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)

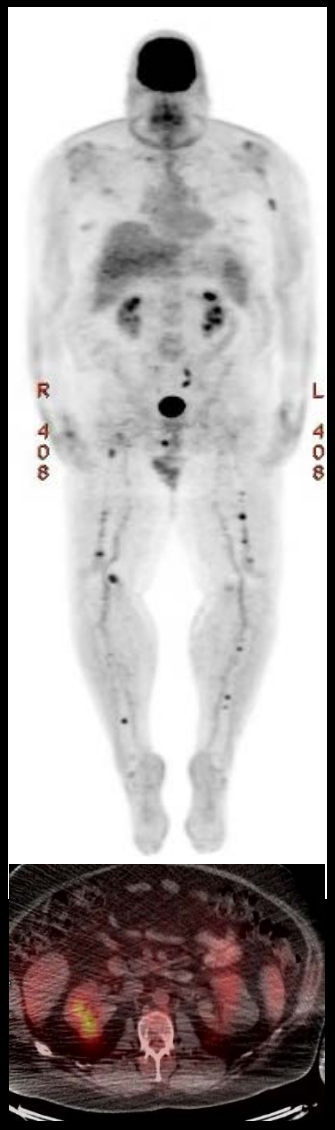
- Chemotherapeutic intervention included VD-PACE induction, PACMED cytoreduction and carfilzomib and melphalan-based autologous stem cell transplant

