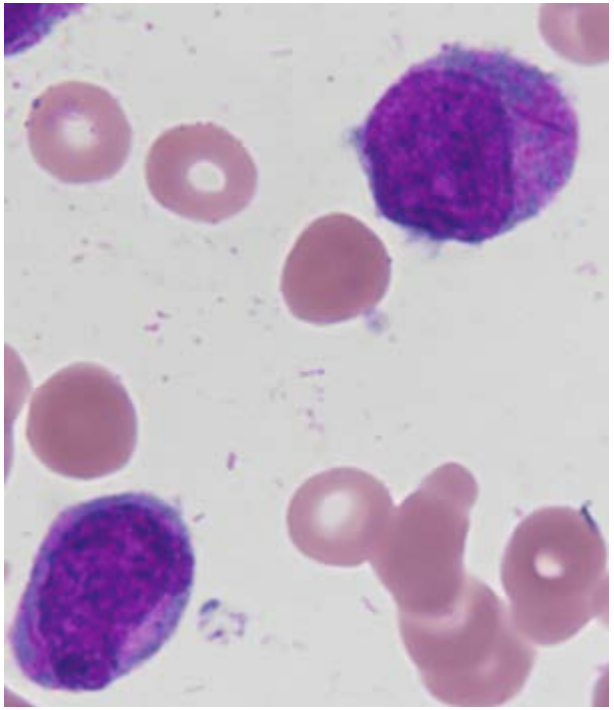
Initial Case: Clinical Presentation

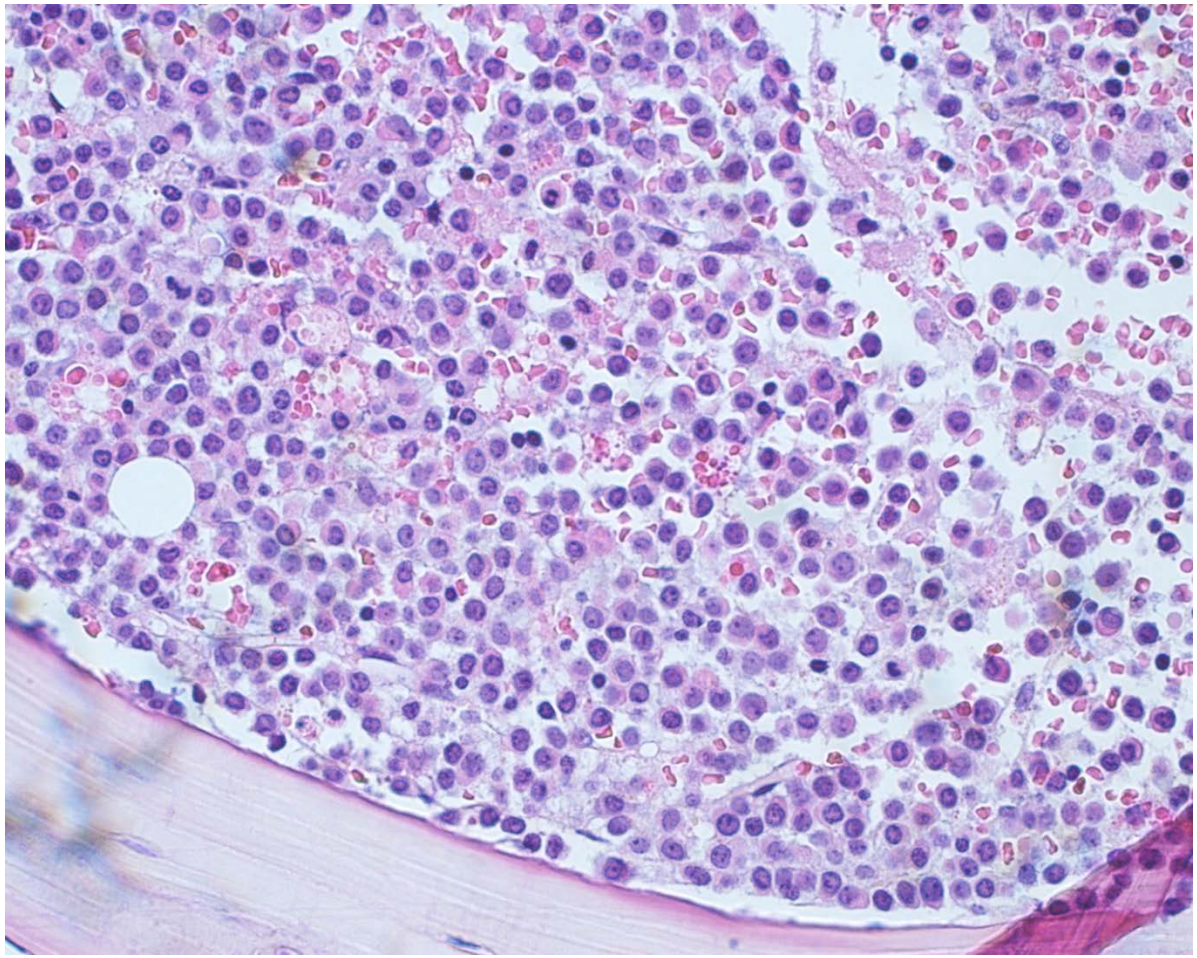
- 44 year old woman presented with a 12 day history of fatigue, epistaxis, gum bleeding, vaginal bleeding.
- CBC: WBC: 1.8 x10^3/µL, Hemoglobin: 6.3 g/dL, Hematocrit 17.9%, Platelets: 21 x10^3/µL
- Clinical concern for DIC.

