An Update on Lymphoproliferative Disorders

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Disclosures

• I have nothing relevant to disclose.

The 2016 WHO classification of lymphomas: What’s old

• Mycosis fungoides
• Sezary syndrome
• CD30+ lymphoproliferative disorders (lymphomatoid papulosis, primary cutaneous ALCL)
  – C-ALCL and Lyp with chromosomal rearrangement of 6p25.3
• Subcutaneous panniculitis like TCL
• Gamma delta TCL

The 2016 WHO classification of lymphomas

• What is no longer provisional?
  – Hydroa vacciniforme like lymphoproliferative disorders (no longer strictly a lymphoma)
• What’s provisional?
  – Primary cutaneous acral CD8+ TCL

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Outline

• Discussion of new entities
  – Hydroa vacciniforme like lymphoproliferative disorder
  – Primary cutaneous ALCL with DUSP22-IRF4 rearrangement on 6p25.3
  – Primary cutaneous acral CD8+ T cell lymphoma
• New techniques for clonality assessment: high throughput sequencing

Hydroa vacciniforme like LPD

• Nine year old Guatemalan boy with waxing and waning skin tumors and ulcers present for 3 years. The lesions start as arthropod like vesicles and subsequently form bullae.
Hydroa vacciniforme like lymphoproliferative disorder (LPD)

• Chronic EBV+ LPD of childhood with risk of progressing to lymphoma (HV-lymphoma) (Doeden K et al. J Cutan Pathol 2008; 35:488)
• Spectrum including classic HV at one end and HV-like lymphoma at the other
• Classic HV=rare, UV related vesiculopapular eruption with scarring

• HV-like lymphoma=HV like lesions but clonal proliferation of T cells
• Inability to demonstrate which patients will only have HV and which will develop overt lymphoma=current terminology introduced into 2016 WHO classification (Gru A et al. (2016),http://dx.doi.org/10.1053/j.sempdp.2016.11.003)

Hydroa vacciniforme like lymphoproliferative disorder (LPD)

• Asian and South Americans more at risk for developing lymphoma
• Most cases seen in children
• Classic HV can have marked facial edema and lesions can be chronic
• While in 2008, the role of systemic symptoms was unclear, in 2016, the presence of hepatosplenomegaly = lymphoma

• The cells are medium sized, hyperchromatic, and centered on the dermis
• Epidermal necrosis and vesicles can be seen
• Some overlap with the lesions of NK-T cell lymphoma, with angiocentricity
• Can express T or NK cell markers (or both)
• EBV+

Hydroa vacciniforme like lymphoproliferative disorder (LPD)

• Differential diagnosis (would only be on morphologic grounds)
  – Aggressive NK leukemia (blood involvement by atypical CD56+ cells; skin involvement rare)
  – Extranodal NK/T cell lymphoma (usually in adults, very aggressive clinical course with death measured in months)

• Differential diagnosis (would only be on morphologic grounds)
  – Subcutaneous panniculitis like T cell lymphoma: This lymphoma is based in the fat (panniculus) and its neoplastic cells show rimming of adipocytes
  – The neoplastic cells express CD8 and are EBV and CD56 negative
  – Dermal involvement is not usually present
Hydroa vacciniforme like lymphoproliferative disorder (LPD)

- Differential diagnosis (would only be on morphologic grounds)
  - Gamma delta T cell lymphoma: This lymphoma has significant epidermal, dermal and subcutaneous involvement
  - It can lack expression of CD4 and CD8; occasionally it is CD8+
  - CD56 is positive but EBV is negative

Hydroa vacciniforme like lymphoproliferative disorder (LPD)

- Take home pearls = Patients are almost always from Central or South America, or Japan/Korea/China
- Pediatric patients
- Morphology/Immunohistochemistry/Molecular=Huge overlap with other NK/T cell entities
- Really a clinical diagnosis!

Orchard Lake

Primary cutaneous anaplastic large cell lymphoma with DUSP22-IRF4 rearrangement

- 55 year old man with a solitary 1.5 cm lesion on his lower left eyelid.
Primary cutaneous anaplastic large cell lymphoma with $DUSP22-IRF4$ rearrangement

- Dense dermal atypical lymphoid infiltrate
- Extensive epidermotropism is appreciated, but the lesion is a solitary papule
- Cells within the dermis are small to medium sized with hyperchromatic, hyperconvoluted nuclei

Lesional cells are strongly CD30+ and CD3+, but lack CD4 and CD8 in the epidermotropic component

A call to the clinician confirmed solitary, relatively large nature of the lesion and its rapid onset

Primary cutaneous anaplastic large cell lymphoma with $DUSP22-IRF4$ rearrangement

- Given unusual histology and immunohistochemistry, we performed $DUSP22-IRF4$ rearrangement testing with break apart FISH probe (6p25.3)
- A rearrangement was present
- After over a year of follow up, the patient is alive and free of disease following excision of the primary lesion

CD30+ Lymphoproliferative Disorders

- CD30+ lymphoproliferative disorders traditionally constitute four entities
  - Primary cutaneous ALCL
  - Lymphomatoid papulosis
  - Transformed mycosis fungoides
  - Systemic ALCL with secondary cutaneous involvement

CD30+ Lymphoproliferative Disorders

- Significant overlap between pcALCL and lymphomatoid papulosis (Lyp)
  - Lyp = waxing and waning small papules that come in crops (groups of lesions) and fade over 2 week period
  - pcALCL = larger (1.5 cm and above) lesion that does not fade over time, or fades very slowly (8 week period or more)
pcALCL with DUSP22-IRF4 chromosomal rearrangements

