A Systematic Approach to the Cutaneous Lymphoid Infiltrates

A Clinical, Morphologic, and Immunophenotypic Evaluation

Alejandro A. Gru, MD; Chauncey McHargue, MD; Andrea L. Salavaggione, MD

Context.—The evaluation of cutaneous lymphoid infiltrates, both neoplastic and inflammatory, occurs very frequently in routine dermatopathologic examination and consultation practices. The “tough” cutaneous lymphoid infiltrate is feared by many pathologists; skin biopsies are relatively small, whereas diagnostic possibilities are relatively broad. It is true that cutaneous lymphomas can be difficult to diagnose and that in many circumstances multiple biopsies are required to establish a correct diagnostic interpretation. As a reminder, one should understand that low-grade cutaneous lymphomas are indolent disorders that usually linger for decades and that therapy does not result in disease cure. It is also important to remember that in most circumstances, those patients will die from another process that is completely unrelated to a diagnosis of skin lymphoma (even in the absence of specific therapy).

Objective.—To use a clinicopathologic, immunopheno-
typic, and molecular approach in the evaluation of common lymphocytic infiltrates.

Data Sources.—An in-depth analysis of updated literature in the field of cutaneous lymphomas was done, with particular emphasis on updated terminology from the most recent World Health Organization classification of skin and hematologic tumors.

Conclusions.—A diagnosis of cutaneous lymphoid infiltrates can be adequately approached using a systematic scheme following the proposed ABCDE system. Overall, cutaneous T- and B-cell lymphomas are rare and “reactive” infiltrates are more common. Evaluation of lymphoid proliferations should start with a good sense of knowledge of the clinical presentation of the lesions, the clinical differential considerations, and a conscientious and appropriate use of immunohistochemistry and molecular tools.

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Advances in histopathologic, immunophenotypic, and molecular studies have created a revolution in diagnosis of hematopoietic disorders.5–10 One should be aware that many of the molecular methods are expensive, and one should ask himself whether the cost of the assay that could be required for the diagnosis is justifiable when it can potentially create a huge economic burden for a process that ultimately has a very indolent behavior. On the other hand, certain presentations and forms of skin lymphomas, although clinically aggressive, can be histologically deceptive and have a strong impact on a patient’s management. In this sense, patients with Sézary syndrome can have very subtle histologic changes, whereas the clinical presentation can be aggressive and the mortality similar to that for common nodal or systemic forms of T-cell lymphomas.

In this review, a clinicopathologic, immunophenotypic, and molecular approach to the evaluation of common
lymphocytic infiltrates will be presented. For this, we would like to propose an approach similar to what dermatologists and pathologists do in the assessment of melanoctytic biopsies (ABCDE). Such an approach starts with: A, age; B, background; C, clinical presentation; D, differential diagnoses; E, histologic and immunophenotypic evaluation. This proposed approach will provide a standardized framework by which to approach common skin lymphocytic infiltrates and hopefully lead to less consternation on the part of the evaluating pathologist.

THE ABCDE APPROACH IN CUTANEOUS LYMPHOCYTIC INFILTRATES

The routine evaluation typically starts with understanding that different processes occur more frequently at different ages. Most cases of mycosis fungoides (MF) and Sézary syndrome typically present in individuals older than 55 to 60 years.5,11 The occurrence of the disease in children is very unusual. However, lymphomatoid papulosis (LpP) and primary cutaneous anaplastic large cell lymphomas (PC-ALCL) can present at an earlier age and even with some frequency in children.12–22 Similarly, cutaneous B-cell lymphomas are very rare in children, and they are characterized by limited to cutaneous marginal zone lymphomas.36,23–27 Older patients can get more aggressive forms of cutaneous lymphomas, including but not limited to diffuse large B-cell lymphoma, leg type (DLBCL-LT), Epstein-Barr virus (EBV)–positive DLBCL (EBV-DLBCL), and plasmablastic lymphoma.28–37 Most cases of cutaneous B-cell lymphomas in general (primary cutaneous follicle center lymphomas [PCFCLs] and cutaneous marginal zone lymphomas [CMZLs]) are more frequent in people around the ages of 40 to 50 years (middle age).

The background of patients is of extraordinary importance. Where is the patient from? Certain geographic regions have a strong association with certain types of cutaneous lymphomas. For instance, Asia (particularly Japan and Central and South America (Jamaica, Haiti, Peru, Brazil) have large endemic areas of human T-lymphocytic infiltrates will be presented. For this, we would like to propose an approach similar to what dermatologists and pathologists do in the assessment of melanoctytic biopsies (ABCDE). Such an approach starts with: A, age; B, background; C, clinical presentation; D, differential diagnoses; E, histologic and immunophenotypic evaluation. This proposed approach will provide a standardized framework by which to approach common skin lymphocytic infiltrates and hopefully lead to less consternation on the part of the evaluating pathologist.