Initial Case: Peripheral Blood and Bone Marrow Morphology

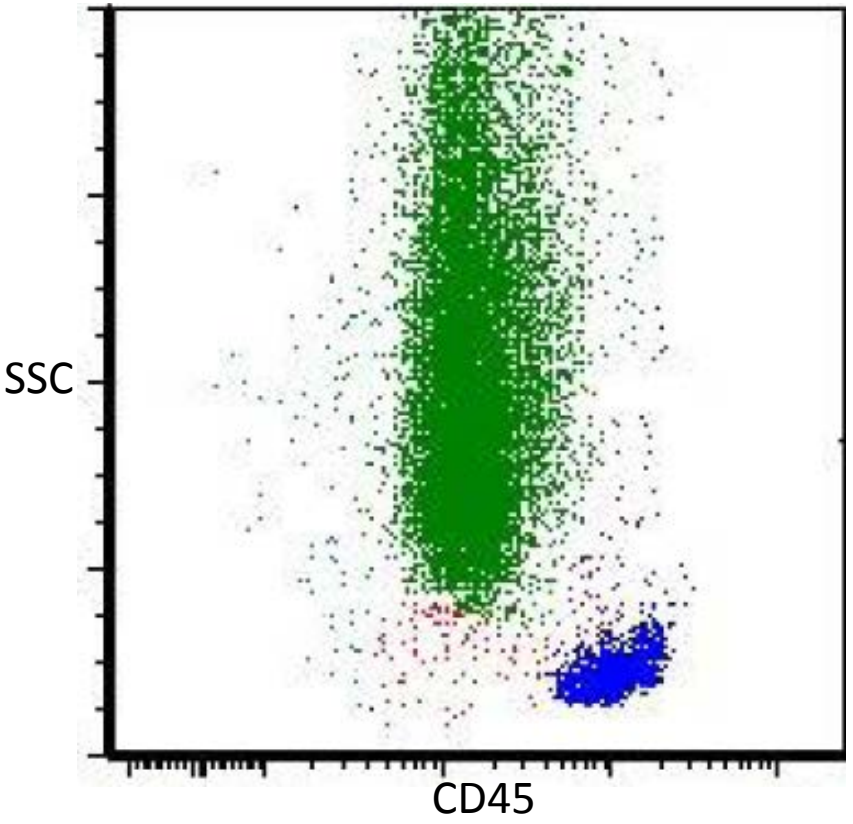




Initial Case: Peripheral Blood and Bone Marrow Morphology

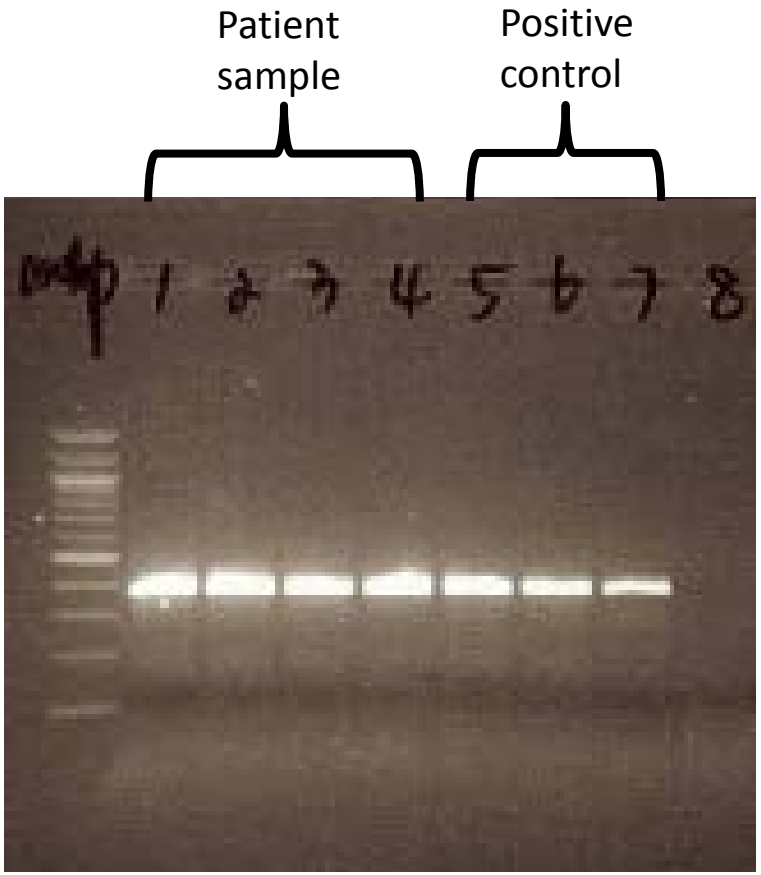


Initial Case Ancillary Studies:
Flow Cytometry and Molecular Tests



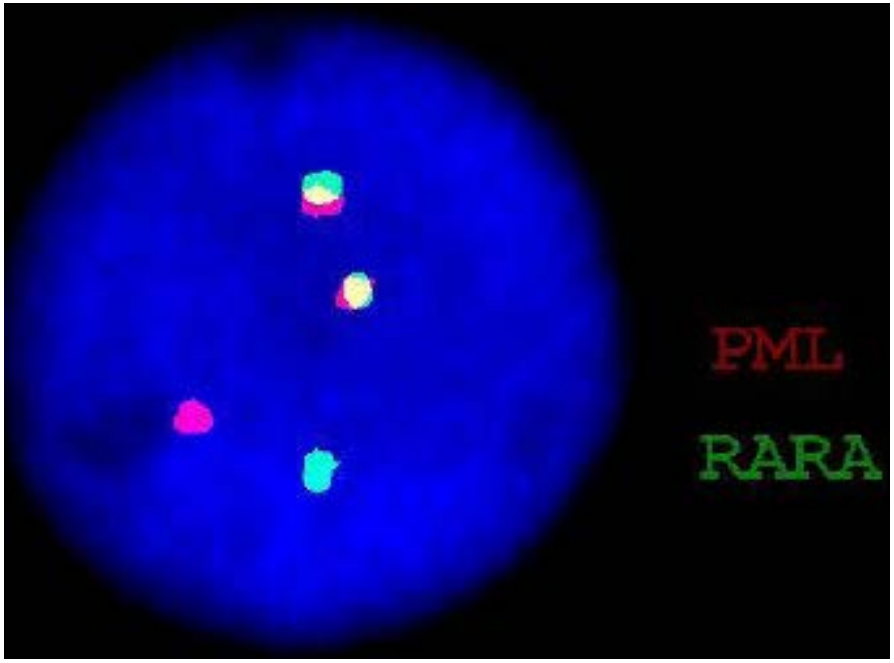
91% of cells expressed CD13, CD33, CD117, and MPO, and lacked HLA-DR, CD34, B-cell and T-cell antigens

