International T-cell Lymphoma Study: Frequency of Subtypes

Study limited to adults

- Peripheral T-cell Lymphoma: 25.9%
- Angioimmunoblastic: 12.2%
- Natural killer/T-cell lymphoma: 10.4%
- Adult T-cell leukemia/lymphoma: 9.6%
- Anaplastic large cell lymphoma, ALK+: 6.6%
- Anaplastic large cell lymphoma, ALK-: 5.5%
- Enteropathy-type T-cell: 4.7%
- Primary cutaneous ALCL: 2.5%
- Hepatosplenic T-cell: 1.7%
- Subcutaneous panniculitis-like: 1.4%
- Unclassifiable PTCL: 0.9%
- Other disorders: 0.9%

JCO 2008;26:4124-4130

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Vose et al. JCO 2008

Overall Survival (%) vs. Time (years)

- Anaplastic large cell lymphoma, ALK+
- Anaplastic large cell lymphoma, ALK-
- All natural killer/T-cell lymphomas
- Peripheral T-cell lymphoma, not otherwise specified
- Angioimmunoblastic lymphoma
- Adult T-cell leukemia/lymphoma

P < .001
Innate Immune System

- γδ T-cells, NK-like T-cells, NK-cells
- Toll like receptors
  - Not MHC restricted
- Cytokines
  - Chemokines
  - Complement
- Apoptotic & necrotic cell death pathways
- First line of defense with a major role in barrier immunity

Adaptive Immune System

- B-cell
- T-cell
- APC
- Ag specific receptors on B + T-cells
- Antigen presentation to T-cells in the context of MHC
- Immunological defense characterized by specificity & memory
Innate Immune System

- Often cutaneous, mucosal, spleen & BM
- Cytotoxic
- Activated cells show frequent apoptosis, necrosis
- Includes most extranodal PTCLs, EBV+ T/NK cell lymphomas

Adaptive Immune System

- Lymphomas may relate to specific effector T-cells
- $T_{FH}$, Treg
- Functional consequences may be clinically apparent
- Includes most nodal PTCLs in adults
Peripheral T-cell Lymphoma, NOS

• A diagnosis of exclusion, by definition a heterogeneous category

• Characterized by a broad morphologic spectrum
  – New approaches include segregation of tumors of TFH origin (follicular variant)
  – Gene expression profiling recognizes tumors of TH1 and TH2 origin

• The “diffuse large B-cell lymphoma” of the PTLs
Lymphoepithelioid variant
Subclassification of PTCL, NOS by gene expression

- **TBX21 / TBET (Th1)**
- Unclassifiable
- **GATA3 (Th2)**
Subclassification of PTCL, NOS: GATA3 & TBX21

Median OS (yrs)

- GATA3: 0.9
- Unclassifiable: 1.41
- TBX21/TBET: 2.08

TBX21/TBET (Th1 cells) - GATA3 (Th2 cells)
Angioimmunoblastic T-cell Lymphoma is a disease of germinal center derived T-cells ($T_{FH}$ cell)

- CD3+
- CD10+
- BCL6 +/-
- CD279/PD-1+
- CXCL13 +

Increased B-cells - both EBV pos and neg

B-cells clonal in up to 50%
Perifollicular Localization of AITL T-cells

CD10
What is the utility of PD-1 immunostaining in differential diagnosis of AITL vs Reactive Hyperplasia?

Exercise caution – Intensity is key!
PD-1+ T-cells are invariably present in reactive paracortical hyperplasia
Reactive paracortical hyperplasia – 18 yo drug hypersensitivity
Strong PD-1 + cells in germinal center
Weak PD-1 in reactive paracortical T-cells
Nodal Peripheral T-cell Lymphomas of TFH origin

- Angioimmunoblastic T-cell lymphoma
- Follicular T-cell lymphoma
- Nodal peripheral T-cell lymphoma with TFH phenotype
- T-zone variant

TFH phenotype requires 2 or more TFH markers

Suggested panel:
- PD1
- ICOS
- CD10
- CXCL13
B-cell proliferations in AITL & TFH-PTCL