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The background of patients is of extraordinary importance. Where is the patient from? Certain geographic regions have a strong association with certain types of cutaneous lymphomas. For instance, Asia (particularly Japan and Central and South America (Jamaica, Haiti, Peru, Brazil) have large endemic areas of human T-
ultraviolet radiation. This explains why it tends to involve sun-protected rather than sun-exposed sites. This is also why phototherapy is one of the most common treatment modalities in the early stages of the disease.\textsuperscript{5,79} It is also important to recognize some of the variants of MF that can have very specific clinical presentations (Figure 2): folliculotropic MF typically presents in the head and neck region as follicular papules (Figure 2, b), patches, and sometimes tumors.\textsuperscript{80,81} Deep and tumorous lesions are associated with a more aggressive behavior. Syringotropic MF and pagetoid reticulosis (Figure 2, c) are typically seen in acral locations.\textsuperscript{82–84} Acral CD8\textsuperscript{+} T-cell lymphoma (an indolent LPD) also occurs in acral sites and ears. An uncommon form of MF, granulomatous slack skin (or granulomatous MF), is characterized by large pendulous areas of skin in the axillary and inguinal folds.\textsuperscript{85,86} Generalized erythroderma (Figure 2, a) implies diffuse reddening of the skin, in common association with marked pruritus and nail changes. Generalized erythroderma of progressive onset is associated with Sézary syndrome and MF with secondary peripheral blood involvement.\textsuperscript{87} However, generalized erythroderma is more frequently associated with other common benign dermatoses; these include pityriasis rubra pilaris, psoriasis, eczematous eruptions, papuloerythroderma of Ofuji, and numerous other causes. Erythroderma is not unique to MF; as previously stated, there is marked clinical and histopathologic overlap between MF and cases of ATLL. Indeed, most patients with ATLL have cutaneous involvement and history of patches and plaques. The main difference between the 2 entities relies on the finding of a positive serology for HTLV-1, because viral integration studies are not currently performed as standard of care in the United States. It is assumed that a positive serologic result implies that the virus is driving the lymphoproliferative process.

The presence of an isolated patch, plaque, nodule, and, less frequently, a tumor, particularly in the head and neck region of a 50- to 60-year-old individual is the very classic and frequent presentation of the newly recognized entity small- to medium-size CD4\textsuperscript{+} LPD (Figure 3, b).\textsuperscript{88} This entity invariably carries an excellent prognosis, and in many cases it disappears spontaneously after the original biopsy is done. A plaque and nodule, either solitary or, less frequently, multiple, in the scalp, face, and upper trunk, is also the presentation of PCFCL.\textsuperscript{89} In counterpart, a tumor, with or without ulceration in the leg, in an older person is the more
characteristic presentation of DLBCL-LT. Although DLBCL-LT is considered a primary form of cutaneous lymphoma, patients who have this uncommon malignancy carry a prognosis similar to those with other subtypes of systemic DLBCL, often requiring chemotherapy (R-CHOP, mini-CHOP). Ulcerated tumors in the trunk and extremities, often solitary or with a small regional number of lesions, are the typical clinical presentation of PC-ALCL. This is an indolent disorder that can be cured with localized forms of therapy (either localized radiation or excision) and can also resolve spontaneously (Figure 3, a).

Multiple papules that occur in crops, that heal spontaneously within 1 to 3 months with or without scarring and ulceration and are present in the trunk and extremities are the most characteristic presentation for LyP (Figure 3, c). Although multiple histologic variants of LyP have been recognized, all of them share the same clinical presentation, course, and therapy. Of course, other clinical entities can have a similar clinical presentation; particularly in children, pityriasis lichenoides chronic (PLC) and pityriasis lichenoides et varioliformis acuta (PLEVA) can share similar clinical features. A diagnosis, then, can subsequently be established using histopathologic and immunophenotypic evaluation of the lesions. A papular and vesicular eruption with scarring, with associated photosensitivity, in children of South America, Central America, and Mexico, in association with EBV infection, is the more classic clinical picture of HV-LPD. The clinical papular presentation is also typical of marginal zone lymphomas. As opposed to PCFCL, which presents in the head and neck area, CMZL is more frequent in the extremities and lower trunk. CMZL can be solitary lesions, but they are more frequently multiple lesions (Figure 4). A nodular or panniculitic (inflammatory) appearance of lesions in the extremities and trunk is the common presentation for SPTCL. Multiple lesions are often present, and careful clinical examination can also reveal lesions compatible with lupus erythematosus. Multiple ulcerated nodules, often in association with systemic symptoms, are also the presentation for primary cutaneous γ-δ T-cell lymphoma (PCGDTCL; Figure 3, d). The latter is an aggressive form of T-cell lymphoma that requires systemic therapy, and the only curative option is the use of a bone marrow transplant. Most patients with this diagnosis are middle-aged (50–60 years). More recently, a subset of such patients can be identified to have a more protracted clinical course and frequently a history of MF-type lesions (long course of patches and plaques). Another subtype of aggressive lymphomas with skin dissemination is the aggressive epidermotropic CD8+ T-cell lymphoma (AETCL), a variant described by Emilio Berti et al, which still remains as a provisional category in the World Health Organization classification. Such patients have a rapid onset of the clinical lesions, frequently disseminated patches, plaques, nodules, and tumors, with ulceration, and often genital, acral, and mucosal involvement. This is another type of T-cell malignancy that has a very poor prognosis and requires aggressive forms of systemic therapy. Lastly, extranodal NK/T-cell lymphoma can often have the appearance of ulcerated nodules on the skin. Extranodal NK/T-cell lymphoma often has involvement of the nasal septum with destruction (in the past this was referred to as midline lethal granuloma) and shows extension and dissemination into the paranasal sinuses. However, in many cases those patients can have lesions outside the head and neck area. The most reliable marker in those patients is the identification of EBV. The EBV blood levels by polymerase chain reaction correlate strongly with the patient’s outcome. Treatment for them is based on the combination of radiation and systemic chemotherapy (SMILE) regimen. The latter has contributed to a significant improvement in the outcome of the disease.

