Aggressive Primary Cutaneous T cell Lymphomas

Uma Sundram, MD, PhD
Professor of Pathology
Oakland University William Beaumont School of Medicine
Beaumont Health Systems, Royal Oak, MI
September 27, 2019
Disclosures

• I have nothing relevant to disclose.
Outline

• An overview of aggressive cutaneous lymphomas
• Transformed Mycosis fungoides
• Sézary syndrome
• CD8+ CTCL: Primary Cutaneous CD8+ Aggressive Epidermotropic Cytotoxic T cell Lymphoma
Outline

- Dermal and Subcutaneous CTCL:
  - Cutaneous Gamma Delta T cell Lymphoma
  - Extranodal NK/T cell lymphoma, nasal type
  - Primary Cutaneous Peripheral T cell Lymphoma, Not Otherwise Specified (NOS)
Aggressive Cutaneous Lymphomas

- Most common CTCL=indolent
- Rare, smaller subgroup of lymphomas known to have poor outcomes (Junkins Hopkins 2017)
- Some ultimately aggressive lymphomas may start with indolent lesions
- If unsure, long term follow up is best
Mycosis Fungoides

- Patients with indolent mycosis fungoides do well with 10 yr DSS of 80% or greater (Benner 2012)
- Transformed MF (tMF) associated with more aggressive clinical course
- Study with 70 tMF patients reported median survival of 8.3 yrs (Agar 2010); a more recent study of 187 patients reported an overall survival of 4.8 yrs (Talpur 2016)
Mycosis Fungoides

- Transformation may be diagnosed at presentation or happen after years of indolence.
- Unusual for stage IA (localized disease, less than 10% BSA) to develop fatal transformation, but not for stage IB (generalized, more than 10% BSA).
Definition of Large Cell Transformation

• Greater than 25% of infiltrate is composed of large cells and/or such large cells are present in microscopic nodules (Salhaney, 1988)

• Large cells are lymphocytes more than 4x the size of ‘regular’ lymphocytes
Large Cell Transformation

- Histiocytes must be discounted (Vergier, 2000)
- Must differentiate from CD30+ ALCL/type C Lyp
- Tumor cells retain CD4 expression with variable expression of CD30
Large Cell Transformation

• CD20 gain documented in several studies in both transformed neoplastic cells and smaller cerebriform cells
• Extracutaneous transformation associated with reduced disease specific survival and overall survival (Vergier 2000)
Large Cell Transformation

• Other adverse factors
  – Development of LCT early in clinical course
  – Transformation in advanced stage (over stage IIB)
  – Reduced CD30 expression
  – Expression of cytotoxic markers
CD30 Positive Lymphoproliferative Disorders

• These include lymphomatoid papulosis, primary cutaneous anaplastic large cell lymphoma, and secondary cutaneous involvement by systemic ALCL.

• TMF not traditionally considered a CD30+ LPD but arises in the differential due to similar presenting environments and sometimes extensive expression of CD30 in large cells.
CD30

• CD30 + transformed MF documented to do better than CD30- transformed MF
• Some studies may have included Lyp/ALCL
• Difficult sometimes to tell CD30+MF from Lyp/ALCL, especially when greater than 75% of cells express CD30
Large Cell Transformation

• tMF vs primary cutaneous ALCL; features favoring tMF include:
  – Tumor arising in plaque of MF
  – Older patients
  – Lack of spontaneous regression of tumors

• *DUSP22* rearrangement seen more often in pcALCL (tMF=0)
Folliculotrophic MF

- Can be associated with aggressive course
- In some studies, 10 yr survival in advanced stage skin limited disease=28% (van Santen 2016)
- In addition to typical lesions of MF, also seen head and neck predominance, follicular/acneiform papules
Folliculotropic MF

- Histology=folliculocentric, folliculotropic
- Follicles expanded/distorted by mucin deposition
- Intrafollicular involvement by atypical, cerebriform cells
Folliculotropic MF

- Compared stage for stage to non follicular MF, FMF patients have been documented to have more aggressive clinical course
- However, tiered differences in outcome have been identified (early skin limited disease does better than FMF presenting with extracutaneous disease)(van Santen 2017)
Sézary Syndrome

