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T-Cell and NK-Cell Lymphomas

From Biology to Novel Therapies

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T-Cell and NK-Cell Lymphomas

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Jasmine Zain is an Associate Clinical Professor of Medicine and the Director of the T-cell Lymphoma Program at the City of Hope National Medical Center. Her focus is to conduct early phase clinical trials of novel small molecules in the treatment of lymphomas and other hematological malignancies in an attempt to define targeted therapies for this group of diseases. Her particular area of interest is in T-cell malignancies and Cutaneous T-cell lymphomas. The lymphomas represent a very diverse group of diseases comprised of approximately 65 different subtypes. T-cell lymphomas in particular are poorly understood and standard therapies to treat this heterogenous group of over 20 subtypes of diseases are lacking. Jasmin Zain is interested in linking emerging concepts in molecular pathogenesis and molecular pharmacology in T-cell lymphomas to clinically relevant information. The major objective is to identify the relevant biological targets which are known to play a critical role in lymphomagenesis, and then to develop targeted small molecules for these agents, with the ultimate goal of evaluating these potential drug candidates in patients. Thus, these targeted therapies will be less toxic and potentially more curative. She is also part of the stem cell transplant program at the City of Hope thus allowing a unique opportunity to integrate the work she does to develop targeted therapies in the Lymphoma program with stem cell transplantation.

Steven T. Rosen, MD, FACP, FASCO is the provost and chief scientific officer for City of Hope in Duarte, California. He is also director of the Comprehensive Cancer Center and the Beckman Research Institute and holds the Irell & Manella Cancer Center Director's Distinguished Chair. He was previously (1989−2014) director of the Robert H. Lurie Comprehensive Cancer Center at Northwestern University Feinberg School of Medicine. Dr. Rosen's laboratory research focuses on experimental therapeutics and hematologic malignancies. He has received funding from the National Cancer Institute (NCI), American Cancer Society, Leukemia and Lymphoma Society (LLS), Multiple Myeloma Research Foundation, and Rising Tide Foundation. Dr. Rosen has published more than 400 scientific papers and is editor-in-chief of *Cancer Treatment and Research*. He is chair of the Medical Science Committee of the LLS and serves on its Board. He also serves on the Board of the American Society of Clinical Oncology's Conquer Cancer Foundation. Dr. Rosen has been an advisor to more than two dozen NCI Comprehensive Cancer Centers. He has been the recipient of a number of awards and in 2017 was inducted to the American Institute for Medical and Biological Engineering's College of Fellows.

Epidemiology and Pathology of T- and NK-Cell Lymphomas

1

Parwiz J. Siaghani, Jerry T. Wong, John Chan, Dennis D. Weisenburger and Joo Y. Song

Abstract

Purpose: This review will describe and update readers on the recent changes in the 2017 WHO classification regarding peripheral T-cell lymphomas.

Recent findings: Signficant advances in molecular studies have resulted in revisions to the classification as well as introduction to provisional entities such as breast implant-associated ALCL and nodal PTCL with T-follicular helper phenotype.

Summary: Major advances in molecular and gene expression profiling has expanded our knowledge of these rare and aggressive diseases.

Keyword

T-cell lymphoma · Classification · Molecular

1.1 Introduction

Peripheral T- and NK-cell lymphoma (PTCL) is relatively rare, usually clinically aggressive, and quite heterogeneous originating from post-thymic T-lymphocytes and NK-cells, representing only 10–15% of all non-Hodgkin lymphomas (NHL)

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Table 1.1 Major lymphoma subtypes by geographic region

Subtype	North America (%)	Europe (%)	Asia (%)
PTCL, NOS	34.4	34.3	22.4
Angioimmunoblastic	16.0	28.7	17.9
ALCL, ALK-positive	16.0	6.4	3.2
ALCL, ALK-negative	7.8	9.4	2.6
NK/T-cell lymphoma	5.1	4.3	22.4
ATLL	2.0	1.0	25.0
EATL	5.8	9.1	1.9
Hepatosplenic	3.0	2.3	0.2
Primary cutaneous ALCL	5.4	0.8	0.7
Subcutaneous panniculitis-like	1.3	0.5	1.3
T-cell, unclassifiable	2.3	3.3	2.4

PTCL, *NOS* peripheral T-cell lymphoma, not otherwise specified; *ALCL* anaplastic large-cell lymphoma; *ALK* anaplastic lymphoma kinase; *ATLL* adult T-cell lymphoma/leukemia; *EATL* enteropathy-associated T-cell lymphoma

Adapted from: International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol 2008:26:4124–4130

(Table 1.1). Our understanding of the pathobiology and diversity of these lymphomas has progressed in the past several decades, and the classification schemes have been continually modified to reflect and incorporate new information. A multiparameter approach integrating morphologic, immunophenotypic, genetic, and clinical features is emphasized in the World Health Organization (WHO) classification (Tables 1.2 and 1.3), which has refined the disease definitions and increased the diagnostic accuracy of these heterogeneous malignancies; however, there are still difficult cases that lack consensus agreement even among experts in the field [1, 2]. Recently, immunophenotypic markers capable of delineating certain functional subsets of T-cells, such as T-regulatory cells (T-regs) and T-follicular helper cells (TFH), as well as gene expression signatures, have been used to delineate biological and prognostically significant subgroups have emerged, further improving diagnostic accuracy, bridging entities with commonalities, and refining the subclassification of these diseases [3, 4]. This review will focus on these recent changes, as well as briefly discuss the more common entities.