Figure 3. Multiple verrucous tumors are present with overinfection with botryomycosis in a case of cutaneous anaplastic large cell lymphoma (a). A small nodule on the ear is seen in a case of small- to medium-sized CD4+ lymphoproliferative disorder (b). Ulcerated papules are seen in a case of lymphomatoid papulosis (c). A large ulcerated tumor is seen on the leg of a patient with primary cutaneous γ-δ T-cell lymphoma (d).
The differential diagnosis is based on the clinical interpretation that the dermatologist performed after obtaining an adequate clinical history and physical examination of those patients. There is nothing more important than a “good” clinical eye and clinical experience in the diagnoses of these types of malignancies. It is without exception capital for the pathologist involved in these cases to obtain a good assessment of the distribution of the lesions, percentage of skin involvement, and often clinical photographs. A summary of common clinical, nonhematolymphoid entities that may have significant clinical overlap with certain specific cutaneous lymphoid diagnoses is provided below:

1. Eczema, psoriasis, atypical psoriasis, parapsoriasis: MF, AETCL.
2. Erythrodermic psoriasis, pityriasis rubra pilaris: Sézary syndrome.
3. Panniculitis: SPTCL, PCGDTCL, AECTL, extranodal NK/T-cell lymphoma.
4. PLEVA and PLC: lymphomatoid papulosis.
5. Different types of nonmelanoma skin cancers in the head and neck (basal cell carcinoma, squamous cell carcinoma): primary cutaneous small to medium CD4+ T-cell LPD, PCFCL, CMZL.
6. Different types of nonmelanoma skin cancers in the trunk and extremities: PC-ALCL, DLBCL-LT.
7. Bug bite: Different lymphoma subtypes and reactive lymphoid infiltrates.

For the histopathologic and immunophenotypic evaluation: although we have used a long “flight of ideas” type of approach to the preceding aspects that happen before a biopsy is reviewed, the next portion of this article will be directed toward addressing the morphologic, immunophenotypic, and molecular features that are characteristic of the most common types of cutaneous lymphomas. It is important to emphasize very strongly that there is no unique molecular or immunophenotypic marker that is diagnostic or pathognomonic of one disorder.

**CUTANEOUS T-CELL LYMPHOMAS**

MF is the most common and classic form of CTCL. The most reproducible pattern of skin involvement is the presence of an epidermotropic infiltrate that shows tagging of cells along the dermal-epidermal junction. Intraepidermal collections of lymphocytes (Pautrier microabscesses) are characteristic, but they are only seen in 25% of cases of MF (Figure 5).\(^5\)\(^1\)\(^1\)\(^3\)\(^6\)\(^8\)\(^6\)\(^1\)\(^3\) Plaques can have associated psoriasiform changes of the epidermis. Poikilodermatous forms tend to
have a sparser infiltrate and marked atrophy of the epidermis. The epidermotropic lymphocytes show atypical hyperchromatic and cerebriform nuclei, with perinuclear halos. The latter is particularly helpful when present but has a relatively low sensitivity value for its diagnosis. Dermal fibrosis is also common and is more prominent in patients who have undergone therapy. Patients who have undergone phototherapy can lose some of the epidermotropic features of the infiltrate. The folliculotropic forms (Figure 6) usually do not have marked epidermotropism and are associated with follicular tropism and frequent follicular mucinosis. Isolated follicular mucinosis, in the absence of a significant infiltrate, can be considered in 2-fold way: (1) a reactive finding (often in association with tumors, inflammatory conditions, etc); or (2) a process that can be a harbinger of the development of MF. Syringotropic MF is characterized by infiltration of the epithelium of the sweat ducts. Granulomatous MF (Figure 7) shows elements of granulomatous inflammation and characteristically elastophagocytosis (which can be seen best with an elastic stain). A diagnosis of large-cell transformation relies on the presence of 25% or more of large cells or large-cell nodules. Large cells are defined as lymphocytes that are 4 times or greater the size of a normal lymphocyte (it is always appropriate to try to identify small “reactive” lymphocytes next to the larger cells to make this type of determination). Cases with large-cell transformation, unfortunately, have a poor interobserver reproducibility and appear to be the only histologic predictor of poor outcome in some studies. It is important to remember that large-cell transformation is not considered part of the staging of the disease, which is ONLY clinical. Therefore, one can identify thin patches or plaques with large-cell transformation and be considered “early” stage, and on the opposite side identify a tumors lesion with small lymphocytes and be regarded as “advanced” stage. It is also important to remember that in many cases repeat biopsies are needed over time to establish the diagnosis of MF, particularly when the pathologic findings are subtle, and there is a strong clinical concern for such diagnosis.

Figure 8 summarizes our own approach to the use of immunostains and molecular tools in the diagnosis of MF. The immunophenotype of MF is characteristically CD4 (Figure 9). Cases with CD8 expression are more frequent in hypopigmented lesions and in pediatric MF, and have an indolent behavior. The CD4/CD8 ratio should be evaluated, whenever possible, at the level of the epidermis (not in the dermis). The normal CD4/CD8 ratio is usually between 2:1 and 4:1, and a ratio of more than 10:1 is usually considered abnormal. The CD4/CD8 ratio should always include a CD3. In many cases an overrepresentation of CD4 is produced by a background of Langerhans cells and macrophages present in the biopsy, and evaluation with additional histiocytic markers (CD68, CD163) or Langerhans cell markers (CD1a, langerin) could be appropriate. Most cases of MF lack a significant proportion of B cells. However, cases with CD4+ /CD8+ phenotype can sometimes show a rich B-cell infiltrate, and expression of T-follicular helper markers (germinal center markers in the T cell: BCL-6, PD-1, CXCL-13, CD10, ICOS). Cases with CD4+/CD8+ can also occur. The main immunophenotypic aberration to look for is the loss of CD7 (in >40% of the T cells). The earlier algorithms proposed a loss of more than 90% for CD7 and more than 50% for CD2, CD3, or CD5, to be considered abnormal. Such criteria are no longer preferred because, although specific, these stringent cutoffs have low sensitivity. Some cases can also show loss of other T-cell markers (CD2 and CD5), a finding that is particularly more common in the setting of large-cell transformation. CD8+ cases have expression of cytotoxic
markers (TIA-1, granzyme B, and perforin). We routinely recommend performing all 3 cytotoxic markers, because in many occasions only 1 of them is expressed. Cytotoxic marker expression also occurs in association with large-cell transformation and tumorous lesions. Cases of MF with an interstitial growth are also more frequently CD8⁺.

