Histopathologic approach to epidermotropic lymphocytic infiltrates

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■ **Abstract**

Mycosis fungoides is the most common and therefore quintessential cutaneous lymphoma and is typically characterized by an epidermotropic infiltrate of atypical monoclonal CD4+ lymphocytes. Classical histopathologic findings include epidermotropism, lymphocytes with convoluted nuclear contours and surrounding perinuclear "halos," and papillary dermal fibrosis. Atypical lymphocytes may occasionally form Pautrier's microabscesses with tagging of lymphocytes along the basal keratinocytes. Unfortunately, a variety of benign inflammatory infiltrates, as well as other cutaneous lymphomas, may demonstrate some similar histopathologic findings. Herein, we review the wide array of epidermotropic T-cell lymphomas and discuss distinguishing features between these entities. We also offer an algorithmic approach utilizing histopathologic, immunophenotypic, and molecular techniques that can be used for analyzing an epidermotropic T-cell infiltrate in order to render a specific diagnosis.

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Given that mycosis fungoides (MF) is the most common and thus quintessential form of cutaneous T-cell lymphoma (CTCL), we will start our review with a discussion of this entity because many of the other entities that follow will be compared to it. MF is defined by the presence of an epidermotropic infiltrate of small-to-medium T lymphocytes.[1,2] The disease typically affects older adults and often has an indolent clinical course. It comes in patch, plaque, and tumor stages. In many cases, patients never progress beyond patch and/or plaque stage. In rare cases, it can progress into a leukemic form with blood involvement in which there are circulating atypical mononuclear cells in the peripheral blood. Unfortunately, the diagnosis of MF can be challenging because many inflammatory disorders demonstrate some similar histopathologic features, and patients may be misdiagnosed for years.[3] Based on literature review and our experience in the diagnosis of MF, we aim to describe an algorithmic approach to the evaluation of epidermotropic lymphoid infiltrates.

The gold standard for the diagnosis of CTCL is light microscopy. Clinical and histopathologic findings are critical in the evaluation of atypical lymphoid infiltrates to exclude the possibility of benign reactive inflammatory disorders. There are many potential mimics, including spongiotic, lichenoid, and psoriasiform disorders, such as chronic allergic contact dermatitis, early lichen sclerosus, or lymphomatoid drug eruptions.[4,5] A key feature in chronic allergic contact dermatitis and lymphomatoid drug eruptions is the presence of increased epidermal spongiosis and dermal edema out of proportion to the lymphoid infiltrate. By contrast, while minimal spongiosis may be seen, especially in the setting of topical treatment of MF, exuberant spongiosis, which is out of proportion to the lymphoid infiltrate, is not commonly encountered in MF. Similarly, vacuolar disruption of the basal keratinocytic layer is not commonly encountered in MF and may be a clue to the diagnosis of an interface process such as early lichen sclerosus. Correlation with the clinical presentation and medication history is absolutely essential also to promote the correct diagnosis.

Histopathological characteristics helpful for making the diagnosis of MF and excluding one of the reactive inflammatory conditions discussed above include identification of haloed lymphocytes, an increase in epidermal mononuclear cells, and a relative lack of spongiosis.[6] Others have also noted the value of identifying disproportional epidermotropism, convoluted lymphocytes, papillary dermal fibrosis, Pautrier's microabscesses, and lymphocytic apposition to the basal keratinocytes.[7,8] Guitart et al developed criteria for the histopathologic diagnosis of MF with a focus on density, epidermotropism, and cytologic atypia.[9] These 3 characteristics were scored on a 0-3 scale and included minor criteria such as reticular fibroplasia, atypical intraepidermal infiltrate, and quality of lymphocytic infiltrate (all assigned 1 point). The International Society for Cutaneous Lymphoma also proposed an algorithm combining clinical and histopathologic features in the diagnosis of MF. However, an analysis of their algorithm by Vandergriff et al showed a strong sensitivity of 87.5% but a specificity of just 60%.[10]

In the evaluation of a new patient without a preexisting diagnosis of MF, we strongly advocate a multidisciplinary approach. We typically have the added benefit of correlating histopathology with the patient's clinical examination in our Multidisciplinary Cutaneous Lymphoma Clinic at Stanford University. Correlation of the clinical features is critical for accurate diagnosis. Nonetheless, histopathologic features important for the diagnosis of MF include (i) lymphocytic epidermotropism with minimal spongiosis, (ii) haloed lymphocytes, (iii) atypical hyperchromatic and hyperconvoluted lymphocytic nuclei, (iv) papillary dermal fibrosis, and (v) dermal band-like lymphocytic infiltrate. Pautrier's microabscesses, while helpful, are not always present.[8]

