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

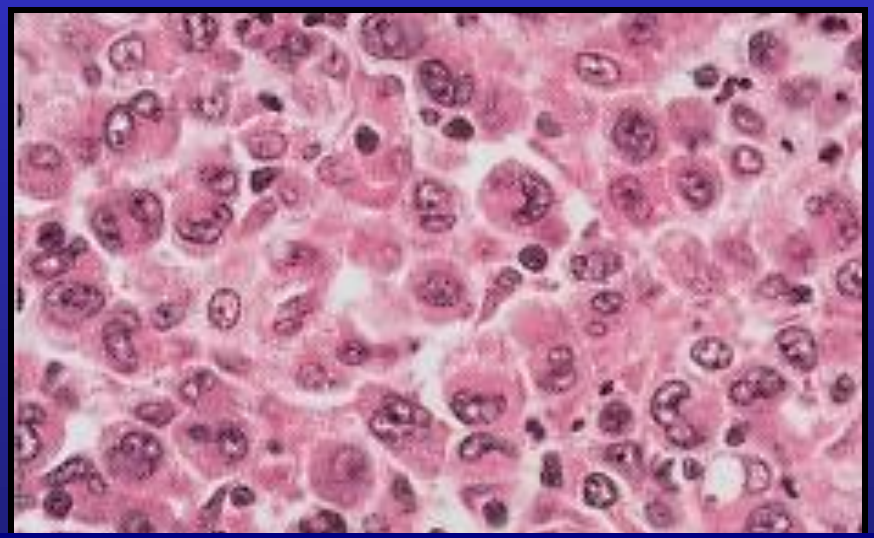
- ALK-positive ALCL frequently involves lymph nodes and extranodal sites
  - Skin (21%)
  - Bone (17%)
  - Soft tissues (17%)
  - Lung (11%)
  - Liver (8%)
- Bone marrow
  - 10% by routine H&E
  - 30% with CD30, EMA and/or ALK
- Extranodal involvement by ALK-negative ALCL is less frequent.

