



Alexey Bobylev. *Hillock*, 2006. Oil on canvas, 80 × 101 cm. Courtesy of the St. Petersburg Art Salon, Russia.

The diagnosis and management of rare, aggressive, and difficult-to-treat lymphomas are reviewed.

Classification and Treatment of Rare and Aggressive Types of Peripheral T-Cell/Natural Killer-Cell Lymphomas of the Skin

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Background: *The classification of cutaneous lymphomas has been contentious. Two major competing classifications were the World Health Organization (WHO) and the European Organization for Research and Treatment of Cancer (EORTC). The principal authors met for a consensus meeting resulted in a combined classification called WHO-EORTC Classification of Cutaneous Lymphoma.*

Methods: *We review the classification of “mature” or peripheral T-cell lymphoma (PTCL) with high predilection to the skin as published by the WHO-EORTC. We also highlight new information and changes from the previous classifications of cutaneous PTCL according to the WHO classification or the EORTC classification. Finally, the salient findings are compared with similar-looking nodal PTCLs with a high frequency of skin involvement.*

Results: *This review focuses on a rare group of cutaneous PTCLs other than mycosis fungoides or its variants. Changes from the previous classifications are discussed, and the rare group of nodal PTCLs with high predilection to the skin are presented. The salient findings, diagnostic features, and treatments are included, along with summary tables and clinical-histopathologic images.*

Conclusions: *This review may serve as a guide for hematologists, oncologists and dermatologists in the diagnosis and management of these rare, aggressive, and often difficult to diagnose lymphomas. Although cutaneous lymphomas are morphologically identical to systemic lymphomas, the former behave differently, require divergent management, and should be recognized as separate entities. The consensus WHO-EORTC classification presents unified terminology and definitions to promote conformity in diagnosing and treating these cases, to foster a multidisciplinary approach to these often-obscure diseases, and to lead to more advances in identifying molecular targets specific to these entities.*

Introduction

According to the International Lymphoma Study Group, approximately 12% of all lymphomas are peripheral T-cell/natural killer-cell non-Hodgkin's lymphomas.¹ Diagnosis of these rare lymphomas is more challenging, especially when they arise at extranodal sites. Moreover, 82% of peripheral T-cell lymphomas (PTCLs) are extranodal, and a majority of them involve the skin.² In the National Cancer Institute's 2005 Surveillance, Epidemiology and End Results (SEER) report, primary cutaneous T-cell lymphomas represented approximately 76.9% of all primary cutaneous lymphomas, whereas primary cutaneous B-cell lymphomas accounted for 22.7% of cases.³

Primary cutaneous lymphomas have an estimated annual incidence of 1.0–1.5/100,000 and are the second most common group of extranodal lymphomas.² The term *primary cutaneous T-cell lymphoma* refers to cutaneous T-cell lymphomas present in the skin without extracutaneous involvement at the time of diagnosis.⁴ Systemic lymphomas occasionally involves the skin early in their course, but they characteristically have important nodal, marrow, or other extracutaneous involvement preceding or concurrent with cutaneous lesions.⁴

Secondary lymphomas that involve both nodal sites and the skin at presentation appear to represent approximately 25% of all cutaneous lymphomas and up to 50% of cutaneous lymphomas other than mycosis fungoides (MF).⁵ In contrast to primary cutaneous lymphomas, secondary cutaneous lymphomas show a B-cell predominance.⁵

Although primary cutaneous lymphoma is morphologically identical to systemic lymphomas, its behavior is

clinically different and requires different management. Therefore, it should be recognized as a distinct entity.⁵

Putative Cells of Origin

Skin is a major portal of entry for infectious organisms. Therefore, it has developed a highly effective but nonspecific immune surveillance that includes natural killer (NK) cells, gamma-delta T cells (γ/δ T cells), and dendritic cells, particularly the DC2 subset that produces interferon alpha (IFN- α).⁶ This “innate” leg of the immune system, in contrast to adaptive immunity, is focused on immediate (minutes to hours) detection and response to pathogens based on nonspecific epitopes.^{6,7} These immune targets include nonhuman glycolipids, glycoproteins, and DNA complexes with novel antigen-presenting molecules.^{6,7}

The adaptive leg of the immune response includes the “classic” alpha-beta T cells (α/β T cells), which comprise 90% of T cells. The “innate” leg includes γ/δ T cells, which comprise 10% of T cells. These cells travel in a recirculation loop to the regional lymph nodes and back to the skin, with T cells homing toward the T cell area or paracortex and B cells toward the cortical follicles of the lymph node.⁵ In the skin, the α/β T cells have predilection to the epidermis and the B cells and NK cells have predilection to the dermis and subcutaneous fatty tissue. The γ/δ T cells are largely located in the dermis, with some in the basal layer of epidermis and outer root sheaths of hair follicles. Although antigen and cognate receptors on γ/δ T cells and NK cells have a limited repertoire, they are adequate in recognizing common microbes.

Antigen receptors on γ/δ T cells and cognate receptors on NK cells have a relatively limited diversity allowing for their role in recognizing common microbial antigens. Dendritic cell maturation mediated by a group of Toll-like receptors is also tuned to recognize broad antigenic patterns. This generic microbial recognition system contrasts with the high level of specificity encoded by the TCR α/β , which largely recognizes protein antigens in the context of the highly conserved and specific HLA class I and class II molecules.

Most of the cutaneous tumors discussed here have putative histogenetic origin from — and perhaps biological behavior attributed to — the distinct cell types of the innate and adaptive immune system.^{6,7,8,9} Various microbial agents have been studied as a possible etiology of CTCLs, but so far, only an association between human T-cell lymphotropic virus (HTLV) and adult T-cell leukemia/lymphoma (ATLL) has been confirmed.⁴

Historical Background

In 1806, Jean Louis Alibert described the first patient with MF.¹⁰ This entity was described in more detail in

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Denileukin diftitox, bexarotene and vorinostat are the only agents listed in the manuscript which received US Food and Drug Administration (FDA) approval for therapy of cutaneous T-cell lymphoma. The remaining agents listed in the manuscript are unlabeled/unapproved for indolent and aggressive T-cell lymphoma/leukemia.

Dr Sokol is a member of the speakers bureau of Merck.

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Abbreviations used in this paper: WHO = World Health Organization, EORTC = European Organization for Research and Treatment of Cancer, PTCL = peripheral T-cell lymphoma, NK = natural killer, MF = mycosis fungoides, IFN = interferon, γ/δ T cells = gamma-delta T cells, α/β T cells = alpha-beta T cells, TCR = T-cell receptor, HTLV = human T-cell lymphotropic virus, SPTCL = subcutaneous panniculitis-like T-cell lymphoma, EBV = Epstein-Barr virus, PTCL-u = peripheral T-cell lymphoma, unspecified.