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*

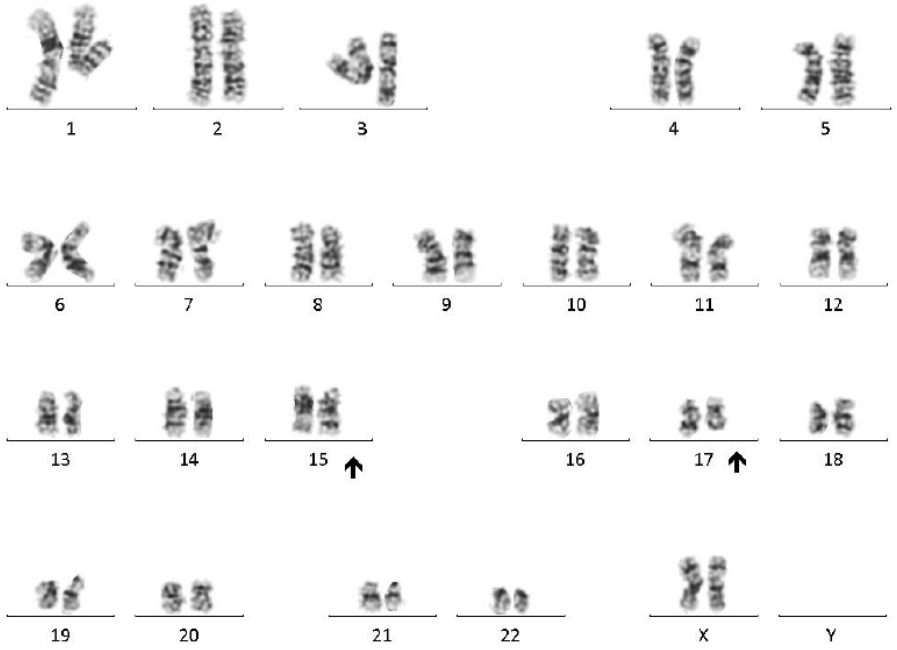


Initial Case Ancillary Studies:
FISH and Cytogenetic Analysis

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

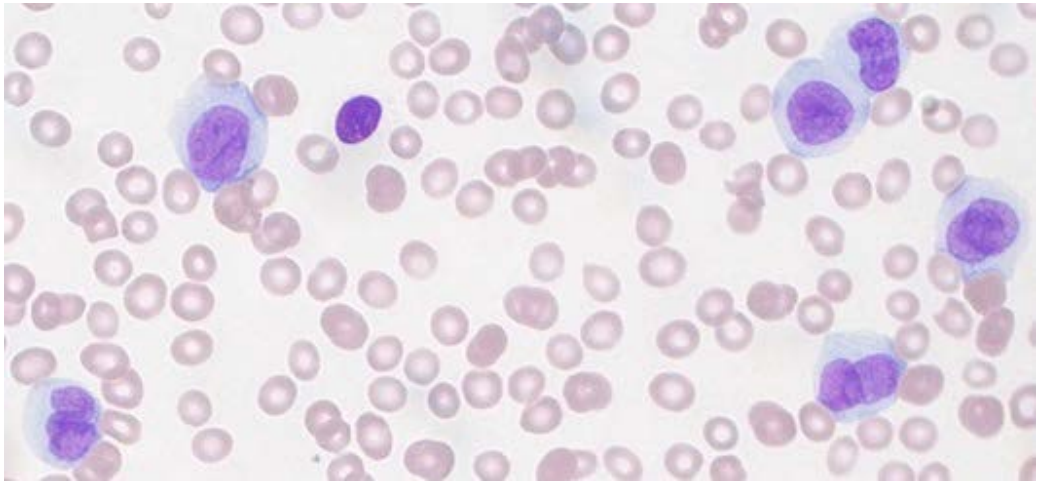
- Acute Promyelocytic Leukemia with t(15;17) *PML-RARA*
- All-trans retinoic acid (ATRA) started on day of presentation.
- Induction chemotherapy with Idarubicin/ATRA
- Two consolidations with Idarubicin/ATRA.
- One consolidation with Mitoxantrone/ATRA.
- Maintenance: three courses of ATRA; four courses methotrexate & 6-mercaptopurine.
- Patient had good response and was in complete remission up to 15 months post induction.