- Variant of CTCL characterized by erythroderma, generalized lymphadenopathy, and related clones in skin, blood, LN
- Required for diagnosis-Sezary count >1000/uL, CD4:CD8 ratio >10:1, and loss of 1 or more T cell antigens (CD7, CD26)
- Poor prognosis, T4 stage
Sézary Syndrome

• Clinical: characterized by intractable pruritus, palmar keratoderma, onychodystrophy, alopecia
• Matching skin and blood clones = more aggressive outcomes
Sézary Syndrome

• Significant blood involvement (B2) has similar outcomes as visceral involvement (M stage)
• Truly requires coordination among clinicians, dermatopathologists and hematopathologists, with flow/morphology analysis of blood
Sézary Syndrome-Histology

• Variable, shows overlap with classic MF
  – Epidermotropism, Pautrier’s microabscess formation

• PCR can be helpful in non diagnostic cases

• CD4+, loss of CD7, CD26; PD1+, express skin homing markers
Sézary Syndrome

• Can have lymph node involvement, visceral involvement, and skin tumors (independent poor prognostic markers)

• Aggressive disease (stage IV, median OS 33-48 months) (Scarisbrick 2015)
CD8+ Epidermotropic TCL

• Mycosis fungoides (hypopigmented variant)
• CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma
• Gamma delta T cell lymphoma
PC CD8+ Aggressive Epidermotropic Cytotoxic TCL

- Generalized papules, nodules, and tumors (Berti 1999)
  - Sudden eruption, often with ulceration
  - Frequently involving oral cavity
- Spread to visceral organs, but not LN
- Aggressive clinical course (22-32 months average survival)
PC CD8+ Aggressive Epidermotropic Cytotoxic TCL

- Usually, preceding MF like patches are not present
- Often middle aged or elderly patients
- Rapid progression
- Prognosis dismal with poor response to therapy (Robson 2015; Guitart 2017)
PC CD8+ Aggressive Epidermotropic Cytotoxic TCL

- Band-like infiltrate of usually medium or large cells
- Pronounced epidermotropism in acanthotic epidermis
- Necrosis and ulceration common
PC CD8+ Aggressive Epidermotropic Cytotoxic TCL

- Lymphoepithelial lesions
- Pleomorphism, blastic morphology common
- True angioinvasion/angiodestruction, like NK/T cell lymphoma, not common
- Absent Pautrier’s microabscesses
PC CD8+ Aggressive Epidermotropic Cytotoxic TCL

- Immunophenotype: CD3+, CD8+, TIA-1+, alpha beta subtype; CD45RA+; CD7+
- Sometimes only one + cytotoxic marker
- CD5, CD2, and EBV are negative
- CD56 typically negative
- Ki 67 usually much higher (75% or greater) than in classic MF (around 5-10%)
PC CD8+ Aggressive Epidermotropic Cytotoxic TCL

- DDX-Other aggressive CTCLs (gamma delta TCL, extranodal NK/T cell lymphoma)
- Transformed MF
- Pagetoid reticulosis (can be CD4+ or CD8+)
  - Localized variant
- ALCL
  - Expression of CD30 helps exclude aggressive CD8+ cytotoxic TCL
PC CD8+ Aggressive Epidermotropic Cytotoxic TCL

• Lyp (type D)
  – Can have weak expression of CD30
  – Will have to check with the clinical setting

• Other indolent entities
  – Hypopigmented MF
  – Subcutaneous panniculitis like T cell lymphoma
  – PC acral CD8+ TCL
Nodular Dermal T-cell Infiltrate

does the patient have a h/o MF?

Yes

cytologic evaluation

MF, tumor stage

small cells

Large cells, more than 25% of infiltrate = MF, large cell transformation

Yes
Nodular Dermal T-cell Infiltrate
does the patient have a h/o MF?