1870 by Bazin.¹¹ In 1975, Edelson¹² suggested the term CTCL for MF and Sézary syndrome without distinguishing the rare entities. The Kiel classification and the Working Formulation did not separately classify primary cutaneous lymphomas.^{13,14} Even the Revised European-American Classification of Lymphoid Neoplasms (REAL classification), published in 1994, included MF and Sézary syndrome with the more unusual variants of primary cutaneous lymphomas.¹⁵

The classification published in 1997 by the European Organization for Research and Treatment of Cancer (EORTC) classified cutaneous lymphomas separately from nodal lymphomas and introduced several new entities.¹⁶ The 2001 World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues included several skin-specific lymphomas but with different approach for some entities.¹⁷ The current WHO-EORTC classification published in 2005 updates these two sources and uses a unified terminology for cutaneous lymphomas.⁴

Classification

There are no radical changes in the new classification for MF/Sézary syndrome or the CD30+ T-cell lymphoproliferative disorders of the skin, which include lymphomatoid papulosis (LyP) and primary cutaneous anaplastic large-cell lymphoma.⁴ This review focuses

on the remainder of primary cutaneous T/NK-cell lymphomas, which represent less than 10% of CTCL, and includes systemic lymphomas that present primarily in the skin such as peripheral T-cell lymphoma, unspecified, adult T-cell lymphoma/leukemia, angioimmunoblastic lymphoma, and extranodal T/NK lymphoma-nasal type in the WHO classification.¹⁷ The WHO-EORTC classifications revised some definitions and introduced three provisional entities separate from the primary cutaneous peripheral T-cell lymphoma, unspecified: cutaneous γ/δ T-cell lymphoma, cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma, and cutaneous CD4+ small- and medium-sized pleomorphic T-cell lymphoma (Table 1).^{4,18-23}

Subcutaneous Panniculitis-Like T-Cell Lymphoma

Changes in Classification: In previous WHO and EORTC classifications, the category of subcutaneous panniculitis-like T-cell lymphoma (SPTCL) included all cases with a panniculitis-like appearance with TCR α/β or TCR γ/δ phenotypes.^{16,17} SPTCL was a provisional entity in the EORTC classification.¹⁶

New Definition: SPTCL is now described as a rare cutaneous T-cell lymphoma with a TCR α/β phenotype, usually T cytotoxic (CD8+), with indolent behavior and restricted to the subcutaneous tissue.⁴

Table 1. — Pathology, Cytogenetics, and Molecular Biology of Rare Subtypes of Mature T/NK-Cell Lymphoma

Lymphoma Type	Morphology	Immunophenotype	Cytogenetics	Molecular Biology	References
SPTCL	Subcutaneous fat rimming, cytophagic histiocytes, karyorrhexis, hyperchromatic lymphocytes	CD3+/CD8+, cytotoxic proteins+ (granzyme B, perforin and TIA-1) /CD4-/CD30-/CD56- β F1+	Nonspecific	TCR genes are rearranged, EBV absent	Willemze et al ⁴ Salhany et al ²⁶
Cutaneous γ/δ T-cell lymphoma	Epidermal, dermal, subcutaneous perivascular cytophagic histiocytes, psoriasiform epidermal hyperplasia	CD3+/CD2+/CD56+/cytotoxic proteins+(TIA-1, granzyme B, and perforin)/CD4-/CD8-/ β F1-/CD5-	Isochromosome 7q	TCR genes are rearranged, EBV absent	Willemze et al ⁴ Toro et al ¹⁸
Primary cutaneous peripheral T-cell lymphoma, unspecified	Medium- to large-sized pleomorphic or immunoblast-like >30%	CD4+/CD30-	Nonspecific	TCR genes are rearranged	Willemze et al ⁴ Bekkenk et al ²⁰ Au et al ²¹
Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma	Band-like/lichenoid, angiocentricity, pleomorphic or blastic nuclei, small to large	β F1+/CD3+/CD8+/perforin+/TIA-1+/CD45RA+/CD56-/CD45RO-/CD2-/CD4-/CD5-	Nonspecific	TCR genes are rearranged, EBV absent	Willemze et al ⁴ Massone et al ²³
Primary cutaneous CD4+ small- to medium-sized pleomorphic T-cell lymphoma	Nodular infiltrates, small to medium lymphocytes <30% large pleomorphic cells	CD3+/CD4+/CD8-/CD30-/cytotoxic proteins- (granzyme B, TIA)	Nonspecific	TCR genes are rearranged	Willemze et al ⁴ Bekkenk et al ²⁰
Extranodal NK/ T-cell lymphoma, nasal type	Angiodestructive necrosis, polymorphous infiltrate admixed with inflammatory cells	CD56+/CD2+/cytoplasmic CD3e+ /cytotoxic granule proteins+ (TIA-1, granzyme B, and perforin) /sCD3-/CD4-/CD8-	del 6(q16-q27), del 13(q14-q34)	TCR genes are germline, EBV+, mutations of k-ras	Willemze et al ⁴ Santucci et al ¹⁹ Au et al ²¹

Epidemiology: SPTCL affects young to middle-aged individuals (median age 45 years), with a male:female ratio of 1:4.^{23,25}

Clinical Appearance of Cutaneous Lesions: Common clinical features of SPTCL include slowly spreading subcutaneous multiple or, less often, solitary erythematous nodules that range in size from 0.5 to 12 cm.²⁶ Ulceration is uncommon. The nodules may wax and wane and are present on the legs, arms, trunk, or face. An association with connective tissue diseases has been reported.^{24,27,28} The indolent form of cytophagic histiocytic panniculitis appears similar to SPTCL.^{29,30}

Pattern of Infiltration: A dense collection of cells is largely confined to the subcutaneous fat (Fig 1). The lymphoid cells characteristically rim individual adipocytes in a "wreath-like" manner (Fig 2).³⁰ Epidermis is usually spared, but minimal infiltration of the dermis and angiocentricity has been reported. Necrosis, karyorrhexis, and lymphohistiophagocytosis are frequent histologic findings. Granulomas may be present.^{24,27,28}

Cytomorphology: A variable mixture of small, medium, and large atypical lymphocytes can be seen, often containing irregular, hyperchromatic nuclei and pale cytoplasm. Numerous vacuolated histiocytes with phagocytized lipid are present. In the early stages, the neoplastic infiltrates may lack significant atypia and a heavy inflammatory infiltrate may predominate.^{25,27,28}

Immunophenotype: The neoplastic cells are usually positive for CD3, CD8, and cytotoxic proteins (granzyme B, perforin, and TIA-1) and negative for CD4, CD30, and CD56.²⁶ The macrophages with hemophagocytosis are CD68+.

