CTCL: Important Diagnostic Tools

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Diagnosis of CTCL

- Clinical Information and Histology
- Immunohistochemistry
  - identify neoplastic lymphocyte population
  - subtype CTCL according to WHO-EORTC criteria
- T cell receptor gene rearrangement studies by polymerase chain reaction (PCR) or Southern blot hybridization
  - identify clonal population
Histologic Features Patch/ Plaque Stage MF

- band-like infiltrate
- focal epidermotropism out of proportion to degree of spongiosis
- Pautrier’s microabscesses
- single cell arrays within basal layer
- papillary dermal fibrosis
- Sézary cells
Diagnosis of Mycosis fungoides

- H&E morphology and clinical correlation
DD of Bandlike Dermal Infiltrates

lymphomatoid drug eruption
treated spongiotic dermatitis
interface dermatitis
lichenoid purpura
actinic reticuloid
lichen striatus
LS & A
Pityriasis lichenoides
type B lymphomatoid papulosis
CD8+ epidermotropic CTCL
Immunophenotyping

- Immunophenotype
  - CD4+, CD7 – (reactive infiltrates can show loss of CD7)
  - CD4/CD8 ratio (reactive infiltrates can have CD4/CD8 ratios of up to 6:1)
Immunophenotyping

- Usually confirmatory in morphologically unequivocal cases
- Least helpful in ambiguous cases
  - Scant infiltrate
  - Intraepidermal neoplastic population with variable reactive infiltrate
  - CD4/CD8 ratios not well established for entities in DD (Stanford study is unique)
Molecular Studies

- Molecular studies
  - T cell receptor clonally rearranged by PCR or Southern Blotting in > 80% of MF
  - Up to 30% false positive rate with PCR (GeneScan analysis)
  - Compare the clone in multiple biopsies (sequential or multifocal)
Diagnosis of Patch/Plaque Mycosis Fungoides

- H&E is gold standard
- biopsies from several sites
- serial biopsies
- close clinicopathologic correlation
- biopsy performed after adequate time off topical therapy (1-2 weeks)
CD8+ Epidermotropic CTCL

- mycosis fungoides (hypopigmented variant)
- Woringer Kolopp disease
- CD8+ epidermotropic T-cell lymphoma (provisional entity)
CD8+ Epidermotropic CTCL

- generalized patches, plaques, nodules
- spread to visceral organs, but not LN
- aggressive clinical course (32 months average survival)

CD8+ Epidermotropic CTCL

- band-like infiltrate
- Medium or large sized cells
- pronounced epidermotropism in acanthotic epidermis
- neoplastic cells CD8+
Phenotype

- CD3+
- CD8+
- TIA-1+
- proliferation rate >> MF (approx. 40%)
DD of Dense Dermal Lymphoid Infiltrates

CD20, CD3

CD20+, CD3-

CD20-, CD3+

CD20-, CD3-

Cutaneous B-cell lymphoma

CTCL
NK/T- cell lymphoma
DD Nodular Dermal T-cell Infiltrate

- tumor stage MF/transformed MF
- Type C lymphomatoid papulosis
- CD30 positive anaplastic large cell lymphoma (primary cutaneous/secondary)
- CD4+ small/medium-sized T-cell lymphoma (provisional entity)
- Peripheral T cell lymphoma, NOS
- Extranodal NK/T lymphoma, nasal-type
- CD8+ aggressive epidermotropic lymphoma
- Cutaneous gamma/delta TCL (provisional entity)
- cutaneous lymphoid hyperplasia
- Leukemia
- If within the subcutaneous tissue only: subcutaneous panniculitis like T cell lymphoma
Nodular Dermal T-cell infiltrate

- Does the patient have a history of MF?
Nodular Dermal T-cell Infiltrate

does the patient have a h/o MF?

Yes

cytologic evaluation

small cells

MF, tumor stage

large cells

MF, large cell transformation
Tumor Stage/Transformed MF

- Antibodies:
  - Ki 67
  - CD30

- Diagnosis of Transformed MF: Infiltrate has to contain >25% large cells
Nodular Dermal T-cell Infiltrate

does the patient have a h/o MF?

Yes

No

Cytologic evaluation

MF, small cells

MF, large cells

MF, large cell transformation

? h/o peripheral T-cell lymphoma

Panel of antibodies
Nodular Dermal T-cell Infiltrate

does the patient have a h/o MF?