1.2 Epidemiology

The incidence of non-Hodgkin lymphoma (NHL) has steadily risen over the past century. Overall, T- and NK-cell lymphomas are underrepresented due to this low incidence compared to B-cell lymphomas and in relative frequency varies in different geographic regions and racial populations [1, 5]. These lymphoid neoplasms comprise only about 6% of all lymphoproliferative disorders. In the United States, the incidence of B-cell lymphomas has plateaued, whereas the rates of T-cell lymphomas have

Table 1.2 2017 WHO classification of mature T- and NK-cell neoplasms

T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK-cells
Aggressive NK-cell leukemia
Systemic EBV+ T-cell lymphoma of childhood[a]
Hydroa vacciniforme-like lymphoproliferative disorder[a]
Adult T-cell leukemia/lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Intestinal T-cell lymphoma Enteropathy-associated T-cell lymphoma Monomorphic epitheliotropic intestinal T-cell lymphoma[a] *Indolent T-cell lymphoproliferative disorder of the GI tract*[a]
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30+ T-cell lymphoproliferative disorders Lymphomatoid Papulosis Primary cutaneous anaplastic large-cell lymphoma
Primary cutaneous peripheral T-cell lymphomas, rare subtypes Primary cutaneous gamma–delta T-cell lymphoma Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma *Primary cutaneous acral CD8+ T-cell lymphoma*[a] *Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder*[a]
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma and other nodal lymphomas of T-follicular helper (TFH) origin Angioimmunoblastic T-cell lymphoma *Follicular T-cell lymphoma*[a] *Nodal peripheral T-cell lymphoma with TFH phenotype*[a]
Anaplastic large-cell lymphoma, ALK+
Anaplastic large-cell lymphoma, ALK−[a]
Breast implant-associated anaplastic large-cell lymphoma[a]

Provisional entities are listed in italics
[a]*Changes from the 2008 classification*
Source Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J (Eds): WHO classification of Tumours of Haematopoietic and Lymphoid Tissues (Revised 4th edition). IARC: Lyon 2017

continued to increase. Based on a 10-year period from 1997 to 2006 recorded in the US Surveillance, Epidemiology, and End Results (SEER) cancer registry, B-cell lymphomas vastly outnumber T- and NK-cell neoplasms (27.96 per 1000 persons compared to 2.09). With the highest incidence of peripheral T-cell lymphoma (0.78) followed by mycosis fungoides/Sézary syndrome (0.54) [6]. Within peripheral T-cell

Table 1.3 Phenotypic summary of reviewed peripheral T-cell lymphoma entities

Entities	Cellular derivation	Phenotype
Nodal		
Peripheral T-cell lymphoma, NOS	Tαβ	CD4 > CD8; CD3±; usually decreased/absent CD5 and CD7; GAT3∓, TBX21∓; cytotoxic granules∓; CD30∓; CD56∓; rarely EBV+
Angioimmunoblastic T-cell lymphoma	Tαβ	CD4; most pan-T-cell antigens+; expression of at least 2 TFH-cell markers (CD10, BCL6, PD1, CD278, CXCL13, CXCR5, SAP); FDC expansion (CD21+ or CD23+); EBV+ B-cells
Nodal peripheral T-cell lymphoma with TFH-cell phenotype	Tαβ	CD4; most pan-T-cell antigens+ with frequent loss of CD7; expression of at least 2 TFH-cell markers (CD10, BCL6, PD1, CD278, CXCL13, CXCR5, SAP); No FDC expansion; EBV+ B-cells±
Anaplastic large-cell lymphoma, ALK-positive	Tαβ	CD30+; ALK+; EMA+; CD25+; CD43+; cytotoxic granules±; CD4±; CD2±; CD7 ±; CD3∓
Anaplastic large-cell lymphoma, ALK-negative	Tαβ	CD30+; ALK−; EMA±; CD25+; CD43+; cytotoxic granules±; CD4±; CD2±; CD7 ±; CD3∓
Extranodal		
Enteropathy-associated T-cell lymphoma	Tαβ > Tγδ	CD3+; CD7+; CD103+; cytotoxic granules +; CD30±; CD4−; CD5−; CD8−; CD56−
Monomorphic epitheliotropic intestinal T-cell lymphoma	Tγδ > Tαβ	CD3+; CD8+; CD56+; cytotoxic granules (TIA+, Granzyme B∓, perforin ∓); CD103 ±; CD30−; CD4−; CD5−;
Breast implant-associated anaplastic large-cell lymphoma	Same as ALCL, ALK-negative	Same as ALCL, ALK-negative

Source Modified from Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J (Eds): WHO classification of Tumours of Haematopoietic and Lymphoid Tissues (Revised 4th edition). IARC: Lyon 2017

lymphoma, the most common type was the not otherwise specified (NOS) category (0.41) followed by anaplastic large-cell lymphoma (ALCL) (0.28). As expected, adult T-cell lymphoma/leukemia (ATLL) was rare in the US (0.04) [6]. Results from the International PTCL Project showed that the most common subtypes of nodal T-cell lymphoma were PTCL-NOS (25.9%), angioimmunoblastic T-cell lymphoma (AITL, 18.5%), ALCL (12%), NK/T-cell lymphoma (10.4%), hepatosplenic T-cell lymphoma (1.4%), and subcutaneous panniculitis-like T-cell lymphoma (0.9%). This difference in prevalence is related to major risk factors that are associated with an increased incidence of T/NK-cell neoplasms, particularly human T-cell leukemia virus type 1 (HTLV-1) and racial predisposition to Epstein–Barr virus (EBV) infection [1, 5] (Table 1.1).

Other populations at increased risk include people of Native American descent in Central and South America who are believed to be genetically related to Asians [1]. Angioimmunoblastic T-cell lymphoma is more common in Europe compared to Asia and North America. ALK+ ALCL is more common in North America, while ALK-negative ALCL is slightly more common in Europe. ATLL is endemic to several regions of the world, particularly Japan, the Caribbean, and parts of Central Africa.

1.3 Nodal Peripheral T-Cell Lymphomas

Nodal peripheral T-cell lymphomas are a heterogeneous and diagnostically challenging group of disorders characterized by a broad morphologic spectrum with significant overlap [7]. They can be broadly grouped by phenotype and postulated cell of origin, segregating those of TFH origin under the new category in the 2017 WHO classification termed "Nodal PTCL with a TFH phenotype" and those of non-TFH origin (PTCL, NOS, and ALCL) [1, 4]. Nodal PTCL with a TFH phenotype is believed to constitute the neoplastic counterpart of TFH-cells, characteristically expressing CD10, CXCL13, ICOS (CD278), BCL6, and PD1 (ideally three TFH markers are required for this designation) [4]. The prototype and best studied of these lymphomas is AITL. Additionally, a few nodal peripheral T-cell lymphomas previously classified as variants of PTCL, NOS (T-zone variant and follicular T-cell lymphoma) in the 2008 WHO classification, have recently been shown to have a TFH-cell phenotype and share morphological, genetic, and clinical overlap with AITL and, thus, have been included under the broad category of nodal PTCL with a TFH-cell phenotype [1, 7–13].