Cytogenetics and Molecular Findings: TCR genes are rearranged (α/β),^{24,28} and karyotypic findings are nonspecific.^{24,28} Epstein-Barr virus (EBV) is absent.^{26,28}

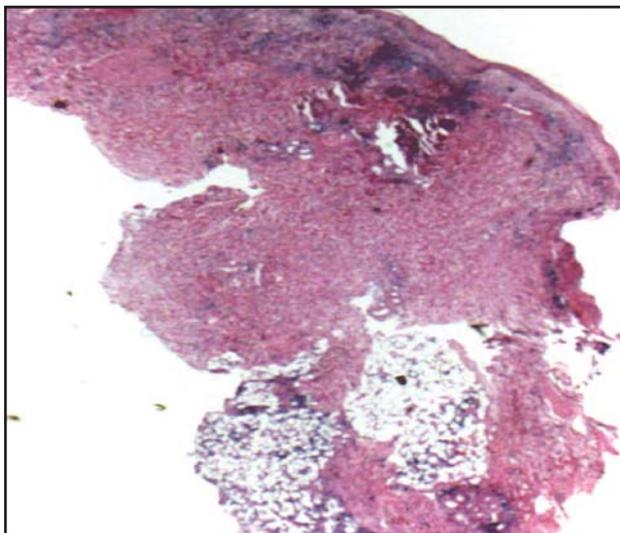


Fig 1. — SPTCL with a dense collection of cells largely confined to the subcutaneous fat. There is a variable mixture of small, medium and large atypical lymphocytes, often containing irregular, hyperchromatic nuclei and pale cytoplasm.

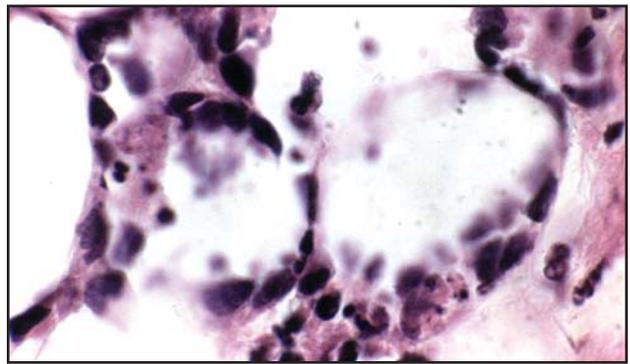


Fig 2. — SPTCL in which the lymphoid cells characteristically rim individual adipocytes in a "wreath-like" manner.

Clinical Behavior: The lesions usually grow locally. In rare cases, a fatal hemophagocytic syndrome signals a rapidly progressive course. Recurrent subcutaneous lesions without extracutaneous dissemination may occur.^{27,28} The estimated 5-year survival rate is 82% to 100%.³⁰

Differential Diagnosis: These include panniculitis, systemic PTCL not otherwise specified, lupus profundus, erythema nodosum, and erythema induratum.^{26,27}

Treatment: Prednisone can be used as an initial therapy in patients with less aggressive disease. For indolent disease, radiotherapy, monotherapy with cyclophosphamide, cyclosporine A, methotrexate, and IFN- α can be used to control the disease. Local external-beam radiation is a less common therapy.^{27,30,31} However, in rare aggressive cases, anthracycline-based chemotherapy regimens were shown to be most effective.³¹

Cutaneous γ/δ T-Cell Lymphoma (Provisional Entity)

Changes in Classification: This subtype is part of SPTCL in the WHO and EORTC classifications.^{16,17}

New Definition: This entity is defined as a lymphoma composed of clonally activated γ/δ T cells with a cytotoxic phenotype, generally with skin plaques with ulceronecrotic nodules and aggressive behavior. A fatal hemophagocytic syndrome may be associated with panniculitis-like tumors.⁴

Epidemiology: Young to middle-aged individuals are affected (median age 49 years), with a male:female ratio of 1.5:1.¹⁸

Clinical Appearance of Cutaneous Lesions: Common clinical presentations include multiple scaly plaques, nodules, or tumors with ulceration. The lesions are commonly located on the extremities. They are often accompanied by constitutional symptoms such as fever, malaise, fatigue, chills, and weight loss. Systemic involvement of mucosal and other extranodal sites has been reported, but involvement of lymph nodes, spleen, or bone marrow is rare.^{32,33}

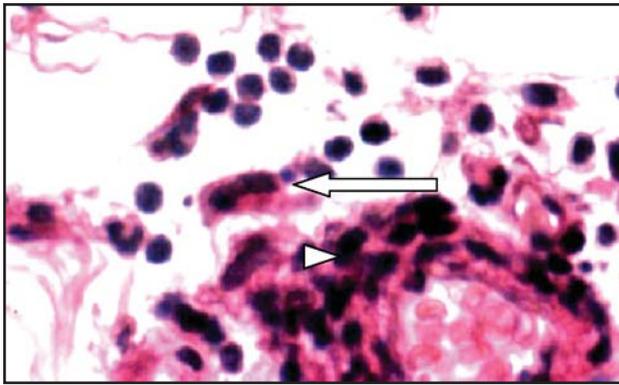


Fig 3. — Cutaneous γ/δ T-cell lymphoma. Lesions are mid-dermal, periadnexal and perivascular and show angioinvasion. Monomorphous population of small or medium-sized atypical lymphocytes with variably irregular hyperchromatic nuclei (arrowhead) and prominent nucleoli admixed with a few large blastic cells. Cytophagic histiocytes (arrow) are present.

Pattern of Infiltration: Infiltration could be epidermal, dermal, subcutaneous or a mixture of some or all of these three. Usually, early-stage lesions are mid-dermal, periadnexal, and perivascular and show angioinvasion (Fig 3).²⁶ In later stages, dense, band-like lymphocytic infiltrate appears centered in the mid-dermis, with variable epidermotropism and extension into subcutaneous tissue.^{18,26} The subcutaneous infiltration may show rimming of fat cells, similar to SPTCL. Apoptosis, necrosis, and psoriasiform epidermal hyperplasia are common.^{26,32,33}

Cytomorphology: Cells consist of a monomorphous population of small or medium-sized atypical lymphocytes with variably irregular hyperchromatic nuclei and prominent nucleoli admixed with a few large blastic cells. In cases with cytophagic histiocytic panniculitis or hemophagocytic syndrome, histiocytes phagocytizing red and white blood cells are present (Fig 4).^{26,29,32,33}

Immunophenotype: The neoplastic cells are usually positive for CD3, CD2, CD56, and cytotoxic proteins, (TIA-1, granzyme B, and perforin),^{26,28,33} and negative for CD4, CD8, β -F1, and CD5.²⁸

Cytogenesis and Molecular Findings: TCR genes are rearranged (γ/δ), and isochromosome 7q is the most common karyotypic abnormality.³³ EBV is absent.^{26,28}