Yes

No

cytologic evaluation

small cells

MF, tumor stage

large cells

MF, large cell transformation

? h/o peripheral T-cell lymphoma

Panel of antibodies

no
First Line Panel of Antibodies

- CD30
- CD56

- CD4
- CD8
- TIA-1
- Ki-67
- \( \beta \)-F1 (Important in gamma/delta T cell lymphoma)
CD30+, CD56-, CD3+/-

CD30+ Lymphoproliferative Disorder

- more than 75% of cells CD30 positive
  - lymphomatoid papulosis type C
  - primary cutaneous anaplastic large cell lymphoma
  - systemic anaplastic large cell lymphoma, alk-negative
  - systemic anaplastic large cell lymphoma, alk-positive
  - (transformed MF)
CD30-, CD56-, CD3+, CD4+/-, CD8+/-,

- CD4+ small/medium-sized T-cell lymphoma
- Peripheral T cell lymphoma, NOS
- CD8+ epidermotropic lymphoma
- cutaneous gamma/delta TCL
CD4+ Small/Medium-sized T-Cell Lymphoma

- Solitary (usually) or multiple tumor nodules
- Not preceded by patches or plaques of MF
- Relatively favorable clinical course
- 60% 5 year survival
CD4+ Small/Medium-sized T-Cell Lymphoma

- deep and diffuse infiltrate
- small-to-medium sized cells
- <30% large cells
- By definition, CD4+
- CD30-
- CD56-
Peripheral T Cell Lymphoma, NOS

- single or multiple tumor nodules
- not preceded by patches or plaques of MF
- aggressive clinical course
- 10-20% 5 year survival
Peripheral T Cell Lymphoma, NOS

- deep and diffuse infiltrate
- >30% large cells
- CD30-
- CD56-
CD30-, **CD56+**, CD3+/-, CD4-, CD8+/-

- cell membrane staining with CD56 in > 50% of cells
  - NK/T-cell lymphoma
  - Gamma delta T-cell lymphoma
NK Cells

- 10-15% of human peripheral blood lymphocytes
- Non-T/ non-B lineage, more closely related to T-lineage
NK Cells

- morphology: large granular lymphocyte
- kills target cell through cytolysis (perforin, granzyme, TIA-1)
- BM derived (CD34+ stem cells)
Histology

- dense dermal infiltrate
- columns of lymphoid cells centered on skin appendages
- often angiocentric/ angiodestructive
- fat commonly involved
- areas of necrosis
- high mitotic and apoptotic rate
Cytology

- small cells with irregular and angulated nuclei
- medium cells with round or folded nuclei
- large cells with vesicular nuclei and prominent nucleoli
- mixture of all cell types
Immunophenotype

- CD56 (N-CAM) +
- CD43 +
- TCRβ -
- CD20 -
- CD30-/+
- CD4 -/+ 
- CD8 -/+ 
- TIA-1 +/-
- CD3 surface -
- CD3 (ε) cytoplasmic +/-
- MDR +/-
CD56

- N-CAM: neural cell adhesion molecule
- Adhesion molecule of immunoglobulin superfamily
- Expressed on: NK cells, NK/T cells, neural and neuroendocrine tissues
- Tumors: NK neoplasms, neuroblastoma, small cell carcinoma (Merkel cell carcinoma), medullary thyroid carcinoma, peripheral nerve tumors
CD3

- discrepant results in frozen and paraffin embedded tissue (negative in frozen, positive in paraffin)
Ancillary Studies

- Clonality cannot be demonstrated with Southern blotting or PCR for TCR
  - Subset of NK/T is clonal with these methods and will also express bF1
  - Distinction from gamma delta T cell lymphoma: these will show a T cell clone
- EBV mRNA often positive (in situ hybridization)
- Less frequently associated with EBV than nasal type T/NK lymphomas
Summary

- Patch and plaque stage MF are best diagnosed with HE.
- Immunophenotyping is essential in the diagnosis and classification of dermal nodular T-cell infiltrates.
- CD56 and CD 30 should be included in the routine panel for immunophenotyping.
Acknowledgements

- Sabine Kohler, MD
- Youn Kim, MD