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Managing Patients with Cutaneous B-Cell and T-Cell Lymphomas Other Than Mycosis Fungoides

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Abstract

Cutaneous lymphomas (CL) are a heterogeneous group of neoplasms characterized with clinical and histopathological variation, as well as overlap with benign dermatoses. Diagnosis and treatment of CLs is challenging and often requires a multi-disciplinary approach. However, prognostic knowledge of these conditions and awareness of treatment options can help optimize appropriate use of available regimens, thereby improving care for patients. Here we review the most recent literature and outline treatment themes for managing patients with cutaneous B-cell and T-cell lymphomas other than mycosis fungoides.

Keywords

Primary cutaneous B- cell lymphoma; cutaneous T- cell lymphoma; non-mycosis fungoides; systemic treatment; skin-directed treatment; multi-disciplinary approach

INTRODUCTION

Cutaneous lymphomas (CL) are a heterogeneous group of neoplasms characterized by an accumulation of mononuclear, mostly lymphocytic cells in the skin.[1] They are the second most prevalent extranodal non-Hodgkin lymphomas (after gastrointestinal), representing

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Conflict of Interest

Meenal Kheterpal, Neha Mehta-Shah, Pooja Virmani, and Patricia L. Myskowski each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent

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approximately 19% of extranodal non-Hodgkin lymphomas[1] with mycosis fungoides (MF) and Sézary syndrome (SS) accounting for over 50% of all cutaneous T-cell lymphomas (CTCL). Non-mycosis fungoides (non-MF) CTCL and cutaneous B-cell lymphomas (CBCL) include several other subtypes and variants, whose clinical and histopathological presentations vary significantly.

While this review will focus mainly on treatment of such non-MF CTCL and CBCL, accurate diagnosis is a crucial, and often challenging, initial step. Given the rarity of these cutaneous lymphomas and the variability in presentations, clinical-pathological correlation is paramount to making a sound diagnosis. Furthermore, there can be significant overlap with reactive benign inflammatory conditions. Application of modern PCR-based methods for determining monoclonality in formalin-fixed tissue has greatly increased our ability to diagnose cutaneous lymphomas. At least 85% of cases demonstrate monoclonality.[2] However, since monoclonality can be seen rarely in reactive processes, interpretation should be performed in clinical, histopathologic and immunophenotypic context[2–4]. At times, long term clinical follow up with multiple biopsies is needed to confirm the final diagnosis.

Once the diagnosis is established, there are some common treatment themes. Our overall approach is to best understand the patient's presenting condition within the realm of the existing World Health Organization-European Organization for Research and Treatment of Cancer (WHO-EORTC) classification, thereby understanding the disease prognosis as indolent or aggressive. For the indolent lymphomas, our approach is to balance efficacy with safety of the available regimens. Given that several indolent conditions have a high rate of relapse with a retained excellent overall prognosis; treatments with low potential of immediate and long-term risks are preferable for early lines of therapy. At times, observation is a reasonable option. In contrast, early diagnosis of the aggressive cutaneous lymphomas, followed by combination chemotherapy and often a strong consideration of hematopoietic stem cell transplant (HSCT) is a mainstay of treatment.

CUTANEOUS T-CELL LYMPHOMA

Primary Cutaneous CD30+ lymphoproliferative disorders (CD 30+ LPD)

Primary cutaneous CD30-positive lymphoproliferative disorders are the second most common form of cutaneous T-cell lymphomas representing about 30% of all CTCLs. They include lymphomatoid papulosis (LyP), primary cutaneous anaplastic large cell lymphoma (PCALCL) and borderline/overlapping cases that may include features of both.[1] Clinical follow up is occasionally the only way to establish the final diagnosis.