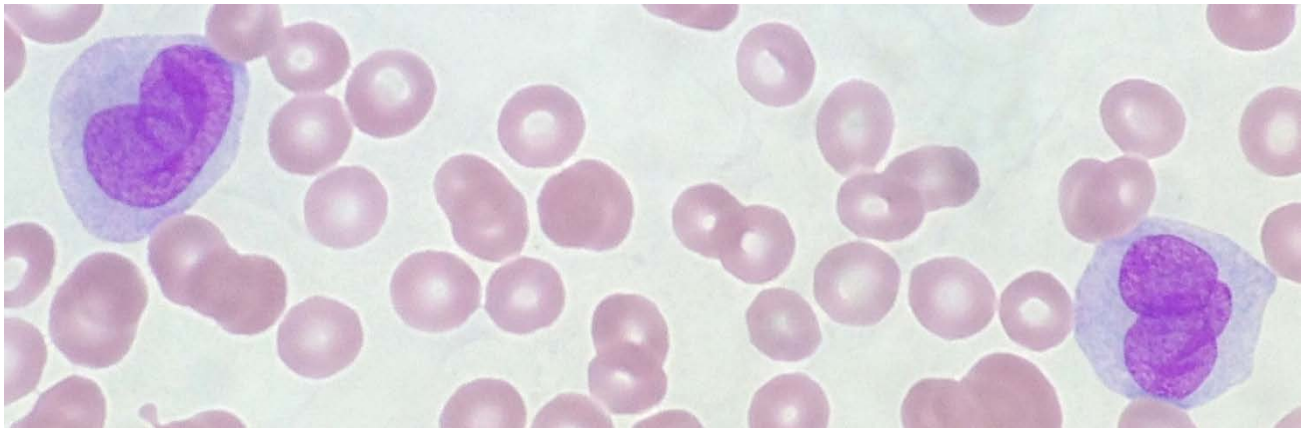
Follow-up Case: Clinical Presentation

- 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

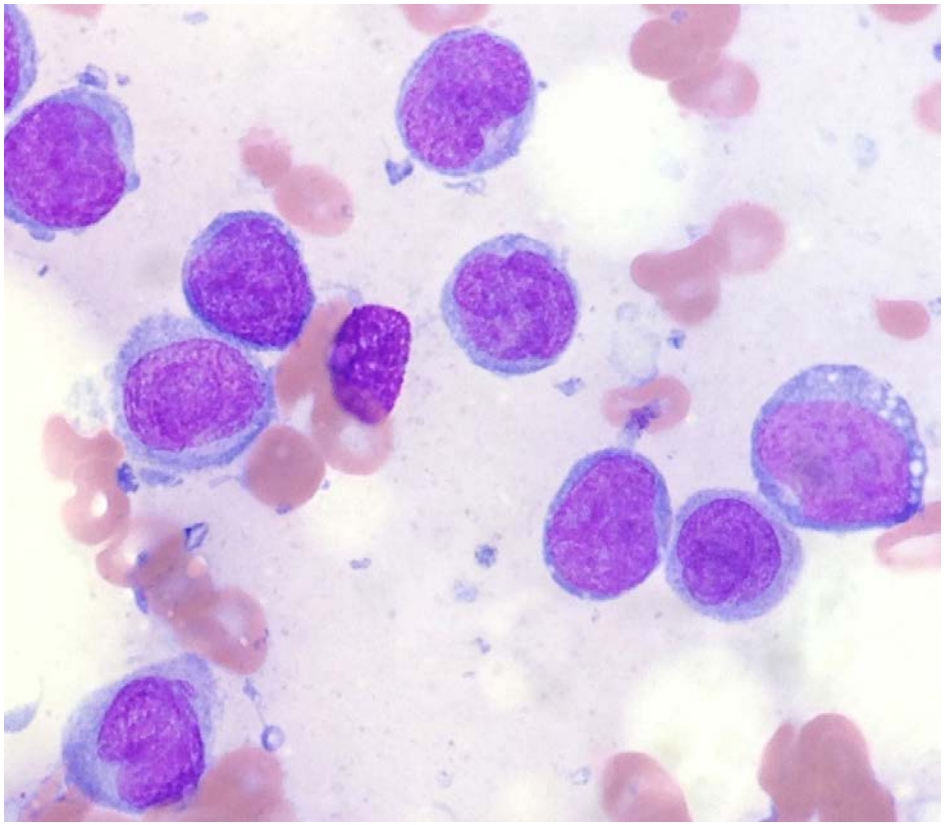




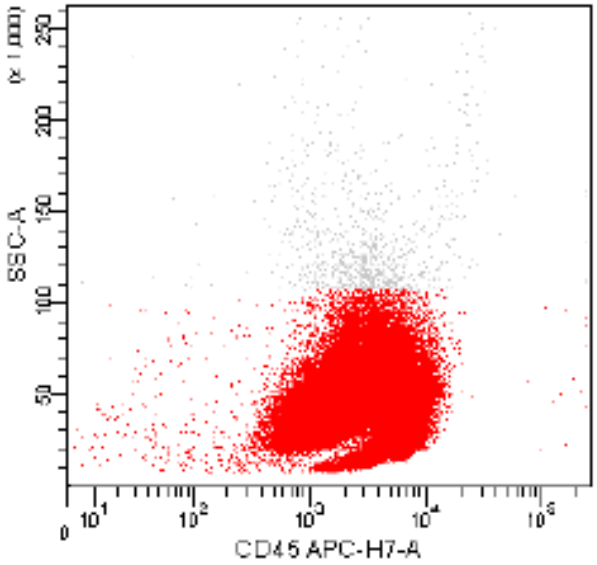
Follow-up Case: Differential Diagnosis

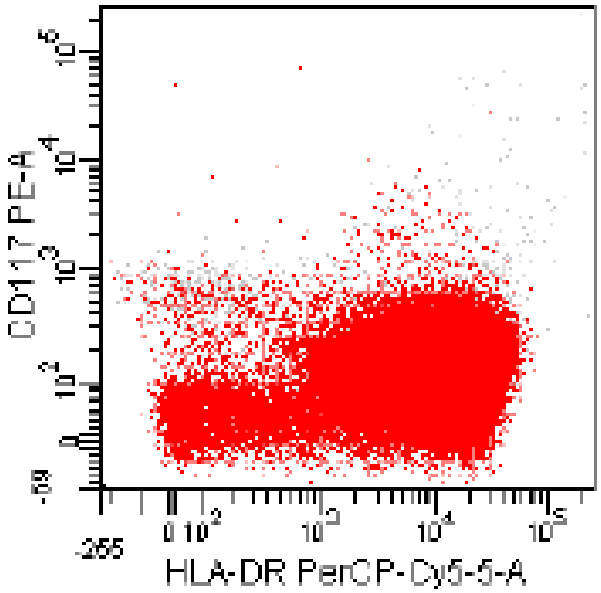
- Relapsed APL now with change to microgranular morphology
- Therapy-related MDS/AML