Immunohistochemical studies may be helpful for distinguishing MF from inflammatory dermatoses. We often, but not always, perform immunostaining with CD3, CD4, CD8, and β-F1 to evaluate the T-cell subsets. Additionally, CD2, CD5, and CD7 may be helpful to evaluate for specific antigen loss in the epidermotropic component (see Figure 1), although such loss is not 100% specific for

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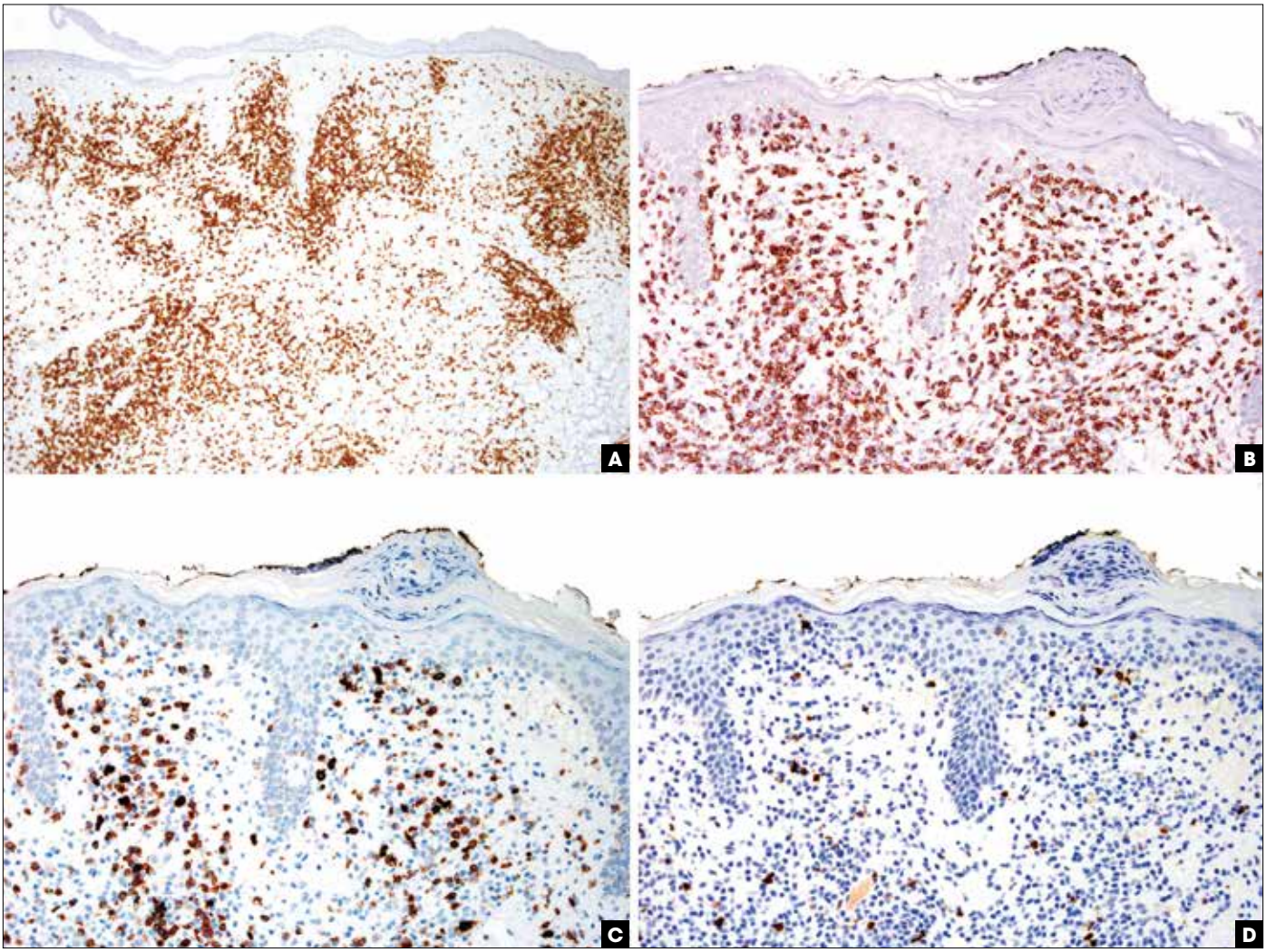