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

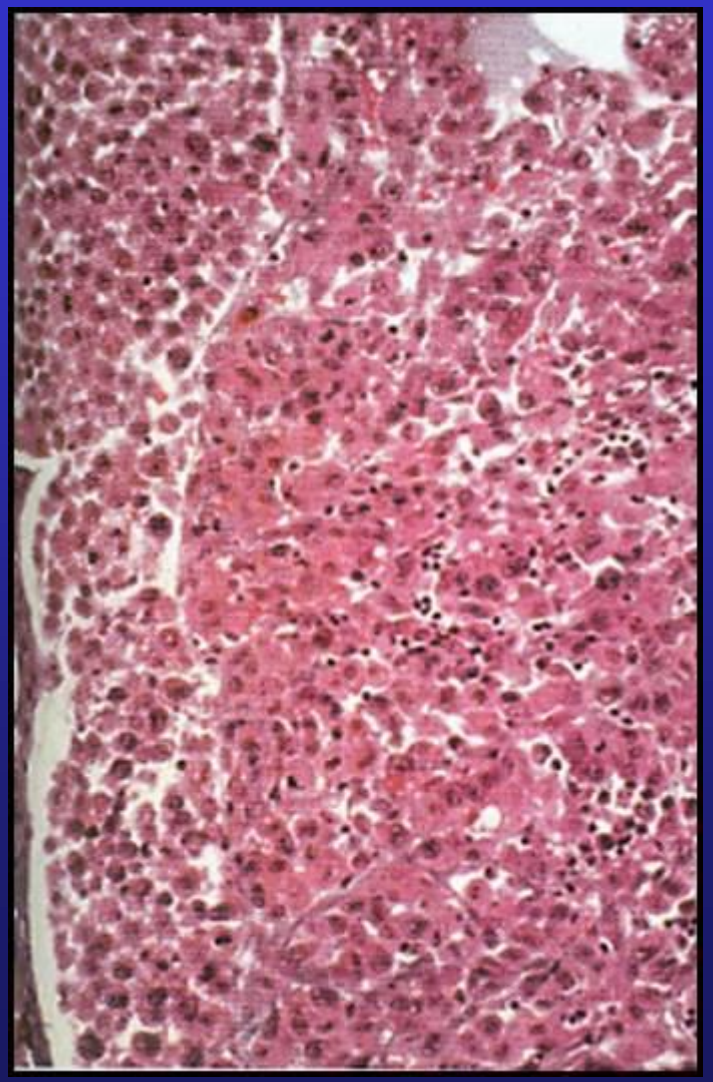


Morphology

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

Morphology

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



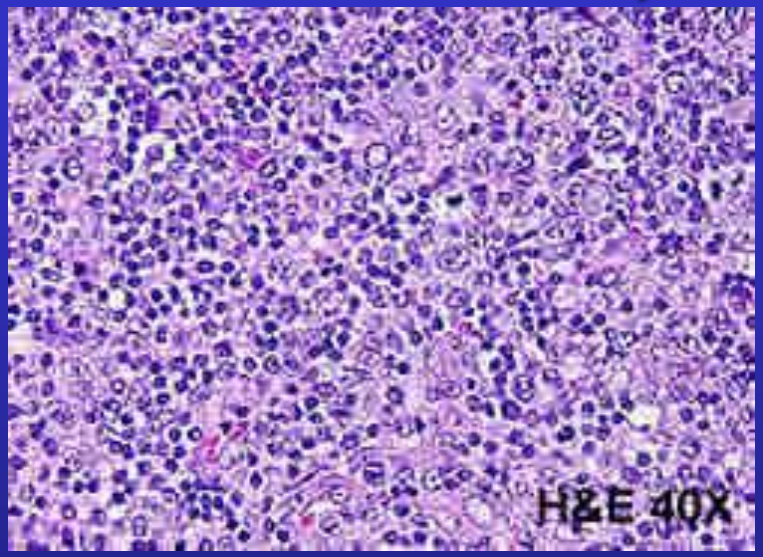
Morphology

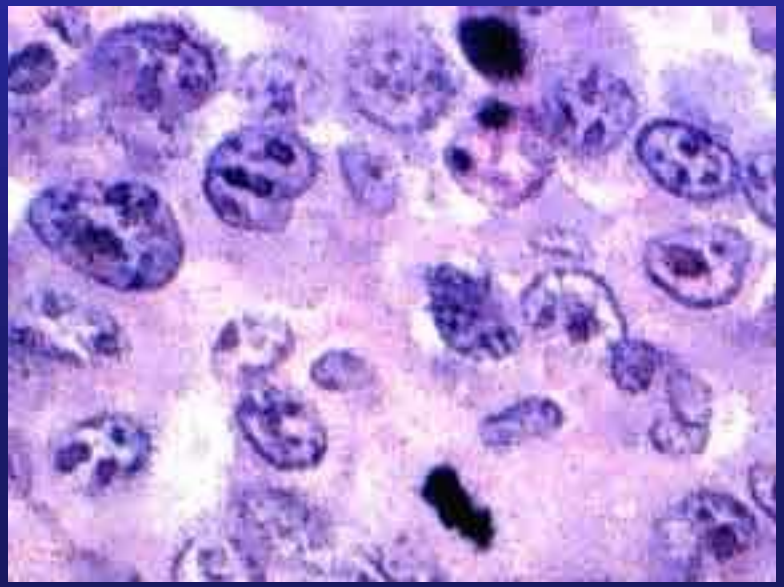
- Cytologic variants
  - Common
  - Lymphohistiocytic
  - Small cell
- 10% may have more than one variant
- Relapses may look morphologically like a different variant

ALCL, Common Variant

- 70% of cases
- Pleomorphic large cells
  - Hallmark features
- Admixed monomophic, round cells
  - May be the prominent population