- **EBV-positive**
  - Variable numbers of EBV+ blasts, may be dominant picture
  - Hodgkin/Reed-Sternberg like cells

- **EBV-negative**
  - B-immunoblasts
  - Polyclonal plasma cells
  - Monotypic/ Monoclonal plasma cells
  - Hodgkin/Reed-Sternberg like cells
EBV neg B-cell proliferations in AITL and PTCL-TFH

CD20 + B-immunoblasts

Plasma cells
Often
Abundant
May be monoclonal & atypical

Balague et al.
Am J Surg Path 2007
Peripheral T-cell lymphoma with EBV+ HRS cells

T-cell population clonal,
Cytologically atypical
Usually has a TFH phenotype
“HRS-cells” are “B-lineage”

CD30
CD15
EBER
• PTCL classified as AITL, PTCL, often with $T_{FH}$ markers

• Intimate relationship between the HRS-like cells & neoplastic T-cells

• HRS-like cells
  – EBV-positive (52 cases)
  – EBV-negative (5 cases)

• Progression to classical Hodgkin’s lymphoma not observed
EBV-negative HRS like cells are also rosetted by neoplastic TFH cells.
Angioimmunoblastic T-cell Lymphoma & PTCL TFH
Take Home Points & Remaining Questions

• AITL is characterized by proliferation and sometimes clonal expansion of B-cells, as well as neoplastic $T_{FH}$-cells
• Recent data indicate that B-cells may carry the same mutations as T-cells?
  – TET2 mutations identified in B-cells of patients with AITL (Schwartz FH J Pathol, 2017)
  – AITL may be a “stem cell” disease
Lymphomas of the Innate Immune System

- Often cutaneous, mucosal, spleen & BM
- Cytotoxic
- Activated cells show frequent apoptosis, necrosis
- Includes most pediatric T/NK neoplasms
Hepatosplenic T-cell lymphoma

- Most common in young males
- May be seen with chronic immune suppression
  - Crohn’s disease, pts treated with anti-TNF, 6-MP, Azathioprine
  - Late occurring PTLD
- Hepatosplenomegaly, cytopenias, systemic symptoms; lack LN and PB involvement
- Aggressive behavior and dismal prognosis (<2y survival)
- Differential Dx: T-LGL in bone marrow, spleen
Recurrent Mutations in HSTCL

- HSTCL
  - STAT5B (33%); STAT3 (10%)
  - SETD2 (71%)
- T-LGL
  - STAT3 (40%); STAT5B (2%)
- T-ALL
  - JAK1, JAK3, STAT5B (subset)
- T-PLL
  - STAT5B (36%)
Subcutaneous Panniculitis-Like T-cell Lymphoma

CLINICAL FEATURES:
Broad age range (1 yr to 57 yrs) Median age - 30
Males = Females
Deep subcutaneous nodules
primarily affecting extremities, trunk
Overall survival > 80% 5 years
Absence of nodal involvement
Subcutaneous Panniculitis-Like T-cell Lymphoma

**MORPHOLOGY:**

Usually confined to subcutis, lobular distribution

Absence of dermal, epidermal involvement

– Helpful in distinction from cutaneous γδ T-cell lymphoma

Necrosis and karyorrhexis prominent

May show vascular invasion
Subcutaneous Panniculitis-like T-cell Lymphoma

**Immunophenotype & Genotype**

**Activated $\alpha\beta$ T-cytotoxic phenotype**

- CD3+, CD8+
- TIA-1+, Granzyme B+, Perforin +
- CD56 negative - *in contrast to $\gamma\delta$*
- EBV-negative
- TCR $\gamma/\beta$ genes rearranged
- Germline mutations in *HAVCR2* encoding TIM-3 in both Asian and European patients with HLH & SPTCL (Gayden et al. 2018)
Differential Diagnosis of SPTCL

