A unique case of B-lymphoblastic leukemia with eosinophilia

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Clinical Presentation

- 51 yo F presents to an outside hospital on 10/6 with a cc of a headache, dizziness, neck pain, and subjective fevers x 10 days
- The patient also endorses joint pain and a 24 lb. weight loss over the last 6 months
- No neurologic deficits or change in mentation were noted
- PMH − asthma, seasonal allergies and hypothyroidism
- SHx – non-contributory
- FHx – non-contributory

Initial Work Up

Test	Result
LP	No RBCs, glucose 55, protein 20, 1 WBC, colorless. Bacterial culture x 3 days no growth
CT head	No acute intracranial abnormalities
CBC	WBC 62K, 70% eosinophils, no circulating blasts, platelets 203K
MRI head/neck	Chronic small vessel ischemic change and T1 hypointensity throughout the visualized marrow concerning for a myeloproliferative disorder
BMBx	Pending

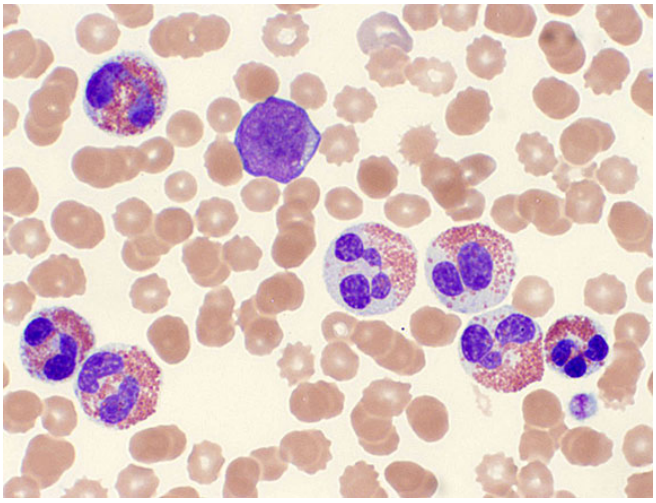
Clinical Course

- Managed symptomatically
- Developed altered mentation
  - Receptive aphasia and left hemiparesis
  - Unknown time of onset
  - CT head repeated – neg
- WBC continued to increase
  - Day 4: WBC 123.3K, 80% eosinophils, Hgb 11.6, platelets 83K
- On 10/10, pt was transferred due to concern of leukostasis
- BMBx results showed “acute leukemia” per verbal report

Clinical Course

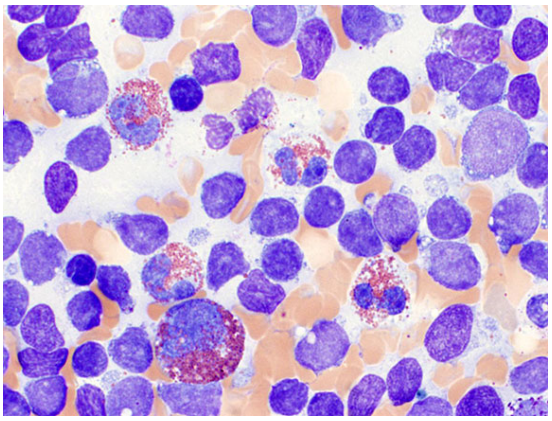
- Intubated for inability to protect airway
- Echocardiogram
  - EF 47% with mild global hypokinesis
  - LV hypertrophy
  - Mild to moderate regurgitation of AV, MV, TVR, and PVR (trace)
- Cardiac MRI
  - Eosinophilic myocarditis
  - RV and LV thrombus
    - Started on bivalirudin
- Brain MRI
  - Multifocal infarcts involving cerebral hemispheres, pons and cerebellum
  - Likely secondary to ventricular thrombi
- Undergoes leukapheresis
- Undergoes repeat BMBx

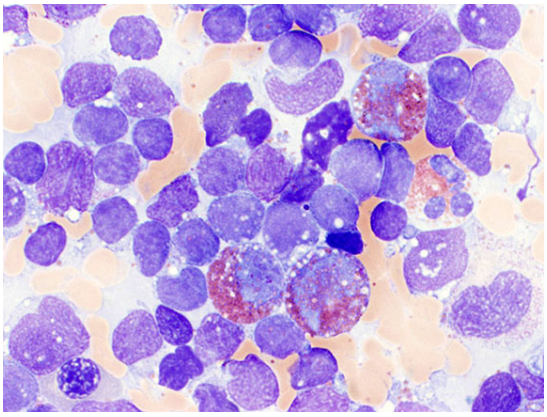
Peripheral Blood Smear



HGB	9.6 g/dL
MCV	79.5 fL
RDW	14.2 %
PLT	40 x 10^9/L
WBC	61.0 x 10^9/L
Blasts	9%
Promyelocytes	0%
Eosinophils	86%
Basophils	0%
Monocytes	0%
Lymphocytes	3%
Neutrophils	2%
Metamyelocytes	0%