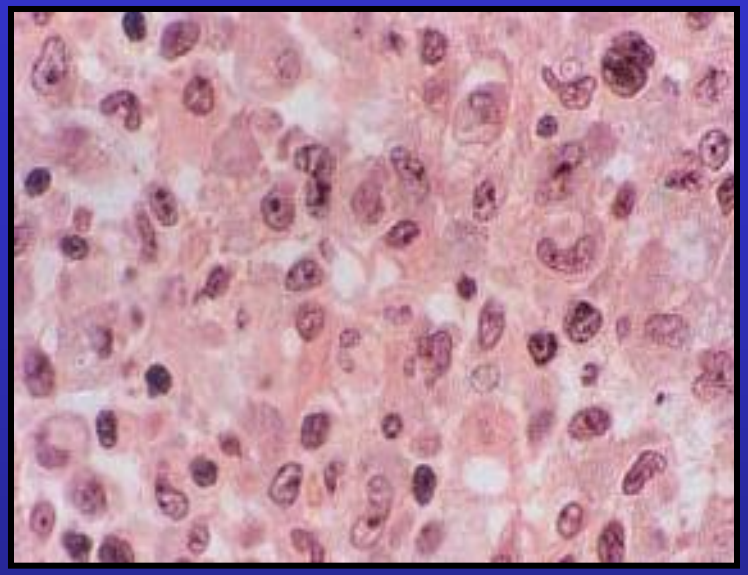
ALCL, common variant

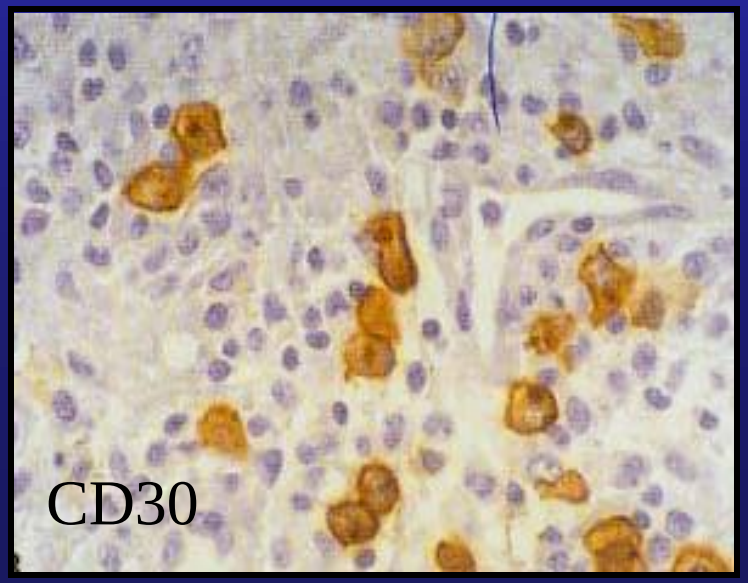




ALCL, Lymphohisitocytic variant

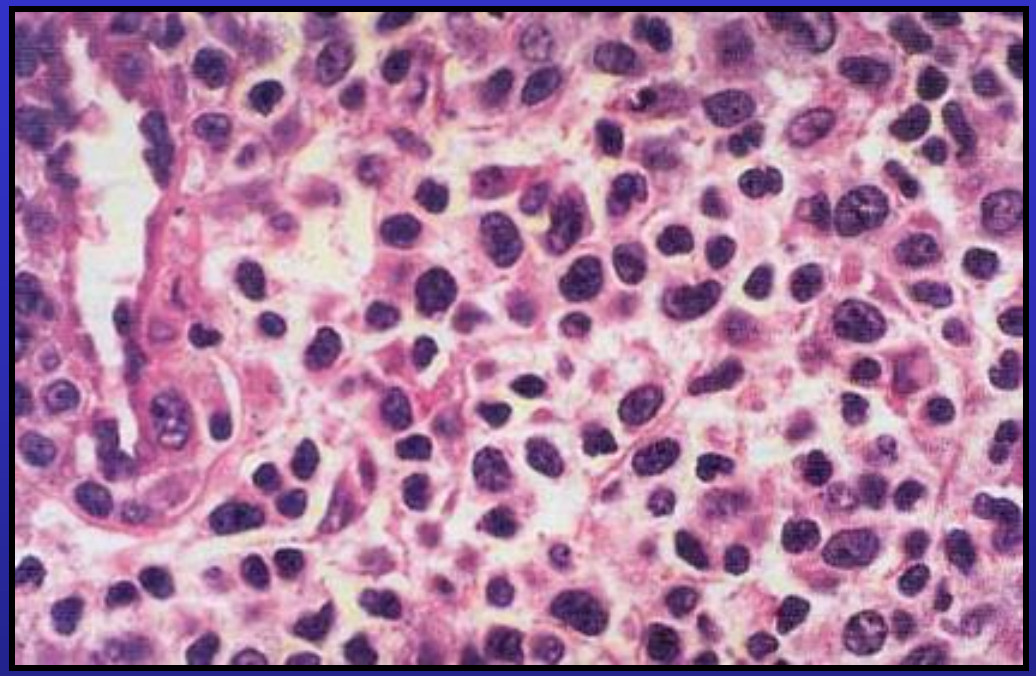
- 10% of cases
- Tumor cells admixed/masked with large numbers of histiocytes
  - Clustering of tumor cells around vessels
  - Erythrophagocytosis