*Lupus profundus*

- Mixture of T-cells, B-cells, plasma cells
- Lobular pattern with preserved septa
- Fibrinoid change in connective tissue
- Interstitial infiltration, but infrequent rimming of fat spaces
- Mixture of CD4+/CD8+ cells
- Scattered gamma-delta T-cells
- Increased PDC’s (CD123+)
Subcutaneous Panniculitis-like TCL vs. Lupus profundus – Not always easy

- Oligoclonal T-cell populations can be seen in some patients with lupus, inclusive of the cutaneous lesions
- Correlate clinical, histological, and genetic features
- One should be cautious about making the diagnosis of SPTCL in a patient with lupus
Enteropathy Associated T-cell Lymphoma (EATL)

- Broad morphological spectrum
  - Adjacent mucosa shows villous atrophy
- CD3+, CD103+, Cytotoxic markers, TCR $\alpha\beta$
  - Often double negative for CD4/CD8
- Often presents with intestinal perforation
- Aggressive clinical course with poor prognosis
Enteropathy-associated T-Cell Lymphoma
[Classical form or Type I]

• Associated with celiac disease
  – 95% of patients have HLA-DQ2 and HLA-DQ8
  – Autoantibodies against tissue transglutaminase
  – Antibodies against gliadin
  – Gluten-free diet may reduce risk of lymphoma
Enteropathy Associated T-cell Lymphoma, Types I & II are distinct

EATL I
Usually αβ
Celiac disease
N European

EATL II
Usually γδ
Epitheliotropic
Asian, Hispanic
Monomorphic epitheliotropic intestinal T-cell lymphoma (EATL II)

- Medium sized cells with clear cytoplasm
- CD56 +, CD8+, CD4-
- Usually gamma delta +
- MAT kinase +
- Mutations in STAT5B, JAK3 SETD2
JAK/STAT Pathway is an attractive target for therapy of Cytotoxic T-cell Lymphomas and Leukemias
T-cell & NK cell Lymphomas of Gastrointestinal Tract

- EATL “Classical”
  - $\alpha\beta > \gamma\delta$

- MEITL
  - $\gamma\delta > \alpha\beta$

- Extranodal NK/T
  - EBV+ NK or T
  - Mainly Asian

- PTCL, NOS
  - ($\alpha\beta$ or $\gamma\delta$ or TCR silent)

- All clinically aggressive
- All cytotoxic

Mainly Asian
Indolent T-cell lymphoproliferative disease of the GI tract (10 cases) (Perry et al. 2013)

- Ages 15-77 (median 48), M:F 6:4
- Oral cavity, stomach, small intestine, colon, esophagus
- Diarrhea, pain, rectal bleeding
  - “Crohn’s disease (2 patients), Colitis
- Follow-up: 9-175 months; Median 38 months
  - 2 pts followed >10 yrs, without progression
- 6 patients received chemotherapy for PTCL, with no response, but no progression
- Optimal therapy uncertain
Superficial infiltrate
Confined to mucosa
No invasion of the wall

Very low proliferation rate
No destruction of the glands
No cytological atypia
Very bland infiltrate

? Optimal management
Do not respond to chemorx

Ki-67
Indolent T-cell LPD of GI tract

Subset of cases are CD4+

- These may be more likely to progress to overt T-cell lymphoma
- Recurrent STAT3-JAK2 fusions in CD4+ cases but not in CD8+ cases (Sharma et al Blood 2018)

Prior reports published as

“Low grade intestinal T-cell lymphoma”

“Lymphomatous polyposis of T-cell type”
  - Carbonnel 1994; Egawa 1995; Hirakawa 1996
  - Margolskee 2013
NK-cell Enteropathy
An atypical proliferative lesion mimicking lymphoma

- 8 cases: M:F 1:3; Median age 49 (27-70)
- Vague GI symptoms, but negative for celiac disease
- Superficial lesions with hemorrhage, edema, ulceration
- Lesions in stomach, small intestine, and colon
- Indolent, relapsing clinical course without dissemination
  - Do not mistake for aggressive NK-cell lymphoma
Colon: Positive for cytoplasmic CD3, CD56, CD7; CD2+/