1.3.1 Angioimmunoblastic T-Cell Lymphoma and Other Nodal Lymphomas TFH-Cell Origin

Angioimmunoblastic T-cell lymphoma (AITL) is a neoplasm of mature TFH-cells which occurs in middle-aged and elderly individuals (M > F) often presenting with generalized lymphadenopathy, hepatosplenomegaly, skin rash, effusions, fever, polyclonal hypergammaglobulinemia, hemolytic anemia, and secondary immunodeficiency [14]. It is one of the most common types of nodal peripheral T-cell lymphomas in the US and Europe, and is characterized by a polymorphous lymphoid infiltrate including atypical T-cells with clear cytoplasm, scattered EBV + B-immunoblasts, plasma cells, and eosinophils with a prominent proliferation of high endothelial venules (arborizing vasculature) and extrafollicular expansion of follicular dendritic cell meshworks, most prominent around the arborizing vasculature [1, 5, 14]. Three overlapping patterns have been recognized: pattern 1, which is fairly rare, the neoplastic cells surround hyperplastic follicles with well-formed germinal centers ("perifollicular distribution"); pattern 2, regressed follicles with the neoplastic cells more readily identified in the expanded paracortex; and pattern

3, diffuse effacement of the normal nodal architecture by the expanded paracortex with few regressed follicles [1, 7, 9]. Multiple patterns in consecutive biopsies have been reported and even in the same specimen [7, 15, 16]. EBV+ B-cells are present in 80–95% of cases and may constitute a significant part of the cellular infiltrate. Hodgkin/Reed-Sternberg-like (HRS) cells may also be present, mimicking classical Hodgkin lymphoma. In rare cases, EBV-negative B-cell proliferations can be seen [7, 17, 18]. Although AITL is primarily nodal, extranodal sites such as skin, spleen, liver, and bone marrow are often involved [19].

Follicular T-cell lymphoma (FTCL) is a rare node-based neoplasm of TFH-cells with a predominantly follicular and perifollicular growth pattern but lacking the characteristic features of AITL [1]. The true incidence of FTCL is unknown but is believed to account for <1% of all T-cell neoplasms. Its clinical presentation can overlap with AITL but FTCL more often presents with localized disease and with fewer systemic symptoms [1, 7, 8, 10, 14, 20]. Two distinct growth patterns have been recognized: follicular lymphoma-like FTCL with the neoplastic T-cells arranged in well-defined nodules lacking the morphologic features of normal follicular center B-cells; and the other mimicking progressive transformation of germinal centers in which the neoplastic T-cells are arranged in well-defined aggregates surrounded by numerous small IgD+ mantle zone B-cells [1, 8]. Unlike AITL, the interfollicular areas lack the polymorphous infiltrate, arborizing vasculature proliferation, and extrafollicular expansion of follicular dendritic cell meshworks. However, scattered B-immunoblasts and, in a subset of cases, HRS-like cells often surrounded by neoplastic T-cells are present [17, 21]. In a limited number of cases, consecutive biopsies from different time points have demonstrated a change in morphology from FTCL to typical AITL that have been observed suggesting that these two entities may constitute different morphologic representations of the same biological process [8]. However, significant clinical and pathological differences remain so that both diagnoses are retained in the 2017 WHO classification [1].

Gene expression profiling studies have identified a strong microenvironmental signature in AITL including a substantial contribution from follicular dendritic cell (FDC)-related and B-cell-related genes, chemokines and chemokine receptors, and angiogenesis-related genes. Although the signature contributed by the neoplastic

Table 1.4 Summary of recurrent mutations in nodal peripheral T-cell lymphomas

Gene	AITL (%)	PTCL with TFH phenotype (%)	PTCL, NOS (%)	ALK+ ALCL (%)	ALK− ALCL (%)
RHOA	53–72	62	18–26	–	–
TET2	33–82	–	20–49	0	0–50
IDH1	0	–	0	–	–
IDH2 R172	13–32	–	<1	–	–
DNMT3A	23–38	–	27, 36	–	16

References [10–12, 23–28]

cells could be relatively minor, it shows features of normal TFH-cells [3, 22, 23]. Furthermore, next-generation sequencing studies have identified recurrent mutations to help unify AITL with other nodal T-cell neoplasms derived from TFH-cells as well as discern AITL from other PTCL subtypes (Table 1.4). In addition, approximately 20% of FTCL and rare cases of AITL carry a t (5;9)(q33;q22) leading to *ITK–SYK* fusion. This translocation has not been seen in other peripheral T-cell lymphomas [24–26].

It has become evident that a subset of PTCL, NOS, has a TFH-cell phenotype as well as some pathological features of AITL. These lymphomas often show a diffuse infiltrative pattern without a prominent polymorphic lymphoid infiltrate in the background and lack the arborizing vascular proliferation or extrafollicular expansion of follicular dendritic cell meshworks characteristic of AITL. In a subset of cases, a "T-zone pattern" may be seen [20]. These cases not only share some morphologic features of AITL but also display genetic alterations seen in AITL (Table 1.4). Although these phenotypic and genotypic features imply a relationship to AITL, currently it is recommended that these cases be classified as nodal peripheral T-cell lymphoma with a TFH-cell phenotype [1].

1.3.2 Peripheral T-Cell Lymphoma, NOS

Mature T-cell lymphomas that do not correspond to any specifically defined entity in the current WHO classification are categorized as PTCL, NOS [1]. These T-cell lymphomas encompass a heterogenous group of malignancies that account for nearly 30% of PTCL in Western countries. The vast majority are older adults with a male-to-female ratio of 2:1 [5]. The postulated normal counterpart are activated mature T-cells, mainly CD4+ central memory type of the adaptive immune system [1]. Most patients present with generalized lymphadenopathy and B-symptoms. Advanced-stage disease is common with involvement of the liver, spleen, bone marrow, and other extranodal tissues. Leukemic and extranodal presentations can occur but are uncommon. The most frequent extranodal sites include the skin and gastrointestinal tract [5, 27]. Rarely, the CNS and lung may be involved [28]. Occasionally, eosinophilia, pruritus, and hemophagocytic lymphohistiocytosis are seen [27].