Lymphomatoid papulosis (LyP)

Overview: Overview: chronic, recurrent self resolving papular necrotic/papular nodular skin disease, with variable histology, and CD3+, CD4+, typically CD8− immunophenotype, with type A and type C revealing large CD30+ cells.[5] Given the spontaneous resolution of these lesions the prognosis is excellent and treatment is often not needed. One series with 118 patients with LyP, reported a 2% mortality over a follow up of 77 months.[6] There is a reported incidence of second lymphomas (most commonly cutaneous lymphomas such as

MF and cALCL) in this subgroup of patient as high as 20–40% but a very low risk of systemic lymphomas.[6,7,8] The risk factors to predict a secondary lymphoma are not well delineated. Number of lesions, severity of symptoms, ethnicity, and lactate dehydrogenase levels did not affect development of lymphoma in one series. Moreover, treatment of LyP provided symptomatic relief but did not prevent progression of lymphoma.[8]

Treatment guidelines: The natural course of LyP is chronic and relapsing, without a curative treatment option. Hence, we support a conservative treatment approach, balancing long- term safety profile and adverse effects of the available treatment regimens. For patients with few or infrequent, non-scarring lesions, active observation should be considered. Occasionally lesions may ulcerate or become infected, in which case topical or oral antibiotics maybe considered. Several anecdotal reports have demonstrated responses to phototherapy modalities such as Psolaren and UVA (PUVA), narrowband ultraviolet B (nbUVB), excimer laser, photodynamic treatment (PDT), however, relapses are common after discontinuation of treatment.[6] In addition, LyP lesions have been reported to appear *de novo* in a PUVA treated field in MF patients.[9] Other reported effected skin directed treatments include topical steroids, intralesional steroids, nitrogen mustard and topical imiquimod with variable treatment responses.[8] Low-dose oral methotrexate (MTX, 5–20 mg/wk) is effective in suppressing the development of new skin lesions and can be considered in patients with widespread disease.[10] Other novel options include oral and topical bexarotene[11], as well as brentuximab vedotin, a CD30−directed antibody-toxin conjugate. In a phase II clinical trial, of brentuximab vedotin in patients with CD30+ lymphoproliferative disorders (n=9 LyP patients), a 100% overall response rate (ORR) was achieved; time to response was 3 weeks (range, 3 to 9 weeks), and median duration of response was 26 weeks (range, 6 to 44 weeks). Grade 1 to 2 peripheral neuropathy was the most common (54%) and ongoing side effect (45%).[12]

Primary cutaneous anaplastic large cell lymphoma (pcALCL)

Overview: Primary cutaneous anaplastic large cell lymphoma is an indolent cutaneous T-cell lymphoma, characterized by large cells characterized by the expression of CD30 antigen in more than 75% of the tumor cells, without history of concomitant MF.[13] Clinically, lesions present as solitary or grouped, rapidly growing and ulcerating tumors or thick plaques, and may involve regional lymph nodes. Histopathology demonstrates non-epidermotropic sheets of large CD30+ cells with anaplastic, pleomorphic, or immunoblastic cytomorphology. Immunophenotype is CD4+ (but can be CD8+), with variable loss of CD3, CD2, and CD5. Cells show expression of cutaneous lymphocyte antigen (CLA), but are negative for epithelial membrane antigen (EMA) and anaplastic lymphoma kinase (ALK). CD 15 staining is negative, distinguishing this entity from Hodgkin's lymphoma.[1]

Clinical course is indolent with 5-year disease-related survival ranging from 96% (skin only) to 91% (skin and regional lymph node involvement). Spontaneous regression (complete or partial) maybe observed in skin lesions in up to 42% of the patients.[6] However, relapse rate after therapy can be as high as 42%.[14] In a small study, extensive limb disease (ELD) and extracutaneous spread were found to be negative prognostic factors for disease specific survival in a multivariate analysis, with an aggressive course and poorer outcomes.[15] A

newly described DUSP22-IRF4 locus on 6p25.3 (DUSP22 rearrangement) in systemic ALK-neg ALCL is associated with an improved prognosis.[16] Although it is also reported in 28% of pcALCL.[17] as well as in LyP[18], the prognostic significance of this remains unclear.

