SH/EAHP WORKSHOP 2017
CASE 210 PRESENTATION

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Clinical History

- 60 year old male with history of c-MAF high-risk IgG lambda plasma cell myeloma (December 2015)

- Chemotherapeutic intervention included VD-PACE induction, PACMED cytoreduction and carfilzomib and melphalan-based autologous stem cell transplant

- Follow up in November 2016
  - Bone marrow was negative for plasma cell myeloma
  - Abnormal findings seen on PET-CT imaging
    - Extramedullary disease progression versus infection
Imaging Studies and Physical Exam

- **PET-CT (November 2016)**
  - Increased uptake in left posterior ilium, right proximal humerus and right perineum

- **PET-CT (January 2017)**
  - Increased uptake in right perineum
  - Mediastinal lymph nodes and lung
  - Left lobe of liver

- Physical exam revealed soft tissue swelling in the left gingiva
Mediastinal Lymph Node

Diff-Quik preparation (×500): Large atypical cells with immature chromatin
CD45 vs side scatter identified a cell population in the monocyte region with high forward scatter comprising 40% of total events (red). This population was positive for CD33, HLA-DR, CD14 (bright), CD11b (bright), CD36 (variable) and negative for CD34 and CD117.

A second population (21%; blue) with decreased forward and side scatter showed variable expression of CD33 and HLA-DR with dimmer CD11b and CD14.
Mediastinal Lymph Node

H&E stain (×40 and ×400): Aggregates of large atypical cells with rare intermingled granulocytes
Mediastinal Lymph Node: IHC

CD163

Lysozyme

CD138

MPO
Left Gingival Biopsy

H&E stain (×20): Dense dermal infiltrate
Left Gingival Biopsy

H&E stain (×200 left; ×400 right): Atypical cellular infiltrate within the dermis
Left Gingival Biopsy
Immunohistochemical Stains

- MPO
- LYSOZYME
- CD163
- CD138
Ancillary Studies

• **FISH Analysis:**
  – Mediastinal lymph node:
    • Positive for t(14;16)(q32;q23) translocation (76%)
    • Negative for t(11q23) and del(17p13.1)
  – Gingival biopsy:
    • Positive for t(14;16)(q32;q23) translocation (73%)
    • Negative for t(9;22)(q34;q11.2) and inv (16)

• **Cytogenetic Analysis:**
  – Unsuccessful due to no growth and low mitotic index

• Concurrent bone marrow and MRD flow cytometry were negative for PCM

Courtesy of Julie Priest
Case Summary

• **Morphology:**
  - Atypical infiltrates resembling monocyte-macrophage cells
  - Multiple locations (left gingiva, mediastinal lymph node, right perineum and liver)

• **Immunophenotype:**
  - Positive for CD68, CD163, lysozyme, CD43, MPO (subset)
  - Negative for CD34, CD117, S-100, Pan-CK, CD138 and CD56

• **Molecular Analysis:**
  - $t(14;16)(q32;q23)$ translocation; IgH and MAF genes
IgH rearrangement (Mediastinal LN)

FR1: 332 bp

FR2: 266 bp

FR3: 131 bp
## Genomic Studies (NGS)

<table>
<thead>
<tr>
<th>Bone marrow 2015</th>
<th>Gingival Lesion 2017</th>
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<tbody>
<tr>
<td><strong>IGH IGH-MAF rearrangement</strong></td>
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<tr>
<td><strong>CDKN2A/B loss</strong></td>
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<tr>
<td><strong>KRAS A146V</strong></td>
<td><strong>KRAS A146V</strong></td>
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<tr>
<td><strong>BRAF1 G469A, BRAF1 G466A</strong></td>
<td><strong>BRAF1 G469A</strong></td>
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<tr>
<td><strong>MAP3K6 Q943, truncation exon 22</strong></td>
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<tr>
<td><strong>TRAF3 R505</strong></td>
<td><strong>TNFAIP3 W85</strong></td>
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<tr>
<td><strong>PTPRO E379K</strong></td>
<td><strong>NF1 R2450</strong></td>
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<tr>
<td><strong>CCT6B splice site 615 2A&gt;G</strong></td>
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c-MAF Role in PCM Oncogenesis

- Located on chromosome 16q23.2
- Member of the AP-1 superfamily
  - Oncogene that is a bZIP transcription factor (Tf)
  - Other AP-1 Tfs include Fos and Jun
- Oncogenesis in PCM
  - MAF translocations are seen in ~5% of PCM, but ~50% of PCM demonstrate MAF overexpression
  - Regulated via post-translational modification (GSK3 and sumoylation)
Cell Transformation/Evolution

• Hematopoietic cells are derived from common precursors that as they differentiate, they become committed to a specific lineage

• However, cases have shown that two hematopoietic tumor populations can share identical genetic abnormalities but be phenotypically distinct\(^1\)
  – Clonal relationship
  – Lineage plasticity

Transdifferentiation

- Three mechanisms/pathways$^{2,3}$:
  1. Direct transdifferentiation
     a) Neoplastic cells differentiate into distinct phenotypic cells via epigenetics and genetics
  2. Two step de-differentiation
     a) Neoplastic cells de-differentiate into an earlier progenitor cell then regain the capability to re-differentiate along a different lineage
  3. Common progenitor cell
     a) Pluripotent neoplastic cell evolves into separate cell lineages at different times
     b) Retains a genotype or genotypic signature linked to the progenitor cell

Proposed Diagnosis
Myeloid sarcoma with monocytic differentiation and IGH-MAF gene rearrangement

Final Panel Diagnosis
Histiocytic sarcoma (with IGH-MAF), likely transdifferentiated from plasma cell myeloma (with IGH-MAF)