Histologically, the lymph nodes show diffuse effacement of the normal architecture by a polymorphous lymphoid infiltrate with a wide spectrum of cytological features. Most cases show medium to large cells with irregular and hyperchromatic nuclei and frequent mitosis in an inflammatory background of small lymphocytes, plasma cells, eosinophils, and histiocytes. Similar to AITL or PTCL with a TFH phenotype, clear cell morphology and scattered HRS-like cells can also be seen [1, 2, 7, 14, 29, 30]. Occasional cases with a monomorphic neoplastic infiltrate and, rarely, with a predominance of small cells have been observed [1]. The arborizing vasculature proliferation and expanded FDC meshworks characteristic of AITL are not seen [1, 2, 7, 8]. The immunophenotype of the neoplastic cells can be as varied as its cytomorphology, but it is usually characterized by a CD4 > CD8 cells and expression of T-cell receptor alpha–beta (beta F1). PTCLs with a cytotoxic phenotype (TIA1, granzyme B,

and perforin) are more likely to be seen with the CD8+ phenotype or an aberrant T-cell phenotype, often with decreased or absent expression of CD5 and CD7, CD4/CD8 double-positivity or double-negativity, as well CD56 expression [1, 2, 7, 31, 32]. CD30 expression is variable and does not have the strong intensity seen in ALCL. CD30 expression in most or all cells has been found to correlate with a poor prognosis [33, 34]. Some cases can also express CD15.

The lymphoepithelial variant (Lennert's lymphoma) is characterized by confluent clusters of epithelioid histiocytes and has a somewhat better prognosis compared to other forms of PTCL, NOS, and has been retained under PTCL, NOS. However, the follicular and the T-zone variants with a TFH-cell phenotype described in the 2008 WHO classification have been moved to the broad category of nodal PTCL with a TFH phenotype (described above) [1, 35, 36]. Cases with a growth pattern of neoplastic T-cells around reactive germinal center are no longer considered a variant, but rather a non-specific morphological pattern of PTCL, NOS [1].

Primary EBV+ nodal T/NK-cell lymphoma is a rare entity, defined by EBV expression in the majority of the neoplastic cells. These cases usually have a monomorphic infiltrate and lack the angiodestruction and necrosis seen in extranodal NK/T-cell lymphomas. They are more commonly seen in the elderly or in the setting of immune deficiency [7, 18, 37, 38]. Currently, these lymphomas are considered a variant of PTCL.

Recently, gene expression and microRNA profiling studies have provided new insights into PTCL, NOS [2, 3, 39–43]. Specifically, overexpression of transcription factors TBX21 (T-BET) and GATA3 have allowed distinctive signatures for two novel subgroups. The TBX21 subgroup shows enrichment in interferon and NF-kappa B pathways, with a subset displaying a cytotoxic profile, and the GATA3 subgroup shows enrichment of cell cycle/proliferation signatures and upregulation of MYC− and PI3K-AKT-mTOR pathways. This distinction has been shown to have prognostic significance with the GATA3 subgroup, and a subset of TBX21 cases with a high cytotoxic signature correlates with a poor prognosis. Immunohistochemical markers for GATA3 and TBX21 have been developed in lieu of gene expression profiling studies and have been shown to be prognostic [1, 3, 43, 44].

1.3.3 Anaplastic Large-Cell Lymphomas

Anaplastic large-cell lymphoma (ALCL) is mature T-cell lymphoma postulated to be derived from activated mature cytotoxic T-cells that are CD30+. The cells of ALCL are typically large with pleomorphic nuclear morphology including typical horse-shoe-shaped or "hallmark cells," prominent Golgi zones, and abundant eosinophilic cytoplasm [1, 7, 14]. ALCL is subcategorized into those that are systemic, primary cutaneous, and those associated with breast implants. Systemic ALCL is further subcategorized into those that express the ALK fusion protein derived from rearrangement at the ALK 2p23 locus versus those that lack expression of ALK protein [1]. The discussion here will be limited to systemic and breast implant-associated ALCLs, more specifically in relation to updates since the 2008 classification.

ALCL, ALK-positive, is most commonly seen in children and young adults with a male predominance, with most presenting with advanced-stage disease and systemic symptoms. Although mostly nodal, extranodal involvement is frequent including bone, soft tissue, skin, and liver [1, 7, 14, 45, 46]. ALK-positive ALCL can be identified by strong expression of CD30 and ALK and, therefore, does not pose a diagnostic challenge in most cases [1, 7, 14]. Cases with variant morphological patterns may be more difficult to recognize including the small cell variant which is often misdiagnosed as PTCL, NOS, cases with sarcomatous features, and rare cases with a hypocellular or myxoid background [47]. Helpful diagnostic clues include looking for the presence of hallmark cells, which are often concentrated around blood vessels in the small cell variant, and the strong uniform expression of CD30 and ALK [1, 7, 14, 47].