CD30 expression is of capital importance in the evaluation of MF for 3 main reasons: (1) diagnostic purposes (MF with large-cell transformation versus other CD30⁺ LPDs); (2) prognostic value (although this is debated); and (3) therapeutic prospective (use of the monoclonal antibody brentuximab vedotin) in the setting of advanced dis-
It is important to remember that CD30 does not define large-cell transformation: only 30% to 40% of cases of transformed MF show CD30 expression at a significant level (>40%).\(^7\) The evaluation of CD30 can vary across clinical lesions, and even within the same lesion. The interobserver agreement and interpretation of the level of expression is also relatively poor.\(^2\) However, an accurate determination of CD30 is important for the use of brentuximab, which is now US Food and Drug Administration approved for the treatment of advanced MF (stage...
IIb or above). Most clinical trials have used a cutoff of 10% expression in the tumor cells (or total infiltrate that includes reactive background immunoblasts), but many patients have shown benefits with treatment with levels below 10% and even below 1%. Another marker of prognostic impact, particularly in patients with advanced-stage disease, is the evaluation of proliferation index by Ki-67 (>20% is associated with a more aggressive clinical course).

Sézary syndrome lacks in many cases the epidermotropic pattern of MF (Figure 10). In such cases, a pleomorphic and cerebriform lymphoid infiltrate in the dermis is noted. Cases of Sézary syndrome are invariably CD4+, and they retain CD7 expression more frequently than ordinary MF. Flow cytometric evaluation of the patient’s peripheral blood is capital to make this diagnostic determination. Such cases show loss of CD26 in nearly all cases. The role of Sézary cell counts in the peripheral blood smear has fallen into disuse. Sézary syndrome can also show large-cell transformation, and in such settings strong expression of CD30 is common.

Molecular diagnostic techniques have been used for a long time to make a diagnosis of MF and Sézary syndrome. The best way to prove clonality using polymerase chain reaction–based T-cell receptor (TCR) rearrangement studies (TCRβ and TCRγ) is to identify the same clonal peaks across 2 separate biopsies from different sites. The sensitivity and specificity of the polymerase chain reaction–based assay for the diagnosis of MF are approximately 77% and 86%, respectively. In the case of Sézary syndrome, the isolation of an identical clone in the blood and skin is also pathognomonic.

CD30+ LPDs include LyP and PC-ALCL (in addition to some cases of MF with large-cell transformation). The morphologic and immunophenotypic profile of cases of LyP (Figure 11) is summarized in Table 1. PC-ALCL is characterized by diffuse expression of CD30 (>75% of cells). As opposed to systemic ALCL, epithelial membrane antigen is more frequently negative. Loss of common T-cell antigens is frequent, and most cases are CD4+. Cases of PC-ALCL show expression of cytotoxic markers and are EBV negative. A rare example of iatrogenic ALCL in association with EBV infection and BRAF V600E mutation has been recently described. A pyogenic variant in the skin can sometimes be difficult to diagnose because the malignant infiltrate can be obscured by a rich acute
inflammatory infiltrate (Figure 12). Such examples are more frequent in immunosuppressed individuals, particularly HIV-positive patients. Rare examples of isolated PC-ALCL with ALK+165–167 have been reported in children, particularly in association with arthropod bites.168–173 However, a diagnosis of ALK+ ALCL should always carry a further staging workup because most cases are systemic lymphomas with secondary cutaneous manifestations. At the molecular level, some cases of PC-ALCL have shown the presence of DUSP22 translocation (20%–25%). This translocation is not specific, as could also be seen in systemic ALCL and some examples of LyP.174,175 However, most cases of CD30+ MF with large-cell transformation lack such translocation.176–178 Regardless, it is important to emphasize that the main distinction between PC-ALCL, LyP, and MF with large-cell transformation relies on clinical and not histopathologic criteria.

SPTCL presents histologically as a lobular and sometimes mixed septal panniculitis (Figure 13).179 The infiltrate shows a characteristic rimming of the lymphocytes around individual adipocytes and an increased proliferative rate by Ki-67.180 Areas of necrosis can also be seen, but SPTCL does not have epidermotropism. If the latter is present, an alternative diagnostic consideration should be explored (tumor-stage MF, extranodal NK/T-cell lymphoma, PCGDTCL). The immunophenotype of SPTCL is CD3+, CD8+, CD4+, CD7+, and positivity for cytotoxic markers. All cases show expression of TCRβ (also referred to as BF1).181 The former examples of SPTCL with TCRβ are now classified as PCGDTCL, the latter being more aggressive. The most important differential diagnosis with SPTCL is lupus panniculitis. Lupus panniculitis is also a lobular or mixed septal/lobular panniculitis that is associated with fibrosis. In lupus panniculitis, lymphoid aggregates can be frequently seen. Adipocyte rimming can also be seen in lupus panniculitis. Immunohistochemistry can also help in the differential diagnosis because lupus panniculitis typically has a predominance of CD4+ T cells, lacks loss of CD7, shows frequent clusters of CD123+ plasmacytoid dendritic cells,60 and lacks increased Ki-67 among the atypical cells (mean Ki-67 is 25% for neoplastic and 7% for reactive T cells).180 Regardless, there are some cases that can be difficult to separate. The most important clinical prognostic marker in SPTCL is the presence or absence of hemophagocytosis, the latter associated with a worse outcome and the need for systemic treatment.103 PCGDTCL is another form of panniculitic-type T-cell LPD (Figure 14). Originally believed to be a subtype of SPTCL, this lymphoma subtype was reclassified on the basis of its aggressiveness and expression of TCRγδ, and it is currently a permanent category in the updated World Health Organization classification.103 This is a very aggressive tumor with a poor 5-year survival rate (median survival time is 31 months). Morphologically, most cases lack significant epidermotropism and show an angiotropic and angiodestructive process, which sometimes can also have pseudoepitheliomatous changes on the surface. The neoplastic cells are medium sized and express CD56, cytotoxic markers, CD3, and TCRγδ. Ki-67 is very high in these tumors (usually >60%).105,106,179,181 They are characteristically negative for TCRβ, CD4, CD8, and EBER. Variable loss of T-cell antigens is present. More recently, several authors have identified some cases with a more protracted clinical course, MF-like clinical lesions, and epidermotropism.182,183 Those cases are negative for CD56 and have expression of CD4 or CD8. It is believed that those cases may have a more indolent behavior compared with the classic forms of PCGDTCL. Another point of interest is that phenotypic switch of cases of MF from TCRβ to TCRγδ can also occur.122 It is important to remember that expression of TCRγδ should not be considered specific for a diagnosis of PCGDTCL: cases of LyP and PLC/PLEVA can also have expression of TCRγδ.184

