Comprehensive Molecular Profiling of an ALK-Negative, Anaplastic Large Cell Lymphoma with *DUSP22* rearrangement

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Clinical History

• 50 year old man with PMH of asthma, GERD, and Lyme disease 6 yrs ago
• Noted right submandibular mass while shaving
• First underwent FNA, then excisional biopsy
H&E 10X – 2.5cm Submandibular Mass
CD_{4} \quad \text{CD}_{8}
CD30  ALK-1
TIA-1  Ki-67
Summary of All Immunostains

• Positive for:
  - CD3, CD4, CD2, CD30 (Strong, diffuse), BCL-2 (weak), MUM-1, TCR-Beta

• Negative for:
  - CD20, CD8, CD5, CD7, CD10, CD56, ALK-1, TIA-1, Granzyme B, EMA, BCL-6, Cyclin D1

• EBV LMP-1 and EBER ISH are negative

• Ki-67 Proliferation index: >90%
**Cytogenetics/FISH Studies**

- *IRF*$_4$ gene rearrangement detected in 68% of the cells (100 cells analyzed)
- The findings are supportive of *DUSP22-IRF*$_4$ (6p25.3) gene rearrangement
Final Diagnosis

- Right Submandibular Lymph Node, Excision
  - Anaplastic Large Cell Lymphoma (ALCL), ALK-Negative, with $DUSP22$-rearrangement
Genetic Alterations in ALK-Negative ALCL

ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes

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- 22/73 (30% of cases) harbor DUSP22 (6p25.3) rearrangements
- 6/73 (8% of cases) harbor TP63 (3q28) rearrangements
- Mutually exclusive gene rearrangements
- Not found in ALK-Positive ALCL cases

“Doughnut cell” in *DUSP22*-rearranged ALCL

- *DUSP22*-rearranged ALCL are:
  - More likely to exhibit “Doughnut cell” morphology
  - Less likely to have pleomorphic cell
  - More likely to have sheet-like growth
  - Less likely to have admixed granulocytes or eosinophils

DUSP22-Rearranged ALCL are more likely to lack TIA1 and Granzyme B expression.

Survival Differences among ALCL subgroups


**Figure A:** Overall Survival by ALK Status
- ALK positive
- ALK negative

**Figure B:** Overall Survival by Genetic Subtype
- ALK
- DUSP22
- TP53
- **-/-**
P < 0.0001

**Figure C:** Overall Survival by Genetic Subtype, Non-transplanted Patients Only
- ALK
- DUSP22
- TP53
- **-/-**
P = 0.0025
Survival Differences among ALCL subgroups

Screening for *DUSP22*- and *TP63*-Rearranged ALCL

- **DUSP22-Rearranged ALCL**
  - Characteristic morphology (“Doughnut cell”, sheet-like growth pattern)
  - Tend to lack TIA1 and Granzyme B expression by IHC
  - FISH for *DUSP22-IRF4* (6p25.3)

- **TP63-Rearranged ALCL**
  - Overexpression of p63 by IHC
  - FISH for *TP63* (3q28)
  - RNA sequencing for fusion detection
Back to our Case - Molecular Findings

- Hybridization-capture based assay, targeting 400 genes, sequencing on an Illumina HiSeq2500 instrument
- Patient’s Nail DNA was used as Matched Normal control to filter out germline variants.

- Mean Overall Coverage: 1089X
- Variants detected:
  1. **CARD11** (NM_032415) exon5 **p.K215del** (c.645_647delGAA) (136/1523 reads, VAF=0.09)
  2. **CARD11** (NM_032415) exon6 **p.K254N** (c.762G>T) (90/1209 reads, VAF=0.07)
  3. **GRIN2A** (NM_001134407) exon13 **p.F1135C** (c.3404T>G) (304/1426 reads, VAF=0.21)
  4. **PIK3R1** (NM_181523) exon15 splicing variant **p.X662_splice** (c.1985+2T>C) (138/638 reads, VAF=0.22)

CARD11 is linked to both B- and T-cell receptor Signaling

NF-κB Pathway Activation

Case Follow-up

- Diagnosed with Stage III disease (>1 extranodal site), IPI score of 1
- Bone marrow: No evidence of lymphoma involvement
- Underwent CHOEP X 4 cycles
- Complete Response (CR) by PET/CT
- Patient was offered consolidation therapy with autologous stem cell transplant.

- However, since *DUSP22*-rearranged ALK-Negative ALCL has better prognosis than other ALK-Negative ALCL cases, the patient decided that he would hold off undergoing marrow transplant.
Final Panel Diagnosis

- Right Submandibular Lymph Node, Excision
  - Anaplastic Large Cell Lymphoma (ALCL), ALK-Negative, with $DUSP_{22}$-rearrangement
Thank You


