What’s new on the horizon in T-cell lymphomas

Elaine S Jaffe
National Cancer Institute, Bethesda MD
Basis of New Information since 2008

- Rapid progress in understanding of molecular pathogenesis
  - NGS studies, Gene Expression profiling
    - Nanostring and other platforms
  - Allow high throughput investigation of paraffin embedded samples
- Large scale clinical studies led to new insights into clinical behavior
  - Interest in more targeted therapy
AITL & other nodal TCL

Intestinal T-cell lymphomas

γδ T-cell lymphomas

ALCL, ALK neg

Cutaneous TCL

EBV+ T/NK disease
Nodal Peripheral T-cell Lymphomas of TFH Origin

- Gene expression profiling and mutation analysis has helped to clarify the interrelationship among nodal T-cell lymphomas of TFH origin.
Gene expression profiling allowed reclassification of 14% of PTCL, NOS as AITL

Gene expression signatures of PTCL; Iqbal et al. *Blood* 2014
Genomic Findings in AITL and TFH derived lymphomas

• 20-45% in *IDH2*, *DNMT3A* and *TET2* in AITL
  – Genes involved in pathogenesis of gliomas, AML
• *TET2* mutations also seen in other PTCL of TFH origin (up to 60%)
• *RHOA* mutations in 60% of AITL and some PTCL, NOS, all with *TET2*

Activating Mutations in TCR Signaling Genes in AITL and TFH lymphomas Vallois et al. Blood 2016

5-14% of cases

- CD28 and TCR signaling
- \textit{PLCG1} – NF kappa B, NFAT pathway
- PI3K pathway
- AP-1/MAPK pathway

Parallels with B-cell signaling in B-cell lymphomas

Also reported in other T-cell lymphomas

ATLL, Cutaneous T-cell lymphomas

- \textit{But JAK/STAT pathway not involved}
Nodal Peripheral T-cell Lymphomas (2008)

PTCL, NOS

T-zone variant

Follicular variant

Lymphoepithelioid cell variant

Angioimmunoblastic T-cell lymphoma
Nodal Peripheral T-cell Lymphomas (2016)

PTCL, NOS

Lymphoepithelioid cell variant

Angioimmunoblastic T-cell lymphoma

Follicular T-cell lymphoma

Nodal peripheral T-cell lymphoma with TFH phenotype

T-zone 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)
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 γδ+
- MAT kinase +
- 8q24(myc) amplifications
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
Recurrent Mutations in Cytotoxic T-cell & NK-cell lymphomas and T-LGL leukemia

Koskela et al., Jerez et al. 2012
• T-cell & NK-cell LGL

Nicolae, et al. 2014
• γδ HSTCL

Kucuk et al. 2015
• γδ cutaneous & HSTCL
• EATL, II (γδ)
• NKTCL

• 40% STAT3; 2% STAT5B

• 33% STAT5B, 10% STAT3

• 33% STAT5B; 8% STAT3
• 36% STAT5B
• 6% STAT3; 6% STAT5B
Recurrent Mutations in Intestinal T-cell Lymphomas

Authors
Nairismagi 2016
• EATL II αβ and γδ

Nicolae 2016
• EATL Type II > I
  – αβ and γδ and TCR silent

Mutations
• 63% STAT5B
• 35% JAK3, 24% GNAI2
• 67% JAK/STAT pathway
  STAT5B/ JAK3/ STAT3
• 24% RAS pathway
  KRAS/ NRAS/ BRAF
JAK/STAT Pathway is an attractive target for therapy of Cytotoxic T-cell Lymphomas and Leukemias
Anaplastic Large Cell Lymphomas
overlapping clinical and biological features

- ALCL, ALK-positive
- ALCL, ALK-negative
- Primary cutaneous anaplastic large cell lymphoma & Lymphomatoid papulosis
- Breast implant associated anaplastic large cell lymphoma
ALK-negative ALCL – No Longer a Provisional Entity
Should have very similar morphology and phenotype as ALK + ALCL

Diagnostic Criteria for ALK neg ALCL vs. CD30+ PTCL have been clarified
Required: Cohesive growth pattern with hallmark-like cells
Strong and uniform CD30 expression
Desirable but not essential: EMA+, Cytotoxic +, Sinusoidal growth, Loss of “T-cell ag”
Constitutive Activation of the JAK/STAT pathway in Systemic and Cutaneous ALK-negative ALCL

Activating mutations of JAK1 or STAT3 or both (20%)
Crescenzo Cancer Cell 2015
Genetic correlates with survival in ALCL, ALK+ / ALK-
Feldman et al. Blood 2014

DUSP22 (# 22)
ALK+ (# 32)
P63 (# 6)
ALK neg, no aberrations (#45)

Subset with DUSP22 R Comparable to ALK+
DUSP22 translocations also seen in primary cutaneous CD30+ T LPD

- **LYP with 6p25.3** (<5%) 11 pts with localized skin lesions (Karai 2013)
  - Same translocation (*DUSP 22* locus), as in systemic ALCL, ALK-