Figure 11. Lymphomatoid papulosis. Classic type A (a and b), type B (c), type C (d), type D (e), and type E (f).
Berti lymphoma, or AETCL, is another subtype of cytotoxic lymphoma with a very aggressive clinical course (Figure 14). This lymphoma subtype is characterized by exquisite epidermotropism. The phenotype shows expression of CD3, CD7, CD8, cytotoxic molecules, and TCRβ. The Ki-67 is markedly elevated. As opposed to CD8+ MF, Pautrier microabscesses are uncommon, the Ki-67 is very high, and there is usually retained expression of CD7.107,109 Clinically, AETCL has numerous ulcerated patches, plaques, and tumors with genital involvement, whereas CD8+ MF is an indolent lymphoma with hypopigmented patches and plaques that do not affect the mucosal sites. In our practice,
a diagnosis of neoplastic CD8⁺ epidermotropic infiltrates is a difficult one to make in the absence of supporting clinical information. In the absence of an adequate clinical description of the lesions, a diagnosis of CD8⁺ epidermotropic T-cell lymphoma should be used, and the inclusion of a differential diagnosis of CD8⁺ MF, pagetoid reticulosis, AETCL, and type D LyP added to the pathology report. If the lesion presents in an acral location, a diagnosis of primary cutaneous acral CD8⁺ T-cell lymphoma can also be included in the differential diagnosis.

In the authors’ personal experience, small- to medium-sized CD4⁺ LPD is perhaps the most common form of cutaneous LPD encountered in the routine clinical practice (Figure 15). This is because the vast majority of the previously called “atypical lymphoid hyperplasias” or “clonal lymphoid hyperplasias” represent examples of this entity. A significant underdiagnosis occurs because routine clonality studies are not typically done in common cutaneous hyperplasias of T and B cells. This indolent form of T-cell dyscrasia is characterized by the expression of germinal center markers among the T cells (T-helper phenotype). This disorder typically shows a dense, nodular, or diffuse infiltrate in the dermis and sometimes the subcutis, with sparing of the epidermis. On some occasions, limited epidermotropism occurs. This process shows a mixture of T and B cells, with admixed plasma cells and eosinophils. Sometimes, small germinal centers can be present (which are positive for BCL-6 and CD10 but negative for BCL-2). Granulomas can also be seen. The T cells typically show expression of CD4, CD3, and the follicular T-helper markers (BCL-6, PD-1, CXCL-13, ICOS, and sometimes CD10). The CD4/CD8 ratio is very high (>10:1). As opposed to other T-cell LPDs, loss of T-cell markers (CD2, CD5, and CD7) is not common. The Ki-67 is typically low (<30%). PD-1 shows rosetting around B cells in a pattern similar to what is seen in nodular lymphocyte–predominant Hodgkin lymphoma. CD30 is usually negative. The rate of positive clonality studies is variable, ranging from 60% to 100%. Some authors used a positive TCR to support a diagnosis, given the hard problems distinguishing from reactive hyperplasias. In the authors’ opinion, a TCR is not required, and it creates a significant economic burden for the patients, given the complete indolent nature of this disorder. Most clinicians will do a watchful waiting approach for treatment, because many such lesions disappear. Limited excision and local radiation are used for persistent lesions. Given the fact that many of these cases can sometimes show a significant proportion of large cells
and subcutaneous involvement, it is common to encounter referrals with a diagnosis of “peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS).” This diagnosis puts patients at risk for an aggressive management of an indolent process, and we have identified many patients who are treated with CHOP for this condition. In this sense, a diagnosis of PTCL-NOS should almost never be issued when dealing with skin lymphomas. Patient care may be optimized by submitting any such not definitely classifiable lymphoid infiltrate to an expert in the field of skin

Figure 13. Subcutaneous panniculitis-like T-cell lymphoma (a through c). A classic lobular lymphocytic panniculitis-like infiltrate is present (a). The classic histologic finding is the presence of prominent adipocyte rimming by the malignant cells (b and c). The infiltrate can be very similar and easily confused with a diagnosis of lupus panniculitis (d through f). There is a mixed lobular and septal panniculitis (d), with adipocyte rimming (e), and a predominance of CD4+ T cells (f).

