Society for Hematopathology

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"Cutaneous Lymphomas: Integrating Morphology with Molecular Advances in Diagnosis"

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1. **Question**: Which specialty do you think is better to take responsibility of reporting cutaneous lymphoma - dermpath or hemepath?
   Answer: That's an excellent question. Since cutaneous lymphomas fall within the scope of hematopathology, I believe hematopathologists should take primary responsibility for diagnostic reporting. However, given the risk of misclassifying certain inflammatory dermatoses as cutaneous lymphomas, this process is best approached collaboratively. At my institution, we have the Cutaneous Lymphoma Program that includes a hematopathologist, dermatopathologist, hematologist-oncologist, dermatologist, and radiologist. We review challenging cases together and make joint diagnostic and management decisions—a model that has proven highly effective and successful.
2. **Question:** I struggle with peripheral blood flow Cytometry cases submitted for circulating Sezary cells, do I need a well- defined population of CD7-/CD26- T cell population with CD4:CD8 ratio of more than 10 or do I report the CD4+|CD26- and CD4+|CD26- cell regardless of CD4:CD8 ratio and well defined population?
   Answer: The current recommendation is an absolute Sézary cell count ≥ 1000/µL, OR an expanded CD4+ T-cell population with a CD4:CD8 ratio > 10, OR an expanded CD4+ T-cell population with an abnormal phenotype (CD4+/CD7− T cells ≥ 40% or CD4+/CD26− T cells ≥ 30%). However, if you have a TRBC1 tube and find clonal populations on the any of these T cell subsets you can report it. On the otherhand, if there are no clonal populations by TRBC1 , we don't report it. If you don't have the TRBC1 tube, then it gets tricky when these T cell subsets don't meet the recommended criteria. In those situations, one may choose to report it with the caveat that these can occur in healthy individuals.

3. **Question:** Is Sezary syndrome a higher stage in MF or is a different disease?
   Answer: Sézary syndrome (SS) and mycosis fungoides (MF) are classified as distinct diseases, not simply as different stages of the same condition, although both are subtypes of cutaneous T-cell lymphoma (CTCL).

4. **Question:** How to differentiate Sezary from angioplasties T cell lymphoma involving the skin?
   Answer: Sézary syndrome (SS) and I presume you mean angioimmunoblastic T-cell lymphoma (AITL) involving the skin can be differentiated by integrating clinical presentation, histopathology, immunophenotype, and molecular findings. SS is a leukemic variant of cutaneous T-cell lymphoma characterized by erythroderma, lymphadenopathy, and significant peripheral blood involvement by malignant T cells. Skin involvement is primary and often precedes nodal disease. In contrast, cutaneous AITL almost always occurs in the setting of established systemic (nodal) AITL, with skin lesions appearing concurrently or after nodal disease, not as the initial manifestation. Histologically, SS can present with epidermotropism and tend to have a CD4+ CD7-CD26- phenotype with frequent loss of expression of T cell markers, whereas AITL does not typically show epidermotropism or frequent loss of T cell markers or CD26, less frequent peripheral blood involvement. Although AITL shows TFH marker expression, Sezary syndrome show strong PD1 expression as well so may not be helpful. Mutations in *RHOA* and *IDH2* will also favor AITL.

5. **Question:** Can Sezary be diagnosed on skin biopsy without epidermotropism (no prior history of MF but history of skin lesions (patches X3 years) now presenting with generalized rash?
   Answer: Sézary syndrome can be diagnosed in a patient with no prior history of mycosis fungoides (MF) and longstanding skin lesions, even if the skin biopsy lacks epidermotropism, provided the clinical and hematologic criteria for SS are met.

6. **Question:** Does MF involves lymph node without any clinical history of Sezary syndrome?
   Answer: Yes, mycosis fungoides (MF) can involve lymph nodes in the absence of any clinical history of Sézary syndrome (see question 3). MF is primarily a cutaneous T-cell lymphoma, but as it progresses, it can extend to lymph nodes, blood, and visceral organs. Lymph node involvement is a recognized feature of advanced-stage MF and is included in the TNMB staging system for MF and Sézary syndrome.