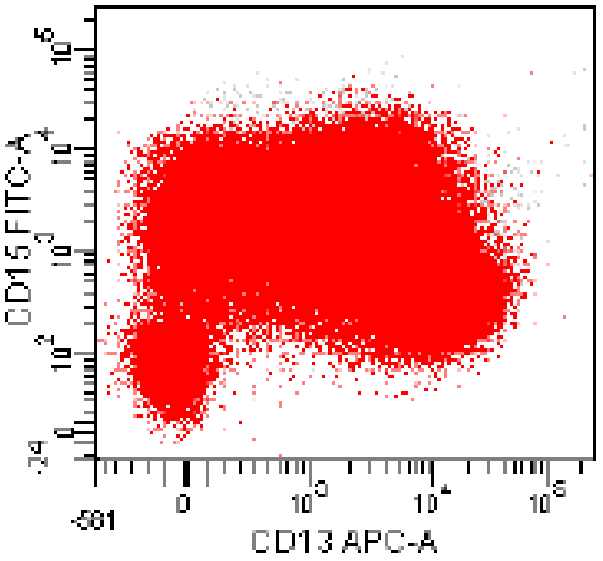
Follow-up Case: Bone Marrow Morphology

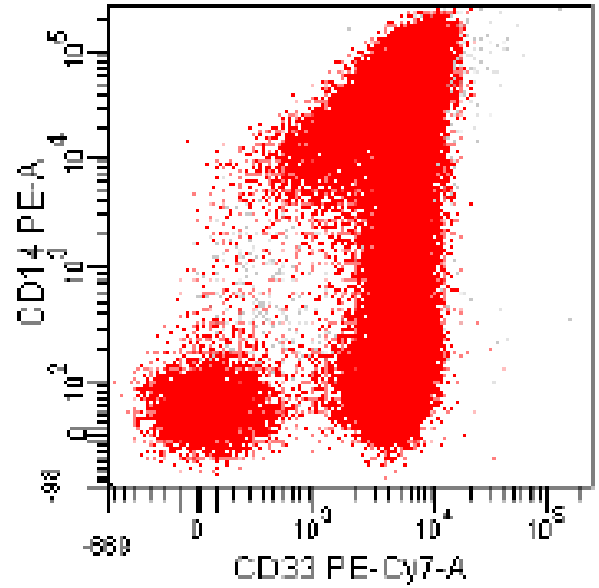


Follow-up Case: Flow Cytometry



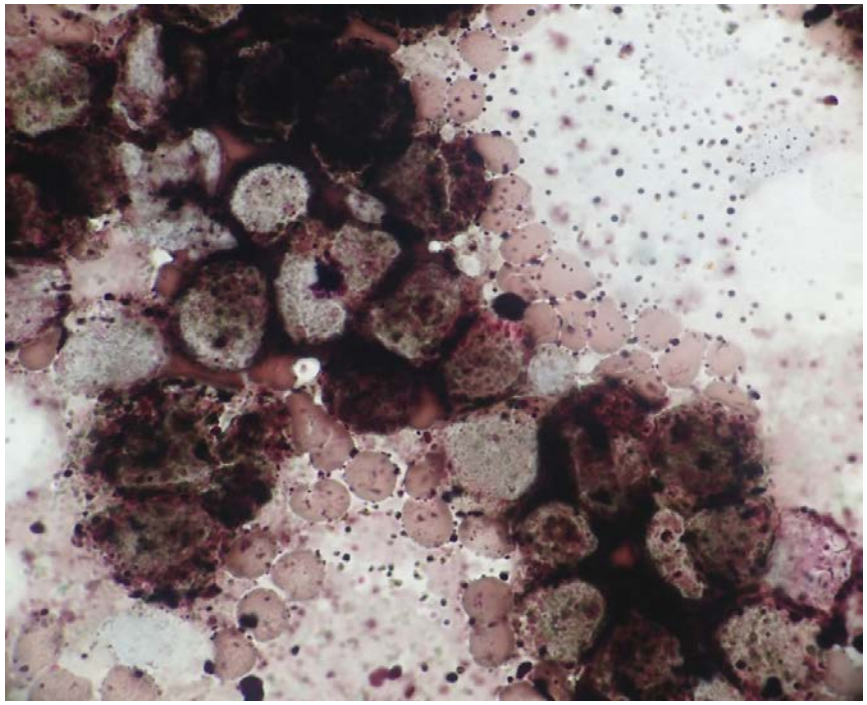




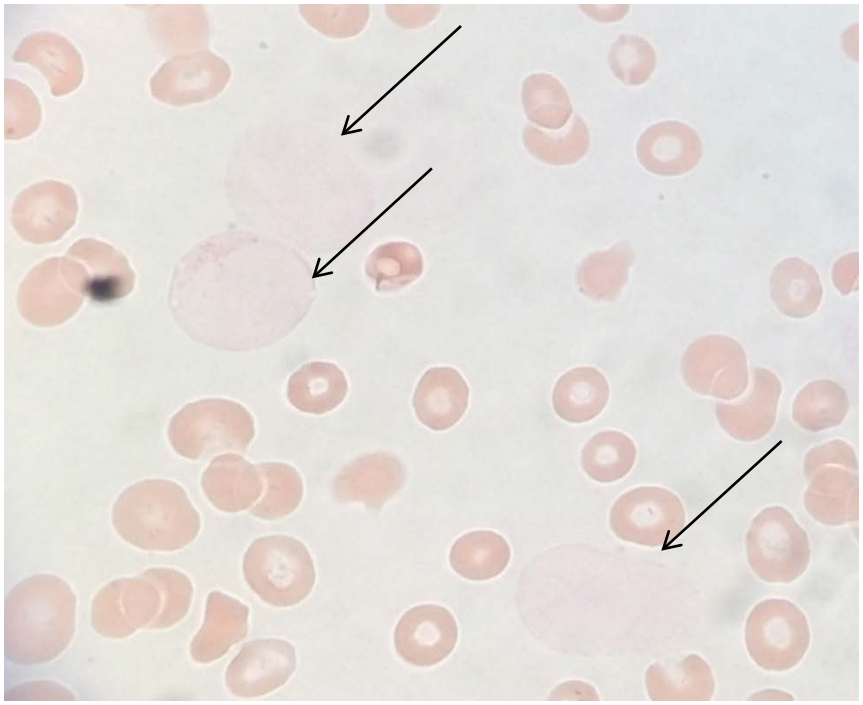


Bone Marrow Aspirate Flow: neoplastic cells expressed variable CD13, CD14, CD15, CD11c, and positive for CD33, HLA-DR, and dim CD4, and were negative for CD34, CD117, B-cell, and T-cell antigens.