Figure 14. Aggressive cutaneous T-cell lymphomas: primary cutaneous γ-δ T-cell lymphoma (a through c) and Berti lymphoma (d through f). In primary cutaneous γ-δ T-cell lymphoma, there is pseudoepitheliomatous changes (a) and angiotropism with angionecrosis (b). The malignant cells are positive for TCRγ (c). Aggressive CD8+ epidermotropic T-cell lymphoma (Berti lymphoma): in this example, there is a dense dermal and markedly epidermotropic infiltrate (d and e). The infiltrate is diffusely positive for CD8 (f).
lymphomas, thereby limiting overdiagnosis and overtreatment with unnecessary morbidity. In the authors’ experience, it is always useful to do EBER by in situ hybridization when encountering this process. Such is done to exclude the possibility of a diagnosis of angioimmunoblastic T-cell lymphoma, a systemic form of PTCL that frequently has skin dissemination. However, EBV by itself is not diagnostic of AITL in the skin because iatrogenic T-cell lymphomas and extranodal NK/T-cell lymphomas can also be EBV positive.

NK-CELL LYMPHOMAS

The prototypic disorder in this group, extranodal NK/T-cell lymphoma, is an aggressive lymphoma with frequent skin dissemination. Morphologically, there is angiotropism and angionecrosis. Limited epidermotropism can be present. The malignant infiltrate is composed of medium-sized cells with abundant and granular cytoplasm. Although NK cells do not express surface CD3, because of CD3ε cytoplasmic expression, most antibodies for CD3 stain positive in the tumor cells. NK cells typically have expression of CD2 and CD7 but lack expression of CD5. Invariably, all tumors are diffusely positive for EBV and CD56. Malignant cells lack expression of TCRαβ and TCRγδ, and have a high Ki-67 proliferation index. Cytotoxic markers are also positive. It is important to emphasize that although most cases show a polyclonal TCR gene rearrangement study, some cases can be clonal. Cases that have a T-cell phenotype with diffuse expression of EBV can also be included under this category, whereas cases that have an NK-cell phenotype but are negative for EBV expression are best classified with the group of T-cell lymphomas.

Another form of T- or NK-cell LPD that occurs in children is HV-LPD. Histologically, there is epidermal spongiosis, intraepidermal vesiculation, and necrosis. Angiotropism without angionecrosis is noted. The infiltrate is both superficial and deep, and has a perivascular distribution. Such cases can be of T- or NK-cell origin and have EBV expression. Cytotoxic markers are typically expressed, and the Ki-67 and EBER+ is lower in comparison with extranodal NK/T-cell lymphoma.

CUTANEOUS B-CELL LYMPHOMAS

The 2 most common subtypes of cutaneous B-cell lymphomas are PCFCL and CMZL, and their frequency is similar overall. PCFCL is a B-cell lymphoma of germinal center origin. Morphologically, the lesions show a dermal-based infiltrate with a follicular, diffuse, or follicular and diffuse growth (Figure 16). Cytologically they are composed of a mixture of centrocytes (small cleaved cells) and centroblasts (larger cells with central prominent nucleoli). Cases with a diffuse appearance have a larger number of centroblasts and can be confused with DLBCL. There is a particular variant of PCFCL with a spindle cell appearance that can be confused with mesenchymal spindle cell neoplasms (Crosti lymphoma, reticulohistiocytoma dorsis). The immunophenotype of this lymphoma is characterized by expression of pan–B-cell markers (CD20, CD19, PAX-5, CD79a) and germinal center markers (BCL-6 and CD10). Cases with a more diffuse growth pattern can lack CD10 expression. BCL-2 is often negative but can be present in 20% to 25% of cases. The expression of BCL-2 correlates with the IGH-BCL2 translocation t(14;18), which is present in approximately 25% to 40% of cases. The Ki-67 is variable, typically in the lower range (<20%) but can be sometimes high in cases where there is abundance of
centroblasts or the spindle cell variant. Invariably the neoplastic follicles of PCFCL show a much lower Ki-67 proliferation index compared with normal germinal centers (>90%). Follicular dendritic networks can be identified in those cases with a follicular component (CD21, CD23, CD35, D2-40). MUM-1 is negative in most of the cells but can stain scattered plasma cells in the background. Dermal eosinophils can be seen.

There are 3 important differential diagnostic considerations in the diagnosis of PCFCL:

1. DLBCL-LT. For DLBCL-LT, as opposed to PCFCL, MUM-1 is positive and p63 is also positive. Cases with a diffuse pattern can have a large proportion of centroblasts and high Ki-67. For years, the controversial diagnosis of a low-grade lymphoma with abundant large cells has remained in the field of skin lymphomas. It is worth remembering the rule, “when speaking about PCFCL, size does not matter.” A lesion with abundant large cells and high proliferation, but otherwise classic features of PCFCL, should be interpreted as such. Perhaps a statement about a large proportion of large cells is warranted in such cases. On the other hand, a lesion with a germinal center phenotype (CD10+, BCL-6+, MUM-1) and perhaps a lower proportion of large cells in the legs can have a more aggressive clinical course. Therefore, such cases should be very carefully examined, and a diagnosis of B-cell lymphoma of germinal center type in the legs can be interpreted as such. Perhaps a statement about a large proportion of large cells is warranted in such cases. On the other hand, a lesion with a germinal center phenotype (CD10+, BCL-6+, MUM-1) and perhaps a lower proportion of large cells in the legs can have a more aggressive clinical course.

2. Systemic FL. Most PCFCLs are BCL-2+/BCL-6+. As opposed to systemic follicular lymphoma, grading on the basis of the number of centroblasts carries no prognostic significance for PCFCL. One should remember that systemic FL with skin dissemination is quite uncommon and typically occurs in the setting of advanced disease. The presence or absence of BCL-2 or IGH-BCL2 translocation should not be used to define a process as systemic. Careful staging procedures typically limited to a computed tomography scan or positron emission tomography can often help to distinguish between the two.

