What’s New in Cutaneous Lymphoma: the 2016 WHO Classification

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Disclosures

• I have nothing relevant to disclose.
The 2016 WHO classification of lymphomas: What’s old (Swerdlow 2016; Sundram, 2019)

- Mycosis fungoides/Sézary syndrome
- CD30+ lymphoproliferative disorders (lymphomatoid papulosis, primary cutaneous ALCL)
  - C-ALCL and Lyp with chromosomal rearrangement of 6p25.3
- Subcutaneous panniculitis like TCL
Hydroa vacciniforme like lymphoproliferative disorders (no longer strictly a lymphoma)

Gamma delta TCL (no longer provisional)
The 2016 WHO classification of lymphomas: What’s provisional

- Primary cutaneous CD8+ aggressive epidermotropic cytotoxic TCL
- Primary cutaneous CD4+ small medium pleomorphic T cell lymphoproliferative disorder (LPD)
- EBV positive mucocutaneous ulcer
- Primary cutaneous acral CD8+ TCL
- Breast implant associated ALCL
Outline

• Discussion of some new entities
  – Hydroa vacciniforme like lymphoproliferative disorder
  – Primary cutaneous ALCL with *DUSP22-IRF4* rearrangement on 6p25.3
  – Breast implant associated ALCL
  – Primary cutaneous acral CD8+ T cell lymphoma
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 (Doeden, 2008)
- Spectrum including classic HV at one end and HV-like lymphoma at the other
- Classic HV=rare, UV related vesiculopapular eruption with scarring
Hydroa vacciniforme like lymphoproliferative disorder (LPD)

- 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, 2016)
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
- Systemic symptoms can occur in the HV-like lymphoma end of the spectrum
Hydroa vacciniforme like lymphoproliferative disorder (LPD)

- 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)
- Can be of $\alpha\beta$ or $\gamma\delta$ origin
- EBV+
Hydroa vacciniforme like lymphoproliferative disorder (LPD)

- Differential diagnosis (on morphologic grounds)
  - Aggressive NK leukemia (blood involvement by atypical CD56+ cells would be present; skin involvement would be rare)
  - Extranodal NK/T cell lymphoma (usually in adults, very aggressive clinical course with death measured in months)
Hydroa vacciniforme like lymphoproliferative disorder (LPD)

- Differential diagnosis (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 (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!
Bond Falls, near Paulding and Ontonagan, MI
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 \textit{DUSP22-IRF4} rearrangement

• Histology is of a dense dermal atypical lymphoid infiltrate
• Extensive epidermotropism is appreciated, but the lesion is a solitary papule (not characteristic of mycosis fungoides)
• Cells within the dermis are small to medium sized with hyperchromatic, hyperconvoluted nuclei
Primary cutaneous anaplastic large cell lymphoma with \textit{DUSP22-IRF4} rearrangement

- Lesional cells are strongly CD30+ and CD3+, but lack CD4 and CD8 in the epidermotropic component.
- The lesional cells retain CD2 and CD5 in the intraepidermal 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)
Different types of Lyp

• None of these types change clinical outcome of Lyp at all!
• They are thought to be different time points of the same disease process
• Type A = wedge shaped dermal infiltrate with scattered CD30+ cells
• Type B = MF like with epidermotropism
Different types of Lyp

• Type C = ALCL like, with dense dermal infiltrate of anaplastic cells
• Type D = similar in cytology to CD8+ cytotoxic lymphomas, with CD8 expression
• Type E = angioinvasive, most of these are CD8+
pcALCL with *DUSP22-IRF4* chromosomal rearrangements

- Recently chromosomal rearrangements have been described in both systemic and primary cutaneous ALCL (Pham-Ledard, 2010)
- 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)
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, 2011)

- 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 \textit{DUSP22-IRF4} chromosomal rearrangements

- \textbf{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
- \textbf{For now, no change in clinical management}
LELAND, MICHIGAN, ON LAKE MICHIGAN
Breast Implant Associated ALCL