- 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

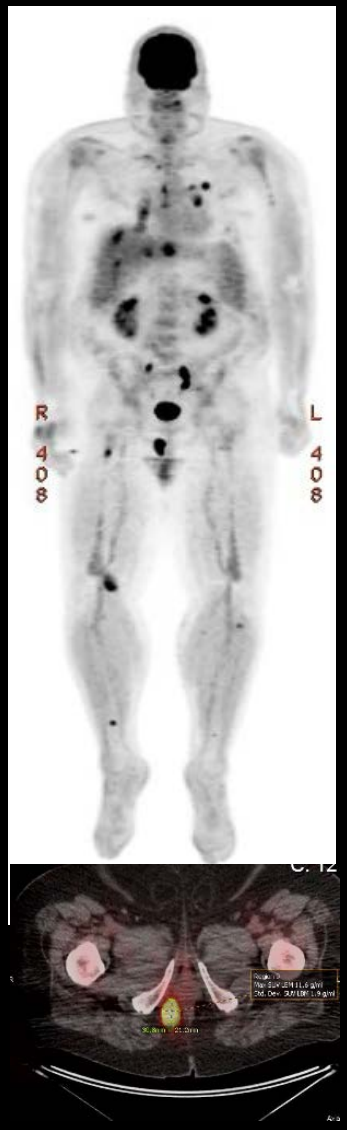
Imaging Studies and Physical Exam

- 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

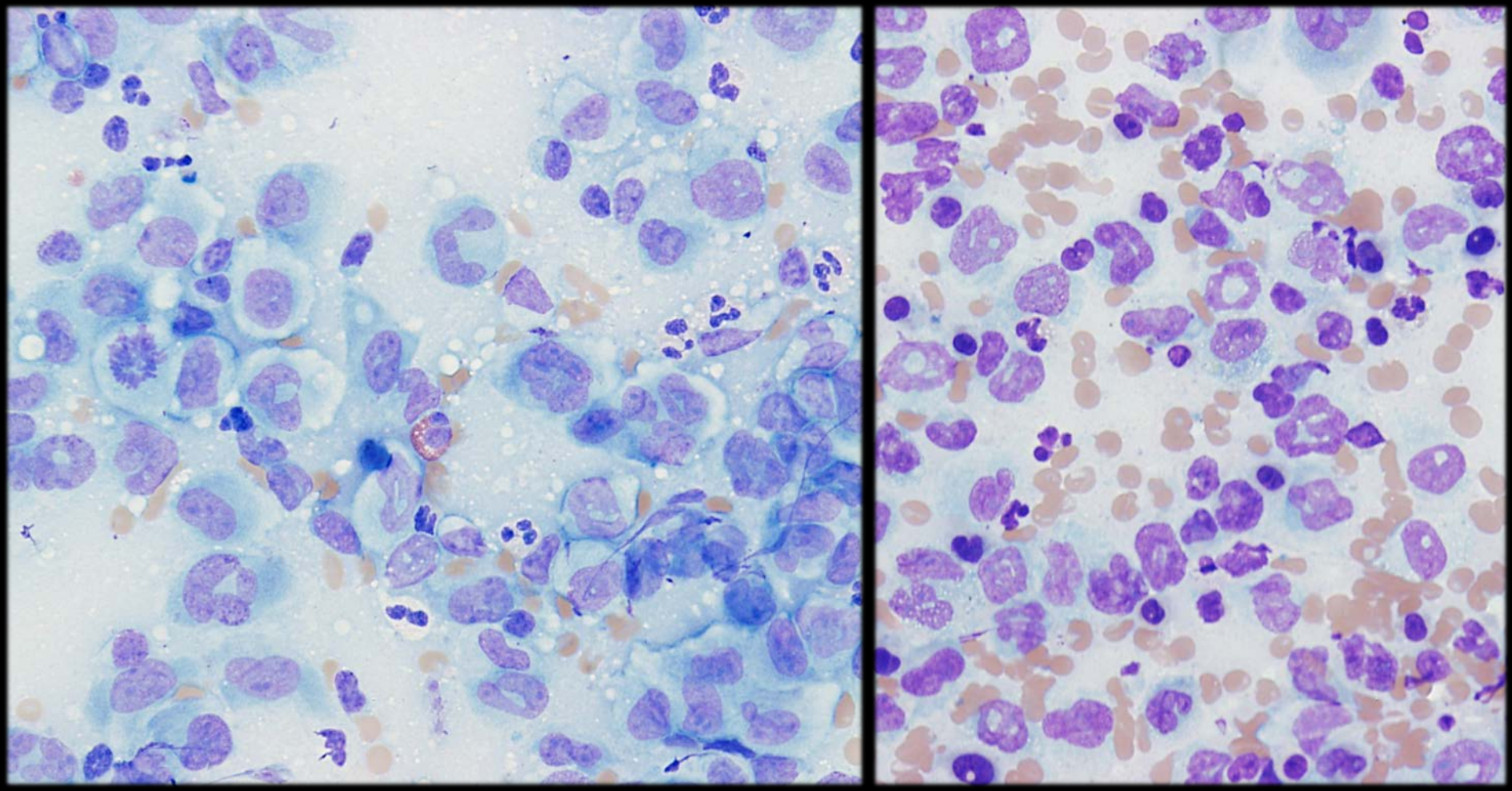


Nov 2016



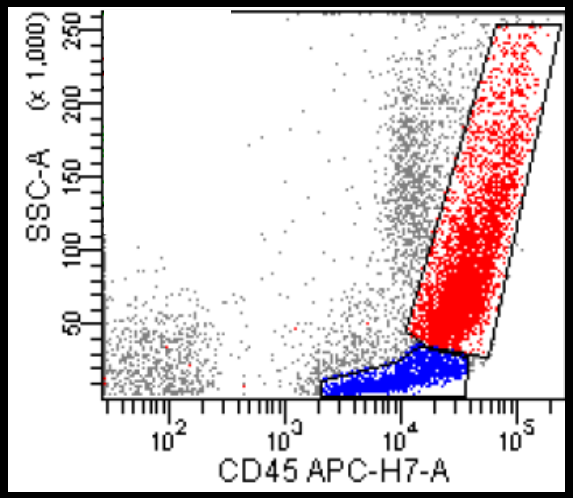
Jan 2017

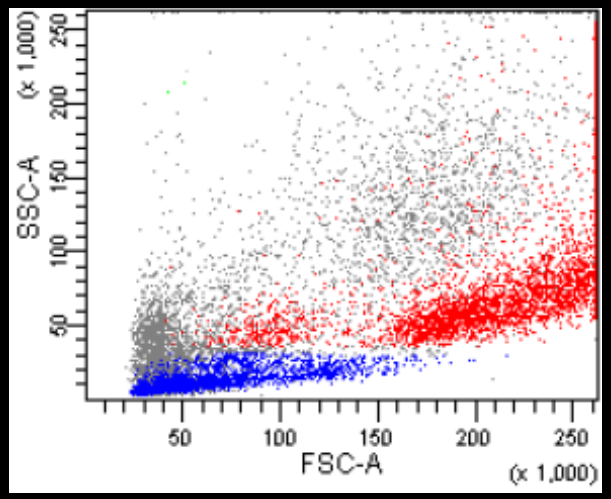
Mediastinal Lymph Node

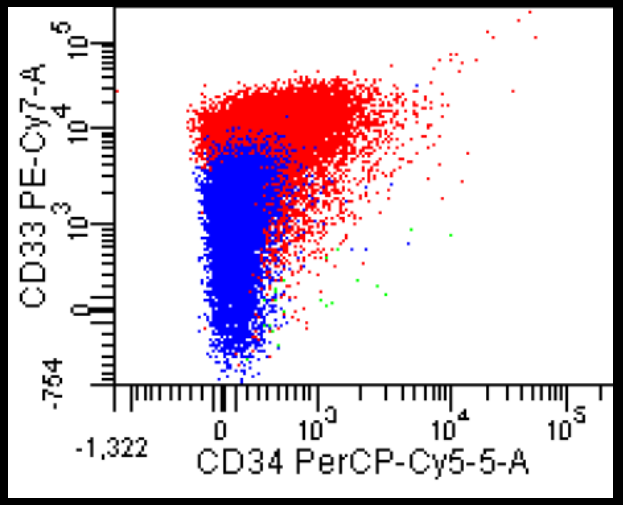


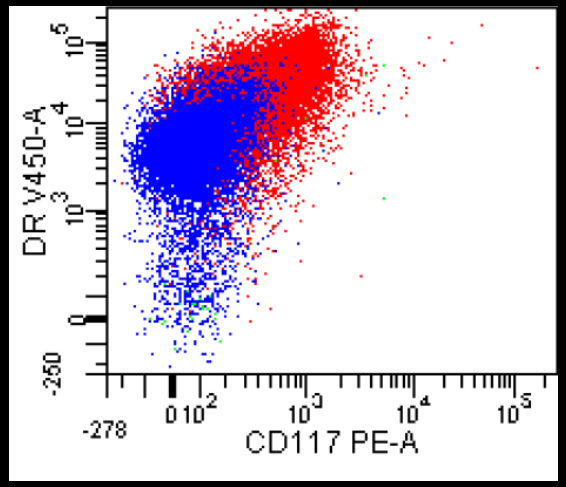
Diff-Quik preparation (×500): Large atypical cells with immature chromatin

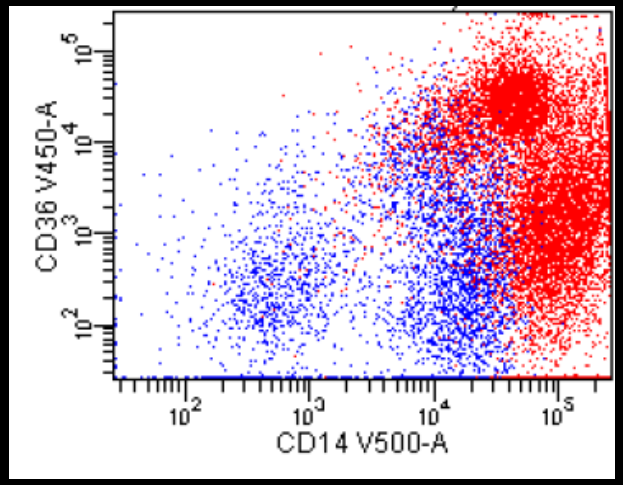
Flow Cytometric Analysis: Mediastinal lymph node