Treatment guidelines: Given that CD30+LPDs demonstrate an overall indolent course. For localized disease, surgical excision for small lesions and/or radiation are considered to be the first line treatment, with 95% complete response rate (CRR). Relapses after local therapy may occur in up to 40% of patients, with no treatment more superior in controlling relapses.[19] Multiagent chemotherapy with CRR of 80–92%, but 62–80% relapse rate in skin and/or draining lymph nodes, has fallen out of favor as first line treatment, due to lack of durable responses. Single agent chemotherapies including MTX (intralesional/systemic), etoposide, gemcitabine in addition to anecdotal reports of response to interferons, imiquimod, thalidomide, bexarotene (alone or in combination with Interferon α), as well as HSCT have been summarized elsewhere.[19]

In the relapsed or refractory pcALCL, Pralatrexate, an anti-folate approved for use in peripheral T cell lymphoma, has shown activity. It is an anti-folate with an acceptable safety profile for continuous long-term dosing. In a dose-de-escalation strategy, Pralatrexate 15mg/m(2)/wk for 3 of 4 weeks showed high activity with acceptable toxicity in patients with relapsed/refractory CTCL.[20] Duvic et al[12] showed that CD30+ LPDs, including primary cutaneous anaplastic T-cell lymphomas (n = 2) showed ORR of 100% to Brentuximab vedotin (BV); time to response was approximately 3 weeks, and median duration of response was 26weeks for LyP/pcALCL patients. Onset of response was faster than MF patients but the duration of response was also shorter.[12] An international, randomized, prospective study of Brentuximab vedotin+methotrexate vs Brentuximab alone has also recently completed accrual with anticipated results on the horizon.

Subacute Panniculitis-like T-cell lymphoma

Overview—Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare primary cutaneous T-cell lymphoma that makes up <1% of T-cell lymphomas.[21] Clinically, lesions presents as non-specific subcutaneous nodules that may regress and remit spontaneously.[22–24] Histopathology shows atypical lymphoid cells rimming individual adipocytes with associated reactive histiocytes often associated with coagulation necrosis. Atypical lymphocytes show CD8+, CD56+, alpha/beta+ immunophenotype. Involvement of lymph nodes, spleen or bone marrow is uncommon. Hemophagocytic syndrome (HPS)/hemophagocytic lymphohistiocytosis (HLH) can be observed and carries a poor prognosis. The gamma/delta expressing phenotype of this disease is now classified as cutaneous gamma/delta T-cell lymphoma, under primary cutaneous peripheral T-cell lymphoma and tends to have a more aggressive clinical course.[24,25]

Treatment guidelines—Therapy for SPTCL remains controversial. Since SPTCL usually follows an indolent course and carries a favorable prognosis similar to MF (particularly when hemophagocytic lymphohistiocytosis is not present), approaches more commonly used for other indolent CTCLs have proven effective. Historically, responses to combination chemotherapy are usually of short duration and CRs are rare.[26,27] There are reports of

successful allogeneic stem cell transplantation[28–30] and prolonged remissions with combination chemotherapy followed by an autologous stem cell transplant.[31] However, the rarity of this disease and the infrequent need for aggressive therapy hampers our understanding of the utility of such approaches. Importantly, as with other indolent lymphomas, relapses often have not correlated with shortened survival. Single agent bexarotene has significant clinical activity in SPTCL with an ORR of 82% including CRs.[32] Other systemic agents as used for CTCL, such as oral methotrexate and histone deacetylase inhibitors also have activity. Anecdotal responses to glucocorticoids, interferon-α, zidovudine, and cyclosporine also have been observed.[33–37] The use of denileukin diftitox in two patients has been reported with evidence of activity.[38]

It has been our approach to treat those with SPTCL or the rare clinically indolent cutaneous gamma-delta T-cell lymphoma with systemic therapies that may be less aggressive but more tolerable for long periods of time. This strategy mimics what we often do for CTCL, in contrast to aggressive systemic PTCL. Therefore, we prefer initial therapy with either bexarotene or oral methotrexate. At times, observation alone may be appropriate. We consider combination chemotherapy, often adding HST consolidation with curative intent, in physically fit patients who continue to progress on these and other milder therapies, show a more aggressive disease course, and/or develop HLH.

Primary Cutaneous Peripheral T-cell lymphoma

Cutaneous gamma/delta T-cell lymphoma

Overview: As mentioned above, the term SPTCL now restricted to the a/b phenotype and the gamma/delta expressing phenotype of this disease is now classified as cutaneous gamma/delta T-cell lymphoma under the classification of PTCL. It often carries a highly aggressive clinical course.[24,25] Clinically, lesions appear as generalized plaques and/or ulceronecrotic nodules or tumors involving the extremities, mucosal sites, other extranodal sites. Immunophenotype of the PTCL, gamma/delta type is represented by a proliferation of mature, activated gamma/delta T-cells w/a cytotoxic phenotype with CD2+, CD3+, bF1−, g/d+, CD5−, CD56+, cytotoxic proteins. It is generally CD4−, CD8−, EBV−.[39] Involvement of lymph nodes, spleen or bone marrow is uncommon.