ALK-negative ALCL is no longer a provisional category as in the 2008 WHO classification [1]. Gene expression profiling studies have provided insight into the distinction of CD30-positive T-cell lymphomas, as well as improved criteria for recognition of ALK-negative ALCL in daily practice [1, 3, 40–42, 45]. Morphologically ALK-negative ALCL is indistinguishable from ALK-positive ALCL, except that it lacks expression of the ALK protein. This disease tends to occur in older adults with a predominately nodal presentation, often in advanced stage with B-symptoms [1, 7, 14]. Strong and uniform staining with CD30 is seen. Although extranodal sites can be involved, it is less common in comparison to ALK-positive ALCL. Most cases show an effaced nodal architecture by solid, cohesive sheets of neoplastic cells with cytological features described above including the presence of hallmarks cells; however, in ALK-negative ALCL, the neoplastic cells tend to be larger and more pleomorphic than those in seen ALK-positive ALCL [7, 47, 48]. Cases with *DUSP22-IRF4* rearrangement may lack the large pleomorphic cells and have more "doughnut cells" (neoplastic cells showing central nuclear pseudoinclusion) [49]. Occasionally, cases where the lymph node architecture is preserved the neoplastic cells typically show a sinusoidal pattern or growth within the T-zone areas commonly in a cohesive pattern. Absence of these features should raise the possibility of a diagnosis of PTCL, NOS [1, 7]. In addition, cases with features of classical Hodgkin lymphoma such as sclerosis and eosinophils in the background with a confirmed T-cell origin are best classified as PTCL, NOS [7]. The variant morphological patterns described in ALK-positive ALCL are currently not recognized in ALK-negative ALCL [1]. In a small subset of cases distinction between PTCL, NOS and ALK-negative ALCL on the basis of morphologic and immunophenotypic features may not always be clear-cut even among experts. In these rare cases, the WHO classification advocates a conservative approach with the recommendation of diagnosing ALK-negative ALCL only if both the morphology and phenotype (with exception of expression of ALK protein) very closely resemble ALK-positive ALCL [1, 7]. Immunophenotypically tumor cells are strongly and diffusely positive for CD30 with a membranous and Golgi pattern, although diffuse cytoplasmic positivity can be seen. Staining of the neoplastic cells should be strong and of equal intensity in all cells a feature that distinguishes it from other peripheral T-cell lymphomas which may also express CD30, typically with

variable intensity in the proportion of cells. In addition, loss of pan-T-cell markers is seen at a greater frequency than other PTCL. In this regard, ALK-negative ALCL is similar to ALK-positive ALCL. CD4 expression is typically seen in a significant proportion of cases, whereas CD8 expression is rare. Cytotoxic markers are expressed in the majority of cases; however, these tend to be absent in cases with *DUSP22* rearrangement. EBV (EBER-ISH and LMP1) is consistently negative in ALK-negative ALCL, and expression of these markers should strongly suggest the possibility of classical Hodgkin lymphoma. Both ALK-negative and ALK-positive ALCL lack T-cell receptor proteins and in this respect different from PTCL, NOS [1, 7, 14, 33, 34, 45–50].

Gene expression profiling studies have shown that ALK-negative ALCL has a signature similar to ALK-positive ALCL and distinct from other NK or T-cell lymphomas [2–4, 40–45, 47, 49]. In addition, ALK-negative ALCL appears to be genetically heterogeneous, with those with *DUSP22* rearrangement (~30% of cases) demonstrating 5-year overall survival rates matching that of ALK-positive ALCL, whereas those with *TP63* rearrangements (~8% of cases) behave more aggressively. These rearrangements have not been reported with ALK-positive ALCL, but can be seen in a small fraction of other PTCLs [45–49, 51].

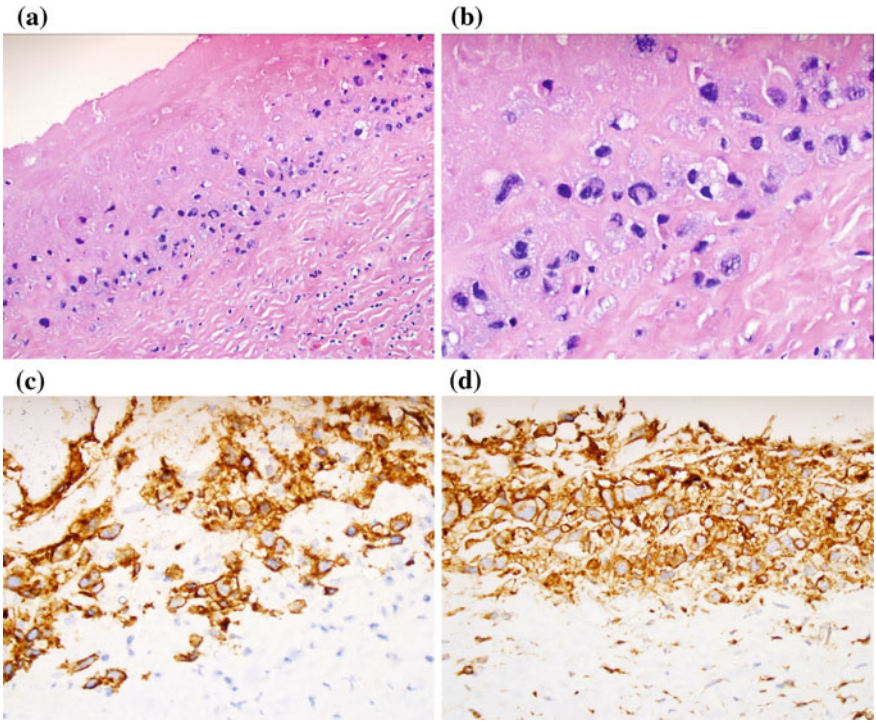

Fig. 1.1 Breast implant-associated anaplastic large-cell lymphoma. **a** Neoplastic cells are infiltrating the fibrous capsule. **b** These tumor cells are pleomorphic with some having hallmark cell morphology. **c** The tumor cells are positive for CD30 and **d** CD4

First described in 1997, subsequent studies in recent years have identified a unique form of ALK-negative ALCL arising in association with breast implants, which is designated a provisional entity in the 2017 WHO classification. This lymphoma shows morphologic and immunophenotypic features indistinguishable from ALK-negative ALCL and is usually localized to the seroma fluid cavity and/or pericapsular fibrous tissue in patients with breast implants, both saline and silicone filled [1] (Fig. 1.1). Overall, the incidence is very low ranging from 1 case per 500,000 to 3 million women with implants. In addition, there has been an association with the textured implants. The mean interval is approximately 11 years from time of implant placement to lymphoma diagnosis; however, this can vary greatly [52–56]. Most patients present with stage I disease and less frequently with a mass. Although approximately one-third of the patients may have axillary lymphadenopathy, not all nodes show evidence of tumor. Rare cases have presented with disseminated disease. Currently, patients with localized disease have excellent outcomes after complete removal of the implant (median overall survival 12 years). The most important adverse prognostic indicators are the presence of a solid mass, which may be an indication for systemic chemotherapy [1, 52, 53, 57, 58].

1.3.4 Intestinal T-Cell Lymphomas

The complexity of the intestinal T-cell lymphoproliferative disorders reflects the complexity of the intestinal T-cells within the lamina propria and epithelial compartments which display characteristics of an effector/memory phenotype and, although they are notoriously heterogenous, two types have characterized.