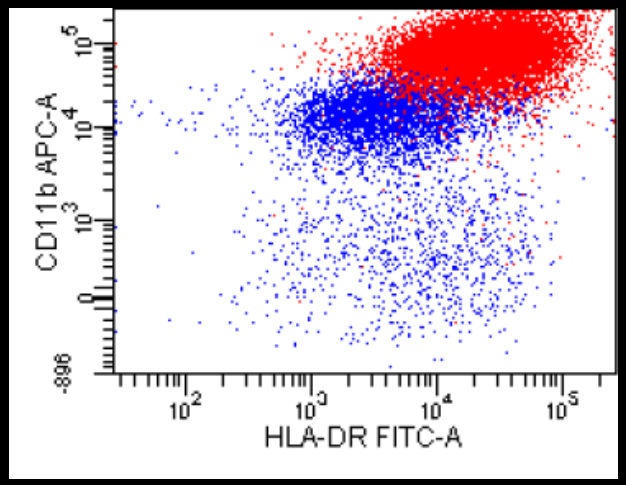






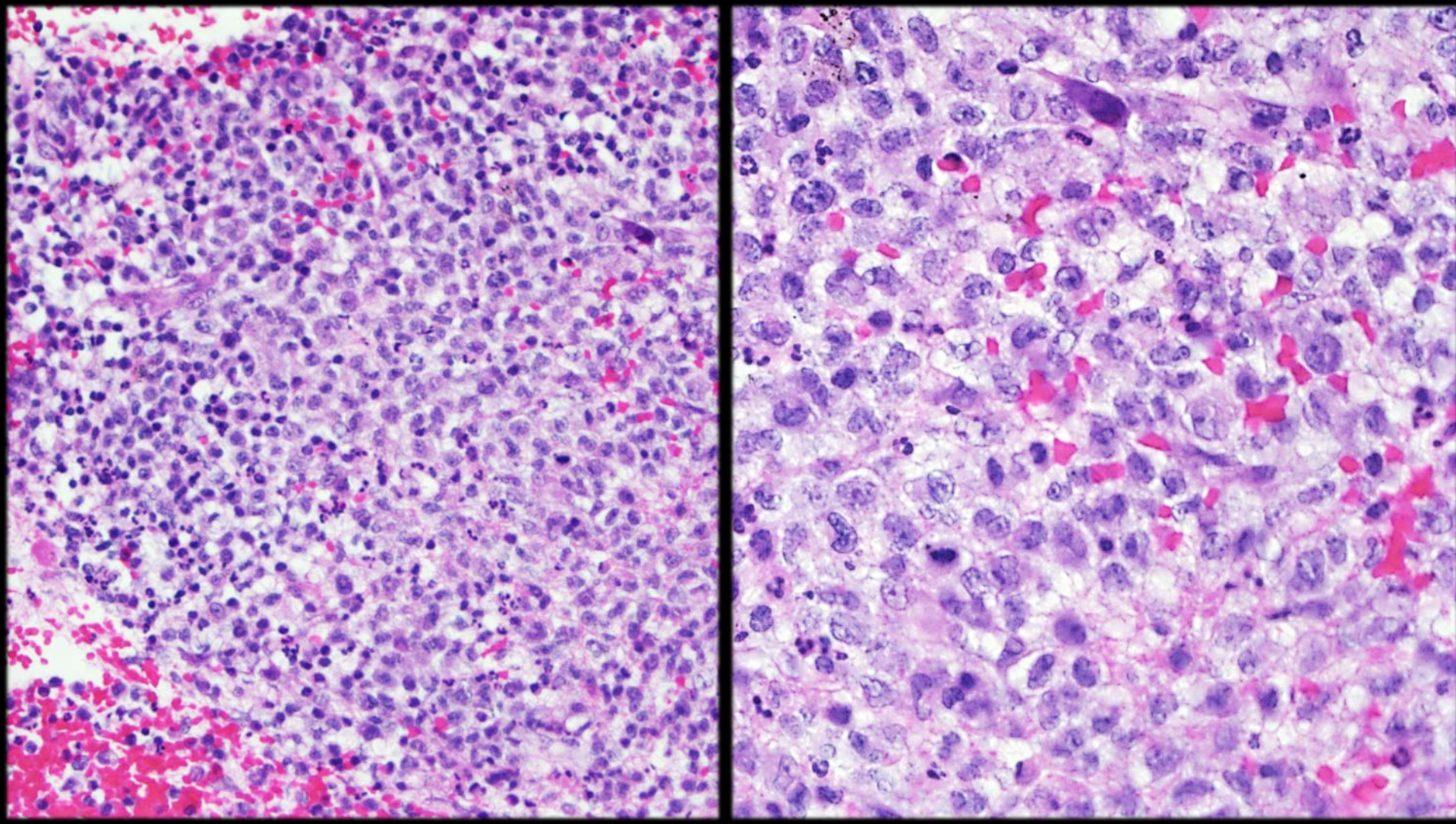






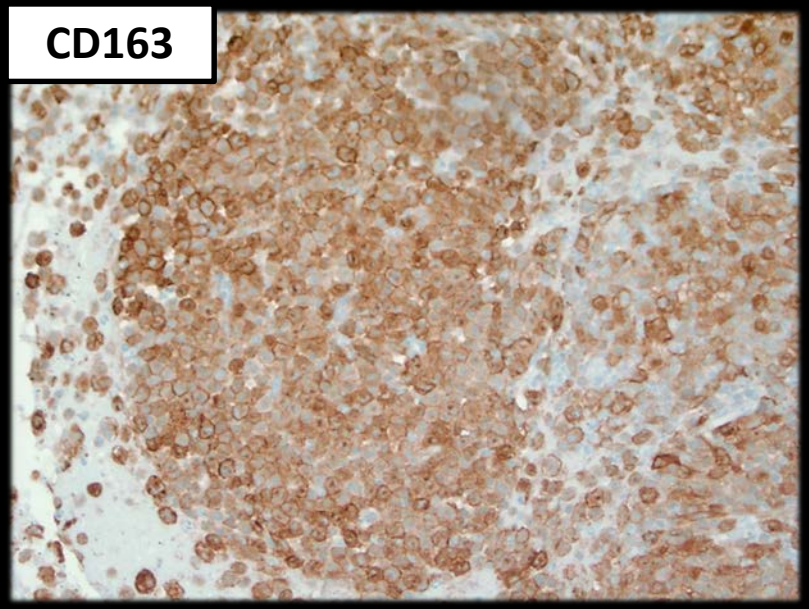
- CD45 vs side scatter identified a cell population in the monocyte region with high forward scatter comprising 40% of total events (red). This population was positive for CD33, HLA-DR, CD14 (bright), CD11b (bright), CD36 (variable) and negative for CD34 and CD117.
- A second population (21%; **blue**) with decreased forward and side scatter showed variable expression of CD33 and HLA-DR with dimmer CD11b and CD14.