Follow-up Case: Cytochemical Stains

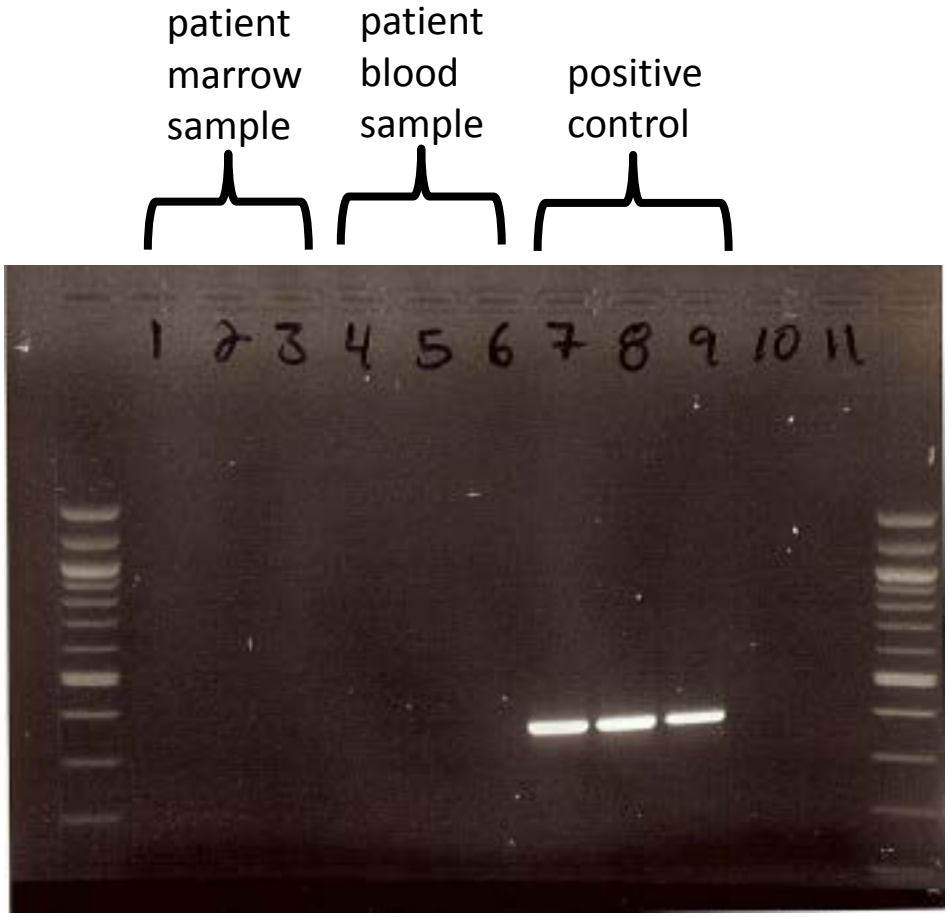


Bone Marrow Aspirate
Non-specific esterase:
strongly positive staining which was inhibited by fluoride.