Treatment guidelines: In contrast to STPCL alpha/beta, cutaneous gamma/delta T-cell lymphoma is more frequently associated with hemophagocytic lymphohistiocytosis (HLH). In the largest multicenter retrospective series of this disorder, the median survival was 31 months but others have cited medium survivals of approximately 1 year.[39,40] Given the poor prognosis, aggressiveness, and poor responsiveness to conventional-dose treatments, we and others prefer to manage most patients with aggressive cutaneous gamma/delta lymphomas patients similarly to other cytotoxic T-cell lymphomas (e.g. HSTCL) with non-CHOP based induction chemotherapy followed by SCT with a preference fir allogeneic over autologous when feasible. More recently, as our ability to perform gamma staining by immunohistochemistry the has become more reliable, it has been observed that there may be a less aggressive form of cutaneous gamma/delta T-cell lymphoma that has histologic features and clinical behavior skin to SPTCL.[41–43]

Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (provisional)

Overview: Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma is a rare subtype representing<1% of cutaneous T-cell lymphoma (CTCL) with about 45 cases[44] reported in the literature, and a more recently, additional 18 cases reported through a EORTC Cutaneous Lymphoma Task Force Workshop[45]. It is characterized by widely distributed ulcerated papules and nodules, with occasional mucosal involvement, with an aggressive and fatal course.[44,46] Histology reveals epidermotropic infiltrates of CD8+ (CD2−/CD4−/CD45RA−/CD45RO−/CD5−/CCD56−) cytotoxic T cells, expressing cytotoxic markers (beta F1+, TIA-1+, granzyme B+, perforin+); EBV is generally negative.[1,45] Clinical course is rapidly progressive, (median survival 12–32 months[45,46]) and usually unresponsive to conventional CTCL treatments. There is a high tendency for spread to extranodal sites, mucosa and central nervous system, generally sparing lymph nodes and bone marrow.[45,46] Of note, there are reported cases of indolent CD8+ lymphoid proliferation of acral sites (CD8+ LP), which are thought to be low grade lymphomas with clinical presentation similar to CD4+ small/medium pleomorphic T-cell lymphoma (see below), comparable disease course, and infrequent need for systemic therapy, which should not be confused with aggressive CD8+ epidermotropic TCL.[47,48]

Treatment guidelines: Optimal treatment for this condition is not defined, due to rarity of this disease and its aggressive course, systemic spread and frequent relapse. In general, skin directed therapies are ineffective, including radiotherapy, unless used in combination with systemic therapy.[44] Partial responses may result with oral bexarotene plus total skin electron beam treatment (TSEBT).[49] Multi-agent CHOP like regimens are used most commonly but rates relapse are high, potentially improved with auto- or allogeneic HSCT.[45] When the clinical aggressiveness is clear is, our approach is to treat them with our same approach for cutaneous gamma/delta T-cell lymphoma.

CD4+ small- medium pleomorphic T-cell lymphoma (CD4+ SMPTCL)/CD8+ lymphoid proliferations of acral sites (CD8+ LP) (provisional)

Overview: Primary cutaneous CD4+ small- medium pleomorphic T- cell lymphoma (CD4+ SMPTCL) is a low grade indolent lymphoma (provisional entity) presenting as solitary papule or nodule, usually located on the head and neck.[47] Trunk and extremities can be involved, and a multifocal presentation has been very rarely associated with a more aggressive course with systemic involvement. No surface markers are predictive of an aggressive course, including Ki-67 index.[50] Histologically, the lesions are characterized by dense dermal infiltrate of small to medium sized atypical lymphocytes (CD4+/CD8+) without significant epidermotropism.[51] Immunohistochemistry reveals expression of T-follicular helper cell markers (PD-1, CXCL-13 and BCL-6) by the lymphocytic infiltrate in CD4+ SMPTCL, which can aide in diagnosis in cases with a polymorphous infiltrate along with a dominant T-cell clone.[51] While CD4+SMPTCL is a provisional entity in WHO-EORTC classification of cutaneous lymphomas, and its true malignant potential is questioned, a discussion of this entity is included here to emphasize the favorable prognosis and indolent nature of these conditions.[50, 52]