FIGURE 1. Mycosis fungoides expression of common T-cell antigens. **(A)** Epidermotropic accumulation of CD3-positive T lymphocytes (150x); **(B)** Retained expression of CD2 in the neoplastic lymphocytes (300x); **(C)** Loss of CD5 expression in neoplastic lymphocytes (300x); **(D)** Complete loss of CD7 in neoplastic lymphocytes (300x).

CTCL. If large-cell transformation (LCT) is considered, we might also utilize Ki67 and CD30, which may be elevated in LCT. CD56 is utilized in cases to evaluate for natural killer (NK)/T-cell lymphoma. Additionally, T-cell receptor delta (TCR-δ) immunohistochemical stains may be used to evaluate for gamma delta T-cell lymphoma (gδ-TCL). In classical MF, the atypical lymphocytes are $CD3^+$, $CD4^+$, $CD8^-$, $CD30^-$, and $CD56^-$. Generally, the overall infiltrate should have a skewed CD4 > CD8 ratio, though it should be noted that this finding may be seen in some benign inflammatory disorders.[11,12] Furthermore, clonal loss of T-cell antigens, such as CD2 and CD5, may be helpful to provide further evidence of neoplasia.[13] In a study by Harmon et al, loss of either CD2, CD3, or CD5 was found in 66% of patients with Sézary Syndrome, 29% of patients with pre-Sézary Syndrome, and no patients with benign dermatoses.[14] However, we interpret loss of CD7 with some caution because it may be lost in a variety of benign dermatoses.[15,16] Finally, it should be noted that there are some aberrant phenotypes observed in MF, including CD8-positive MF ($CD4^-CD8^+$), double negative MF ($CD4^-CD8^-$), and CD56-positive MF.[17-19] In these clinical scenarios, histomorphology and clinical correlation is critical because aberrant immunohistochemical results support the diagnosis of MF.

One final diagnostic tool that is increasingly utilized is high-throughput sequencing of the T-cell receptor genes (HTS-TCR), which has been demonstrated to be an effective way to diagnose CTCL from a differential that includes inflammatory dermatoses.[20] We utilize HTS-TCR as an ancillary technique useful in cases with high clinical suspicion for MF without definitive histopathologic findings. Preliminary results demonstrate improved sensitivity and specificity using HTS-TCR in establishing the diagnosis of CTCL.[20]

Histopathologic evidence of folliculotropism and LCT should be noted because these 2 entities may portend a worse clinical prognosis. Epidermotropism is not always present in folliculotrop-

ic MF, however, and one study demonstrated evidence of epidermotropism in just 54% of biopsies.[21] LCT occurs in approximately 20%-50% of cases and is defined as the presence of large cells (>4 times the size of a small lymphocyte) exceeding 25% of the infiltrate or formation of microscopic nodules.[22-24] The diagnosis of LCT is clear when the infiltrate is predominantly composed of enlarged cells but may be more challenging when the percentage of large cells is in the 20%-40% range or composed of medium-sized cells. CD30 has been cited as a marker for LCT, and while being a useful clinical/treatment target, numerous studies have shown it is not a reliable marker.[25-28] We have recently shown that Ki67 and tumor protein 53 (p53) can be of value in making a diagnosis of LCT.[29] In our study, Ki67 was 13% in MF and 57% in MF with LCT. p53 overexpression was not found in any of the standard MF biopsies and present in 48% of the MF with LCT biopsies. In keeping with the literature, CD30 was 4% in the MF group and 22% in the MF with LCT group. We envision that Ki67 and p53 can be used in addition to CD30 to aid in making a diagnosis when the percentage of large cells is in the challenging 20%-40% range.

Additional considerations

There are numerous other cutaneous lymphomas that are histopathologically characterized by epidermotropic T-cell infiltrates, discussed below.

