What’s new on the horizon in T-cell lymphoma
Elaine S Jaffe
National Cancer Institute, Bethesda MD
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Dr. Elaine S Jaffe declares that she has no conflict(s) of interest to disclose.
AITL & other nodal TFH lymphomas

Intestinal T-cell lymphomas

HSTCL / γδ

ALCL, ALK-negative

EBV+ T/NK disease

1° Cut CD4+ T-LPD
• 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

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<th>Relative Level of Expression (x median value)</th>
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<td>AITL</td>
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Gene expression signatures of PTCL; Iqbal et al. *Blood* 2014
Genomic Findings in AITL and TFH derived lymphomas

- *IDH2, DNMT3A* and *TET2* mutated in 25-40% 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*

Nodal Peripheral T-cell Lymphomas (2008)

PTCL, NOS
- T-zone variant
- Lymphoepithelioid cell variant
- Follicular variant

Angioimmunoblastic T-cell lymphoma
Nodal Peripheral T-cell Lymphomas (2015)

- PTCL, NOS
- T-zone variant
- Lymphoepithelioid cell variant
- Angioimmunoblastic T-cell lymphoma & other
  Nodal PTCL of TFH origin
- Follicular T-cell lymphoma (provisional)
• Primary cutaneous CD4 positive small/medium T-cell lymphoma
• Was provisional in 2008
• Another TFH derived neoplasm
TFH phenotype, PD-1+, more rarely CD10+

Contains abundant B-cells, fewer plasma cells

Clonal TCR with rare B-cell clonality
Primary cutaneous small/medium CD4 positive T-cell proliferations

- Vast majority of patients have an isolated single lesion
- 75% head and neck area
- Excellent prognosis following simple excision
  - Only patients with multiple or bulky disease had an aggressive clinical course
- Proposal: Primary cutaneous CD4+ T-cell lymphoproliferative disease (not 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

γδ
Monomorphic epitheliotrophic intestinal T-cell lymphoma (EATL II)

- Medium sized cells with clear cytoplasm
- CD56 +, CD8+, CD4-
- Gamma delta +
- MAT kinase +
- 8q24(myc) amplifications
T-cell & NK cell Lymphomas of Gastrointestinal Tract

- EATL
  - "Classical" αβ
- Monomorphic epitheliotropic intestinal T-cell lymphoma γδ
- Extranodal NK/T EBV+ NK or T
  - Mainly Asian
- PTCL, NOS (αβ or γδ or TCR silent)

All clinically aggressive
Indolent T-cell Lymphoproliferative diseases of low malignant potential

Indolent T-LPD of the GI Tract
Perry et al., Blood 2013

Multiple mucosal polyps
Can affect entire GI Tract

Most common in:
small intestine
colon

Less often:
stomach
oral mucosa
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 Lymphoproliferative Disorder of the Gastrointestinal Tract

A new provisional entity
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
38 yo. male with lesion of ear

CD8
Primary cutaneous acral CD8+ T-cell lymphoma

A new provisional entity

38 yo. male with lesion of ear
Lymphomas of the Innate Immune System

- Includes γδ T-cells, NK-like T-cells, NK-cells
- Commonly involve
  - Skin, mucosa & other extranodal sites
  - Spleen & BM
  - Infrequent lymphadenopathy

Similarities in gene expression profile and in genetic features
Overlap in the Gene Expression Profile of $\gamma\delta$ T-cell and NK-cell lymphomas

Extranodal NKTL

Gene expression signatures in peripheral T-cell lymphoma; Iqbal et al. Blood 2014
Recurrent Mutations in γδ T-cell & NK-cell lymphomas and T-LGL leukemia

Nicolae, et al. 2014
• γδ HSTCL

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

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

Mutations
• 33% STAT5B, 10% STAT3
• 33% STAT5B; 8% STAT3
• 36% STAT5B
• 6% STAT3; 6%STAT5B
• 40% STAT3; 2% STAT5B
JAK/STAT Pathway is an attractive target for therapy of Cytotoxic T-cell Lymphomas and Leukemias

Similar rate of mutations in STAT5B (33%) in most γδ T-cell lymphomas (Hepatosplenic, Intestinal, Cutaneous)
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”
Overall survival of ALCL, ALK+ / ALK- Pediatric and Adult cases

ALK1+
$n=215$

ALK1-
$n=28$

$P = 0.001$
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+

p<0.0001
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
Breast implant assoc. ALCL
A provisional entity
Biological & Clinical 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 & capsule is probably adequate therapy in most cases, e.g. no invasion
  – Miranda et al. JCO 2014 (review of 60 cases from literature)
Most EBV+ T-cell and NK-cell neoplasms share a similar epidemiology (WHO 2008)

- **Chronic Active EBV-infection**
  - Systemic CAEBV of T or NK cell type
  - Hydroa vacciniforme-like lymphoma (T>NK)
  - Mosquito-bite allergy (NK >T)
- **Extranodal NK/T-cell lymphoma, nasal type**
- **Aggressive NK-cell leukemia**
- **Systemic EBV+ T-cell lymphoproliferative disease of childhood**
Variation in Clinical Aggressiveness from Chronic to Fulminant

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- **Aggressive NK-cell leukemia**
- **Systemic EBV+ T-cell lymphoma of childhood**
  - Terminology changed from systemic EBV+ T-cell LPD to emphasize the aggressive clinical course
CAEBV vs acute EBV-associated HLH vs Systemic EBV+ T-cell Lymphoma

- Challenging differential diagnosis
  - All can have clonal EBV-infection of T-cells or NK-cells
- CAEBV requires > 6 mos symptoms
- Poor prognostic factors in HLH include marked elevations of Ferritin, Bilirubin (Kogawa et al. 2014)
- Clonality of T-cells is helpful but not definitive
EBV-associated HLH vs. Systemic EBV+ T-cell Lymphoma

3 y.o. Hispanic female
Acute presentation
Laboratory Findings

- WBC 2.7 K/uL, RBC 2.9 M/uL, HGB 7.7 G/DL, HCT 22.1, PLT 24 K/uL
- Ferritin > 40,000 ng/ml, Triglycerides 324 mg/dl
- Bili 11.2/ Direct 8.3; LDH 5744 IU/L
- EBV DNA > 2 million
- EBV localized to T-cells, but no clone by PCR
- Rx according to HLH 94 protocol

EBV viral load returned to normal, no EBER + cells detected in bone marrow, currently in CR – favoring acute HLH
What’s new in the WHO classification ....

- Integrated approach to AITL and other TFH lymphomas
- Altered terminology for primary cutaneous CD4+ T-cell LPD
- Formal separation of EATL Types I and II
- Introduction of new provisional entities for indolent T-cell LPD’s in the GI tract & Skin
- New Insights into the genetics of γδ T-cell lymphomas
- ALK-negative ALCL no longer provisional entity
  - More clearly defined & new genetic findings
- Breast implant associated ALCL - a provisional entity
- Improved definition of EBV+ T-cell and NK-cell malignancies
What’s new in the WHO classification 

- Many questions remain ....
- New insights will lead to more accurate diagnosis and improved therapy
Thank You!

& Now the speakers are ready for your questions

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