Bone Marrow Aspirate
Myeloperoxidase: negative in neoplastic cells.

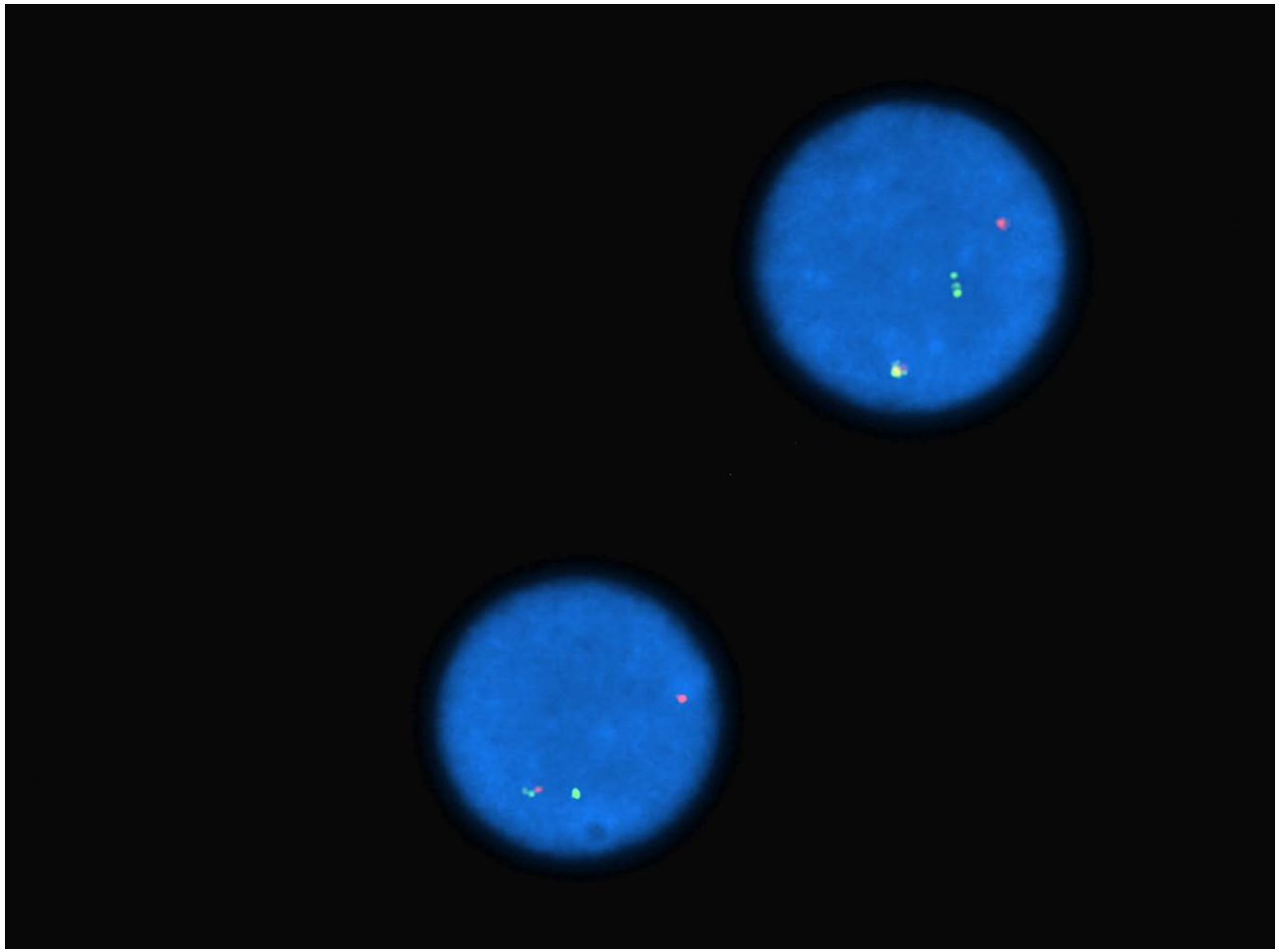
Follow-up Case: Molecular Analysis
Negative RT-PCR for *PML-RARA*