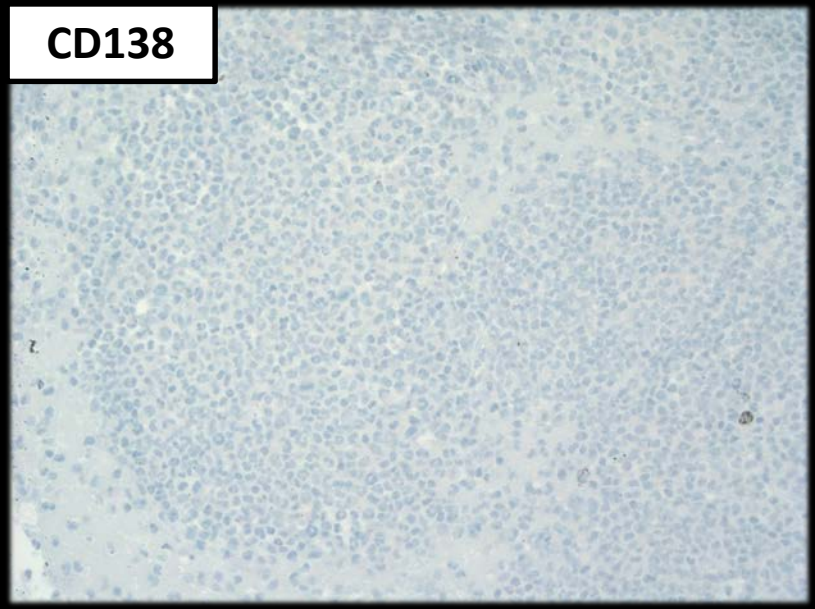
Mediastinal Lymph Node

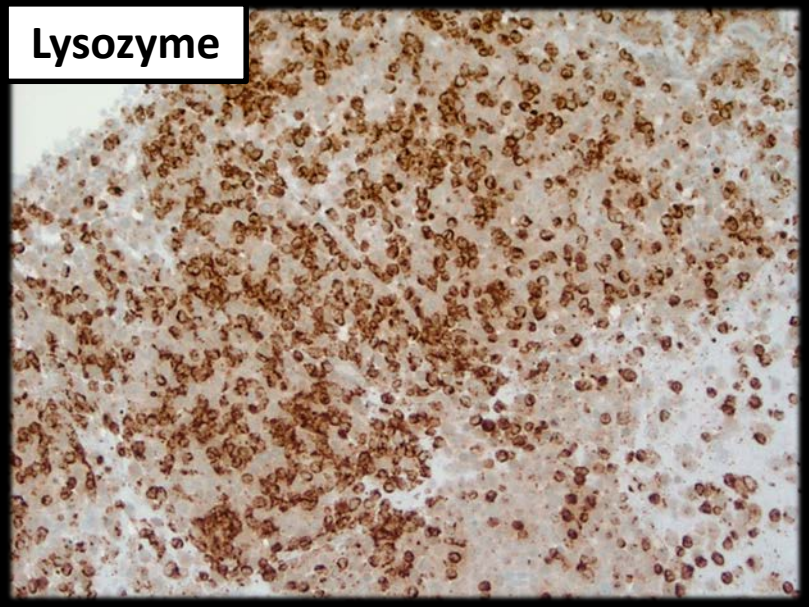


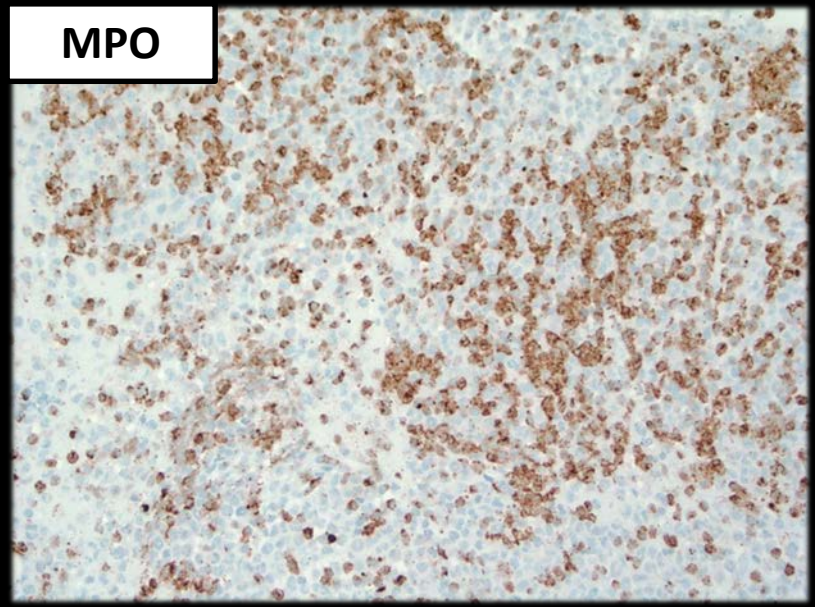
H&E stain (×40 and ×400): Aggregates of large atypical cells with rare intermingled granulocytes