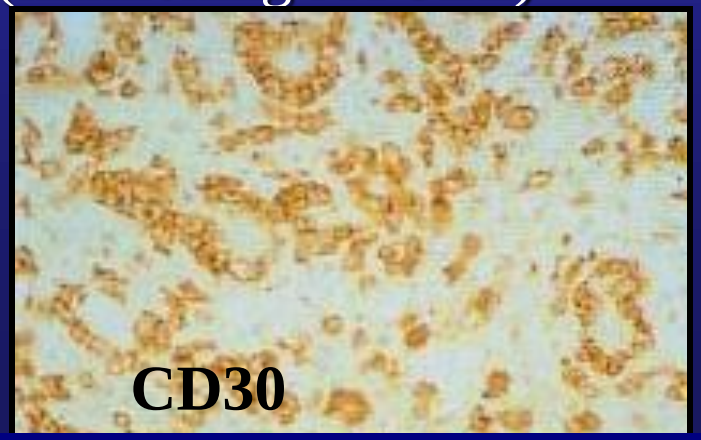


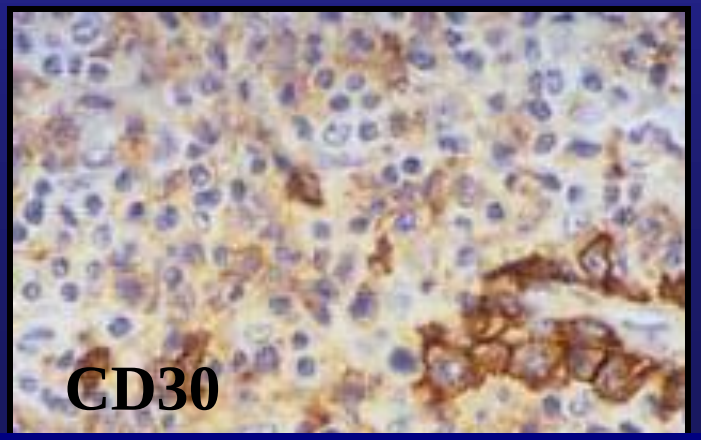


ALCL, Small Cell Variant

- 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)