Clinical Behavior: Prognosis is poor, with a median survival of 15 months.^{18,33} Hemophagocytic syndrome with resulting pancytopenia is a life-threatening complication that is present in more than 25% of patients.²⁶ Patients with subcutaneous fat involvement may have a worse prognosis compared to those with only epidermal or dermal involvement.²⁶

Differential Diagnosis: These include primary cutaneous CD4 small- to medium-sized pleomorphic T-cell lymphoma, SPTCL, and nasal-type extranodal NK/T-cell lymphoma.³³

Treatment: Systemic combined anthracycline-based therapy should be first-line treatment for this disease with aggressive behavior. Although transient responses

were achieved using topical corticosteroids, psoralen and ultraviolet A (PUVA), radiation therapy, IFN- α , and retinoids, durable complete remissions to any of these treatments have not been reported.³¹ Also, investigational therapies including anti-CD25 or UCN-01 (7-hydroxy analog of staurosporine, a tyrosine kinase inhibitor) have not achieved better treatment outcomes.³¹

Primary Cutaneous Peripheral T-Cell Lymphoma, Unspecified

Changes in Classification: In the WHO classification, peripheral T-cell lymphoma, unspecified (PTCL-u) includes most of the provisional entities of the new classification.¹⁷ These cases are classified as part of primary, cutaneous CD30-, large T-cell lymphomas and pleomorphic small- to medium-sized cutaneous T-cell lymphoma (provisional entity) in the EORTC classification.^{16,20} For the remaining cases that do not fit the above designations, the recommended diagnosis is PTCL, unspecified. The PTCL, small to medium size, is separate from this category in the new classification. All cutaneous T-cell neoplasms that do not fit into other subtypes of T-cell lymphoma/leukemia, and presenting with medium to large cells.⁴

Epidemiology: PTCL-u affects middle-aged to elderly individuals (median age 68 years, range 20 to 87 years), with a male:female ratio of 2.5:1.²⁰

Clinical Appearance of Lesions: Localized but more frequently generalized plaques or nodules are present. These cases may be associated with systemic lymphoma, especially on relapse.^{20,34}

Pattern of Infiltration: Diffuse, nodular, or band-like pattern infiltrates occur in the dermis, in decreasing frequency. Epidermotropism is generally mild or absent.

Cytomorphology: Medium- to large-sized pleomorphic or immunoblast-like T cells are present in variable numbers.^{34,35} For the designation of PTCL, the large-cell type (the large neoplastic cells in which the nuclei are larger than macrophage nuclei) represents at least 30% of the total tumor cell population.^{20,36}

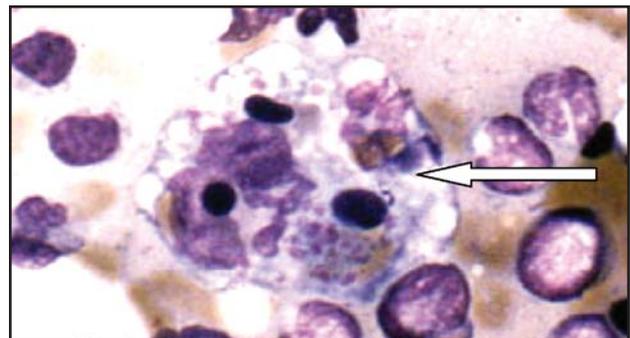


Fig 4. — Cutaneous γ/δ T-cell lymphoma. In cases with cytophagic histiocytic panniculitis and hemophagocytic syndrome, histiocytes (arrow) phagocytizing red and white blood cells are present in the bone marrow.

Immunophenotype: The neoplastic cells are usually positive for CD4 and negative for CD30. In most cases, one or more “mature” T-cell antigens such as CD5 or CD7 is lost.^{37,38} Rare CD56 expression or cytotoxic proteins (granzyme B, TIA-1) are observed.²⁰

Cytogenesis and Molecular Findings: TCR genes are rearranged, and karyotypic lesions are uncharacterized.

Clinical Behavior: Prognosis is poor, with a 5-year survival rate of less than 20%.⁴ No difference has been observed between patients who present with solitary and those who have generalized skin involvement.²⁰

Differential Diagnosis: MF in transformation to diffuse large-cell lymphoma is the differential diagnosis.

Treatment: Multiagent chemotherapy is recommended.^{4,39} For isolated skin lesions, radiotherapy was previously used as the treatment of choice, with a complete remission in up to 71% of cases. However, these responses were short-lived followed by systemic dissemination of disease.³⁷ CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or a similar doxorubicin-based chemotherapy with additional radiotherapy has been used in some cases.^{31,37,39} Gemcitabine as a single agent has been used for treatment of relapsed or refractory disease.³¹ Denileukin diftitox (Ontak), a recombinant fusion protein consisting of peptide sequences of diphtheria toxin and recombinant interleukin-2 ligand (CD25), achieved a 40% overall response rate in patients with relapsed/refractory PTCL-unspecified (PTCL-u) in a phase II trial.³¹ In refractory patients treated with alemtuzumab, a response rate of 36% has been reported.^{31,39}

Primary Cutaneous Aggressive Epidermotropic CD8+ T-Cell Lymphoma (Provisional Entity)

Changes in Classification: In the WHO classification, these cases are included in the PTCL-u category.¹⁷ In the EORTC classification, they are included with primary, cutaneous CD30-, large T-cell lymphomas, or pleomorphic small- to medium-sized cutaneous T-cell lymphomas.¹⁶

Definition: This type of lymphoma is described as primary cutaneous proliferation of epidermotropic CD8+ cytotoxic T cells.⁴

Epidemiology: Middle-aged to elderly patients are affected, with a median age 53 years. The male:female ratio is 1.4:1.²²

Clinical Appearance of Lesions: A common clinical feature includes rapidly spreading localized hemorrhagic papulonodular or generalized nodules or tumors. Occasionally, they have central ulceration and necrosis with spontaneous central resolution²² or superficial, hyperkeratotic patches and plaques that present on the face and upper arms.⁴⁰

Pattern of Infiltration: Early lesions show intraepidermal pagetoid spread of atypical lymphocytes. Fully developed lesions are characterized by a band-like/lichenoid infiltrate of an acanthotic or atrophic epidermis. The central part of the lesion frequently shows intercellular edema, blistering, and necrosis, whereas the border shows a pagetoid spreading of lymphocytes.²² Subcutaneous tissues, sweat glands, and hair follicles are frequently involved, but nerves are usually spared. A perivascular distribution of neoplastic cells is seen, and angiocentricity and angioinvasion may be present. Dissemination has been reported in lung, testis, central nervous system, and oral mucosa. Lymph node involvement is rare.^{18,22,40}

Cytomorphology: T cells are small-medium or medium-large with pleomorphic or blastic nuclei. A variable number of reactive macrophages and dendritic cells, rare eosinophils, and plasma cells are seen.^{22,40}

