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

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGB</td>
<td>9.6 g/dL</td>
</tr>
<tr>
<td>MCV</td>
<td>79.5 fl</td>
</tr>
<tr>
<td>RDW</td>
<td>14.2 %</td>
</tr>
<tr>
<td>PLT</td>
<td>40 x 10⁹/L</td>
</tr>
<tr>
<td>WBC</td>
<td>61.0 x 10⁹/L</td>
</tr>
<tr>
<td>Blasts</td>
<td>9%</td>
</tr>
<tr>
<td>Promyelocytes</td>
<td>0%</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>86%</td>
</tr>
<tr>
<td>Basophils</td>
<td>0%</td>
</tr>
<tr>
<td>Monocytes</td>
<td>0%</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>3%</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>2%</td>
</tr>
<tr>
<td>Metamyelocytes</td>
<td>0%</td>
</tr>
</tbody>
</table>
Bone Marrow Aspirate

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

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
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 \textit{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 \textit{CRLF2}, or rearrangements of \textit{EPOR}
  - \textit{CRLF2} rearrangements have been identified in approximately half of cases
    - \textit{CRLF2} translocations are more common in Hispanics and in Native Americans
    - Tyrosine-kinase type translocations involving \textit{ABL1} with partners other than \textit{BCR} have been reported
    - Other kinases including \textit{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 10⁹/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


DDx of hypereosinophilia with increased blasts

• Myeloproliferative Neoplasms
  • Chronic Myeloid Leukemia
  • Polycythemia Vera
  • Chronic Eosinophilic Leukemia, NOS
    • Eosinophil count ≥ 1.5 x 10^9
    • 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 PDGFR, PDGFRB, FGFR1, or PCM1-JAK2
  • Eosinophilia characteristic but not invariable
    • >85% have eosinophil count ≥ 1.5 x 10^9
    • 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