Mediastinal Lymph Node: IHC

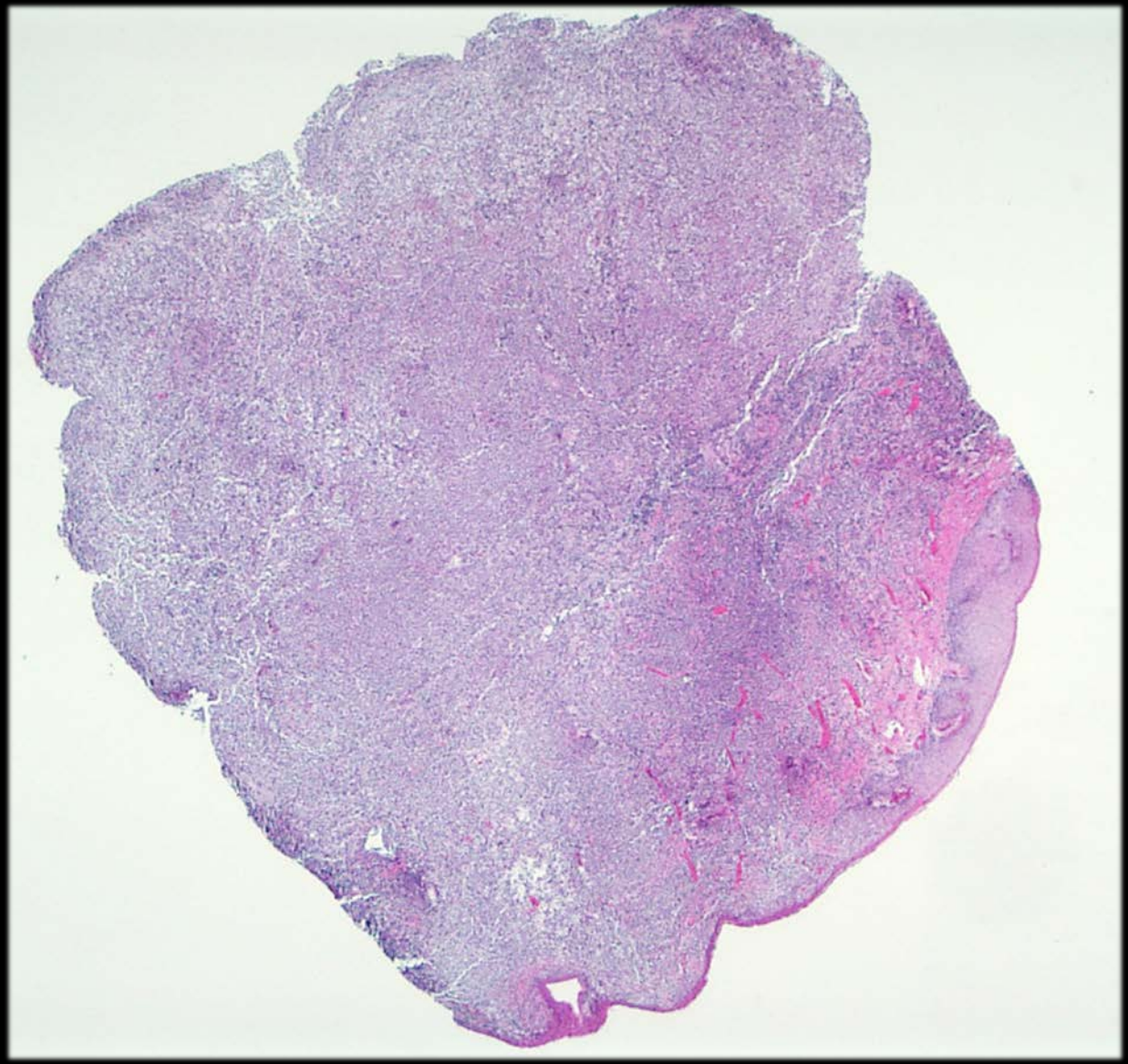






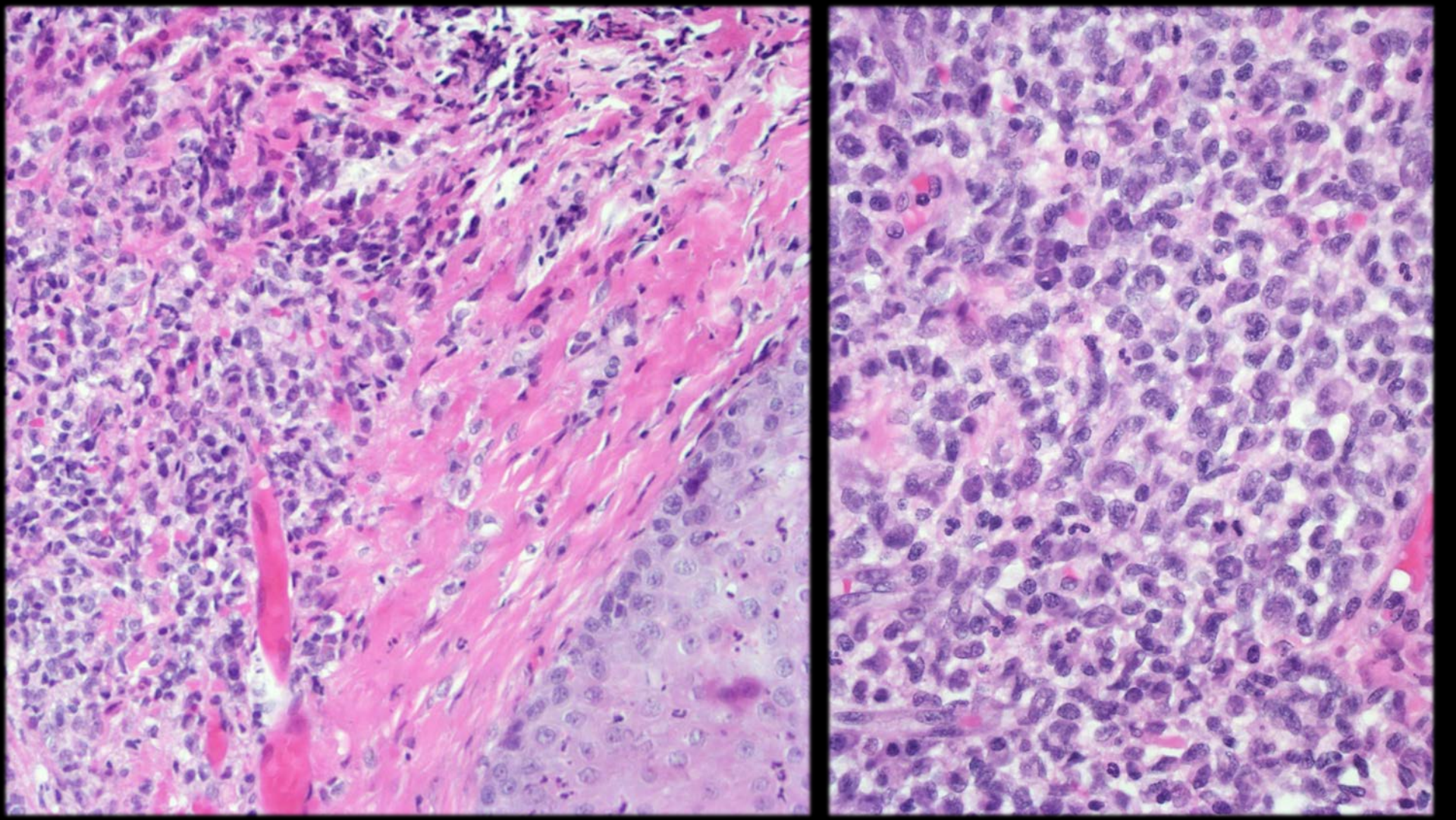


Left Gingival Biopsy



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

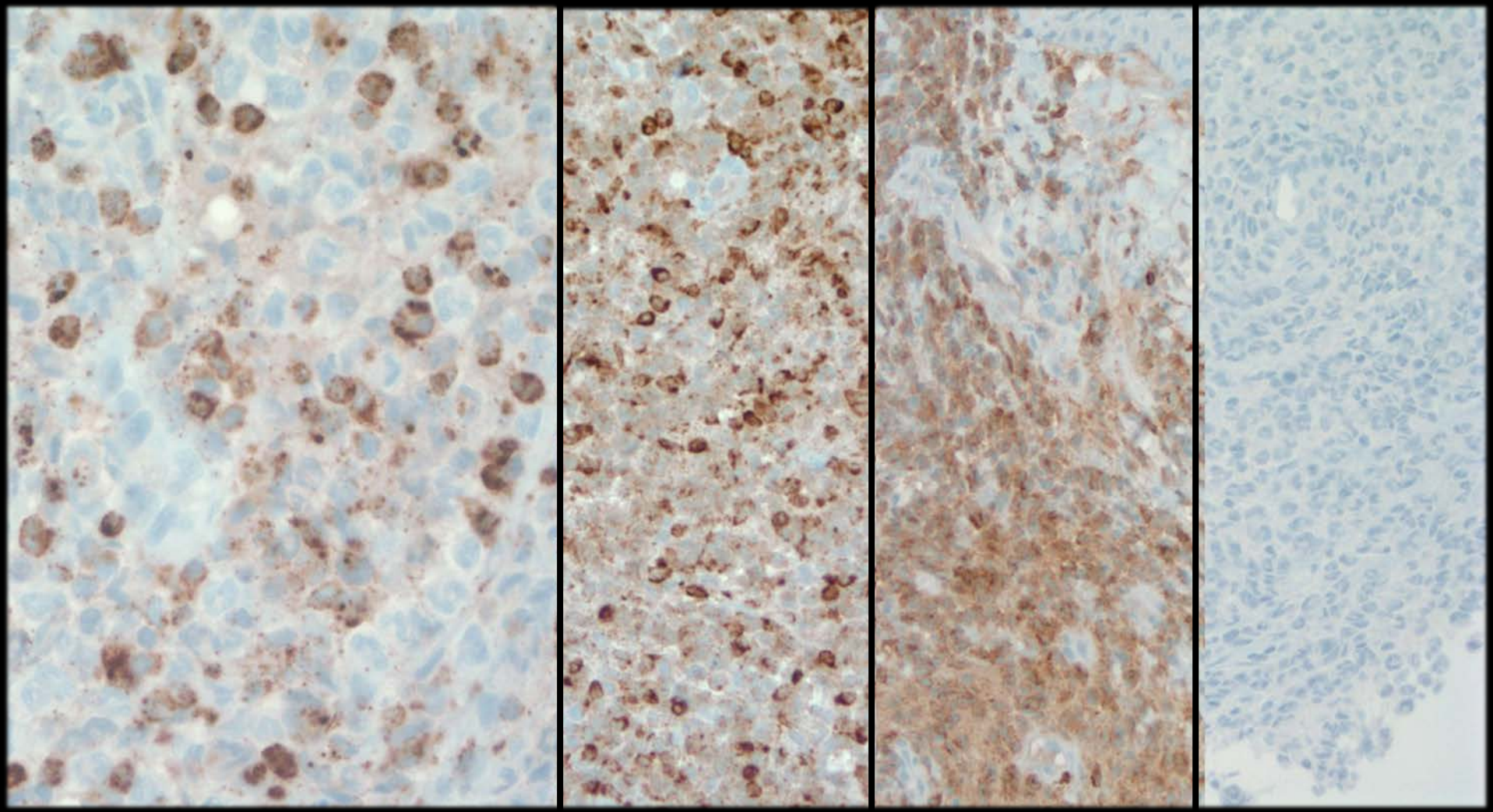
Left Gingival Biopsy



H&E stain (×200 left; ×400 right): Atypical cellular infiltrate within the dermis