Immunophenotype: The neoplastic cells are usually positive for β F1, CD3, CD8, perforin, TIA-1, and CD45RA characteristic of cytotoxic T cells. Some show weak granzyme B and are negative for CD56, CD45RO, CD2, CD4, CD5 and usually negative for CD30.²² The CD2-/CD7+ immunophenotypes appear to predict aggressive disease. They show high proliferation index using Mib-1 (Ki-67).²²

Cytogenetic: TCR genes are rearranged,²² karyotypic findings are nonspecific,²² and EBV is absent.²²

Clinical Behavior: This entity has an aggressive clinical course, with a median survival of less than 32 months. There is no difference in survival between cases of small- or large-cell morphology. Metastasis to the oral cavity, lungs, testis, and the central nervous system is common, but lymph nodes usually are not involved.^{22,40}

Differential Diagnosis: This includes MF, other types of CTCLs expressing a CD8+ cytotoxic T-cell phenotype, pagetoid reticulosis, LyP, and cutaneous anaplastic large-cell lymphoma.^{22,40}

Treatment: Multiagent anthracycline-based chemotherapy is recommended for these aggressive cases.³¹

Primary Cutaneous CD4+ Small- to Medium-Sized Pleomorphic T-Cell Lymphoma (Provisional Entity)

Changes in Classification: The EORTC classification includes small- to medium-sized pleomorphic CTCL.¹⁶

Definition: This entity is defined as small- to medium-sized pleomorphic CTCL with a CD4 T-cell phenotype.⁴

Epidemiology: The median age is 69 years (range 45 to 87 years), with a male:female ratio of 0.5:1.²⁰

Clinical Appearance of Lesions: Common clinical presentations include multiple papules and nod-

ules or a solitary plaque or tumor without a history of patches, that appear on the face, neck, or upper trunk.

Pattern of Infiltration: Infiltrates are dense, diffuse, or nodular within the dermis, with a tendency to infiltrate the subcutaneous tissue (Fig 5). There is minimal or no epidermotropism.

Cytomorphology: Cells are pleomorphic small- to medium-sized lymphocytes; less than 30% are large pleomorphic cells (Fig 6).⁴¹ Reactive small lymphocytes and histiocytes are frequently seen.^{31,20}

Immunophenotype: The neoplastic cells are usually positive for CD3 and CD4 and negative for CD8, CD30, and cytotoxic proteins (granzyme B, TIA). Pan-T-cell markers are lost in some cases.^{41,42}

Cytogenetics and Molecular Findings: TCR genes are rearranged.⁴¹

Clinical Behavior: Localized lesions have a good prognosis with local treatments.³¹ A disease-specific 5-year survival rate of up to 75%³¹ and an overall 5-year survival rate of 45% have been reported.²⁰

Differential Diagnosis: These include MF, PTCL, unspecified.

Treatment: Surgical excision and radiotherapy³¹ are options for localized disease. IFN- α 2a and/or chemotherapy are recommended for larger tumor or disseminated disease.⁴³

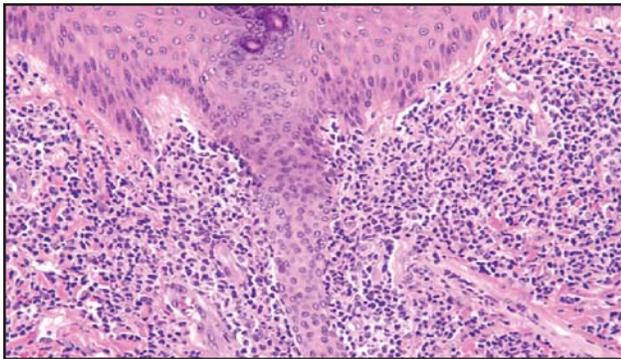


Fig 5. — Primary cutaneous CD4+ small medium pleomorphic T cell lymphoma with dense, diffuse, or nodular infiltrates within the dermis.

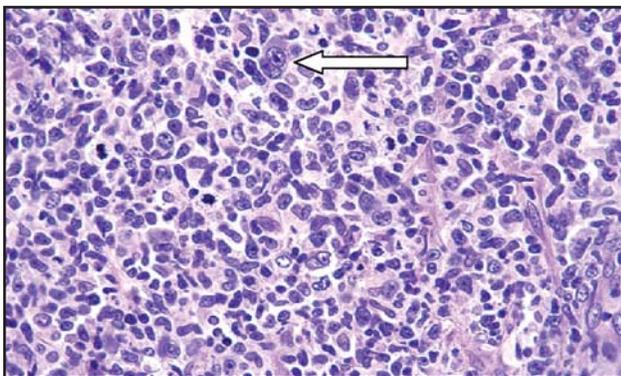


Fig 6. — Primary cutaneous CD4+ small- to medium-sized pleomorphic T-cell lymphoma with pleomorphic small- to medium-sized lymphocytes with less than 30% large cells (arrow). Reactive small lymphocytes and histiocytes are frequently seen.

Extranodal NK/T-Cell Lymphoma, Nasal Type

Changes in Classification: In the WHO classification, these cases were classified among cutaneous NK-cell lymphoma (NK/T-cell lymphoma) or PTCL-u.¹⁷ In the EORTC classification, they were part of CD30-cutaneous large T-cell lymphoma.¹⁶

Definition: This entity is defined as an extranodal lymphoid neoplasm derived from NK cells or, less commonly, from cytotoxic T cells.⁴² Skin involvement may be a primary or secondary manifestation of the disease.⁴⁴ Nasal cases and extranasal cases are two major types of extranodal NK/T-cell lymphomas designated as “nasal type.” These diseases are currently separated from the extranodal blastic NK cell types that are different and likely derived from precursor plasmacytoid dendritic cells (hematodermic).³⁵

Epidemiology: Middle-aged to elderly individuals are predominantly affected (median age 50 years), with a male:female ratio of 3:2.^{35,42} Five pediatric cases with cutaneous involvement have been reported.⁴⁵

Race Predislection: Extranodal NK/T-cell lymphoma (nasal and extranasal) and aggressive NK-cell leukemia are rare. The nasal and nasal types were originally described in Oriental Asia, but individuals of Mexican and South American descent,^{46,47} as well as European Caucasians,^{45,48} have also been reported.

Clinical Appearance of Lesions: Clinical features include multiple indurated, erythematous plaques, tumors, or nodules that may ulcerate. Lesions are located on the extremities, trunk, and, less frequently, the head and neck.⁴² Rare cases with bruise-like skin lesions have been reported.⁴⁹ Systemic symptoms such as fever, malaise, and weight loss may be present, and cytopenia due to hemophagocytic syndrome has been reported in some cases.