7. **Question:** Could you please share the PD-1 clone and instrument you use?
   Answer: Abcam, clone NAT105

8. **Question:** Do you know of any geographic locale where most cases of MF are CD8 rather than CD4?
   Answer: Some studies have reported that CD8+ pediatric MF and CD8+ hypopigmented MF, are common in Black and Asian populations, and may be associated with a more indolent course.

9. **Question:** In patient presenting with skin tumorous lesion, do you require the history of patch and plaque stage to call it mycosis fungoides tumor stage (if immunophenotype fits)?
   Answer: No, a documented history of patch and plaque stages is not required to diagnose tumor-stage mycosis fungoides (MF) if a patient presents with a tumorous skin lesion and an immunophenotype consistent with MF. They can arise from patches or plaques or occur on their own.

10. **Question:** MF often takes repeated biopsies over many years to diagnose. How should we integrate the molecular test during workup in order to arrive at the diagnosis avoiding the multiple biopsies? How specific for lymphoma is it if the same clonal peak is demonstrated in skin biopsies from two sites?
    Answer: Molecular testing for T-cell receptor (TCR) gene rearrangement should be integrated as a supportive tool in the diagnostic workup of suspected mycosis fungoides (MF), especially when clinicopathologic findings are equivocal or repeated biopsies are non-diagnostic. However, TCR clonality alone is not definitive for lymphoma diagnosis and must be interpreted in the context of clinical, histopathologic, and immunophenotypic data. It is well recognized that TCR gene rearrangement analysis is useful to support the diagnosis of MF and Sézary syndrome, particularly when identical clonal peaks are demonstrated in skin biopsies from different sites. This finding increases the specificity for a clonal T-cell process and is highly suggestive of lymphoma, especially if the same clone is also found in blood or lymph node samples.

11. **Question:** I was wondering how useful Ki67 staining is in the evaluation of large cell transformation in MF?
    Answer: Some studies have demonstrated that Ki-67 immunostaining can aid in the diagnosis of large cell transformation (LCT), as transformed lesions typically show a higher proliferative index compared to non-transformed mycosis fungoides. However, the diagnosis ultimately relies on the morphologic identification of increased large cells, which should comprise at least 25% of the infiltrate.

12. **Question:** In cases with multiple cutaneous lesions, do you recommend taking more than one biopsy as a means to prove clonality?
    Answer: Yes, our clinicians typically obtain at least two biopsies from different sites. Detection of the same clonal T-cell receptor peak across multiple specimens greatly increases the likelihood that the process represents a T-cell lymphoma rather than a reactive condition.

13. **Question:** How do you go about with skin biopsies from two different sites at different points of time with two different clonal peaks? Are they same or different lesions?
    Answer: The presence of different T-cell receptor (TCR) clonal peaks in skin biopsies from two different sites or time points in a patient with suspected mycosis fungoides (MF does not necessarily indicate distinct, unrelated lesions; it can still represent the same disease process, reflecting clonal heterogeneity or subclonal evolution within MF. If the case is challenging then correlate with the clinical presentation for final diagnosis.

14. **Question:** What do you do when the clinical team has ordered T-cell clonality studies (which are positive) on peripheral blood prior to your work-up? Would these be enriched for oligoclonal/reactive populations limit the significance of clonality testing results?
    Answer: Positive T-cell receptor (TCR) clonality in peripheral blood prior to pathology work-up should be interpreted with caution, as it may reflect either malignant (MF/SS) or reactive/oligoclonal T-cell populations, and is not by itself diagnostic of cutaneous T-cell lymphoma. However, the advantage of having that clonal peak is that you can compare it to the skin biopsy to determine if it is the same clonal process, which will put the patient into the B1 or B2 category.