Left Gingival Biopsy

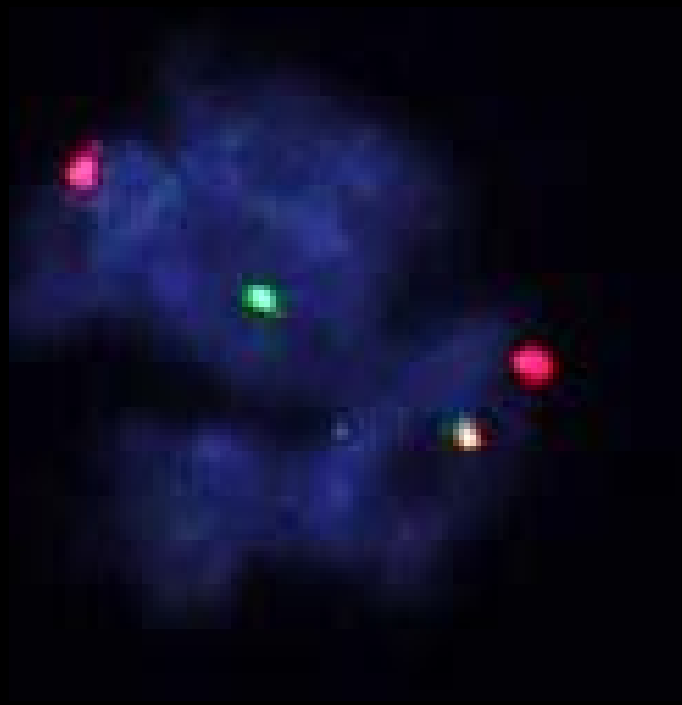
Immunohistochemical Stains



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**

MEDIASTINAL LYMPH NODE



FISH with dual color probes showing IGH (14q32; green) and MAF (16q23; red) gene rearrangement (pattern 2R1G1F)