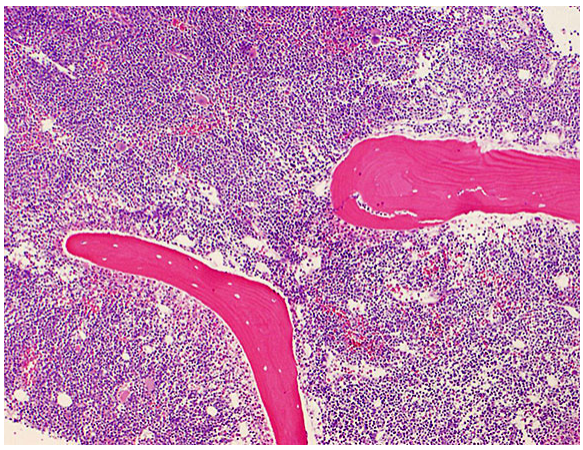
Bone Marrow Aspirate

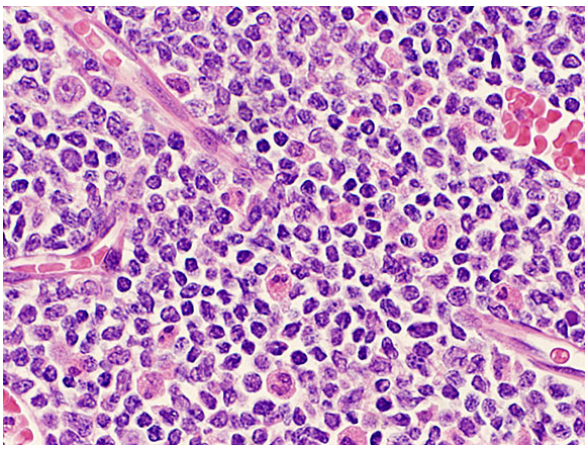




Blasts	51%	Lymphocytes	13%
Eosinophils	28%	Plasma cells	0%
Basophils	1%	Erythroid Precursors	2%
Monocytes	0%	PMNs and Precursors	5%

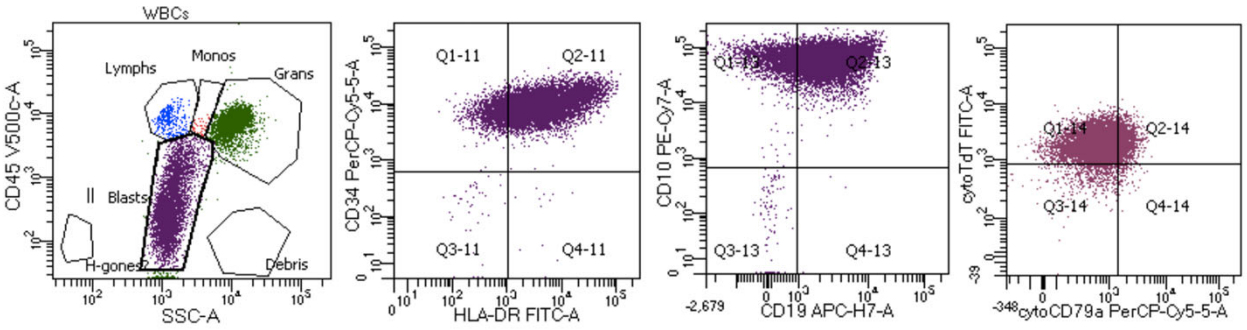
Bone Marrow Biopsy





Flow Cytometric Analysis

- Blast Immunophenotype
  - CD10+ (bright), CD19+, CD20+ (partial/dim), cCD22+, CD34+, cCD79+ (partial/dim), HLA-DR+, TdT+
  - CD33+ (partial/dim)



BMBX

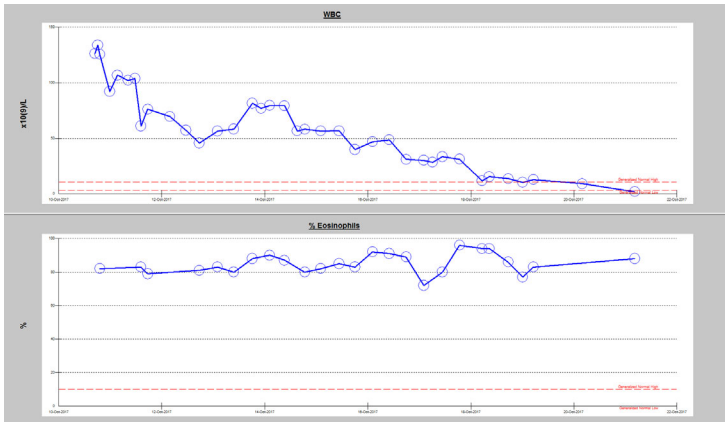
A-D. Bone marrow, left iliac crest aspirate with clot preparation and biopsy with touch imprints, and peripheral blood smear:

1. B lymphoblastic leukemia/lymphoma.
2. Bone marrow and peripheral blood eosinophilia, marked.
3. Hypercellular marrow (95%) with 51% lymphoblasts, 28% eosinophils, and diminished hematopoiesis.

Comment: Please correlate also with the pending results of cytogenetic analysis and FISH testing. If any WHO-defined recurrent genetic abnormality is identified, an amended report documenting a more specific subclassification in this case (i.e. B-ALL with recurrent genetic abnormality) will follow.

Hospital Course

- Started on induction chemotherapy with hyper-CVAD + rituximab + IT chemotherapy
- Slow decrease in WBC count

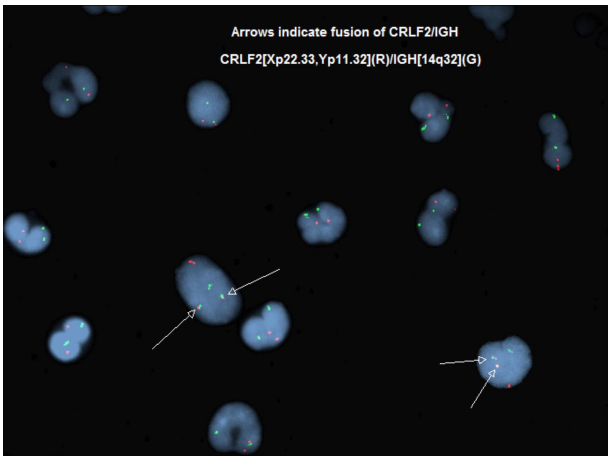


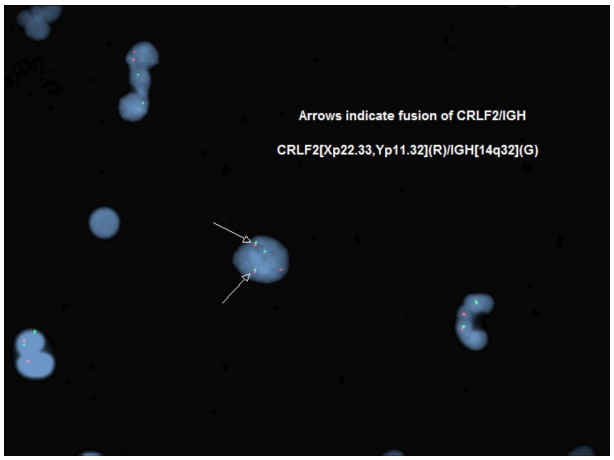
Courtesy of Dr. Talal Hilal

FISH/cytogenetics

- Approximately 12% of nuclei have *CRLF2/IGH* fusion
- *ETV6* rearrangement (at 12p13)
- *CDKN2A* deletion (at 9p21)
- The identification of *CRLF2/IGH* fusion usually indicates a "cryptic" X;14 translocation that is associated with Ph-like ALL
- Patients with this abnormality may be sensitive to kinase inhibitor therapy (Roberts, JCO, 34:1-8, 2016).

