t(14;18) Negative Follicular Lymphoma with 1p36 abnormality associated with In Situ Follicular Neoplasia with t(14;18) translocation

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Clinical History

- May 2013
  - 35 y/o female presented with a painless mass in her right groin.
  - No c/o fever, night sweats or unexplained weight loss
- Laboratory Findings:
  - CBC (WBC: 6.6 K/ul; Hgb: 13.3 g/dl; Hct: 37.3%; MCV: 93 fl; Platelet: 359 K/ul)
  - LDH: 188 U/L
Localized mass: Right Groin: 3.5 x 2.4 cm; SUV: 4
Lymph node excision and bone marrow biopsy were performed.

**Diagnosis:** At outside institute
- **Lymph node:** Marginal zone lymphoma
- **Bone marrow:** No morphologic or immunophenotypic evidence of Lymphoma

**Clinical Stage 1A**

We received slides for consultation at MSKCC.
H&E: Area with Follicular Lymphoma, In Situ Follicular Neoplasia and Reactive Follicles

- Follicular Lymphoma
- In Situ Follicular Neoplasia
- Reactive follicles
Morphologic and immunohistochemical features of Follicular Lymphoma and In Situ Follicular Neoplasia

H&E section shows FL with diffuse areas on right, ISFN (center) and reactive follicles on left (20x)
Follicular Lymphoma: Diffuse Growth Pattern
Morphologic and immunohistochemical features of Follicular Lymphoma (FL)

- H&E
- CD20
- CD10
- BCL2
- CD23
- BCL6
- Ki67

FISH studies using BCL2 Break apart probe: Negative for BCL2 gene rearrangement
Morphologic and immunohistochemical features of In Situ Follicular Neoplasia (ISFN)

FISH studies using BCL2 Breakapart probe: Positive for BCL2 gene rearrangement
Genetic Studies

- SNP (Single Nucleotide Polymorphism) array analysis

1. Copy Neutral – Loss of Heterozygosity (CN-LOH) in 1p35.1p36.33 that harbors TNFRSF14 gene
2. Coexistence of Copy Neutral – Loss of Heterozygosity (CN-LOH) in 16p involving CREBBP gene
Two mutations were detected in this patient:

1. **TNFRSF14 p.Q158* (A change in nucleotide resulting in a premature stop codon), variant frequency 27.9%**

2. **CREBBP p.S1436R (Missense mutation), variant frequency 29.5%**

Patient’s normal control (blood) is also sequenced to filter germline variant.
## Summary of Findings

<table>
<thead>
<tr>
<th></th>
<th>Follicular Lymphoma Diffuse Growth Pattern</th>
<th>In situ Follicular Neoplasia (ISFN)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immunostains</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD20</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>BCL2</td>
<td>Weak to negative</td>
<td>Strong</td>
</tr>
<tr>
<td>CD10</td>
<td>Dim</td>
<td>Strong</td>
</tr>
<tr>
<td>BCL6</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>CD23</td>
<td>Strong</td>
<td>Negative</td>
</tr>
<tr>
<td><strong>Cytogenetic Studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCL2 gene rearrangement</td>
<td>Not detected</td>
<td>Detected (57% of the cells)</td>
</tr>
<tr>
<td>SNP array analysis</td>
<td>Detected (CN- LOH in chromosome 1p35.1p36.33 and 16p)</td>
<td>??</td>
</tr>
<tr>
<td><strong>Comprehensive Genomic Analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNFRSF14 p.Q158*</td>
<td>??</td>
<td></td>
</tr>
<tr>
<td>CREBBP p.S1436R</td>
<td>??</td>
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</tbody>
</table>
Diagnosis

- t(14;18) Negative Follicular Lymphoma with 1p36 abnormality associated with In Situ Follicular Neoplasia with t(14;18) Translocation

Follow Up

- Patient was treated with 24 Gy of involved field radiation therapy (IFRT), completed in August 2013.
- CT scan after treatment- August 2013

Follow up examination showed no clinical or radiological evidence of disease- Complete remission after 45 months
In Situ Follicular Neoplasia (ISFN)

(1) How should in situ follicular neoplasia be defined and diagnosed?
(2) Is in situ neoplasia an early step of lymphomagenesis?
(3) How should patients with in situ neoplasia be managed
   ▪ “in situ” follicular neoplasia without overt lymphoma:
     ▪ No evidence for starting therapy: “wait-and-watch policy” is strongly suggested.
   ▪ For patients with concomitant overt lymphoma:
     ▪ Staging and treatment: based on malignant counterpart.
t(14;18) Negative Follicular lymphoma with Diffuse Growth Pattern

