Initial Presentation

- 55 yo M diagnosed with AML after 5 years of thrombocytopenia
- CBC at presentation:
  - Hb > 9.0 (102.4) < 86
  - Diff: N 30, Ly 14, Mo 14, Ba 7
  - Meta 2, Myelo 2, Pro 6, Blast 25
- BMBx: >95% cellularity, 80% blasts, micromegakaryocytes
- Normal karyotype

Flow cytometry:
- Positive: CD45(dim), CD13, CD33, CD34, CD117, HLA-DR
- Negative: CD3, CD5, CD7, CD11b, CD14, CD15, CD19, CD20, CD64

Initial Molecular Results

- Brigham and Women’s Hospital Rapid Heme Panel
- 95 gene amplicon-based assay
- Illumina MiSeq
- Identification of SNVs and CNVs
- TAT <7d (2-3 runs/week, 30 patients/run)
- Typical run
- Average coverage: 1500-2000X
- >200x coverage: >90%
- <50x coverage: <5%

Somatic Variant | Variant allele (c.) | Variant allele (p.) | Diagnosis (BM) |
---|---|---|---|
ASXL1 | c.2070_2071delTC | p.D690fs*49.6% |
FLT3 | -ITD present | |
IDH1 | c.394C>T | p.R132C | 14.0% |
KRAS | c.34G>C | p.G12R | 4.0% |
NRAS | c.37G>T | p.G13C | 41.7% |
SRSF2 | c.284C>T | p.P95L | 33.3% |

Interval History

- Induction (7+3) and re-induction due to residual blasts on days 15 and 27
- At end of re-induction, less than 5% blasts
- In the following 9 months, CBCs during these 9 months were notable for a leukocytosis (up to 55 K/µL) with a monocytes (up to 32%), thrombocytopenia (12-36 K/µL), and anemia (7.0-10.9 g/dL)
- Subsequent bone marrow biopsies showed 5-10% blasts
- Hypercellular marrow
- Dysplasia (small hypolobated megakaryocytes, atypical monocytes)
- Rx: Chronic myelomonocytic leukemia (CMML-1)

Bad Skin

- Over a 5 month period, the patient noted slowly progressive pink-yellowish papules on the trunk and extremities while on decitabine. Some became necrotic, other became coalescent.
- Skin biopsies were performed.
- CBC: 5.42 > 8.3 (91.3) < 39
  (N 52 Ly 15 Mo 20 Eo 2 Ba 4 Meta 3)

Skin Molecular Results

**ASXL1**
- c.2070_2071delTC
- p.D690fs
- 49.6%
- 51.2%
- 41.0%
- 46.0%

**ETV6**
- c.459_460insG
- p.E153fs
- 21.0%
- 15.1%

**FLT3**
- ITD present

**IDH1**
- c.394C>T
- p.R132C
- 14.0%
- 31.2%

**KRAS**
- c.34G>C
- p.G12R
- 4.0%
- 5.4%
- 24.5%
- 24.5%

**NRAS**
- c.35G>A
- p.G12D
- 22.1%
- 21.6%
- 2.2%
- 2.2%
- 7.8%

**NRAS**
- c.37G>T
- p.G13C
- 41.7%
- 24.3%
- 26.5%
- 7.8%

**RUNX1**
- c.736_737insC
- p.P245fs
- 37.2%
- 25.3%
- 11.9%

**SRSF2**
- c.284C>T
- p.P95L
- 33.3%
- 26.2%
- 22.9%
- 16.1%
### Differential Diagnosis of Skin Lesions in Patients with Leukemia

**Unrelated to Leukemia**
- Unrelated SCC
- Unrelated BCC
- Other unrelated neoplasm or proliferation

**Secondary to Treatment**
- Graft-versus-host disease
- Infection
- Drug eruption

**Associated with Leukemia**
- Sweet's syndrome (neutrophilic)
- Sweet's syndrome (histiocytic)
- Langerhans cell histiocytosis
- Other accumulations of histiocytes/dendritic cells

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### Histiocytoid Processes Associated with Hematopoietic Neoplasms