Courtesy of Julie Priest

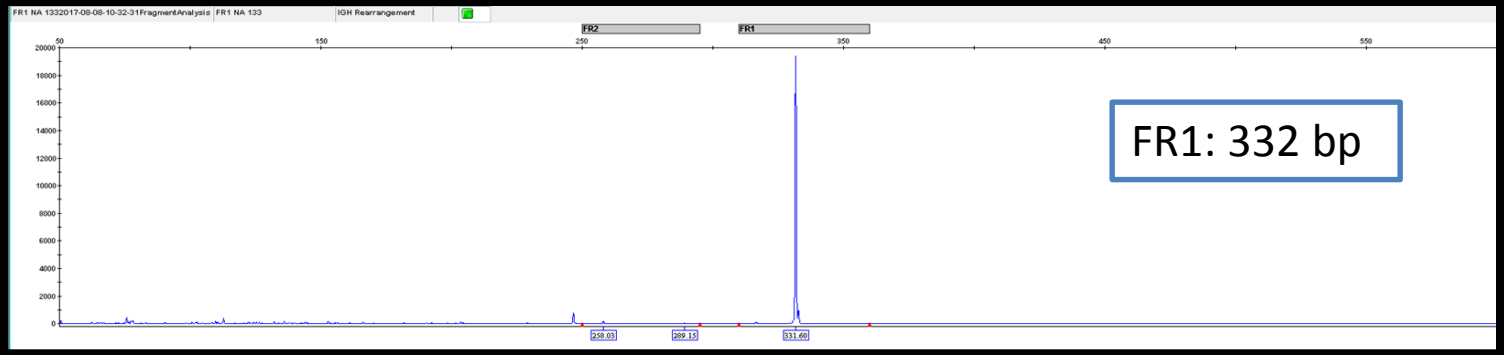
Case Summary

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

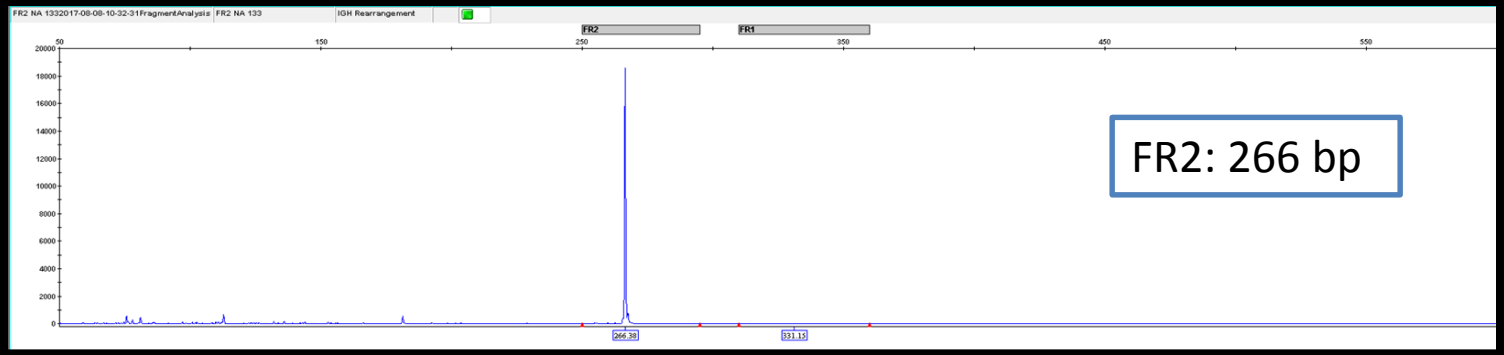
- **Immunophenotype:**
  - Positive for CD68, CD163, lysozyme, CD43, MPO (subset)
  - Negative for CD34, CD117, S-100, Pan-CK, CD138 and CD56

- **Molecular Analysis:**
  - t(14;16)(q32;q23) translocation; IgH and MAF genes

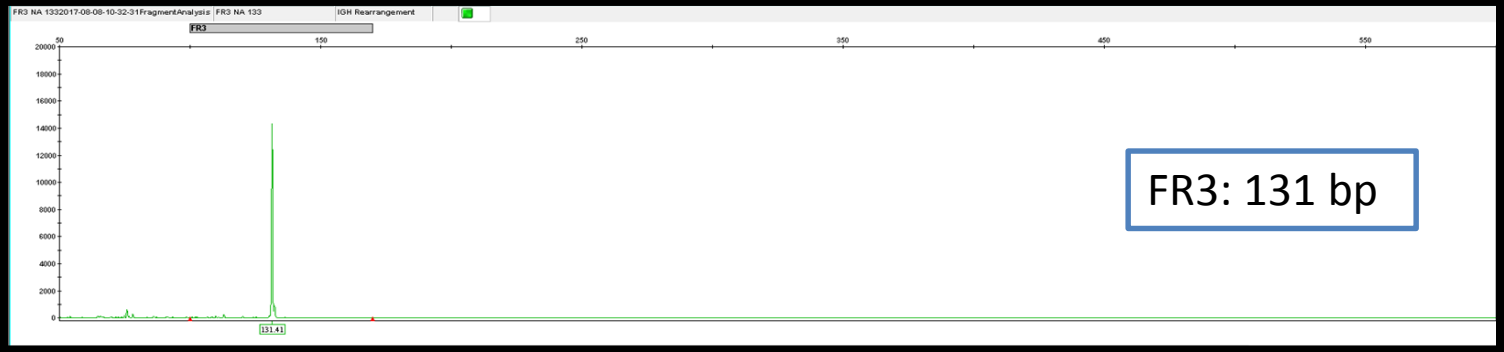
IgH rearrangement (Mediastinal LN)



FR1: 332 bp



FR2: 266 bp



FR3: 131 bp

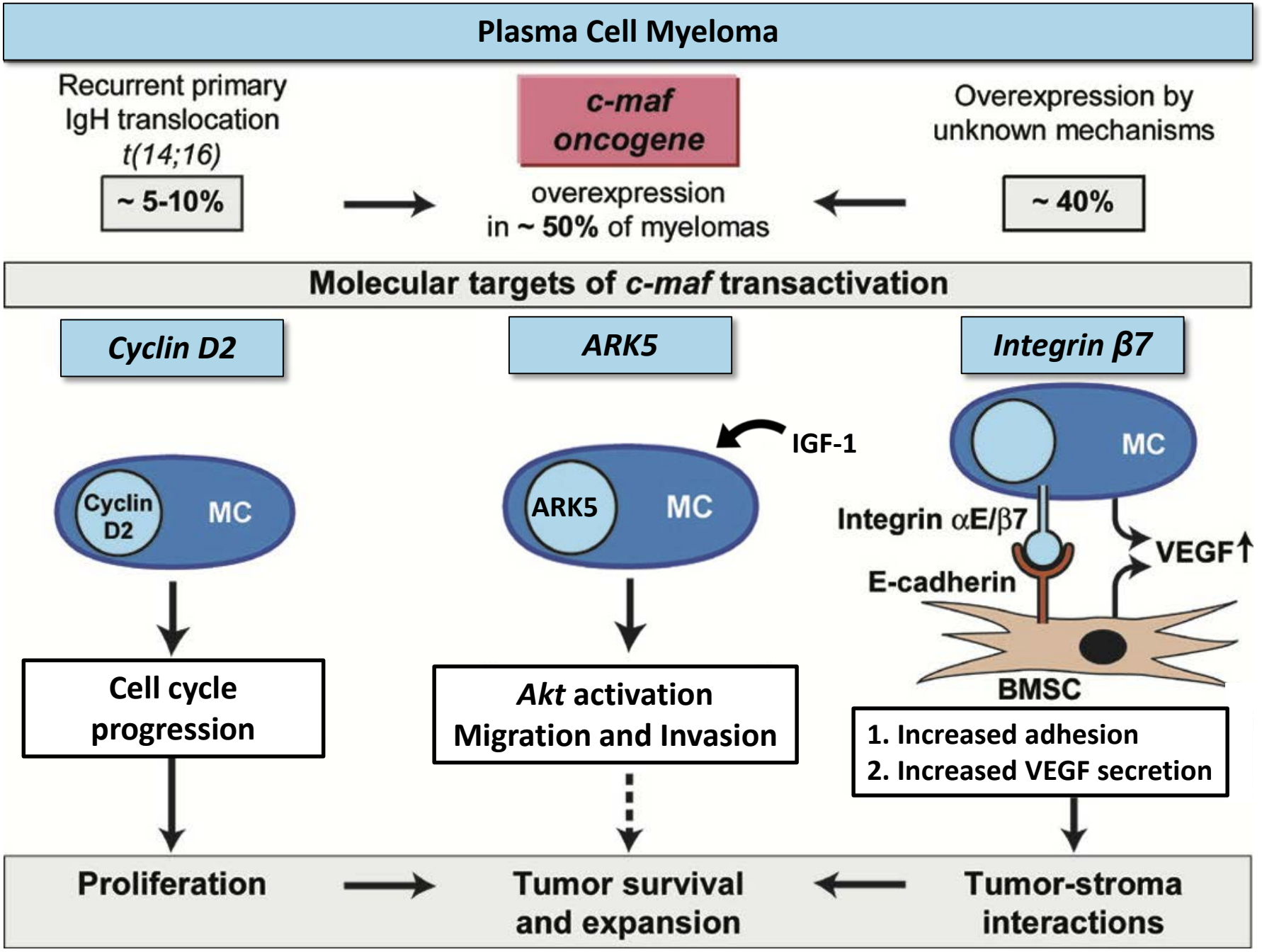
Courtesy of Stacie Delaune and Molly Robbins