• 40 year old woman with history of saline implants, now with new left breast swelling
Breast Implant Associated ALCL

• Associated with patients with history of saline or silicone implants
• Localized breast swelling
• Imaging shows mass, fluid collection adjacent to implant, or both
Breast Implant Associated ALCL

• Important-if lymphoma cells are confined to capsule or extend beyond capsule
• Lymph node involvement considered adverse finding
• ALCL-type hallmark cells found in aspirate or in capsule
• CD30+Alk-
Breast Implant Associated ALCL

- Added as a provisional category to the 2016 WHO classification
- Rare and new
- Outcomes different from both cutaneous and systemic ALCL
SPRING FLOWERS IN UPPER MICHIGAN
Primary Cutaneous CD4+ Small/Medium T cell Lymphoproliferative Disorder

• 45 year old woman with solitary erythematous lesion on right cheek.
Primary Cutaneous CD4+ Small/Medium T cell Lymphoproliferative Disorder

- Patients usually have a single or multiple plaques or tumors, without patches of MF
- Head and neck favored
- Excellent prognosis, over 80% 5 year survival (Beltraminelli 2009; Mattoch 2009; Maurelli 2017)
- Redesignated as a lymphoproliferative disorder in 2016 to reflect indolent course
Primary Cutaneous Small/Medium-sized CD4+ TCL

- Dense diffuse skin infiltrates composed primarily of small to medium sized T cells
- Histologically heterogenous, unlike acral CD8+ lymphoma
- A Grenz zone is usually present
- Lymphocytes express CD3 and CD4, without loss of T cell antigens
Primary Cutaneous Small/Medium-sized CD4+ TCL

• There can be a surprising number of B cells and/or plasma cells (Rodriguez Pinilla 2009; Mattoch 2009; Magro 2019)
• Ki 67 rate is relatively low
• PD-1 (marker of T follicular helper cells) is expressed
• Some controversy in the literature whether these represent a version of follicular T cell lymphoma
SCOTT FALLS, NEAR AU TRAIN, MICHIGAN
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

- New provisional category in the 2016 WHO classification of hematopoietic disorders
- Initially described as lesions on the ear that are indolent, have a Grenz zone, and express CD8 (Petrella, 2007)
- Several case series by Dr Robson and his colleagues further define this entity (Ally 2014)
Primary cutaneous acral CD8+ lymphoma

• Erythematous papules and nodules on the ear, nose, and acral sites (hands/feet) (Li 2014)
• Solitary or multiple lesions
• Can be rarely recurrent
• While lesions on the ear were described first, there is overlap with acral lesions
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
- No folliculotropism or syringotropism
Primary cutaneous acral CD8+ lymphoma

- CD8+ cells with TIA-1 expression
- EBV negative
- Follicular T helper cell markers such as CXCL13 and PD-1 are negative
- Ki67 can be low or high (up to 40%)
Primary cutaneous acral CD8+ lymphoma

- Clonal rearrangements
- No systemic involvement
- Long term follow up = recurrences can occur but no other adverse events
Primary cutaneous acral CD8+ lymphoma

- NOT related to CD4+ small medium pleomorphic T cell lymphoma
- This latter lymphoma expresses PD1, ICOS and CXCL13, unlike acral CD8+ lymphoma (Greenblatt 2013; Kluk 2016)
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
Summary

• Changes have been made to:
  – establish new provisional entities (EBV+ mucocutaneous ulcer)
  – designate aggressive entities as lymphomas (gamma delta T cell lymphoma)
  – inject appropriate uncertainty into certain categories (hydroa vacciniforme like LPD)
  – rename indolent entities (CD4+ small-medium T cell LPD)
Summary

- Expectations exist that in the future, new entities may be carved out of current ‘waste basket’ designations (PTCL-NOS).
- Molecular signature studies may further inform classification, treatment approaches, and understanding of clinical outcome.