Pagetoid reticulosis

Pagetoid reticulosis is a rare variant of MF that is characterized by an intraepidermal proliferation of atypical lymphocytes with $CD3^+/CD4^+/CD8^-$ or $CD3^+/CD4^-/CD8^+$ immunophenotypes.[30] The lesional cells are large with ample cytoplasm and demonstrate marked pagetoid scatter with overlying epidermal acanthosis. The lesions are often solitary, erythematous, and verrucous and are usually present on the distal extremities, which is distinct from MF. CD2 and CD7 may be lost, and there is T-cell receptor clonality. It can be difficult to distinguish pagetoid reticulosis from unilesional MF; some useful tips include the presence of a single lesion on the distal extremities (in contrast with conventional MF, in which the lesions are usually on the central trunk), lack of atypical dermal lymphocytes, and the strong CD8 positivity.

Primary cutaneous $CD30^+$ lymphoproliferative disorders

This group of neoplasms is characterized by the presence of large atypical lymphocytes that are $CD30^+$ and includes primary cutaneous anaplastic large cell lymphoma (PC-ALCL), systemic anaplastic large cell lymphoma (S-ALCL), and lymphomatoid papulosis (LyP). The distinction between these 2 entities requires clinical correlation, as definitive diagnosis of PC-ALCL requires exclusion of S-ALCL by staging. In PC-ALCL, lesions are typically composed of large sheets of irregular polygonal cells in the dermis and subcutaneous tissue with minimal epidermotropism. These large cells are classically $CD3^+/CD4^+/CD8^-$ and are strongly CD30 positive.[31] Because minimal epidermotropism is usually present, neither PC-ALCL nor S-ALCL typically fall into the differential diagnosis of epidermotropic T-cell lymphomas.

LyP is a chronic lymphoproliferative disorder characterized by waxing and waning eruptions of papules and plaques that undergo self-regression. There are various subtypes that are distinguished histopathologically; however, of all the types, LyP type D is the type that typically demonstrates marked epidermotropism by atypical $CD8^+$ lymphocytes and thus is mentioned in this article. This type may be mistaken for $CD8^+$ MF or aggressive epidermotropic cytotoxic CD8-positive T-cell lymphoma.[32] Correlation with the clinical presentation of small papules that undergo spontaneous regression is needed to render a correct diagnosis for this entity and to distinguish it from other epidermotropic T-cell lymphomas.

Primary cutaneous aggressive CD8 epidermotropic T-cell lymphoma

Primary cutaneous aggressive $CD8^+$ epidermotropic T-cell lymphoma is a disorder characterized by a brisk epidermal infiltrate of pagetoid atypical lymphocytes with overlying epidermal acanthosis, spongiosis, and even occasionally necrosis. The atypical lymphocytes are $CD3^+/CD8^+$ and also express TIA-1, granzyme B, and perforin, thus displaying a cytotoxic phenotype.[33] This disorder is aggressive, with median survival of 32 months; therefore, early diagnosis is crucial. The distinction from CD8-positive MF largely rests on the clinical presentation because in CD8-positive MF, patients usually have a long-standing history of patches and plaques, while primary cutaneous aggressive CD8 epidermotropic T-cell lymphoma usually presents with de novo onset of plaques and tumors without preexisting patches.

Cutaneous γ/δ-TCL

Cutaneous γ/δ-TCL is a rare cutaneous lymphoma composed of plaques and tumors most commonly on the trunk and upper extremities. It has a very aggressive clinical course with an 11% 5-year survival rate.[34] It is histologically characterized by the presence of large atypical lymphocytes in the epidermis, dermis, and/or subcutaneous tissue. Epidermotropism is often present, and thus this condition is on the differential diagnosis of an epidermotropic T-cell infiltrate. The lymphoma is a clonal proliferation of γ/δ T cells that are most commonly $CD3^+/CD2^+/CD56^+$ and are typically $CD4^-$ and $CD8^-$. The lesional lymphocytes express TCR-γ or TCR-δ and the cytotoxic markers TIA-1 and granzyme. TCR-β-F1 is negative. This condition can be distinguished from many other forms of epidermotropic T-cell lymphoma by the immunophenotype because the lymphocytes in MF, pagetoid reticulosis, primary cutaneous $CD30^+$ lymphoproliferative disorders, and primary cutaneous aggressive $CD8^+$ epidermotropic T-cell lymphoma typically label with TCR-β-F1, which is an immunostain to alpha/beta T cells, but not with GM3, which is a marker of gamma/delta T cells. By contrast, the lymphocytes in cutaneous γ/δ T-cell lymphoma label with GM3 and not TCR-β-F1. Nevertheless, there are rare reports of the lesional lymphocytes in MF labeling with the GM3 immuonstain, and thus labeling with GM3 is not 100% specific for MF.[35] Nonetheless, these are exceptional cases, and most of the time, γ/δ T-cell lymphoma can be distinguished from other epidermotropic T-cell lymphomas by immunostaining with GM3 and TCR-β-F1. Of note, extranodal NK/T-cell lymphoma, discussed below, can also sometimes label with GM3. However, extranodal NK/T-cell lymphoma is distinguished from γ/δ T-cell lymphoma by the presence of Epstein-Barr virus (EBV) via in situ hybridization.