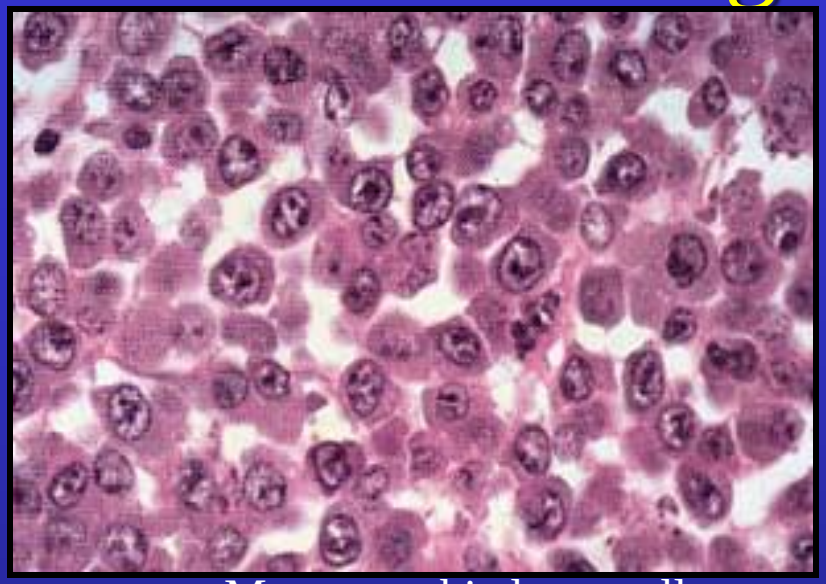




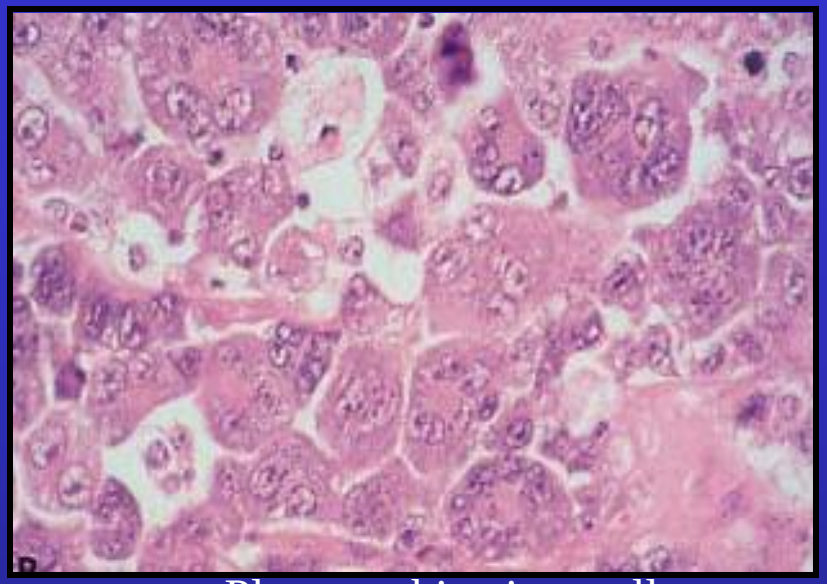
Other ALCL Variants

- Pleomorphic giant cells
- Monomorphic large cells
- Sarcomatoous
- Signet ring cells
- Rare cases with myxomatous stroma and fibroblasts, or capsular thickening and nodular fibrosis (mimicking cHL, NS)