Pattern of Infiltration: A dense infiltrate of atypical CD56+ lymphocytes in the dermis extending to subcutaneous tissue (Fig 7) is seen.¹⁹ Epidermotropism may be present. Angiodestructive growth pattern and

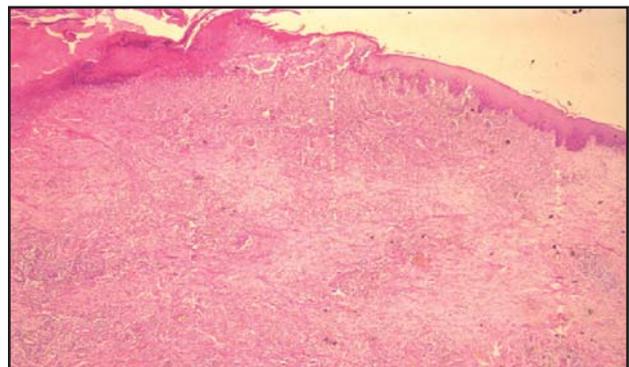


Fig 7. — Extranodal NK/T-cell lymphoma, nasal type. An infiltrate of atypical perivascular lymphocytes in the dermis with frequent necrosis and ulceration.

occlusion of the vessel lumen by lymphoid cells are common but not evident in all cases. Vascular occlusion can cause ischemic necrosis of both tumor cells and normal tissue (Figs 8 and 9).^{19,42,50}

Cytomorphology: These cases feature polymorphous infiltrate admixed with inflammatory cells, with the malignant cells composed of a mixture of normal-appearing small lymphocytes and atypical lymphoid cells of varying size with irregular nuclei, moderately dense granular chromatin, and pale to clear to finely granular cytoplasm with high mitotic activity (Fig 8).^{42,50}

Immunophenotype: EBV is often positive.^{45,48} EBV positivity is helpful since it is rare in other cutaneous lymphomas. The neoplastic cells are usually positive for CD56, CD2, cytoplasmic CD3ε, and cytotoxic granule proteins (TIA-1, granzyme B, and perforin).⁵⁰ They are usually negative for surface CD3, CD4, and CD8¹⁹ but some may express EBV+ CD56- CD4+, and/or CD7+, CD30+ immunophenotype.^{45,48}

Cytogenetics and Molecular Findings: TCR genes are germ-line since NK cells do not have rearrangement of TCR genes.^{45,48,50} Deletions of chromosomes 6(q16-q27) and 13(q14-q34) are common

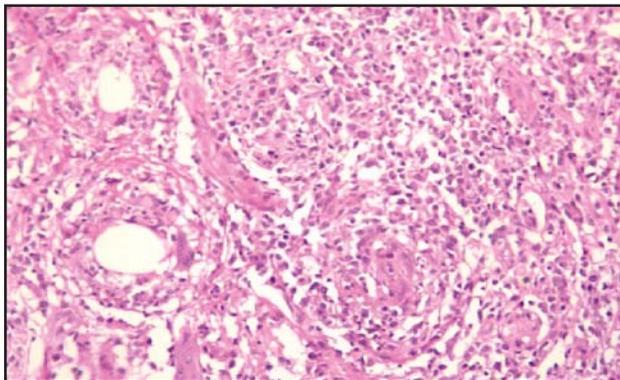


Fig 8. — Extranodal NK/T-cell lymphoma, nasal type. Polymorphous infiltrate, admixed with inflammatory cells, with the malignant cells composed of a mixture of normal-appearing small lymphocytes and atypical lymphoid cells of varying size with irregular nuclei, moderately dense granular chromatin, and pale to clear to finely granular cytoplasm.

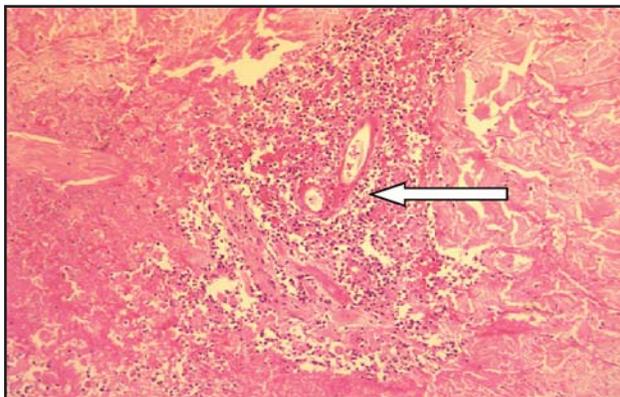


Fig 9. — Extranodal NK/T-cell lymphoma, nasal type. Angiodestructive growth pattern and occlusion of the vessel lumen by lymphoid cells is present. Hemorrhagic ischemic perivascular necrosis (arrow) is characteristic.

karyotypic findings.⁵¹ Mutations of *k-ras* have been described, and p53 is overexpressed in many patients.⁵²

Clinical Behavior: Prognosis is variable. Patients without extracutaneous involvement have the best prognosis, with median survival of less than 27 months.^{45,48} Cases with metastases to oropharynx, testes, or other organs have a poor prognosis. Patients with tumors associated with aggressive NK-cell leukemia have the worst outcome, with a median survival of 6 months. The presence of EBV does not have any prognostic significance in this tumor.⁴²

Differential Diagnosis: These include cutaneous anaplastic large-cell lymphoma, primary cutaneous PTCL, unspecified and aggressive epidermotropic CD8+ T-cell lymphoma.^{45,48}

Treatment: Response rates of up to 85% have been reported with radiation alone for patients with localized disease (stage I and II). However, more than 50 % of patients experience local or systemic relapse with a predilection to extranodal sites.³⁷ Combined modality with anthracycline-based chemotherapy with or without radiation therapy has been used for advanced stage (stage III and IV).^{31,37,53}

Subtypes of Primary Nodal Aggressive PTCL

The following subtypes of primary nodal aggressive PTCL have a high predilection to the skin and should be considered in the differential diagnosis. A full description of these systemic diseases is described in more detail elsewhere in this issue.

PTCL-u: This is the most frequent subtype, with an incidence rate of about 4% among all non-Hodgkin's lymphomas. This entity is heterogeneous in pathology but mostly expresses CD4+, CD8-, CD30+/- immunophenotype, with a high predilection to involve extranodal sites such as the liver, bone marrow, gastrointestinal tract, and skin. The 5-year survival rate is 30% to 35% using standard chemotherapy.³⁵ Extranodal presentations predict a poor prognosis. Cases with skin involvement as a primary that has progressed with systemic disease have a poorer prognosis, with a 5-year survival rate of less than 20%.⁴ No difference has been observed in patients presenting with solitary or generalized skin involvement.²⁰

Angioimmunoblastic T-Cell Lymphoma (AITL): This lymphoma primarily presents in lymph nodes but often at a disseminated stage with involvement of the liver, spleen and with associated hypergammaglobulinemia and fever. Originally included in the atypical lymphoproliferative disorders, this entity is now firmly included in the PTCLs based on clonal molecular and karyotypic findings. The pathologic distinction from PTCL-u is problematic but could be resolved by observing morphologic and phenotypic features. The main

findings in favor of AITL include arborizing prominent vascularization, expansile CD21+ dendritic cell networks, and coexpression of CD10 (a precursor and follicular lymphoma associated antigen) with the neoplastic T cells. EBV association has been described with secondary oligoclonal or monoclonal EBV+ B-cell lymphomas in some patients. The 5-year overall survival rate, as well as the 3-year median survival rate, is about 30%.³⁵

Cutaneous Adult T-Cell Leukemia/Lymphoma

Changes in Classification: No changes have been made in the WHO classification.¹⁷ This issue will be discussed in more detail in a separate article. A short description is provided here with a pathology description and figures.