15. **Question:** Any recommendation for IHCs algorithm or main panels for cutaneous lymphomas?
    Answer: The essential IHC panel includes: CD2, CD3, CD4, CD5, CD7, CD8, CD20, and CD30. This panel helps establish T-cell lineage, assess for aberrant antigen loss (especially CD7 and CD26 in MF/SS), and identify CD30+ lymphoproliferative disorders.

    Additional markers may be used in selected cases: CD25, CD56, TIA1, granzyme B, perforin, TCRβ, TCRδ, IRF4/MUM1, EMA, CCR4, CXCL13, ICOS, PD-1. These help further

classify rare subtypes (e.g., TFH phenotype, cytotoxic variants) and distinguish between MF, Sézary syndrome, and other entities.

16. **Question:** Some of the mutations are very rare in the lymphomas you described. Common multi gene targeted NGS panels may lack gene coverage. Do you have any opinion on whole exome or whole genome studies?
    Answer: Targeted next-generation sequencing (NGS) panels are may be used as the first-line approach for routine lymphoma diagnostics due to their clinical utility, cost-effectiveness, and rapid turnaround; however, these panels may miss rare mutations if the relevant genes are not included in the panel design. Whole exome sequencing (WES) and whole genome sequencing (WGS) provide much broader coverage (usually up to 500 gene panel) and can identify novel, rare, or structural variants not captured by standard panels. These approaches may be particularly valuable in diagnostically challenging or unclassified cases, or when panel testing is inconclusive.

17. **Question:** What percentage of positivity for TFH markers do you use for assigning TFH lineage to a T-cell lymphoma?
    Answer: Assignment of T follicular helper (TFH) lineage to a T-cell lymphoma requires coexpression of at least two or three TFH markers. However, there is no established threshold of quantification of immunoreactivity. Based on my prior studies and personal experience, a threshold of ≥30% immunopositivity is reasonable. However, it is equally important to ensure that the antibody clones used are well-validated for strong, reliable staining and that no pre-analytic issues are affecting the results**.**

18. **Question:** I have a case of CD30+ T cell lymphoma in an inguinal lymph node. Patient has a history of epidermotropic T cell cutaneous lymphoma. How do I confirm if this is from the same location such as a transformed MF?
    Answer: You can perform T cell clonality in both the skin and lymph node biopsies to see if they are the same clonal peak, thus proving the same clonal process. It is also very important to look at the clinical presentation here because primary cutaneous ALCL will be in the differential diagnosis. Although they are indolent, on occasion, they can spread to the regional lymph nodes. Clinical correlation will be important here.

19. **Question:** At UVA do you do molecular/NGS studies on all of the cases for which you are suspicious of lymphoma?

Answer: No, we do not routinely perform NGS. Instead, we typically perform clonality studies to compare findings across different biopsies. The results are then integrated with the clinical, morphologic, and immunophenotypic features to reach a diagnosis. NGS is reserved for particularly complex or challenging cases.

Question: "Any comments about ""acral type"" CD8+ LPD (indolent?), and discriminating it from pcAETCL? Reports of CD68 ""dot-like"" pattern have been published as perhaps discriminating - but we have seen a very aggressive case."
Answer: In acral-type $CD8^+$ T-cell lymphoproliferative disorder (TLD), the infiltrate is typically confined to the dermis, with the epidermis largely spared. However, focal minimal epidermotropism and focal folliculotropism may be present—features that help distinguish it from primary cutaneous aggressive epidermotropic cytotoxic T-cell lymphoma (PCAETL), which characteristically exhibits prominent pagetoid epidermotropism. Clinical presentation is also an important differentiator: lesions are usually solitary, non-ulcerated nodules occurring at acral sites. Immunohistochemically, CD68 demonstrates a distinct Golgi dot-like staining pattern within the tumor cells, a feature described as almost unique to this entity in the 5th Edition of the WHO Classification.