3. CMZL. This differential diagnosis can be particularly challenging in cases located in the head and neck region. CMZL can show atrophic germinal centers, which are BCL-2+, or disrupted ones, which can produce an irregular pattern of BCL-6 staining in the dermis. When faced with that dilemma, a CD123 immunostain can be useful (clusters of plasmacytoid dendritic cells are frequent in CMZL but not in PCFCL).

CMZL is a low-grade form of B-cell lymphoma that includes the combination of monocytoid cells, plasmacytoid lymphocytes, and mature plasma cells (Figure 17). Some examples of CMZL can show marked plasma cell differentiation, and in the past some of these cases have been erroneously diagnosed as cutaneous plasmacytoma. We now understand that all those cases are examples of CMZL. Morphologically, CMZL is centered in the dermis and shows an adnexotropic growth. In some circumstances, epidermotropism can be present. A helpful clue in the diagnosis of the disease is the presence of atrophic germinal centers. Dermal eosinophils can also be seen in many of the cases. Immunophenotypically, these lesions show expression of pan-B-cell antigens, and they lack CD5 and CD10. A blastoid variant has been described that can sometimes show CD5+. The atrophic germinal centers are positive for BCL-6 and CD10 but are negative for BCL-2. The Ki-67 in the lesional cells is low (<20%), but it is very high in the germinal centers (>90%). In situ hybridization for κ and λ can be helpful in proving clonality among the B cells and plasma cells. More recently, high-

Figure 16. Primary cutaneous follicle center lymphoma, histopathologic and immunophenotypic features. There is a nodular and diffuse infiltrate in the dermis (a). Poorly formed germinal centers that lack both polarization and a mantle zone are seen (b and c). The infiltrate is composed of a mixture of centrocytes (small cleaved cells) and centroblasts (larger cells; c). The nodular pattern of B cells is highlighted by a CD20 immunostain (d). The nodules are positive for BCL-6 (e) but negative for BCL-2 (f).
resolution in situ mRNA (RNA scope technique) also has been able to be used to demonstrate clonality. Clusters of plasmacytoid dendritic cells are typically present. Another helpful immunophenotypic clue is the abundance of immunoglobulin G4+ (IgG4+) plasma cells found in a subset of such cases. Clonality studies for immunoglobulin heavy-chain gene rearrangement (IGH) can be used in challenging cases where determination of clonality cannot be done by other methods.

The last subtype of cutaneous B-cell lymphoma is DLBCL-LT, an aggressive type of lymphoma that requires systemic therapy. Pathologically, there is a diffuse dermal infiltrate composed of sheets of large cells (Figure 18) and immunoblastic cells (large pleomorphic cells with a vague

Figure 17. Primary cutaneous marginal zone lymphoma, histopathologic and immunophenotypic features. There is a diffuse, mostly interstitial infiltrate with sparing of the epidermis (a). Focal nodular aggregates of atrophic germinal centers are seen (b and c). Scattered eosinophils are present (c). The infiltrate is positive for CD19 (d). In situ hybridization for κ (e) and λ (f) show κ restriction.

Figure 18. Diffuse large B-cell lymphoma, leg type, histopathologic and immunophenotypic features. Sheets of immunoblastic-appearing large cells (large lymphoma cells with a vague plasmacytoid appearance) are seen in the dermis and extending into the subcutis (a through c). The infiltrate is positive for CD20 (d), MUM-1 (e), and BCL-2 (f).
plasmacytoid appearance). The malignant cells are positive for pan-B-cell markers, BCL-2, BCL-6, and MUM-1, a classic non–germinal center phenotype in accordance with the Hans algorithm. The Ki-67 is very high (usually >70%). The tumor has rearrangements in the MYC gene in up to 32% of cases in the absence of IGH-BCL2 translocations. EBV is also negative. Cases with a germline center phenotype (CD10, BCL-6, MUM-1) should not be diagnosed as DLBCL-LT, but rather as DLBCL, not otherwise specified. However, many such cases may fall under the category of PCFCL with a diffuse growth pattern, and a predominance of large cells. The latter carries a much better prognosis compared with DLBCL-LT. Excluding other types of aggressive B-cell lymphomas is important in this condition, particularly systemic B-cell lymphomas (DLBCL, mantle cell lymphoma, EBV-positive DLBCL, plasmablastic lymphoma, etc). MYD88 mutations are typical of DLBCL-LT (they are not exclusive to DLBCL-LT because they can also be identified in lymphoplasmacytic lymphomas, splenic marginal zone lymphoma, and chronic lymphocytic leukemia). The mutation is associated with a worse prognosis.

**PSEUDOLYMPHOMATOUS INFILTRATES**

In the approach to “reactive” lymphoid infiltrates one should take into consideration whether the predominant pattern is epidermotropic, dermal-based, or mostly subcutaneous. Such patterns can be helpful in determining a list of differential diagnostic considerations that can be confused with both T- and B-cell lymphomas.

Epidermotropic reactive lymphocytic infiltrates can create significant diagnostic challenges, particularly in the diagnosis of eczematous (spongiotic) dermatoses. It is important to remember that intraepidermal collections of Langerhans cells can sometimes be confused with Pautrier microabcesses. When the biopsy is clearly inflammatory (not neoplastic), the term *lymphoid exocytosis* as opposed to *epidermotropism* is preferred to indicate a “benign” pattern. When a histopathologic pattern suggests a reactive (non-neoplastic) process and there is a low index of clinical suspicion for MF, TCR gene rearrangement studies ARE NOT recommended. Drug and viral exanthems can also have a mixture of spongiotic and interface changes, and the dense infiltration of the surface epidermis mimics a diagnosis of MF. Perhaps an important consideration in the differential diagnosis at both a clinical and a histopathologic level is a diagnosis of actinic reticuloid (chronic actinic dermatitis). Clinically, actinic reticuloid differs in the sun-exposed distribution of the clinical lesions, and the fact that many such cases are seen in the setting of HIV. Histologically, the lesions can very much resemble MF, with a prominent pattern of lymphoid tropism into the epidermis. However, actinic reticuloid has a classic CD8 phenotype and does not show loss of T-cell antigens. Pityriasis lichenoides (PLC and PLEVA) can also be a mimic. Both entities are characterized by the presence of interface changes and a lymphocytic vasculitis. Epidermal necrosis is typical of PLEVA. Both disorders are also frequent in children and can show a dense intraepidermal infiltrate. As opposed to MF, they do not show significant loss of T-cell antigens. In the past, some suggested that the infiltrate was CD4 for PLC and CD8 for PLEVA.