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*

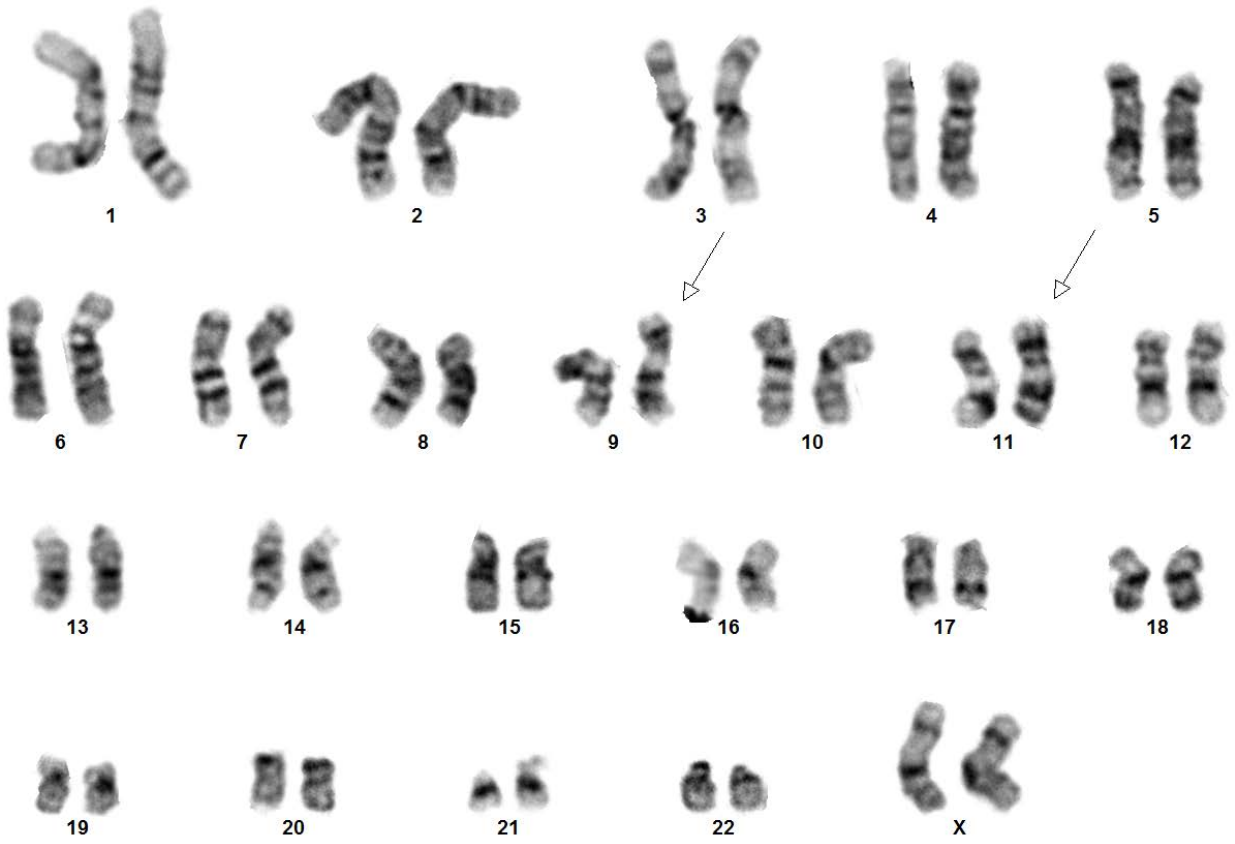
Negative result with sensitivity as low as 1 in 10,000 cells

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.

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Thank You

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