Pattern of Infiltration: Diffuse infiltration of dermis and subcutaneous tissue are seen. Epidermotropism and microabscesses have been reported (Fig 10A).^{38,54}

Cytomorphology: The skin lesions of leukemic and lymphomatous variant show medium to large neoplastic cells with nuclear pleomorphism and amphophilic, basophilic or pale cytoplasm (propeller, flower, or hyperlobated cells) (Fig 11A-B). The skin lesions of

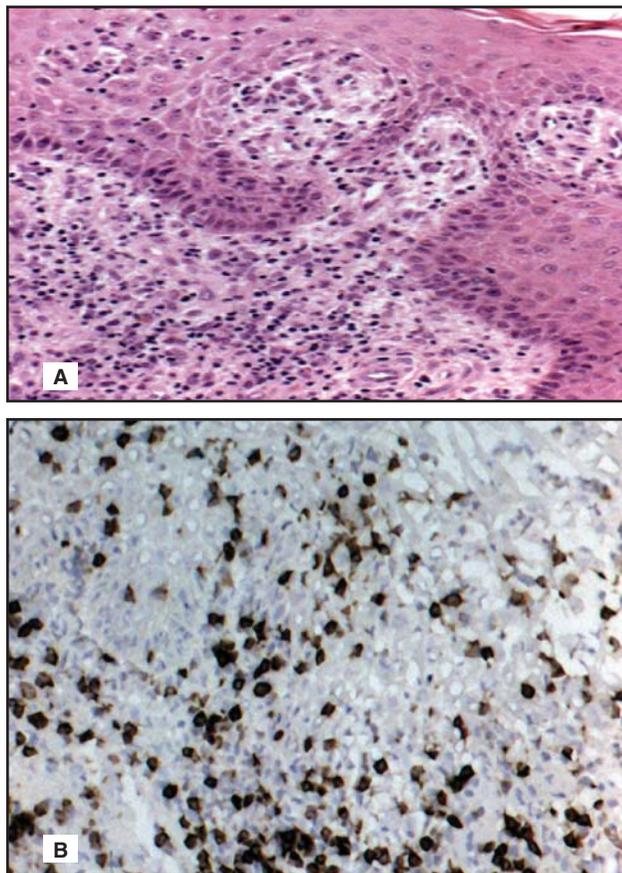


Fig 10A-B. — (A) Cutaneous adult T-cell leukemia/lymphoma (ATLL) showing diffuse infiltration of dermis and subcutaneous tissue with epidermotropism. (B) CD25+ T-helper cells are characteristic findings in ATLL.

the smoldering and chronic subtype show small lymphocytes with minimal atypia or nuclear pleomorphism (Fig 10A).^{38,54} CD25+ T-helper cells are characteristic phenotype of ATLL (Fig 10B).

Differential Diagnosis: MF is the principal differential diagnosis.^{38,54}

Conclusions and the Role of Targeted Therapy

Overall, only SPTCL- α/β and primary cutaneous CD4 positive small- to medium-sized pleomorphic T-cell lymphoma have a better prognosis in this group, regardless of the therapy used. These two entities are the only diseases where localized therapy can be of benefit (Table 2).^{4,18,20,22,23,55} Cutaneous γ/δ T-cell lymphoma, primary cutaneous PTCL-u, and primary cutaneous aggressive epidermotropic CD8+ T-Cell lymphoma behave aggressively (early dissemination) regardless of the therapy used. First-line therapy for these diseases should be systemic combined chemotherapy.

Limited-stage extranodal NK/T-cell lymphoma, nasal type is responsive to radiation therapy; however, among patients with limited-stage disease, approximately 50% will relapse. Those with disseminated-stage disease are

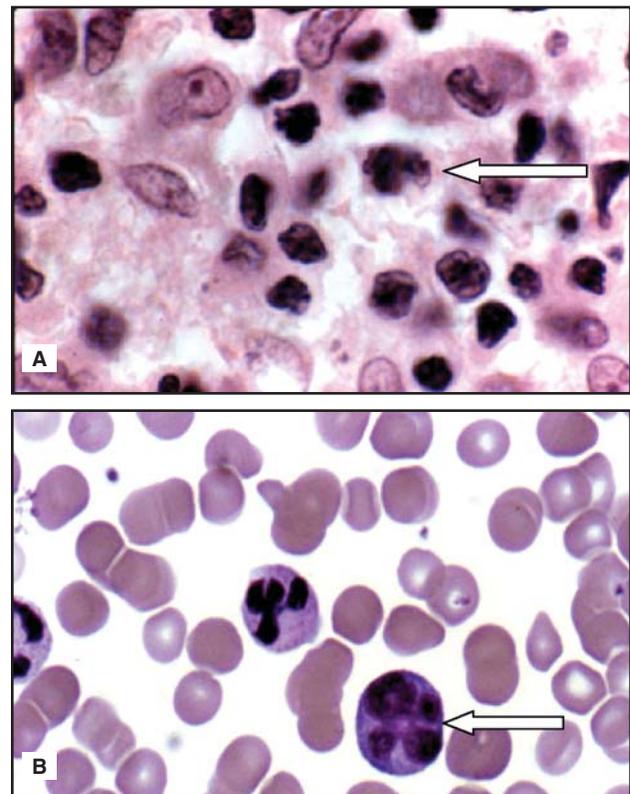


Fig 11A-B. — (A) Cutaneous adult T-cell leukemia/lymphoma medium to large-size neoplastic cells with nuclear pleomorphism (arrow) and amphophilic, basophilic or pale cytoplasm. (B) Clover leaf or propeller pathognomonic T-helper circulating cells. ATLL cells (arrow).

usually treated with combined chemotherapy with or without radiation therapy. No standard of care has been established for the remaining five entities, except for extranodal NK/T-cell non-Hodgkin's lymphoma, due to their rarity and recent reclassification. The role for targeted therapy needs to be explored.