Yes

No

cytologic evaluation

MF, tumor stage

small cells

Large cells, more than 25% of infiltrate

MF, large cell transformation

Panel of antibodies

Beaumont HEALTH
Important Antibodies to Employ

- CD30
- CD56
- CD4
- CD8
- TIA-1
- Ki-67
- β-F1, TCR gamma
- CXCL13
- EBV in situ
- PD-1
- Other pan T cell antigens, i.e., CD5, CD2, CD7
DD Nodular Dermal T-cell Infiltrate

- Tumor stage MF/transformed MF
- CD30 positive anaplastic large cell lymphoma (primary cutaneous vs secondary)
- Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder
- PC CD8+ aggressive epidermotropic cytotoxic TCL (provisional)
DD Nodular Dermal T-cell Infiltrate

- Cutaneous gamma/delta TCL
- Peripheral T cell lymphoma, NOS
- Extranodal NK/T lymphoma, nasal-type
- Cutaneous adult T cell leukemia/lymphoma
Cutaneous Gamma Delta TCL

• Very rare, highly aggressive lymphoma with skin and mucosal involvement
• Usually patients have ulcerating plum colored nodules or deeply placed “panniculitic” lesions; sometimes plaques may be present
Cutaneous Gamma Delta TCL

• Upgraded and is no longer provisional in 2016 WHO classification
• Nodal, bone marrow involvement at presentation uncommon
• Hemophagocytic syndrome can occur (Guitart 2012)
Cutaneous Gamma Delta TCL

- Neoplastic cells are T cells of gamma delta origin (rather than alpha-beta) (Toro 2003)
- Lesions can be primarily epidermotropic, involve epidermis and dermis, or have large panniculitic component
Cutaneous Gamma Delta TCL

• Can have associated lichenoid infiltrate; Pautrier’s microabscesses absent
• Cells are medium to large with “smooth” chromatin; may be deceptively bland
• Necrosis and angioinvasion commonly seen
Cutaneous Gamma Delta TCL

- Immunophenotype
  - CD2+, CD3+, TIA1+, CD4-, CD8 usually negative, CD5-, βF1- 
  - CD7, CD45RA +; CD56 or CD30 can be positive 
  - EBV is negative 
  - Express gamma-delta chains on cell surface (currently delta antibody available for FFPE tissue)
Peripheral T Cell Lymphoma, NOS

• T cell lymphoma that is difficult to classify
• Limited to the skin
Peripheral T Cell Lymphoma, NOS

- Clinical presentation is not that of MF; usually tumor nodules, may be necrotic/ulcerative
- Dense dermal infiltrate of medium to large T cells that are CD30 – but express TCR beta
Peripheral T Cell Lymphoma, NOS

• Histology variable—Can have band like superficial infiltrates or deep dermal infiltrates
• Angiocentrism
• Can have small, medium or large cells
Peripheral T Cell Lymphoma, NOS

- Can have CD4 or CD8 expression
- Of alpha beta or TCR null type
- Can express cytotoxic markers
- Unfavorable prognosis (Tolkachjov 2016)
SPRING IN CADILLAC, MICHIGAN (NEAR TRAVERSE CITY)
Extranodal NK/T cell lymphoma, Nasal Type

- EBV+ aggressive extranodal lymphoma which expresses NK markers (CD56)
- Nasal: so called lethal midline granuloma
- Central American/Asian subgroups affected commonly
Extranodal NK/T cell lymphoma, Nasal Type

- Tumor nodules, plaques, with B symptoms
- Hemophagocytic syndrome
- Median survival of less than 15 months
Extranodal NK/T cell lymphoma, Nasal Type

- Dense dermal infiltrate, centered on skin appendages and blood vessels
- Necrosis, angiocentricity common
- Subcutis involvement
- Medium sized “blastic” cells, significant mitoses and apoptosis
Extranodal NK/T cell lymphoma, Nasal Type

• Immunophenotype
  – CD56+, CD2+, CD4-, CD8-, surface CD3-
  – EBV +, TIA-1 +
  – CD3 (epsilon chain) expressed (cytoplasmic)
  – βF1 negative
Extranodal NK/T cell lymphoma, Nasal Type

- **Immunophenotype**
  - T cell antigens usually absent (i.e., CD5, CD7 negative)

- **TCR rearrangement in germline configuration if pure NK**
Summary

• Aggressive T cell lymphomas can arise from mycosis fungoides (transformation) but can also be *de novo* entities

• Immunophenotyping is essential in the diagnosis and classification of dermal nodular T-cell infiltrates

• Clinical correlation and complete clinical staging work up is paramount