<table>
<thead>
<tr>
<th>Histiocytoid Process</th>
<th>Immunophenotype</th>
<th>Associated Hematologic Neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized Histiocytosis</td>
<td>S100+, CD68+, CD163+, CD14+, CD56-</td>
<td>AML, MDS, PMF, CMML*</td>
</tr>
<tr>
<td>Langerhans Cell Histiocytosis</td>
<td>S100+, CD1a+, Langerin+, CD68-</td>
<td>AML, MDS, PMF, CMML*</td>
</tr>
<tr>
<td>Langerhans Cell Sarcoma</td>
<td>S100+, CD1a+, Langerin+, CD68-</td>
<td>AML, MDS, PMF, CMML*</td>
</tr>
<tr>
<td>Myeloid Dendritic Cell Dyscrasia</td>
<td>CD4+, CD56+, CD123+, CD68+</td>
<td>CMML*, AML*, MPN*, MPN/MPN*</td>
</tr>
<tr>
<td>Plasmacytoid Dendritic Cells</td>
<td>CD4+, CD56+, CD123+, CD68+</td>
<td>CMML*, AML*, MPN*, MPN/MPN*</td>
</tr>
<tr>
<td>Blastic Plasmacytoid Dendritic Cell Neoplasms, Blastic Indeterminate Dendritic Cell Tumors, Myelomonocytic Cell Tumors</td>
<td>CD123+, CD4+, CD56+</td>
<td>CMML (all terms from 1 paper)</td>
</tr>
</tbody>
</table>

*Proven to be clonally related by cytogenetics or molecular methods.

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### Sweet's Syndrome

- Histocytoid slightly more prevalent in HMs

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### Diagnosis - What is in a name?

- Cutaneous involvement by the patient's known myeloid neoplasm (leukemia cutis) (with partial Langerhans cell differentiation)

### Why is this an Evening Symposium Case?

- Differential diagnosis of skin lesions in a patient with leukemia
- Leukemias with cutaneous histiocytic lesions
- Clonal relatedness: stage of maturation matters...

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### Associated with Leukemia

- Sweet's Syndrome
- Myeloid Neoplasms
- Other Histiocytic Proliferations

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### But wait, there is more…

- What is in a name?
  - Cutaneous involvement by the patient's known myeloid neoplasm (leukemia cutis) (with partial Langerhans cell differentiation)
Passengers, Drivers, Backseat Drivers, and Boston Drivers

**PRESENTATION TITLE**
Passengers, Drivers, Backseat Drivers, and Boston Drivers

**RNA Splicing**
- SRSF2, SF3B1, U2AF1, ZRSR2

**Epigenetic**
- TET2, ASXL1

**Initiation**
- Evolution
- Defining
- RAS pathway
- JAK2/CALR
- KIT
- CSF3R

**Transcription**
- Progression

**PRESENTATION TITLE**
Mastocytosis

- Acquisition of KIT variant is a late event and, except in ASM-AHN, occurs only in more differentiated mast cells.

**PRESENTATION TITLE**
BRAF

- p.G596R found in colon, lung, bladder, and skin (cell line) INACTIVATING variant in vitro

**PRESENTATION TITLE**
Take Home Messages

- Leukemia cutis is a very broad term and does NOT mean cutaneous involvement by an acute leukemia
- Processes may demonstrate a spectrum of maturation, and many cases just don’t fit into a box
- Clonal evolution can be implied by sampling multiple samples over time and comparing mutations and variant allele fractions (VAFs)
- This case involves at least three different clinical, morphologic, immunophenotypic, and molecular stages of differentiation… of the same myeloid neoplasm
- Maybe pathologists should be lumpers and not splitters (or lumpers and splitters…)

**PRESENTATION TITLE**
Case 3 – Panelists’ Diagnoses

- Langerhans cell sarcoma (DDx: histiocytic sarcoma, CMML) possibly related to AML
- Residual AML (5-10% blasts, dysmegakaryopoiesis) on decitabine showing monocytosis in peripheral blood and differentiation to Langerhans cells in skin
- Underlying CMML with cutaneous involvement
References

- Ziegler et al. JAMA Dermatol. 2015;151:766-768. (GEH with FGFR1)
- Yu et al. J Cutan Pathol. 2015;42:924-928. (LCH with CMML)

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Thank You