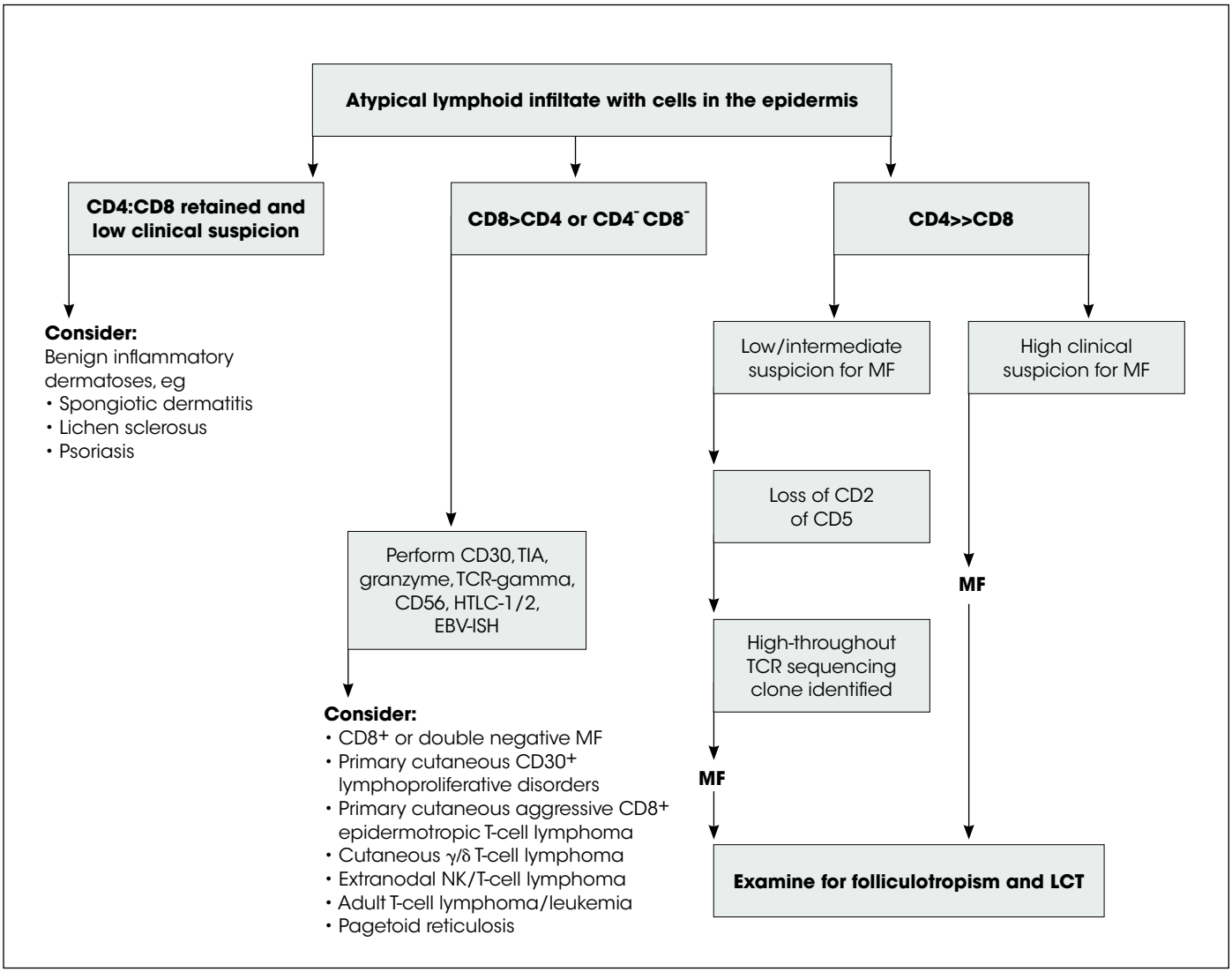

FIGURE 2. Algorithmic approach to an epidermotropic lymphocytic infiltrate. Abbreviations: EBV, Epstein–Barr virus; ISH, in situ hybridization; LCT, large-cell transformation; MF, mycosis fungoides; NK, natural killer; TCR, T-cell receptor.