Treatment guidelines: Data suggests excellent prognosis in these patients and durable response to skin directed treatment modalities.[48,50,52–57] Treatment options include local excision, topical/intra-lesional steroids and local radiation. The rates of remission are high irrespective of the treatment modality used, and the relapse rates are low. Patients with multifocal progressive disease and/or symptoms suggestive of systemic involvement should be evaluated with staging studies such as computed tomography (CT), or positron emission tomography (PET) scan to exclude PTCL, NOS with subsequent dissemination to the skin as opposed to CD4+ SMPTCL.[50]

CUTANEOUS B-CELL LYMPHOMAS (CBCL)

Primary cutaneous B-cell lymphomas represent less than one third of cutaneous lymphomas[1,58]. The WHO-EORTC has categorized primary cutaneous B-cell lymphomas to 3 main subtypes (Table 1). The relevance to distinguish these subtypes is in the different treatment options as well as different prognosis[59]. Primary cutaneous marginal zone lymphoma (PCMZL) and primary cutaneous follicle center lymphoma (PCFCL) are characterized as indolent diseases with 99%–95% 5 year survival in comparison to DLBCL, leg type that has a more aggressive disease course and less than a 50% 5year survival[60]. The diagnosis of primary cutaneous B-cell lymphoma is only established when the staging is negative after the initial clinical and histopathological diagnosis. Of note, a bone marrow biopsy is often not required as routine staging in indolent CBCL, such as PCMZL, but is required in clinically intermediate to aggressive forms of cutaneous B-cell lymphomas.[61]

Primary cutaneous marginal zone lymphomas (PCMZL)

Primary cutaneous marginal zone lymphomas of MALT-type (PCMZL), previously known as primary cutaneous immunocytomas, comprise 24% of all primary cutaneous B-cell lymphomas[60]. Clinically, they present as single or multiple, red to violaceous infiltrated cutaneous or subcutaneous papules, plaques or multi-focal nodules with 2 cm or less in diameter (70%), with multifocal lesions being most common (72%).[62] The lesions are slow growing and usually do not ulcerate. Biopsies (i.e. punch biopsy or surgical excision) should be adequately deep in order to evaluate the extent of the infiltrate. Some authors have suggested an association of MZL is associated with chronic inflammatory processes or infections.[63,64] In Europe there have been cases of PCMZL associated with *Borrelia burgdorferi* infection however, recent reports are contradictory[62,65], however, recent reports are contradictory.[66–69]

Immunohistochemistry reveals CD19+, CD20+, CD5−, CD10− with monotypic immunoglobulin light chains often demonstrable in paraffin sections. The cells are often class-switched (IgG, IgA, IgE), unlike other types of extranodal marginal zone B-cell lymphomas. BCL2 is expressed in most cases[70–72]. The characteristic presence of reactive follicles can be highlighted by a CD21 stain that marks follicular dendritic cells.

Primary cutaneous follicle center lymphoma (PCFCL)

PCFCL is the most common type of primary cutaneous B-cell lymphomas, making up 57% of cases in a recent large study. The median age at diagnosis is 58 years with a male:female

ratio of 1.8.[60] It presents as an erythematous papule, plaque, or nodule most commonly located on the trunk or head/neck. Lesions may be single or multiple but are localized when multiple. It is only rarely seen on the upper (2.3%) or lower (6.4%) extremities. The latter is at times difficult to differentiate from diffuse large B-cell lymphoma, leg type (DLBCL – LT). Immunohistochemistry reveals pan-B-cell markers CD19 and CD20, with coexpression of BCL6. Other germinal center B-cell markers are also often expressed including CD10 and human germinal center –associated lymphoma (HGAL)[73] Unlike nodal follicular lymphoma, in which BCL2 expression is a hallmark that reflects a t(14;18)(q32;q21) translocation, PCFCL is characteristically negative for BCL2. However, in examples that are follicular, especially when predominantly small cleaved cells, BCL2 is expressed in approximately 40% of cases.[73,74]

Primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBL-LT)

PCDLBCL-LT comprises approximately 20% of primary cutaneous B-cell lymphomas and has several distinctive clinical features. Compared to the above two types, this lymphoma occurs in an older population (median age 78 years) and has a striking female predominance (M:F ratio of 0.5). As the name implies, it presents most commonly (88% of patients) on the lower extremity. However, it can occur at other sites including the head/neck, trunk, and upper extremities in 5–12% of patients[1,60]. Clinically it presents as a nodule, either singly or as multiple regional lesions. Multifocal disease is seen in 20% of cases. Uncharacteristic to other cutaneous lymphomas, PCDLBCL-LT will often disseminate to nodal and visceral sites, which likely portends a transition in its already aggressive behavior[75,76]. Immunohistochemistry reveals expression of CD19 and CD20. Unlike PCFCL, expression of BCL2 is the rule and the post-germinal center B-cell maker MUM1 is usually expressed. BCL6 is expressed by most cases but CD10 is not.[73,77–80]

Molecular genetics—t(11;18)(q21;q21) translocation involving *API2-MALT1* and t(3;14)(p14;q32) involving *FOXP1* and *IGH@* are seen in less than 10% of cases. The t(14;18)(q32;q21) also involving *IGH@* and *MALT1* is present in less than 15% of cases.[72,81] The *IGH@-BCL2* translocation typically seen in nodal follicular lymphoma can be seen in 0–40% of cases PCFCL with a follicular growth pattern.[74,82,83] Variation may be related to technique.[82] Gene expression profiling studies have shown that the profile resembles germinal center-like diffuse large B-cell lymphomas.[84]

PCDLBL-LT lacks translocations seen in MALT-type lymphomas or follicular lymphoma. However, translocations of *BCL6, MYC*, and *IGH@* and amplification of BCL2 are commonly seen. Deletion in the region of cell cycle inhibitors *CDKN2A* and *CDK2NB* (chromosome 9p21.3) or promoter methylation is frequent and associated with poor outcome.[85,86] Gene expression profiling shows a distinct profile from PCFCL and similarity to activated B-cell type of diffuse large B-cell lymphoma.[84]

Treatment guidelines: The standard treatment for indolent cutaneous B-cell lymphoma (MZL and FCL) depends on number and size of the lesions. Although there is no strong support in the literature for “watch *and* wait”, it is recommended by the National

Comprehensive Cancer Network (NCCN) guidelines[87] and practiced by some experts for multifocal lesions or extensive disease.

Excision and local radiotherapy is commonly considered as first line therapy especially for solitary lesions. Recent studies have shown treatment with radiation could result in 99% complete response rate but the relapse rate in these studies widely varied.[88] Neelis et al used low dose (2×4Gy) radiation in 18 indolent CBCL patients with 72% complete response rate.[89] Low-dose local radiation may have fewer side effects and moreover, it provides the possibility of repeating radiation when there is evidence of relapse.

In small studies, intralesional interferon α[90], intralesional adenovirus-interferon γ[91], intralesional steroids[92–94], intralesional rituximab[95,96] have been administered successfully with an acceptable relapse rate. Systemic rituximab monotherapy is often administered when there is multifocal disease or other therapies are contraindicated or unwanted[97–99]. Topical imiquimod, an immune response modulator, is an option in certain cases[100,101].

In cases with high suspicion for an infectious trigger such as *Borrelia or H.pylori*, appropriate antibiotic therapy can be attempted as first line therapy with anecdotal responses reported.[102–105] Systemic mono- or multi-agent chemotherapy such as chlorambucil[106] or CHOP-like regimens have been used in the past when the true indolent nature of this lymphoma was less well understood. These are now only considered in cases of extensive disease, failure prior therapies, and extracutaneous spread, in which case their management is similar to the more common systemic indolent B-cell lymphomas.[88]