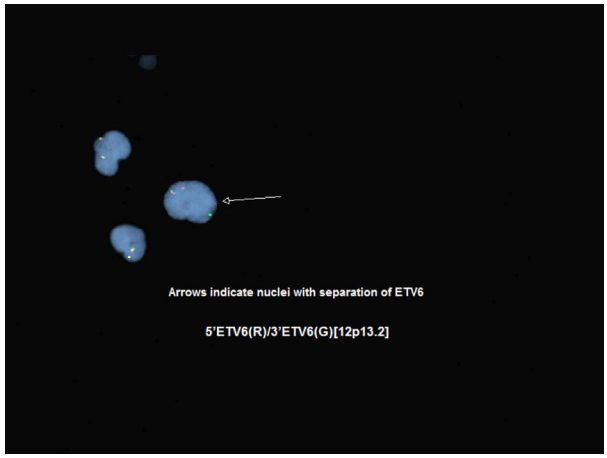
FISH Results

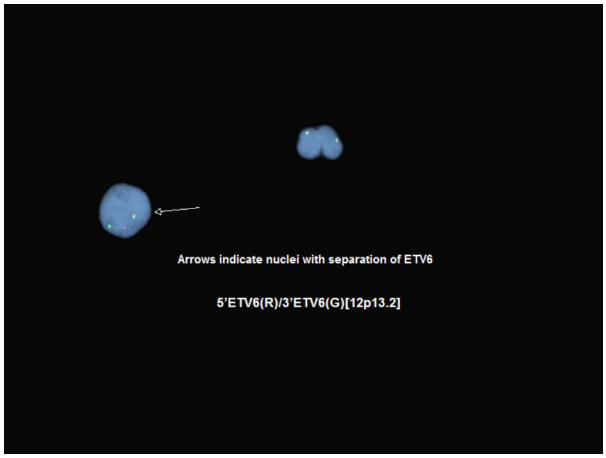




Images courtesy of Dr. Rhett Ketterling

FISH Results





Images courtesy of Dr. Rhett Ketterling

B-lymphoblastic leukemia, BCR-ABL1-like

- A new provisional entity with recurrent genetic abnormalities that has been incorporated into the WHO 2016 updates
- Neoplasm of B-lymphoblasts that lack the *BCR-ABL1* translocation but show a similar gene expression pattern to Ph+ ALL
- Occurs in 10-25% of patients with ALL
  - Prevalence significantly increases with age
- Clinical presentation similar to patients with other ALLs
  - Higher WBC at presentation
- Significantly inferior outcomes across all age groups
- May be amenable to tyrosine kinase inhibition

Genetic Profile

- Significant genetic heterogeneity involving many different genes
- Commonly harbor translocations involving other tyrosine kinases, translocations involving *CRLF2*, or rearrangements of *EPOR*
  - *CRLF2* rearrangements have been identified in approximately half of cases
    - *CRLF2* translocations are more common in Hispanics and in Native Americans
    - Tyrosine-kinase type translocations involving *ABL1* with partners other than *BCR* have been reported
    - Other kinases including *ABL2, PDGFRB, NTRK3, TYK2, CSF1R,* and *JAK2*
      - >30 partner genes have been observed
- Testing for these genetic alterations utilizing standard diagnostic methods is challenging due to the diversity and occasionally cryptic nature

Back to our patient…

- On 10/22, started on Imatinib
  - Several days later WBC < 0.1 x 10^9/L with no measurable eosinophils
- Follow up BMBx on 11/9
  - Hypocellular bone marrow (10%) with no overt evidence of residual leukemia
- Discharged on 12/5 with several re-hospitalizations
- 4/2018
  - Patient remains in heart failure
    - Echocardiogram showed improved EF and resolution of thrombi
  - Continued hemiparesis
  - Continues on maintenance chemotherapy regimen

Thank you!

- Dr. Kelemen, Dr. Conley, and the rest of the hematopathology team at Mayo, Scottsdale
- Dr. Spier, Dr. Fuchs, Dr. Proytcheva & the remainder of the BUMC-T faculty

References

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DDx of hypereosinophilia with increased blasts

- Myeloproliferative Neoplasms
  - Chronic Myeloid Leukemia
  - Polycythemia Vera
  - Chronic Eosinophilic Leukemia, NOS
    - Eosinophil count ≥ 1.5 x 10^3
    - Evidence of clonality of myeloid cells or increase in myeloblasts in blood or BM
      - <20% blasts
    - If no increase in blasts, idiopathic hypereosinophilic syndrome appropriate dx
- Myeloid and lymphoid neoplasms w/eosinophilia and abnormalities of *PDGFRA, PDGFRB, FGFR1,* or *PCM1-JAK2*
  - Eosinophilia characteristic but not invariable
    - >85% have eosinophil count ≥ 1.5 x 10^3
  - Usually present as a MPN but can also present as an AML, T or B ALL, MPAL, CMML, or have a lymphomatous picture
- Systemic Mastocytosis with Associated Clonal Hematologic Non-Mast Cell Lineage Disease
  - Meet criteria for SM as well as a second d/o (MPN, CMML, MDS, and AML)
  - 30-40% of cases associated with eosinophilia
    - Should be distinguished from *PDGFRA* translocation-associated myeloid neoplasms via molecular studies
- Acute Myeloid Leukemia
  - t(8;21)
  - inv(16)

DDx of hypereosinophilia with increased blasts

- B-Lymphoblastic leukemia with t(5;14)
  - Translocation between *IL3* and *IGH* gene results in variable eosinophilia
  - Blasts may be absent in the peripheral blood
  - Dx can be made based on immunophenotypic and genetic findings even in absence of high blast count in BM