20. **Question:** How often do you see loss of CD5 in mycosis fungoides and do you routinely order it in the initial workup?
    Answer: We routinely do the full T cell panel including CD5 and I do observe on rare occasion, loss of expression of CD5 in MF. It is not as frequent as loss of CD7 but they do occur. Finding both CD5 and CD7 loss of expression in MF increases specificity for the diagnosis of lymphoma especially in early patch cases.

21. **Question:** Is a partial loss of, for example, CD8 in mycosis fungoides still considered a loss?
    Answer: I'm not entirely sure I understand the question, but CD4 and CD8 expression are typically evaluated in relation to each other. Cases are generally interpreted as CD4-positive or CD8-positive, and less commonly as double-positive ($CD4^+/CD8^+$) or double-negative ($CD4^-/CD8^-$).
22. **Question:** Do you think TRBC1 is helpful in establishing clonality by flow for both skin biopsy and PB staging?
    Answer: In our practice, we currently use TRBC1 only for flow cytometric analysis of peripheral blood and it is helpful in establishing clonality. We do not yet perform TRBC1

immunohistochemistry (IHC) on skin biopsies in routine clinical practice, although we hope to implement this in the future.

23. **Question:** Do you have a standardized IHC panel for cases for which you are suspicious for cutaneous lymphoma? I've found the approach to be very heterogeneous across pathologists even within the same institute, which hinders future research application.
    Answer: See question 15

24. **Question:** What is the frequency of B-cell monoclonality in cutaneous MALT lymphoma, and how should one approach cases where the differential diagnosis between cutaneous MALT lymphoma and primary cutaneous CD4+ T-cell lymphoma is difficult, especially when both T-cell and B-cell clones are detected?
    Answer: B-cell monoclonality is detected in the majority of cutaneous MALT (marginal zone) lymphomas. However, a subset of cases may be negative by molecular or flow methods, especially if the neoplastic B-cell population is small or obscured by a prominent reactive infiltrate. When both B and T cell clones are present, one needs to integrate clinical, histopathologic, and immunophenotypic features. Both cutaneous MALT lymphoma and CD4+ TLPD can show overlapping features, including mixed B- and T-cell infiltrates and indolent clinical behavior. Careful assessment of the dominant cell type, architectural pattern, and immunophenotype is essential. For MALT lymphoma, lesions are often multiple, located in trunk and extremities, reactive germinal centers are more common as well as IgG4 positive plasma cells. By NGS mutations in FAS or TNFAIP3 genes may be observed. Are often solitary lesions, often in the head and neckareas and spontaneous resolution are also very common after the initial biopsy.

25. **Question:** How do you report cases in which you don´t have any clinical information but just clinical question about mycosis fungoides, but the histology looks like a lichenoid dermatitis?
    Answer: If a case is morphologically consistent with lichenoid dermatitis and shows no features suggestive of mycosis fungoides (MF), it should be reported as such. However, if there is some epidermotropism and uncertainty about whether this represents early MF, the case can be reported as an atypical lymphoid infiltrate, with a differential diagnosis including lichenoid dermatitis and early evolving patch-stage MF—particularly if a clonal T-cell population is detected.

26. **Question:** Do you consider loss of bcl-2 as a sign of aberrant T- cell phenotype?

Answer: I typically do not evaluate BCL2 in the context of T cell lymphomas and this concept is not popular in hematopathology.

27. **Question:** Can you please provide insight on how to differentiate CHIP from T cell lymphomas (TFH) when it comes to mutations?
    Answer: Differentiating clonal hematopoiesis of indeterminate potential (CHIP) from T-cell lymphomas of T follicular helper (TFH) phenotype relies on the specific types and patterns of mutations detected, their allelic burden, and their cellular context. CHIP is most commonly defined by mutations in CH driver genes such as DNMT3A, TET2, and ASXL1, typically at low variant allele frequency (VAF), and without evidence of overt hematologic malignancy or dysplasia. The presence of RHOA G17V and/or IDH2 R172 mutations, especially in combination with DNMT3A/TET2 and in the context of TFH immunophenotype and clonal TCR rearrangement, strongly favors TFH lymphoma over CHIP.