Generally, the international prognostic index has been applied to PTCLs (similar to that of diffuse large B-cell lymphomas), noting prognostic relevance with 5-year survival rates ranging from 18% (with 3 to 4 factors) to 62% (with no factors).⁵⁶ In the treatment protocols for PTCL by the Groupe d'Etude des Lymphomes de l'Adulte (GELA), the T-cell phenotype was associated with an adverse result compared with the B-cell phenotype with the exception of anaplastic large-cell lymphoma, which was found to have an even better prognosis than high-grade B-cell lymphomas.^{57,58} Most PTCLs express the CD7 antigen, with the exception of CTCL. Data on anti CD7 *Pseudomonas exotoxin* suggest that the CD7 antigen may be a potential target.⁵⁹

Other monoclonal antibodies directed against chemokine receptors, activation antigens, and common T-cell antigens are also tested in early clinical studies. The chemokine receptor CCR4, which is expressed on cells of the immune system, plays a critical role in T-cell migration to several sites including the skin. A phase I clinical trial of anti-CCR4 monoclonal antibody KW-0761 is being conducted for patients with CCR4+ T-cell leukemia/lymphoma in Japan (ClinicalTrials.gov identifier: NCT00355472).

Monoclonal antibodies directed against the α chain (Tac/CD25) of the interleukin-2 receptor are an emerging therapy for T-cell malignancies. LMB-2 is a recombinant immunotoxin that is a fusion of a single-chain Fv fragment of the anti-Tac anti-CD25 monoclonal antibody to a truncated form of the bacterial *Pseudomonas exotoxin*. A phase II study of LMB-2 is open for patients who have CD25+ cutaneous T-cell lymphoma (ClinicalTrials.gov identifier: NCT00085085). A phase I/II study of yttrium Y90-labeled humanized anti-Tac monoclonal

Table 2. — Clinical Features of Rare Subtypes of Mature T/NK-Cell Lymphoma

	SPTCL	Cutaneous γ/δ T-Cell Lymphoma	Primary Cutaneous Peripheral T-Cell Lymphoma, Unspecified	Primary Cutaneous CD8+ T-Cell Lymphoma	Primary Cutaneous T-Cell Lymphoma CD4+ Small/Medium	Extranodal NK/T-Cell Lymphoma, Nasal Type
Median age, yrs (range)	48 (22–73)	49 (13–82)	68 (20–87)	53–58 (31–81)	69 (45–87)	47 (16–86)
M/F ratio	0.25	1.3	2.5	1.4	0.5	1.5
Clinical presentation	Solitary or multiple nodules and plaques; predilection in lower extremities, trunk	Disseminated plaques, nodules, tumors with ulceration, necrosis	Solitary or generalized nodules, tumors	Generalized patches, plaques, papules, tumors, central ulceration	Solitary plaques tumors, papules	Localized: destructive tumor of nasal cavity/nasopharynx Disseminated: plaques, tumors \pm ulceration
Therapy	Corticosteroids, RT, cyclosporin A, methotrexate, cyclophosphamide, IFN- α	Systemic combined CT	Anthracycline-based combined CT \pm RT	Anthracycline-based combined CT, PUVA, TSEB, IFN- α	Solitary lesion: excision, RT Disseminated: PUVA, IFN- α , cyclophosphamide	Limited stage: RT \pm CT Disseminated: CT or CT+RT
5-yr overall survival rate	80%	0%	12%	18%	75%	36%
Median overall survival (mos)	Not Available	15	22	32	56	12
References (no. of cases)	Massone et al ²³ (10)	Willemze et al ⁴ (13) Toro et al ¹⁸ (33)	Willemze et al ⁴ (46) Bekkenk et al ²⁰ (47)	Willemze et al ⁴ (14) Berti et al ²² (17)	Willemze et al ⁴ (39) Bekkenk et al ²⁰ (19)	Cheung et al ⁵⁵ (77)
OS = overall survival RT = radiation therapy CSA = cyclosporine A MTX = methotrexate IFN- α = interferon alpha PUVA = psoralen, ultraviolet A TSEB = total skin electron beam radiation therapy CT = chemotherapy						

antibody and pentetic acid calcium in patients with Tac-expressing hematologic malignancies other than adult T-cell leukemia is accruing patients (ClinicalTrials.gov identifier: NCT00019305).

T/NK cell-specific surface antigens including CD2 and CD4 became therapeutic targets of several recently developed monoclonal antibodies. Two phase I studies with sipilizumab (MEDI-507), an anti-CD2 antibody, in patients with CD2+ lymphoproliferative disorders are open at the National Cancer Institute (ClinicalTrials.gov identifier: NCT00075361) and as a multicenter study sponsored by Medimmune, Inc. A multicenter international study is testing the efficacy of human monoclonal anti-CD4 antibody HuMax-CD4 in patients with MF refractory or intolerant to treatment with bexarotene (Targretin) and one other standard therapy.

Molecular targets implicated in intracellular signal pathways are also being studied. Several groups of intracellular targeting agents, including retinoids and histone deacetylase (HDAC) inhibitors, have been investigated for the treatment of cutaneous T-cell lymphomas.⁶⁰ Retinoids target retinoid-responsive elements in the upstream regulatory regions of a multitude of cellular genes,⁶⁰⁻⁶² cause apoptosis of various cell lines,^{39,60-62} and may improve immunity by various mechanisms.⁶⁰⁻⁶² Bexarotene alpha-retinoid X receptor ligand is effective in patients with CTCLs. HDAC inhibitors modulate gene expression by inhibiting the deacetylation of histone proteins associated with DNA.⁶² These in turn induce apoptosis of malignant lymphocytes. They also may upregulate the expression of the interleukin-2 receptor on malignant T cells, resulting in enhanced susceptibility to killing by denileukin diftitox. Two examples of HDAC inhibitors available for therapy of T-cell lymphomas are suberoylanilide hydroxamic acid (SAHA, vorinostat, Zolinza), which was recently approved by the US Food and Drug Administration (FDA) for CTCL, and depsipeptide (FK228), tested in phase II clinical studies.⁶³

Purine nucleoside phosphorylase (PNP) is an intracellular enzyme with a key role in purine degradation. Hereditary PNP defects in humans result in a fatal T-cell immunodeficiency neurological symptomatology. Forodesine (BCX-1777), a potent PNP inhibitor, showed promising activity in both indolent and aggressive T-cell lymphoma/leukemia.⁶⁴

Nelarabine (Arranon), a water-soluble prodrug of ara-G (9-beta-D-arabinofuranosylguanine), has recently been approved by the FDA for the treatment of relapsed/refractory precursor T-cell acute lymphoblastic leukemia and precursor T-cell lymphoblastic lymphoma in adults and children. This agent acts by inhibiting DNA synthesis and inducing apoptosis in susceptible cells with increased accumulation of ara-GTP in T cells compared with B cells. Earlier studies also confirmed potential activity of this agent in refractory/relapsed PTCL.⁶⁵

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