Negative for CD5, CD4, CD8, EBER
Let’s switch gears ......
EVOLUTION OF ANAPLASTIC LARGE CELL LYMPHOMA, ALK+

Initial Description

HD

PTCL

MH

Immunophenotypic Studies

CD30+
EMA+
LCA+
CD15-
CD3 -/+ 

Molecular Pathogenesis

t(2;5)
NPM;ALK

Definition of Entity

Hallmark cells
ALK+

Ki-1+
Sinusoidal lymphoma
ALCL

Bone marrow Involvement

Scattered single cells in biopsy & smear

Adverse prognostic factor – best diagnosed with IHC of bone marrow
<table>
<thead>
<tr>
<th>Translocations and fusion proteins involving ALK</th>
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<tr>
<td><strong>Nucleophosmin Anaplastic Lymphoma Kinase</strong></td>
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<tr>
<td>t(2;5)</td>
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<tr>
<td>NPM</td>
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<tr>
<td>ALK</td>
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<td>Staining: cytoplasmic/nuclear/nucleolar</td>
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<td>Tropomyosin 3</td>
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<td>TPM3</td>
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<td>ALK</td>
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<td>Staining: cytoplasmic</td>
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<td>Frequency: 10-20%</td>
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<td>Trk Fusion Gene</td>
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<td>Inv2</td>
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<td>ATIC (Pur H gene)</td>
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<td>Frequency: 2-5%</td>
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<td>Clathrin heavy chain</td>
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<td>t(2;19)</td>
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<td>TPM4</td>
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<tr>
<td>ALK</td>
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<tr>
<td>Staining: cytoplasmic</td>
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<td>Frequency: 1-2%</td>
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Histological Spectrum of ALCL, ALK+

- Anaplastic large cell lymphoma
  - Common
  - Lymphohistiocytic
  - Small cell
- Other histological patterns
  - Sarcomatoid appearance with myxoid stroma
  - Hypocellular with edematous background
Lymphohistiocytic variant of ALCL

CD30
Small Cell Variant of ALCL
Time to treatment failure curve according to the presence of a small-cell (SC) and/or lymphohistiocytic (LH) component (n = 361 patients).

Lamant L et al. JCO 2011;29:4669-4676
Genetic correlates with survival in ALCL, ALK+/ ALK-
Feldman et al. Blood 2014

Subset with DUSP22 R Comparable to ALK+

DUSP22 (# 22)
ALK+ (# 32)
P63 (# 6)
ALK neg, no aberrations (#45)
DUSP 22 Mutated ALCL has distinctive morphology and phenotype

Classical Hallmark cells

Granzyme B negative
WHO Classification of T/NK cell neoplasms

**Leukemic/ Systemic**
- T-cell prolymphocytic leukaemia
- T-cell large granular lymphocytic leukaemia
- Chronic lymphoproliferative disorder of NK cells
- Aggressive NK cell leukaemia
- Systemic EBV+ T-cell Lymphoma of childhood
- Hydroa vacciniforme-like lymphoproliferative disorder
- Adult T-cell leukaemia/lymphoma
- Hepatosplenic T-cell lymphoma

**Extranodal**
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Monomorphous epitheliotropic intestinal T-cell lymphoma
- Indolent T-cell lymphoproliferative disorder of the GI tract
- Breast implant-associated anaplastic large cell lymphoma

**Cutaneous**
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides/ Sézary syndrome
- Primary cutaneous CD30 positive T-cell lymphoproliferative disorders
  - Lymphomatoid papulosis
  - Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous gamma-delta T-cell lymphoma
- Primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma
- Primary cutaneous acral CD8+ T-cell lymphoma
- Primary cutaneous CD4 positive small/medium T-cell lymphoproliferative disorder

**Nodal/ Extranodal**
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- Follicular T-cell lymphoma
- Nodal peripheral T-cell lymphoma with TFH phenotype
- Anaplastic large cell lymphoma, ALK positive
- Anaplastic large cell lymphoma, ALK negative