One of the most challenging and still debatable diagnostic considerations is the diagnosis of parapsoriasis. Today, large-plaque parapsoriasis is MF (so the former term should no longer be used). A diagnosis of small-plaque parapsoriasis is still regarded by many as perhaps an early form of MF or a pre-MF stage. Small-plaque parapsoriasis is also referred to as digitate dermatitis to highlight the appearance of the lesions in the trunk and limbs. The histopathologic findings are relatively nonspecific, and they include spongiosis, acanthosis, and a sparse perivascular infiltrate. Foci of epidermotropism and tagging of cells along the dermal-epidermal junction are seen in 10% of cases. Other features of MF, haloed lymphocytes (82%), fibrosis and dermal edema (30%), and cerebriform nuclei, can be present. Clonality studies are variable but more typically polyclonal.

Reactive, nonneoplastic dermal infiltrates include diagnostic mimickers of both CTCL and CBCLs. One of the most common causes of deep dense lymphoid infiltrates with a large proportion of eosinophils includes arthropod bite reactions. Such reactions tend to have a wedge-shaped appearance, and on some occasions arthropod parts. As opposed to CTCLs, loss of T-cell antigens is not typical. Given the abundance of histiocytic cells in the dermis, the CD4/CD8 ratio is often high. A more accurate assessment of the ratio among the T cells is better done using the CD3/CD8 ratio. Many dermatopathologists confuse the presence or absence of eosinophils as a clue for reactive inflammatory disorder (presence of eosinophils) versus lymphoma (absence of them). This is an absolute misconception. Most T- and B-cell lymphomas will show eosinophils in the background. Indeed, in cases of folliculotropic mycosis fungoides with progression, when follicular rupture occurs, a very large proportion of eosinophils can be noted. In addition, the pyogenic variant of PC-ALCL can display a large proportion of background inflammatory cells (neutrophils and eosinophils) and the neoplastic population obscured. Perniosis and polymorphous light eruptions can also show heavy dermal lymphoid infiltrates. A normal immunophenotypic profile can help in the distinction with lymphoma. Both perniosis and PLC/PLEVA have very dense perivascular infiltrate (also described as “lymphocytic vasculitis”), and vasculitis is not typical of CTCLs. The main differential diagnostic considerations in panniculitic disorders have been previously discussed.

It is always a good reminder that finding CD30+ cells in abundance in the dermis should not be considered diagnostic of lymphoma. Many reactive inflammatory conditions can have an abundance of CD30+ cells, and those include infections (molluscum, HSV, pox virus, fungal, scabies), medications (phenytoin, other anticonvulsants), arthropod bites, tattoo reactions, contact dermatitis, etc. PLEVA can also show an abundance of CD30+ cells. Table 2 summarizes a list of common pseudolymphomatous processes for (1) epidermotropic, (2) dermal, and (3) subcutaneous infiltrates.

**CONCLUSIONS**

A diagnosis of cutaneous lymphoid infiltrates can be adequately approached using a systematic scheme following the proposed ABCDE system. Overall, cutaneous T- and B-cell lymphomas are rare and “reactive” infiltrates more common. Evaluation of lymphoid proliferations should start with a good sense of knowledge of the clinical presentation of the lesions, the clinical differential considerations, and a
conscious and appropriate use of immunohistochemistry and molecular tools.

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Table 2. Pseudolymphomas

| Epidermotropic | Dermal Based | Panniculitic |
|----------------|--------------|--------------|
| B cells and plasma cells | Borrelia-associated lymphocytoma cutis | IgG4-related disease |
| NA | Cutaneous lymphoid hyperplasia | Lupus panniculitis |
| Lichenoid contact dermatitis | Pseudolymphomatous contact dermatitis (eg, parapsychomyelinid) | Cold panniculitis |
| Reactions to vaccines | Small to medium CD4+ lymphoproliferative disorder | Drug reactions |
| IgG4-related disease | Drug reactions | |
| Lympomatoid drug reactions | Cutaneous plasmacytosis | |
| CDB+ pseudolymphoma in immunodeficiency | Syphilis | |
| Borrelia-associated T-cell pseudolymphoma | Tibial lymphoplasmacytic plaque | |
| Papuloverrucodermia of Ofuji | Cutaneous Rosai-Dorfman disease | |
| Lichen sclerosus et atrophicus | Zoon balanitis/plasma cell vulvitis | |

T cells
- Actinic reticuloid (chronic actinic dermatitic)
- Pityriasis lichenoides chronic
- Pityriasis lichenoides et varioliformis acuta
- Lichenoid contact dermatitis
- Lymphomatoid drug reactions
- CD8+ pseudolymphoma in immunodeficiency
- Borrelia-associated T-cell pseudolymphoma
- Papuloverrucodermia of Ofuji
- Lichen sclerosus et atrophicus

Abbreviations: HSV, herpes simplex virus; IgG4, immunoglobulin G4; NA, not applicable; VZV, varicella zoster virus.
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