Intestinal T-cell lymphomas are believed to arise from intraepithelial T-cells which can be of either gamma–delta or alpha–beta derivations [1, 7, 59]. They generally have a poor prognosis with a suboptimal response to chemotherapy. In the 2008 WHO classification, enteropathy-associated T-cell lymphomas (EATL type 1 and type 2) were categorized as variants. However, more recent data has emerged which has demonstrated that although there is immunophenotypic overlap, these two entities are clearly distinct, leading to changes in the categorization of intestinal lymphomas in the 2017 WHO classification [1, 7, 31, 59–65]. EATL type 1 is now designated as EATL and is associated with celiac disease, whereas EATL type 2 is now designated as monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) and not associated with celiac disease.

1.3.5 Enteropathy-Associated T-Cell Lymphoma (EATL)

Enteropathy-associated T-cell lymphoma, formerly type I EATL, is a neoplasm of intraepithelial T-cells that is linked to celiac disease and is primarily seen in individuals of N European origin. It is the most common intestinal T-cell lymphoma in Western countries and occurs in adults between 50 and 60 years of age [1, 4, 7, 60, 65–69]. The association between EATL and celiac disease is supported by the

detection of anti-tissue transglutaminase and anti-endomysial antibodies, as well as gluten sensitivity in individuals with EATL. In addition, the presence of HLA-DQ2 or HLA-DQ8 alleles and the clinical findings of dermatitis herpetiformis are also supportive of the link between celiac disease and EATL. Furthermore, the protective effects of a gluten-free diet in the development of EATL have been observed [66, 68–72]. The most common presentation is that of abdominal pain, malabsorption, and diarrhea not responsive to gluten-free diet. Symptoms of intestinal obstruction and perforation are also commonly seen. The duration of symptoms prior to diagnosis is less than 3 months in most cases, but can vary widely. In some, a period of refractory celiac disease accompanied by ulcerative jejunitis is seen [60, 68, 73]. Hemophagocytic lymphohistiocytosis has been reported in 16–40% of individuals [74].

The small intestine, most commonly the jejunum and ileum, is involved in greater than 90% of cases, with a proportion of showing multifocal involvement. The tumor may present as ulcerating nodules, strictures and, rarely, as an exophytic mass. Extra-gastrointestinal dissemination to intraabdominal lymph nodes can occur in approximately 30% of cases. Other sites (bone marrow, skin, spleen, liver, and even CNS) may be involved [1, 31, 60, 68, 73, 75, 76]. Microscopically, the neoplastic cells demonstrate a broad spectrum and pleomorphic cytomorphology usually consisting of medium to large cells with abundant cytoplasm. Angiocentricity and areas of extensive necrosis can be frequently seen. Most cases show admixed inflammatory cells in the background. Intraepithelial spread of the neoplastic cells can range from scattered single cells to striking epitheliotropism. The adjacent intestinal mucosa often shows features of celiac disease especially in the jejunum. The neoplastic cells often express CD3, CD7, and CD103, as well as cytotoxic markers and are usually double negative for CD4 and CD8. However, there are cases with phenotypic variability including a subset that is CD8+. The frequency of CD30 expression varies; however, those with large-cell morphology are usually CD30-positive [1, 7, 14, 31, 33, 60, 65, 68, 69, 77–79]. In most cases, the neoplastic T-cells are derived from the alpha–beta lineage, although more recent studies show a minority of cases that may be derived from gamma–delta T-cells or possibly immature T/NK-cell precursors [80, 81].

Unlike nodal PTCLs, most EATLs display gains of 9q34 region or deletions of 16q12 (these changes may also be seen in MEITL) as well as gains of chromosomes 1q and 5q (seen less frequently in MEITLs) [72, 82]. Recent studies have shown recurrent mutations in the JAK–STAT signaling pathway as well as detection of *JAK1* and *STAT3* mutations in type II refractory celiac disease supports deregulation of JAK–STAT signaling to be an early event in disease pathogenesis [83, 84]. (We did not study EATL but Sandeep Dave recently published a series with both EATL and MEITL … should be referenced and discussed briefly.)

1.3.6 Monomorphic Epitheliotropic Intestinal T-Cell Lymphoma (MEITL)

MEITL is a clinically aggressive primary intestinal T-cell lymphoma derived from intraepithelial lymphocytes with no clear association with celiac disease. The vast majority of cases are reported in Asia, but with apparent increase in frequency in

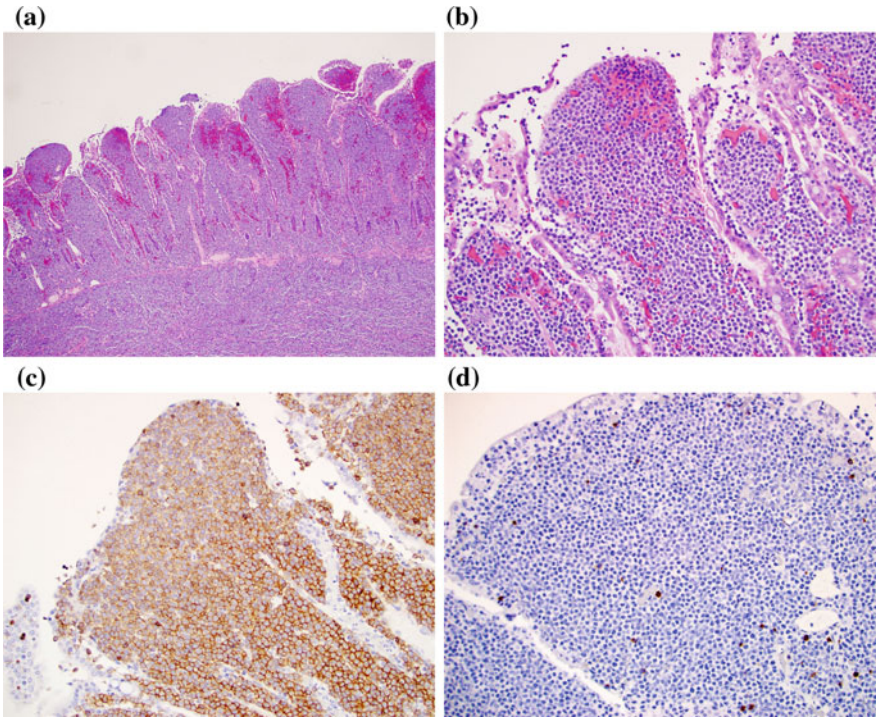

Fig. 1.2 Monomorphic epitheliotropic intestinal T-cell lymphoma. **a** and **b** Diffuse monomorphic infiltrate is expanding the small intestinal villi and invading the submucosa. The tumor cells are positive for **c** CD3 and **d** negative for CD5