- Presents as large, localized tumors in inguinal region
- Diffuse growth pattern
- CD20, BCL2 (dim to negative), CD10 (dim), BCL6 with CD23 co-expression
- Lacks BCL2 gene rearrangement
- Deletion in the terminal parts of the short arm of chromosome 1 (1p36).
- Low clinical stage, indolent disease
MSKCC t(14;18) Negative Inguinal/ Groin Follicular Lymphoma

- Inguinal/ groin FL cases were retrieved from archives of Department of Hematopathology at MSKCC
- Morphologic and immunohistochemical stains were reviewed.
- FFPE inguinal/ groin follicular lymphoma tissue samples were analyzed by BCL2-rearrangement FISH assay (Abbott molecular).
- Genomic DNAs extracted from FFPE tumor material were used for copy number and allelic imbalance analysis by SNP-array (OncoScan, Affymetrix).
<table>
<thead>
<tr>
<th>Case No.</th>
<th>FISH studies: BCL2 gene rearrangement</th>
<th>SNP array analysis: Chromosome 1p</th>
<th>SNP array analysis: Chromosome 16p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Negative</td>
<td>CN-LOH of 1p</td>
<td>CN-LOH of 16p12.1-ter</td>
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<tr>
<td>2</td>
<td>Negative</td>
<td>CN-LOH of 1p36.23-ter</td>
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<tr>
<td>3</td>
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<td>CN-LOH of 1p36.31-ter</td>
<td>CN-LOH of 16p13.13-ter</td>
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<td>4</td>
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<td>CN-LOH of 1p35.2-ter</td>
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<tr>
<td>5</td>
<td>Negative</td>
<td>CN-LOH of 1p36.11-ter</td>
<td>CN-LOH of 16p11.3-ter</td>
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<td>6</td>
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<td>CN-LOH of 1p36.11-ter</td>
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<tr>
<td>7</td>
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<td>del of 1p36.33-36.32 (2.7 Mb)</td>
<td>CN-LOH of 16p11.2-ter</td>
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<tr>
<td>8</td>
<td>Negative</td>
<td>CN-LOH of 1p35.2-ter</td>
<td>CN-LOH of 16p11.2-ter</td>
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<tr>
<td>9</td>
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<td>CN-LOH of 1p36</td>
<td>CN-LOH of 16p13.3-p13.11</td>
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<tr>
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<tr>
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<td>CN-LOH of 16p13.13-ter</td>
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<td>16</td>
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<tr>
<td>17</td>
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<td>deletion of 1p35.1-ter</td>
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<tr>
<td></td>
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<td>Focal homozygous deletion of</td>
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<tr>
<td></td>
<td></td>
<td>TNFRSF14</td>
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<tr>
<td>18</td>
<td>Negative</td>
<td>-</td>
<td>CN-LOH of 16p13.13-ter</td>
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</tbody>
</table>
Cell Biology of TNFRSF14/HVEM: 1p36 Follicular Lymphoma

Disruption of the HVEM-BTLA axis in lymphoma

- HVEM
- BTLA
- BCR activation
- LTα/LTβ/TNFα
- FDC/FRC
- CXCL13/CCL19
- IL4/IL21
- Tfh cell

CAR-T cells engineered to secrete soluble HVEM for lymphoma treatment

- CD19
- solHVEM
- CAR-T cell
- aCD19
- B cell
- BTα

Diagram representing the concept of CAR-T cells that produce solHVEM locally and continuously at the lymphoma site in vivo.

Take home message: Inguinal/Groin Follicular Lymphoma with 1p36 abnormality

1. Clinical features
   - Isolated large inguinal/groin mass

2. Phenotype
   - CD20, BCL2 (dim to negative), CD10 (dim), BCL6 with CD23 coexpression

3. Molecular work up
   - FISH Studies: BCL2 gene rearrangement
   - SNP Array: Deletion or CN-LOH in chromosome 1p36
     - SNP array, not FISH would be the test of choice for this aberration.
   - Comprehensive Genomic Analysis: TNFRSF14 gene mutation
Final Panel Diagnosis

\[ t(14;18) \] Negative Follicular Lymphoma with 1p36 deletion
Thank You