The treatment of PCDLBCL-LT is extrapolated from the diffuse large B-cell lymphoma, the most common systemic non-Hodgkin lymphoma. Therefore, if manageable, immunotherapy with rituximab plus multiagent anthracycline based chemotherapy is recommended.[75,107] Localized radiation therapy to a solitary lesion or grouped lesions is an option as an adjuvant treatment to systemic chemoimunotherapy or alone in cases where comorbidities preclude chemotherapy. The most common regimens used in the up-front management of PCDLBCL-LT are R-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or the infusional regimen, dose adjusted R-EPOCH (cyclophosphamide, doxorubicin vincristine, etoposide, and prednisone). Commonly, full course therapy with 6 cycles is used as there is a lack of evidence for “short-course” combined modality therapy in PCDLBCL-LT despite its use extensively in localized DLBCL.[108] Rituximab monotherapy for PCDLBCL-LT is thought to be inferior therapy, however, remains an option for patients who are unable to tolerate multi-agent chemotherapy.[109] To date, there are no randomized studies to provide guidance.

CONCLUSION

Given the rarity of these lymphomas, prospective data comparing treatments is lacking. Randomized trials are rare and our management decisions are often extrapolated from very imperfect data. In addition, clinical trials evaluating novel therapies frequently accrue CTCL patients across several subtypes. However, despite lack of high-level evidence, patients need treatment. While a strict algorithm cannot be written, we attempt to highlight themes and

principles that have emerged through the existing literature, coupled with clinical experience, allowing reasonable and logical decisions.

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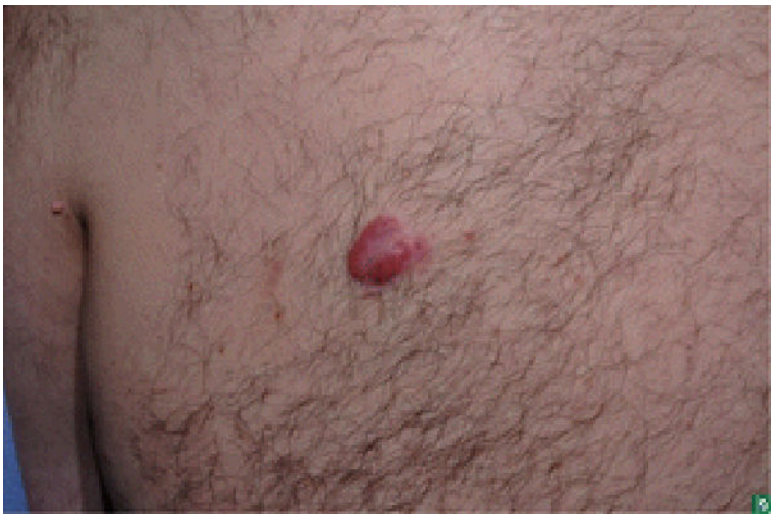

Figure 1.
Lymphomatoid papulosis: lesions in different stages of healing, one active lesion on R calf (arrow).