Extranodal NK/T-cell lymphoma

Extranodal NK/T-cell lymphoma is an aggressive disease rarely seen in the United States and Europe but common in Asia and Central and/or South America. It presents most commonly in the nasal region, but extranasal manifestations of the disease can be seen in the skin with a diverse appearance, presenting as plaques, patches, purpura, bullae, and ulcerations.[36] Histologically, there is a dermal and/or subcutaneous infiltrate of variably sized atypical lymphocytes; pleomorphism is not always marked, and eosinophils and plasma cells may be seen. Epidermotropism can be seen, and thus this condition is on the differential diagnosis of an epidermotropic T-cell infiltrate.[37] The atypical lymphocytes are $CD2^+/CD56^+$ and surface $CD3^-$ (though cytoplasmic $CD3\varepsilon$ is expressed). There is variable expression of CD7, CD8, TIA-1, and granzyme. The atypical cells are usually positive for EBV via in situ hybridization, and the presence of EBV positivity helps to distinguish this entity from other epidermotropic T-cell lymphomas.

Adult T-cell lymphoma/leukemia

Adult T-cell leukemia-lymphoma (ATLL) is a peripheral T-cell neoplasm associated with infection by the human T-lymphotropic virus, type I (HTLV-1). This disease course is variable, with a spectrum from aggressive to quite indolent, and it is found in the blood (leukemia), lymph nodes (lymphoma), or skin. The HTLV-1 virus is prevalent in parts of Japan, the Caribbean, and areas of South and Central America and Africa. ATLL is an important disorder because the clinical characteristics may be similar to MF, and the most common extralymphatic site is skin (>50%). In addition, the histopathologic features can be similar to those seen in MF, including the presence of marked epidermotropism. ATLL is characterized by a clonal expansion of $CD4^+/CD25^+$/forkhead box protein P3 ($FOXP3^+$) regulatory T cells. The condition can be distinguished from other forms of CTCL by its association with HTLV-1.

Conclusion

In summary, there are numerous T-cell lymphomas with epidermotropism and superficial dermal infiltrates. The most common of these lymphomas is MF, and it can sometimes be challenging to distinguish early MF from benign inflammatory dermatoses with lymphocytes within the epidermis. Other forms of cutaneous lymphoma that often demonstrate an epidermotropic T-cell infiltrate include pagetoid reticulosis, type D LyP, primary cutaneous aggressive $CD8^+$ epidermotropic T-cell lymphoma, cutaneous γ/δ-TCL, extranodal NK/T-cell lymphoma, and ATLL. An algorithmic approach to hone in on these diagnoses entails utilization of histopathologic features, immunohistochemistry, and clinical features, as well as ancillary molecular testing (HTS-TCR or standard TCR; see Figure 2).