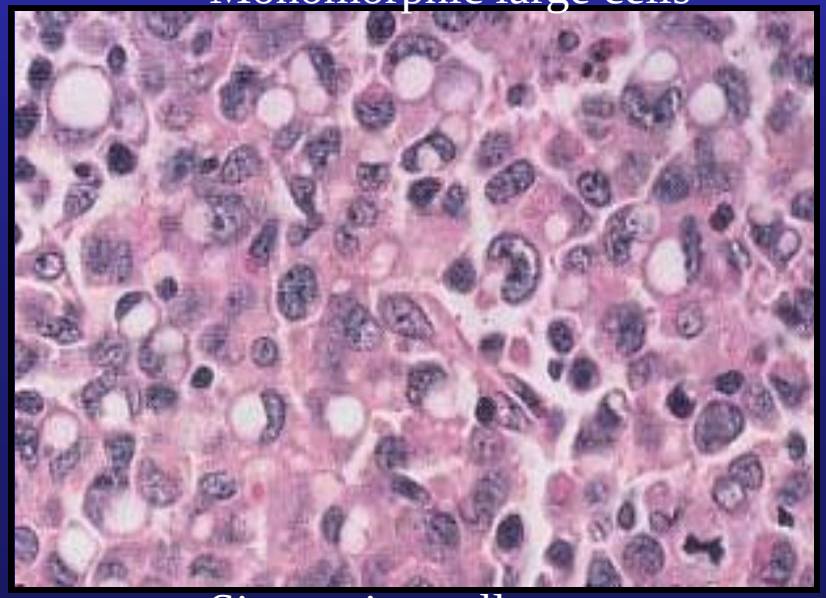
Other Histologic Patterns of ALCL



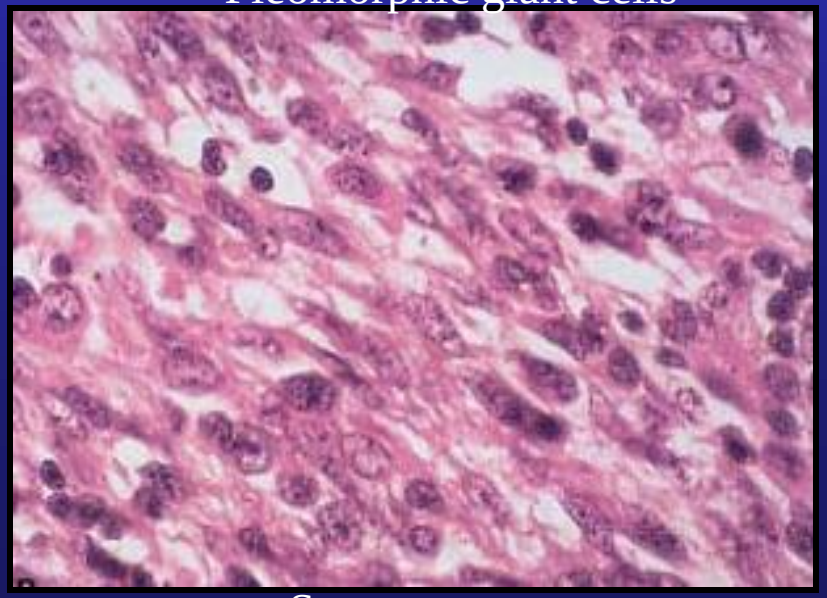
Monomorphic large cells



Pleomorphic giant cells



Signet-ring cells



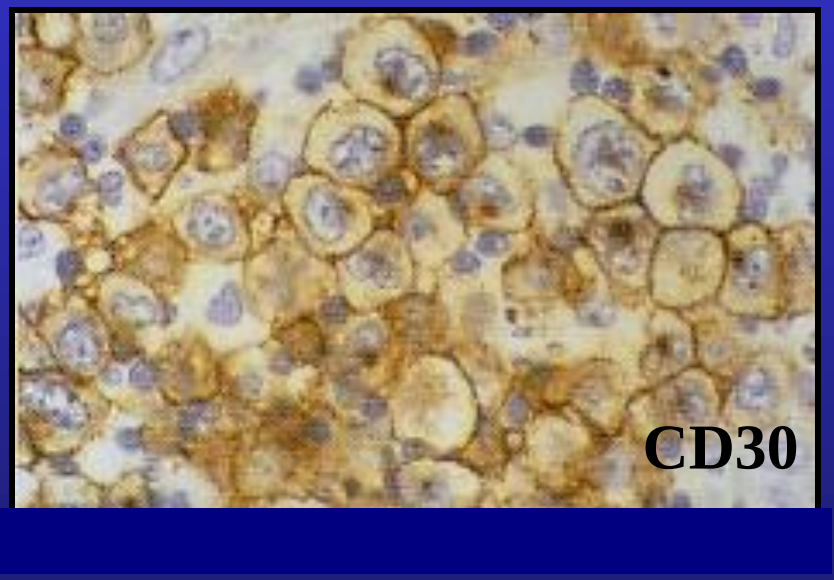
Sarcomatous

Differential DX: Immunostains

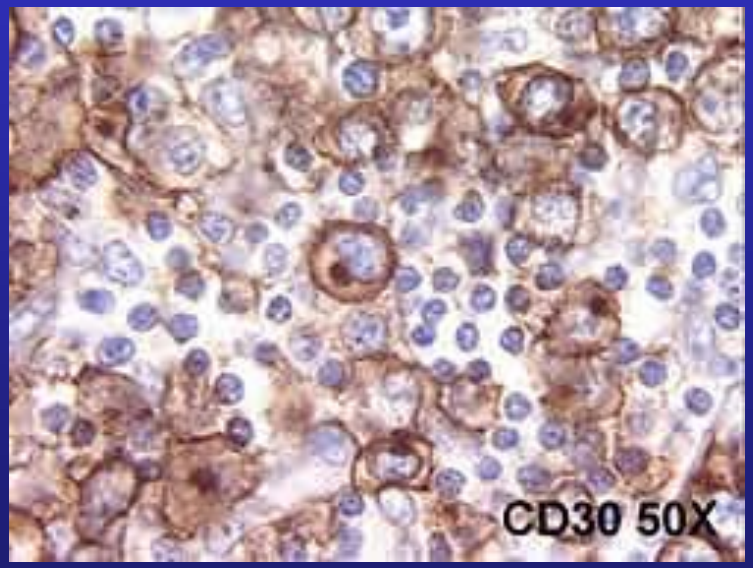
NLPHL CD45+ CD20+ CD15- CD30- EMA+	CHL CD45- CD15+ CD30+ PAX5+