individuals of Hispanic or indigenous origin [63, 85, 86]. Individuals often present with abdominal pain, weight loss, diarrhea, gastrointestinal bleeding, and obstruction or perforation. Commonly, the tumor presents as a mass with or without ulceration in the small intestine, more frequently in jejunum versus ileum, and with involvement of the mesenteric lymph nodes [63, 86]. Microscopically, the neoplastic cells are medium in size and monomorphic with generally round nuclei, finely dispersed chromatin, and ample pale cytoplasm. There is prominent epitheliotropism with distortion of the adjacent villi. Unlike EATL, an inflammatory background and areas of necrosis are uncommon. MEITL has a distinctive phenotype with expression of CD3, CD8, and CD56, and lack of CD5 in the vast majority of cases (Fig. 1.2). Although the cytotoxic marker TIA1 is usually positive, expressions of granzyme B and perforin are less consistent. The majority of cases are of gamma–delta T-cell derivation but some cases are of alpha–beta type, whereas others lack expression of these markers, so-called "TCR silent." In addition, a study reported that most cases express megakaryocyte-associated tyrosine kinase (MATK) and, if present in >80% of tumor cells, maybe a helpful marker in distinguishing it from the EATL. Approximately, 20% of cases show aberrant

CD20 expression. EBV is negative in the neoplastic T-cells, unlike extranodal NK/T-cell lymphomas, but EBV expression may sometimes be seen in background reactive B-cells [1, 7, 61, 87–90].

In addition to gains of 9q34 region, extra signals at 8q24 (MYC) are commonly seen. However, compared to EATL, gains chromosomes 1q and 5q are far less frequent. The most commonly mutated gene is *SETD2*, seen in up to 90% of cases. Activating mutations in *STAT5B* have also been identified in up to 63% of cases, including those of both gamma–delta and alpha–beta derivations [65, 82, 84, 91, 92] (significant overlap with EATL).

1.3.7 Intestinal T-Cell Lymphoma, NOS

Cases of intestinal lymphomas that do not meet the diagnostic criteria for the entities above may be designated as intestinal T-cell lymphoma, NOS. However, it should be noted that this is not considered a specific disease entity [1]. Most cases assigned to this category involved the colon and showed a heterogeneous morphology and immunophenotype, often expressing cytotoxic markers. Some cases have widespread disease, so the intestines may not have been the primary site. All cases appear to be clinically aggressive [1, 7].

1.3.8 Indolent T-Cell Lymphoproliferative Disorder of the Gastrointestinal Tract

This clonal T-cell lymphoproliferative disorder involves the mucosa and all sites in the gastrointestinal tract, but is most commonly seen in the small intestine and colon of adults, more frequently in men than women. No ethnic or genetic factors have been identified; however, some patients may have a history of Crohn's disease. Patients often present with abdominal pain diarrhea, vomiting, dyspepsia, and weight loss. Peripheral adenopathy is generally not present but a subset of patients may show enlarged mesenteric nodes [93–95]. Microscopically, a monotonous T-cell infiltrate composed of small, round lymphocytes expand the lamina propria and may show focal infiltration of the muscularis mucosa and submucosa. Although the mucosal epithelium may be displaced by the lymphoid infiltrate, destruction is typically not seen. Occasionally, epitheliotropism may be seen but is not typical. Admixed inflammatory cells are also rare; however, epithelioid granulomas may be focally present. Some cases may show some histologic changes that are seen in Crohn's disease, but whether these patients may have preceding inflammatory bowel disease remains uncertain. The atypical T-cells have a mature T-cell phenotype (CD2+, CD3+, CD5+, and variable expression of CD7) with a greater proportion of cases being positive for CD8 versus CD4. The CD8+ cases may express TIA1, but generally lack expression of granzyme B. CD56 and EBER are

negative and all reported cases thus far have expressed the alpha–beta T-cell receptor. The proliferative index is generally very low. Most patients have a chronic relapsing clinical course with little response to conventional chemotherapy. However, patients have an indolent clinical course with prolonged survival despite persistent disease. A small subset of cases has progressed to high-grade T-cell lymphomas which may spread beyond the gastrointestinal tract. These cases are more frequently seen in those expressing CD4 rather than CD8, although currently the data is limited in such cases [1, 93–95].

1.3.9 Hepatosplenic T-Cell Lymphoma

Hepatosplenic T-cell lymphoma (HSTL) is a subtype of extranodal lymphoma which is characterized by hepatic and splenic involvement without lymphadenopathy, and usually has an aggressive clinical course and poor outcome. There is a male predominance, and the mean age is approximately 35 years [96]. Approximately, 20% of HSTL arises in the background of long-term immunosuppressive therapy or prolonged antigenic stimulation, and can also be seen as a late-onset posttransplant lymphoproliferative disorder [97, 98]. There have also been reports of HSTL in patients with Crohn's disease treated with immunosuppressive therapy.

Most patients present with marked splenomegaly and hepatomegaly but without lymphadenopathy. The bone marrow is almost always involved and may be accompanied by cytopenias. Morphologically, the cells are medium in size with pale cytoplasm, inconspicuous nucleoli, and infiltrates the cords and sinuses of the splenic red pulp. The liver also shows a sinusoidal pattern, which can also be seen in the bone marrow. Occasionally, the cytologic atypia is minimal and involvement is highlighted with immunohistochemical stains.