References

1. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. *Blood*. 2005;105(10):3768-3785. doi: 10.1182/blood-2004-09-3502.
2. Robson A. The pathology of cutaneous T-cell lymphoma. *Oncology (Williston Park)*. 2007;21(2 Suppl 1):9-12.
3. Olerud JE, Kulin PA, Chew DE, et al. Cutaneous T-cell lymphoma. Evaluation of pretreatment skin biopsy specimens by a panel of pathologists. *Arch Dermatol*. 1992;128(4):501-507.
4. Arps DP, Chen S, Fullen DR, Hristov AC. Selected inflammatory imitators of mycosis fungoides: histologic features and utility of ancillary studies. *Arch Pathol Lab Med*. 2014;138(10):1319-1327. doi: 10.5858/arpa.2014-0298-CC.
5. De Silva BD, McLaren K, Kavanagh GM. Photosensitive mycosis fungoides or actinic reticuloid? *Br J Dermatol*. 2000;142(6):1221-1227.
6. Sanchez JL, Ackerman AB. The patch stage of mycosis fungoides. Criteria for histologic diagnosis. *Am J Dermatopathol*. 1979;1(1):5-26.
7. Nickoloff BJ. Light-microscopic assessment of 100 patients with patch/plaque-stage mycosis fungoides. *Am J Dermatopathol*. 1988;10(6):469-477.
8. Smoller BR, Bishop K, Glusac E, Kim YH, Hendrickson M. Reassessment of histologic parameters in the diagnosis of mycosis fungoides. *Am J Surg Pathol*. 1995;19(12):1423-1430.
9. Guitart J, Kennedy J, Ronan S, Chmiel JS, Hsiegh YC, Variakojis D. Histologic criteria for the diagnosis of mycosis fungoides: proposal for a grading system to standardize pathology reporting. *J Cutan Pathol*. 2001;28(4):174-183.
10. Vandergriff T, Nezafati KA, Susa J, et al. Defining early mycosis fungoides: validation of a diagnostic algorithm proposed by the International Society for Cutaneous Lymphomas. *J Cutan Pathol*. 2015;42(5):318-328. doi: 10.1111/cup.12470.
11. Michie SA, Abel EA, Hoppe RT, Warnke RA, Wood GS. Discordant expression of antigens between intraepidermal and intradermal T cells in mycosis fungoides. *Am J Pathol*. 1990;137(6):1447-1451.
12. Wood GS, Bahler DW, Hoppe RT, Warnke RA, Sklar JL, Levy R. Transformation of mycosis fungoides: T-cell receptor beta gene analysis demonstrates a common clonal origin for plaque-type mycosis fungoides and CD30+ large-cell lymphoma. *J Invest Dermatol*. 1993;101(3):296-300.
13. Florell SR, Cessna M, Lundell RB, et al. Usefulness (or lack thereof) of immunophenotyping in atypical cutaneous T-cell infiltrates. *Am J Clin Pathol*. 2006;125(5):727-736. DOI: 10.1309/3JK2-H6Y9-88NU-AY37.
14. Harmon CB, Witzig TE, Katzmann JA, Pittelkow MR. Detection of circulating T cells with CD4+CD7- immunophenotype in patients with benign and malignant lymphoproliferative dermatoses. *J Am Acad Dermatol*. 1996;35(3 Pt 1):404-410.
15. Ormsby A, Bergfeld WF, Tubbs RR, Hsi ED. Evaluation of a new paraffin-reactive CD7 T-cell deletion marker and a polymerase chain reaction-based T-cell receptor gene rearrangement assay: implications for diagnosis of mycosis fungoides in community clinical practice. *J Am Acad Dermatol*. 2001;45(3):405-413. doi: 10.1067/mjd.2001.116342.
16. Murphy M, Fullen D, Carlson JA. Low CD7 expression in benign and malignant cutaneous lymphocytic infiltrates: experience with an antibody reactive with paraffin-embedded tissue. *Am J Dermatopathol*. 2002;24(1):6-16.
17. Ada S, Güleç AT. CD8+ poikilodermatous mycosis fungoides with a nonaggressive clinical behaviour and a good response to psoralen plus ultraviolet A treatment. *Br J Dermatol*. 2007;157(5):1064-1066. doi: 10.1111/j.1365-2133.2007.08165.x.
18. Hodak E, David M, Maron L, Aviram A, Kaganovsky E, Feinmesser M. CD4/CD8 double-negative epidermotropic cutaneous T-cell lymphoma: an immunohistochemical variant of mycosis fungoides. *J Am Acad Dermatol*. 2006;55(2):276-284. doi: 10.1016/j.jaad.2006.01.020.