- **Primary cutaneous ALCL with 6p25.3**
  - 3 patients, pagetoid reticulosis-like pattern (Onaindia 2015)
  - C-ALCL, intralymphatic localization, skin limited (Samols 2014)

- Evidence for close relationship between some cases of systemic and cutaneous ALCL
Breast Implant-associated anaplastic large cell lymphoma, ALK-negative

- Seen with a variety of breast implants, both saline and silicone
- Usually years after implant
- Symptoms related to accumulation of seroma fluid in cavity surrounding the implant
- Diagnosis best made by cytology
- Cells grow within cavity and on surface of cavity lining, usually without invasion
Location of ALCL Adjacent to Breast Implant

Modified from Thompson PA et al Haematologica 2010
Breast implant assoc. ALCL
A provisional entity
Biological Features

- Clonal TCR reported in most but not all cases
- Surprisingly indolent course, despite very atypical cytological features
- Therapy varies in literature
  - Chemo, Radiation, Observation following removal
- Removal of implant is probably adequate therapy in most cases – if no invasion of capsule
CD30
Breast implant–associated anaplastic large-cell lymphoma
Long Term Follow up in 60 Patients
Miranda R N et al. JCO 2014;32:114-120

93% CR in patients with disease confined to the capsule
72% CR in patients with a mass
No difference in OS or PFS in patients who had chemorx

Recommended rx: Implant removal with capsulectomy
Other clonal T-cell proliferations of limited malignant potential

- Primary cutaneous CD4+ T-cell LPD
- Primary cutaneous acral CD8+ T-cell lymphoma
- Indolent T-cell lymphoproliferative disease of the gastrointestinal tract
Primary cutaneous CD4 positive small/medium T-cell lymphoma (Provisional 2008)
Primary cutaneous CD4+ small/medium “T-cell lymphoma” (2008)

- Usually localized, often involving head and scalp
- Distinction with atypical hyperplasia often difficult
- Lesions sometimes contain numerous B-cells
- Good prognosis if single lesion, most < 3 cm
  - Infrequent recurrences, no deaths
  - Patients with bulky or advanced disease (very few) had aggressive course
TFH phenotype, PD-1+, more rarely CD10+

Contains abundant B-cells, fewer plasma cells

Clonal TCR with rare B-cell clonality
Lacks genetic changes of other TFH lymphomas
Reassessment of Primary cutaneous CD4+ small/ medium “TCL”

WHO 2016

Primary cutaneous CD4 positive small/medium T-cell lymphoproliferative disorder (not lymphoma)
Indolent CD8+ lymphoid proliferation of the ear (Petrella et al, 2007)

- Dense, non-epidermotropic; Clonal
- Rx with local radiotherapy or excision
- Local recurrence in some, but no progression
- Also involves other acral cutaneous sites
Primary cutaneous acral CD8+ T-cell lymphoma

A new provisional entity

38 yo. male with lesion of ear
Primary cutaneous acral CD8+ T-cell lymphoma

Other acral sites  (contributed by T. Petrella)
Indolent T-cell lymphoproliferative disease of the gastrointestinal tract
Perry et al. Blood 2013

A provisional entity - WHO 2016
38 yo male with lesions of stomach, sm bowel, colon over 2 yrs

No invasion of epithelium
Indolent T-cell lymphoproliferative disease of the GI tract (10 cases)

- 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
- 6 patients received chemotherapy for PTCL, with no response, but no progression
  - 1 patient with “acquired double neg phenotype” progressed systemically and expired after > 10 yrs.
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

CD8+, TIA1+
GranB, Perforin negative
EBV neg, TCR αβ
TCR gamma PCR – Two lesions 13 years apart

Oral Bx 1999

Intestine 2012
Indolent CD8+ T-cell LPD of GI tract
Perry et al. Blood 2013

- Important to distinguish from EATL and other intestinal T-cell lymphomas
  - Indolent and non-progressive clinical course
  - Optimal therapy uncertain; do not respond to conventional chemotherapy
- Etiology underdetermined – may be related to antigen drive
- Relationship to inflammatory bowel disease uncertain
- Similar in phenotype and clinical behavior to CD8+ LPD of the “ear”
EBV+ T/NK cell lesions – WHO update (2016)
Y-H Ko, L Quintanilla Martinez, H Kimura, ES Jaffe

- Cutaneous CAEBV
  - Hydroa Vacciniforme **LPD** (T/NK)
  - Severe Mosquito Bite Allergy (NK)
- Systemic CAEBV, T-cell or NK-cell
- Systemic EBV+ T-cell **lymphoma** of childhood
- Aggressive NK-cell leukemia
- Extranodal NK/T-cell lymphoma, nasal type

Marked variation in clinical behavior from indolent to highly aggressive
With acknowledgment to the many contributors &

**Lymphoid Editors**
- Steven H. Swerdlow
- Elias Campo
- Stefano Pileri
- Nancy Lee Harris
- Harald Stein
- Reiner Siebert

**Clinical Advisory Committee Chairs**
- Ranjana Advani
- Michele Ghielmini
- Gilles Salles
- Andrew Zelenetz