- Recently chromosomal rearrangements have been described in both systemic and primary cutaneous ALCL (Pham-Ledard A et al. J Invest Dermatol 2010; 130:816)
- In systemic ALCL, rearrangements of DUSP22 and IRF4 at chromosome 6p25 leads to a relatively monomorphic tumor with lack of cytotoxic granules
- Superior prognosis

pcALCL with DUSP22-IRF4 chromosomal rearrangements

- This translocation has been identified in pcALCL and lymphomatoid papulosis (Lyp)
- 20% of tested cases of pcALCL
- Does not change prognosis or clinical outcome (Kempf W. (2016) http://dx.doi.org/10.1053/j.semdp.2016.11.005)

pcALCL with DUSP22-IRF4 chromosomal rearrangements

- Wada et al. observed that FISH for 6p25.3 rearrangement is highly specific for pcALCL in comparison to other cutaneous LPD (Wada et al. Mod Pathol 2011 24: 596)
- Only 1 of 32 (3%) of cases of Lyp had this translocation

pcALCL with DUSP22-IRF4 chromosomal rearrangements

- pcALCL with this translocation often have a dense epidermotropic infiltrate of atypical cells
- Loss of CD4 and CD8 are documented
- Cells within the dermis are composed primarily of small to medium sized CD30+ cells, as opposed to ‘anaplastic’ cells often seen in ALCL

pcALCL with DUSP22-IRF4 chromosomal rearrangements

- Take home pearl: Consider FISH if the lesion is a solitary cutaneous lesion that is CD30+ but has unusual histology for both ALCL and Lyp
- For now, no change in clinical management

Sleeping Bear Dunes Lakeshore
Primary cutaneous acral CD8+ lymphoma

- 55 year old woman with erythematous lesions on the ear and nose (case kindly shared by Dr Alistair Robson).
- Subsequently she developed small pinpoint erythematous lesions on the heel.
Primary cutaneous acral CD8+ lymphoma
• Initially described by Petrella et al. as lesions on the ear that are indolent, have a Grenz zone, and express CD8 (Petrella T et al. Am J Surg Pathol 2007; 31:1887)
• Several case series by Dr Robson and his colleagues further define this entity

Primary cutaneous acral CD8+ lymphoma
• Erythematous papules and nodules on the ear, nose, and acral sites (hands/feet)
• Solitary or multiple lesions
• Can be rarely recurrent
• While lesions on the ear were described first, overlap with acral lesions, and now thought the same biological entity

Primary cutaneous acral CD8+ lymphoma
• In the ear and on the nose = Grenz zone and monomorphous population of cells with folded nuclei
• Interstitial growth pattern, perinuclear halos
• Acral sites=Pautrier’s microabscesses
• CD8+ cells with TIA-1 expression
Primary cutaneous acral CD8+ lymphoma

- Clonal rearrangements
- No systemic involvement
- Long term follow up = recurrences can occur but no other adverse events
- New provisional category in 2016 WHO classification scheme

Primary cutaneous acral CD8+ lymphoma

- NOT related to CD4+ small medium pleomorphic T cell LPD, which is a LPD of follicular T helper cells

Primary cutaneous acral CD8+ lymphoma

- Take home pearl: Entity to consider if solitary, small lesion on head and neck or acral site, with expression of CD8

Primary cutaneous acral CD8+ lymphoma

- Clonality Assays in Cutaneous T cell lymphomas (CTCL)
  - Early mycosis fungoides (MF) is difficult to diagnose and requires combination of clinical, histopathologic, immunophenotypic, and molecular analysis
  - Most patients with established MF do well long term
  - Significant overlap between MF and reactive entities such as lymphomatoid drug eruption

Clonality Assays in Cutaneous T cell lymphomas (CTCL)

- Increasingly, clonality assays are part of the diagnostic approach
- Positive clone DOES NOT mean lymphoma
Clonality Assays in Cutaneous T cell lymphomas (CTCL)

• Current technology misses cutaneous lymphoma (not sensitive enough) and has false positives (up to 30% of reactive cases)
• Role of sequencing in clonality assays for cutaneous lymphomas?

Clonality Assays in Cutaneous T cell lymphomas (CTCL)

• High throughput sequencing can detect TCR clones, relative frequency of each clone, and sequence clones (Kirsch IR et al, Sci Transl Med 2015; 7:308ra158).
• Different from PCR, it is a bead based amplification process that sequences simultaneously
• Can pick up 100% of established cases of MF (46/46)

Clonality Assays in Cutaneous T cell lymphomas (CTCL)

• Frequency of top T cell clone measured against fraction of total nucleated cells in sample
• Reactive entities tend to have clones, but not large frequency of dominant clone relative to nucleated cells
• Malignant entities tend to have dominant clones that dwarf nucleated cells

Clonality Assays in Cutaneous T cell lymphomas (CTCL)

• Some entities such as pityriasis lichenoides et varioliformis acuta, known to have T cell clones, may be T cell dyscrasias
• Up to 40% of tested cases with HTS still retained detectable clones

Clonality Assays in Cutaneous T cell lymphomas (CTCL)

• Take home pearls: High throughput sequencing (HTS) is an efficient way to amplify and sequence TCR genome
• More effective than current PCR techniques
• Price is going down
• Greater availability in the future

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Au Sable River, MI