ALCL CD45+ CD20- CD3- CD4+ CD30+ ALK+ EMA+	DLBCL CD45+ CD20+ CD3- CD30+/-

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

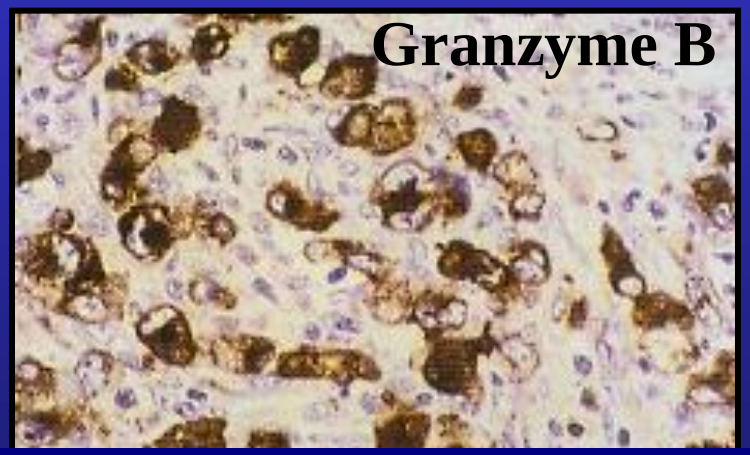


Anaplastic Large Cell Lymphoma



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 phophatase and NSE positive
  - Strong perinuclear activity