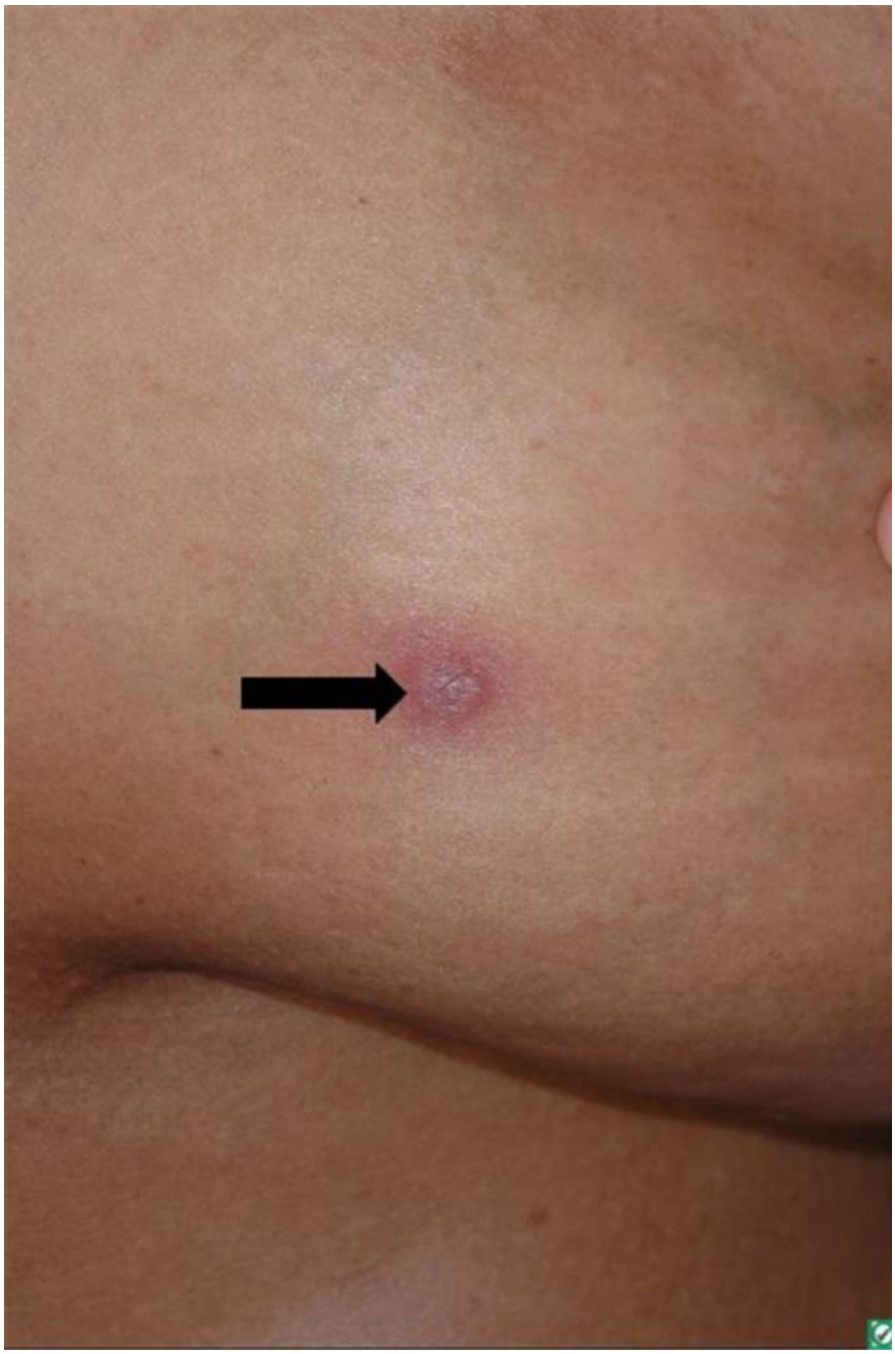

Figure 2.
Primary cutaneous marginal zone lymphoma: solitary non-ulcerated, erythematous nodule.

Table 1

The WHO/EORTC classification for cutaneous lymphomas[1]

Mature T-cell and NK-cell neoplasms
Mycosis fungoides (MF)
Variants of MF
Pagetoid reticulosis (localized disease)
Folliculotropic
Subtype of MF
Granulomatous slack skin
Sezary syndrome
CD30+ T-cell lymphoproliferative disorders of the skin
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma – alpha/beta origin
Primary cutaneous peripheral T-Cell lymphoma (PTL), unspecified
Subtypes of PTL
Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (provisional)
Cutaneous gamma/delta-positive T-cell lymphoma (provisional)
Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma (provisional)
Extranodal NK/T-cell lymphoma, nasal type *
Hydroa vacciniforme-like lymphoma (variant) *
Adult T-cell leukemia/lymphoma *
Angioimmunoblastic T-cell lymphoma *
Mature B-cell neoplasms
Cutaneous marginal zone B-cell lymphoma
Primary cutaneous follicle center lymphoma
Growth patterns
Follicular
Follicular and diffuse
Diffuse
Cutaneous diffuse large B-cell lymphoma, leg type
Cutaneous diffuse large B-cell lymphoma, others
Subtype of DLBCL, other
Intravascular large B-cell lymphoma *
Immature hematopoietic malignancies
Blastic NK-cell lymphoma CD4+/CD56+ hematodermic neoplasm (Blastic NK lymphoma) *

* This table also contains entities of extracutaneous lymphomas frequently involving the skin as a secondary site, thereby excluded from discussion in this review.