19. Klekotka PA, Faulkner-Jones B, Heffernan MP. A case of CD56+ mycosis fungoides. *Arch Dermatol*. 2006;142(10):1370-1372. doi: 10.1001/archderm.142.10.1370.
20. Kim J. High-throughput sequencing of T cell receptor gene rearrangement shows high specificity in the diagnosis of cutaneous T cell lymphoma. In submission. 2017.
21. Lehman JS, Cook-Norris RH, Weed BR, et al. Folliculotropic mycosis fungoides: single-center study and systematic review. *Arch Dermatol*. 2010;146(6):607-613. doi: 10.1001/archdermatol.2010.101.
22. Diamandidou E, Colome M, Fayad L, Duvic M, Kurzrock R. Prognostic factor analysis in mycosis fungoides/Sézary syndrome. *J Am Acad Dermatol*. 1999;40(6 Pt 1):914-924.
23. Diamandidou E, Colome-Grimmer M, Fayad L, Duvic M, Kurzrock R. Transformation of mycosis fungoides/Sezary syndrome: clinical characteristics and prognosis. *Blood*. 1998;92(4):1150-1159.
24. Benner MF, Jansen PM, Vermeer MH, Willemze R. Prognostic factors in transformed mycosis fungoides: a retrospective analysis of 100 cases. *Blood*. 2012;119(7):1643-1649. doi: 10.1182/blood-2011-08-376319.
25. Kadin ME. CD30-rich transformed mycosis fungoides or anaplastic large cell lymphoma? How to get it right. *Br J Dermatol*. 2015;172(6):1478-1479. doi: 10.1111/bjd.13808.
26. Kadin ME, Hughey LC, Wood GS. Large-cell transformation of mycosis fungoides-differential diagnosis with implications for clinical management: a consensus statement of the US Cutaneous Lymphoma Consortium. *J Am Acad Dermatol*. 2014;70(2):374-376. doi: 10.1016/j.jaad.2013.09.007.
27. Pulitzer M, Myskowski PL, Horwitz SM, et al. Mycosis fungoides with large cell transformation: clinicopathological features and prognostic factors. *Pathology*. 2014;46(7):610-616. doi: 10.1097/PAT.0000000000000166.
28. Mehra T, Ikenberg K, Moos RM, et al. Brentuximab as a treatment for CD30+ mycosis fungoides and Sézary syndrome. *JAMA Dermatol*. 2015;151(1):73-77. doi: 10.1001/jamadermatol.2014.1629.
29. Raghavan SS, Kim J, Kim YH. Utility of CD30, Ki67 and p53 in the diagnosis of Mycosis fungoides with Large Cell Transformation. In submission. 2017.
30. Jacyk WK, Grayson W, Dinkel JE, Requena L. Pagetoid reticulosis with CD30 positivity and cytotoxic/suppressor cells. *J Cutan Pathol*. 2007;34(8):644-647. doi: 10.1111/j.1600-0560.2006.00698.x
31. Brown RA, Fernandez-Pol S, Kim J. Primary cutaneous anaplastic large cell lymphoma. *J Cutan Pathol*. 2017;44(6):570-577. doi: 10.1111/cup.12937.
32. Saggini A, Gulia A, Argenyi Z, et al. A variant of lymphomatoid papulosis simulating primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma. Description of 9 cases. *Am J Surg Pathol*. 2010;34(8):1168-1175. doi: 10.1097/PAS.0b013e3181e75356.
33. Berti E, Tomasini D, Vermeer MH, Meijer CJ, Alessi E, Willemze R. Primary cutaneous CD8-positive epidermotropic cytotoxic T cell lymphomas. A distinct clinicopathological entity with an aggressive clinical behavior. *Am J Pathol*. 1999;155(2):483-492. doi: 10.1016/S0002-9440(10)65144-9
34. Endly DC, Weenig RH, Peters MS, Viswanatha DS, Comfere NI. Indolent course of cutaneous gamma-delta T-cell lymphoma. *J Cutan Pathol*. 2013;40(10):896-902. doi: 10.1111/cup.12091.
35. Rodríguez-Pinilla SM, Ortiz-Romero PL, Monsalvez V, et al. TCR-γ expression in primary cutaneous T-cell lymphomas. *Am J Surg Pathol*. 2013;37(3):375-84. doi: 10.1097/PAS.0b013e318275d1a2.
36. Li S, Feng X, Li T, et al. Extranodal NK/T-cell lymphoma, nasal type: a report of 73 cases at MD Anderson Cancer Center. *Am J Surg Pathol*. 2013;37(1):14-23. doi: 10.1097/PAS.0b013e31826731b5.
37. Assaf C, Gellrich S, Whittaker S, et al. CD56-positive haematological neoplasms of the skin: a multicentre study of the Cutaneous Lymphoma Project Group of the European Organisation for Research and Treatment of Cancer. *J Clin Pathol*. 2007;60(9):981-989. doi: 10.1136/jcp.2006.042135.