Genetics

- 90% of ALCL show clonal TCR rearrangements

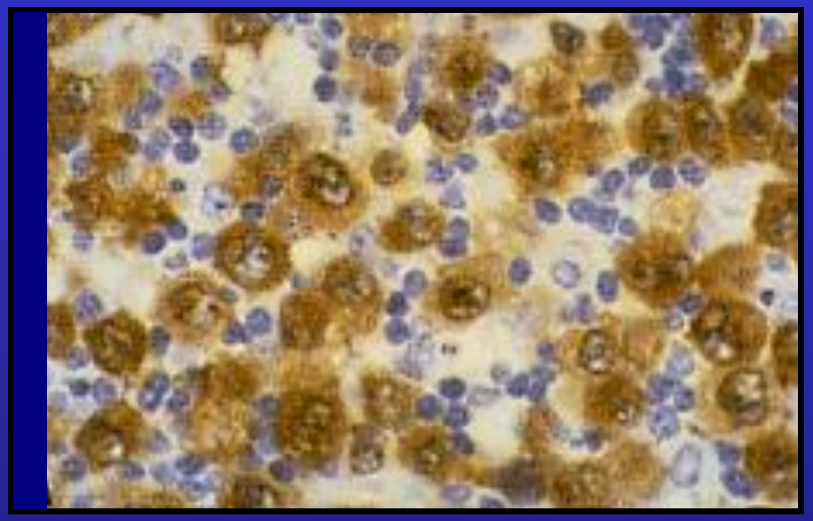
ALK

- 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

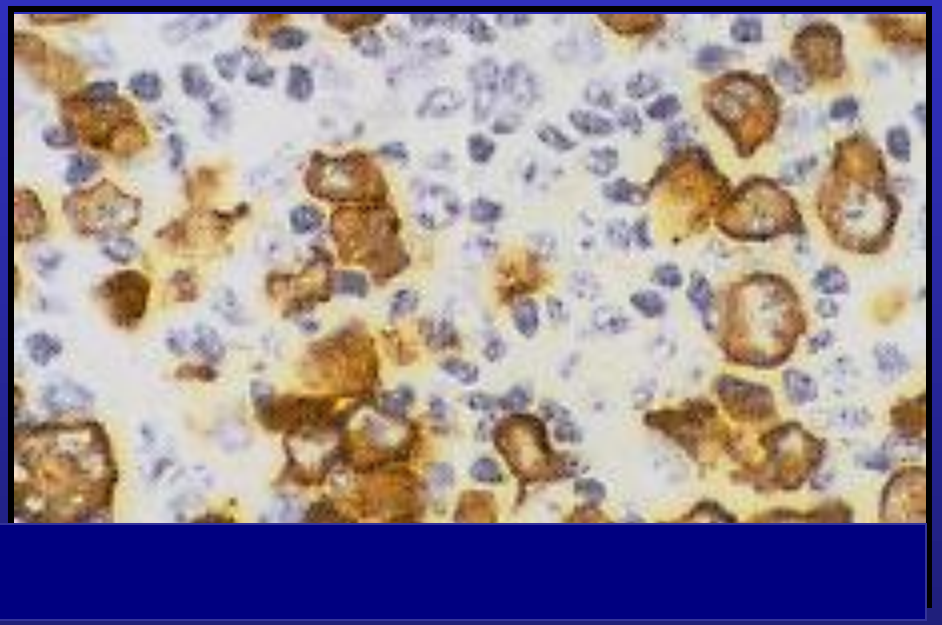
ALK Staining Patterns



- 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

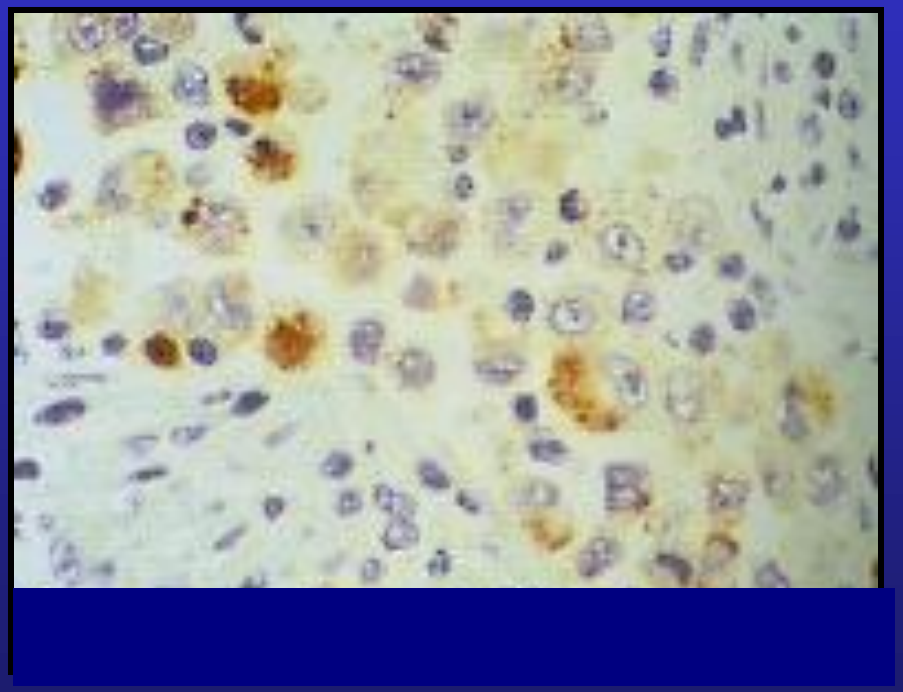
- t(2;3)(p23;q35)
  - Cytoplasmic, diffuse
  - 2-5%
  - TFG/ALK

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