Anaplastic Large Cell Lymphoma (of T cell lineage)
Definition

- T-cell lymphoma comprised of large cells with abundant cytoplasm and pleomorphic, often horseshoe-shaped nuclei
- CD30+
- Most express cytotoxic granule-associated proteins
- Majority are positive for ALK.
- WHO 2008: ALCL, ALK-pos, and ALCL, ALK-neg
Epidemiology

• 3% of adult non-Hodgkin lymphomas

• 10-30% of childhood lymphomas
  – ALK-positive ALCL most frequent in first three decades
  – Male:Female (first three decades) = 1.5:1

• ALK-negative ALCL in older individuals
  – Male:Female = 0.9:1
Etiology

- Not known
Sites of Involvement

- **ALK-positive ALCL** frequently involves lymph nodes and extranodal sites
  - Skin (21%)
  - Bone (17%)
  - Soft tissues (17%)
  - Lung (11%)
  - Liver (8%)

- **Bone marrow**
  - 10% by routine H&E
  - 30% with CD30, EMA and/or ALK

- **Extranodal involvement by ALK-negative ALCL** is less frequent.
Clinical Features

• 70% show advanced stage III or IV disease
  – Peripheral and/or abdominal LAD
  – Extranodal sites
  – Bone marrow involvement

• 75% B-symptoms, especially fever
Morphology

• Broad morphologic spectrum
• All cases contain a variable proportion of hallmark cells
  – Horse-shoe or kidney-shaped nuclei
  – Eosinophilic region near the indented nucleus
• Nuclear cytoplasmic inclusions (invagination of nuclear membrane): “doughnut cells”
• Abundant cytoplasm
  – Clear, basophilic or eosinophilic
• Multinucleated wreath-like or Reed-Sternberg cells
Morphology

- Nuclei
  - Finely clumped or dispersed chromatin
  - Multiple, small basophilic nucleoli
Morphology

- Sinusoidal distribution
  - Resembling metastatic tumour
- Paracortical colonization
- Cohesive sheets
Morphology

- Cytologic variants
  - Common
  - Lymphohistiocytic
  - Small cell
- 10% may have more than one variant
- Relapses may look morphologically like a different variant
ALCL, Common Variant

• 70% of cases
• Pleomorphic large cells
  – Hallmark features
• Admixed monomorphic, round cells
  – May be the prominent population
ALCL, common variant
ALCL, Lymphohisitocytic variant

- 10% of cases
- Tumor cells admixed/masked with large numbers of histiocytes
  - Clustering of tumor cells around vessels
  - Erythrophagocytosis
ALCL, Small Cell Variant

- 5-10% of cases
- Small to medium-sized cells with irregular nuclei
- Hallmark cells (often clustered around vessels)
- Often misdiagnosed as PTCL, unspecified
- May involve peripheral blood as flower-like cells (mimicking ATCLL)

CD30
Other ALCL Variants

- Pleomorphic giant cells
- Monomorphic large cells
- Sarcomatous
- Signet ring cells
- Rare cases with myxomatosus stroma and fibroblasts, or capsular thickening and nodular fibrosis (mimicking cHL, NS)
Other Histologic Patterns of ALCL

- Monomorphic large cells
- Pleomorphic giant cells
- Signet-ring cells
- Sarcomatous
### Differential DX: Immunostains

<table>
<thead>
<tr>
<th>Lymphoma Type</th>
<th>Immunostains</th>
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<tbody>
<tr>
<td><strong>NLPHL</strong></td>
<td>CD45+ CD20+ CD15- CD30- EMA+</td>
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<tr>
<td><strong>CHL</strong></td>
<td>CD45- CD15+ CD30+ PAX5+</td>
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<tr>
<td><strong>ALCL</strong></td>
<td>CD45+ CD20- CD3- CD4+ CD30+ ALK+ EMA+</td>
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<tr>
<td><strong>DLBCL</strong></td>
<td>CD45+ CD20+ CD3- CD30+/-</td>
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ALCL: Immunophenotype

- CD30 positive
  - Membrane plus golgi
  - Strongest in largest cells
- ALK expression detected in 60-85% (ALCL, ALK pos)
- EMA (+) in majority
- Positive for T-cell Antigens
  - Rarely null phenotype
    - Evidence for T-cell phenotype at molecular level
  - CD3 negative in 75% of cases
  - CD5 and CD7 more often negative
  - CD2 and CD4 more often positive
  - CD8 usually negative
Anaplastic Large Cell Lymphoma
Immunophenotype (cont.)

- Most positive for TIA1, granzyme B or perforin
- CD43 in 2/3 of cases
  - Lack lineage specificity
- Variably positive for CD45
- CD15 rarely positive
  - Only in small proportion of cells
- Negative for EBV
- Clusterin pos. (absent in C-ALCL)
Enzyme Cytochemistry

- Acid phosphatase and NSE positive
  - Strong perinuclear activity
Genetics

- 90% of ALCL show clonal TCR rearrangements
ALK

- ALK positivity relatively specific for ALCL
  - Rarely seen in other tumors (all lacking CD30)
    - Rare DLBCL
      - Cytoplasmic IgA
      - Immunoblastic/plasmablastic morphology
    - Rhabdomyosarcoma
    - Inflammatory myofibroblastic tumors (IMT)
ALK

• Encodes a tyrosine kinase receptor of the insulin receptor family
ALK Staining Patterns

- **t(2;5) (p23;q35)**
  - 70-80%
  - Cytoplasmic and nuclear
  - Fusion NPM-ALK protein
  - Results from the fusion of ALK gene (normally transmembrane) on Chr 2 with nucleophosmin (nuclear transport protein) gene on Chr 5.
ALK Staining Patterns

• t(1;2) (q25;p23)
  – Tropomyosin 3/ALK
  – 10-20%
  – Cytoplasmic
Other Translocations Involving ALK

- \( t(2;3)(p23;q35) \)
  - Cytoplasmic, diffuse
  - 2-5%
  - TFG/ALK
Other Translocations Involving ALK

- Inv(2)(p23 q35)
  - 2-5%
  - Cytoplasmic, diffuse
  - ATIC/ALK gene
    - ATIC gene plays a role in *de novo* purine biosynthesis
Other Translocations Involving ALK

- t(2;17)
  - Cytoplasmic, granular
  - 2-5%
  - CLTC/ALK
  - CLTC (clathrin heavy polypetide)
    - Structural protein of coated vesicles
ALK-negative ALCL

- ALK-negative ALCL
  - Larger and more pleomorphic cells
  - More prominent nucleoli
  - ALK-negative ALCL a separate entity?
  - A final common pathway in diverse T-cell malignancies?
    - Morphologic features (and CD30-positivity) seen as a secondary phenomenon in other T-cell lymphomas
    - Currently a provisional entity in WHO 2008

- A difficult diagnosis to make, no help with molecular testing -> most pathologists would report as PTCL, NOS
- Also important to rule out primary cutaneous ALCL with clinical information
Postulated Cell of Origin

• Activated mature cytotoxic T-cell
Prognosis and Predictive Factors

- IPI has some predictive value
- ALK-positivity most important for favorable prognosis (sensitivity to Adriamycin)
  - Irrespective of translocation
- Overall 5-year survival in ALK-positive ALCL = 80% except for small cell variant due to disseminated disease
- 5-year survival in ALK-negative ALCL = 40%
- Relapses uncommon (30%)
  - Usually remaining sensitive to therapy; BMT for refractory cases