Genomic Studies (NGS)

Bone marrow 2015	Gingival Lesion 2017
***IGH* IGH-MAF rearrangement**	***IGH* IGH-MAF rearrangement**
CDKN2A/B loss	***CDKN2A/B loss***
KRAS A146V	***KRAS A146V***
BRAF1 G469A, *BRAF1* G466A	***BRAF1* G469A**
***MAP3K6* Q943, truncation exon 22**	***MAP3K6* Q943, truncation intron 22**
TRAF3 R505	*TNFAIP3 W85*
PTPRO E379K	*NF1 R2450*
	CCT6B splice site 615 2A>G

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)



Kienast J, Berdel WE. *c-Maf* in multiple myeloma: an oncogene enhancing tumor-stroma interactions. *Cancer cell* (2004)
Pouponnot C, Rocques N, Eychene A. A new MAFia in cancer. *Nature Reviews Cancer* (2008)

Cell Transformation/Evolution

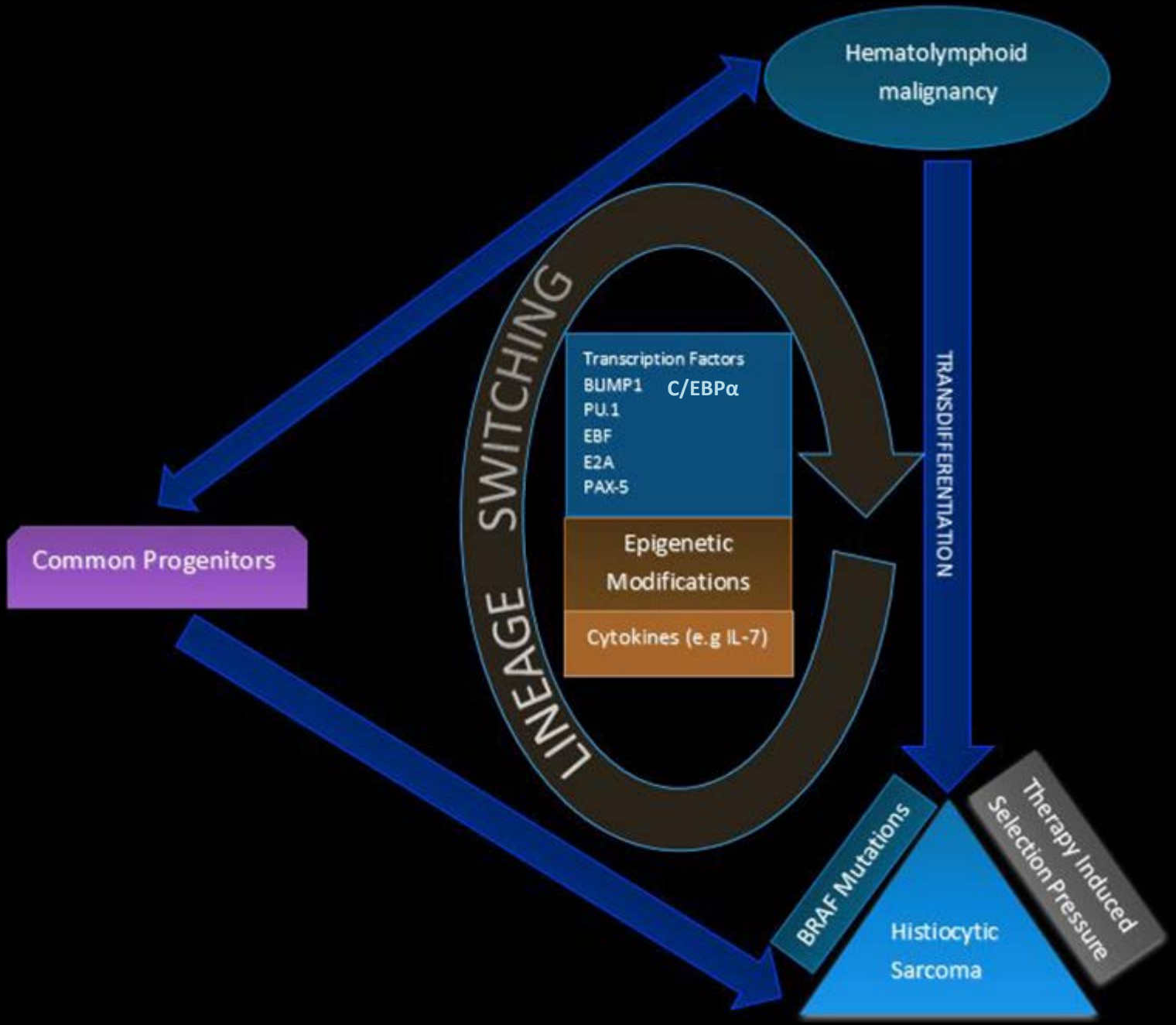
- Hematopoietic cells are derived from common precursors that as they differentiate, they become committed to a specific lineage
- However, cases have shown that two hematopoietic tumor populations can share identical genetic abnormalities but be phenotypically distinct[1]
  - Clonal relationship
  - Lineage plasticity

1. Feldman, A. L., Arber, D. A., Pittaluga, S., Martinez, A., Burke, J. S., Raffeld, M., Camos, M., Warnke, R., & Jaffe, E. S. Clonally related follicular lymphomas and histiocytic/dendritic cell sarcomas: evidence for transdifferentiation of the follicular lymphoma clone. *Blood,* (2008).

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 a 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

2. Ansari J *et al*. Histiocytic sarcoma as a secondary malignancy: pathobiology, diagnosis and treatment. *European J of Haematology* (2016).
3. Stoecker M, Wang E. Histiocytic/Dendritic cell transformation of B-Cell Neoplasms. *Arch Pathol Lab Med* (2013).



Ansari J *et al*. Histiocytic sarcoma as a secondary malignancy: pathobiology, diagnosis and treatment. *European J of Haematology* (2016).
Collombet S *et al*. Logical modeling of lymphoid and myeloid cell specification and transdifferentiation. *PNAS* (2017).

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*)