The neoplastic cells usually have a gamma–delta T-cell phenotype expressing CD3, gamma–delta TCR, and CD56, and negative for CD4, CD5, and CD8 (Fig. 1.3). The cells usually express the cytotoxic marker TIA1 but lack granzyme B and perforin. A minority of cases may be of the alpha–beta type but have a similar GEP as the gamma–delta type [99]. It may be difficult to differentiate HSTL from T-cell large granular lymphocytic leukemia (T-LGL) with a gamma–delta phenotype but the latter lacks atypia with expression of CD8, CD57, and granzyme B. Also, the interstitial and sinusoidal infiltrate is much less prominent. T-cell receptor genes are clonally rearranged, and isochromosome 7q is present in most cases. Missense mutations involving *STAT5B* have been found in 40% of cases as well as mutations in chromatin modifying genes [84, 100], particularly *SETD2*.

The clinical course is usually aggressive, and the vast majority of patients will relapse despite initial response to chemotherapy [101]. The median survival is typically less than 2 years.

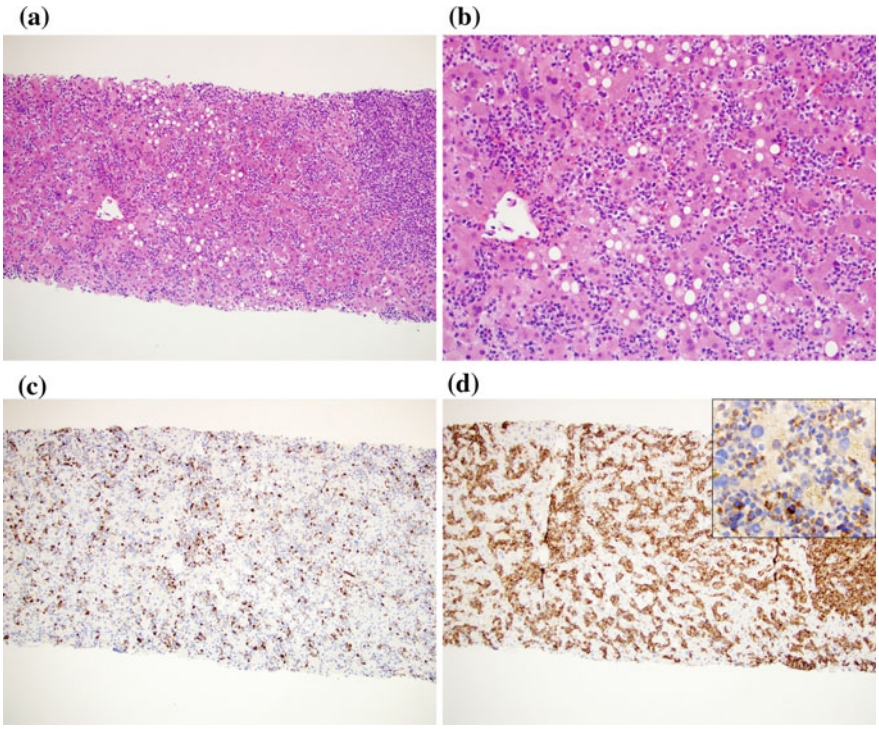

Fig. 1.3 Hepatosplenic T-cell lymphoma involving the liver. **a** and **b** Sinusoidal infiltration of atypical lymphoid cells. **c** A subset express CD3 and **d** many express CD8 with a minor subset positive for TCR gamma immunostaining (inset)

1.4 Cutaneous T-Cell Lymphoproliferative Disorders

1.4.1 Subcutaneous Panniculitis-like T-Cell Lymphoma (SPTCL)

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare T-cell lymphoma that preferentially affects young and middle-aged females. SPTCL infiltrates subcutaneous tissue and generally spares the overlying epidermis and dermis. A characteristic feature of SPTCL is the rimming of subcutaneous adipocytes by variably sized lymphoma cells. The SPTCL cells are cytotoxic alpha–beta T-cells with expression of CD3, CD8, BetaF1, and cytotoxic proteins granzyme B, perforin, and T-cell restricted intracellular antigen-1 (TIA-1). While the CD8-positive phenotype is vastly predominant for SPTCL, occasional CD4-positive and CD4/CD8-double-negative SPTCL cases have been reported [102]. Aberrant loss of other T-cell markers such as CD2 (10% of cases), CD5 (50% of cases), and CD7 (44% of cases) can be seen [103]. CD56 is negative. Ki-67 staining shows a

variable proliferation index, with many unequivocal cases of SPTCL demonstrating high Ki-67 of greater than 50% [103]. Aggregates of subcutaneous lymphoid cells with greater than 30% Ki-67 staining in areas of "Ki-67 hotspots" may be characteristic of SPTCL [104]. SPTCL is generally indolent with a good prognosis. Therefore, the distinction of SPTCL from primary cutaneous gamma–delta T-cell lymphoma is important.

No clinical or histologic feature is pathognomonic for SPTCL, but a characteristic feature of SPTCL is the rimming of subcutaneous adipocytes by atypical lymphoid cells. SPTCL generally localizes to the subcutis and spares the overlying epidermis and dermis. Karyorrhexis and fat necrosis are present in most cases. Admixed benign histiocytes are frequently present. Clonal T-cell receptor (TCR) gene rearrangement is present in the majority of cases [105]. Hemophagocytic syndrome (HPS) can be seen and is a major cause of morbidity and mortality in patients with SPTCL [103, 105]. HPS is an uncontrolled systemic hyper-inflammatory reaction associated with hemophagocytosis. Clinical characteristics of HPS include fever, splenomegaly, and specific laboratory findings (cytopenias; elevated ferritin, triglycerides, soluble CD25; decreased fibrinogen; reduced or absent natural killer cell cytotoxicity) [106].

Consensus recommendations for treatment of SPTCL vary based on the stage and associated prognostic factors [107]. For solitary or localized cutaneous lesions, electron beam radiotherapy is recommended. SPTCL generally is sensitive to radiation, which can produce long-term remissions in patients with localized disease [105]. Systemic steroids or other immunosuppressive agents are recommended for SPTCL without associated HPS. Immunosuppressive agents, such as prednisone and cyclosporine, and single chemotherapeutic agents, such as cyclophosphamide, methotrexate, and chlorambucil, have been used [105]. The use of steroids produced short-lived responses in patients, but relapses and disease progression occur once the steroid doses were tapered. More recently, patients with SPTCL showed a high response rate to bexarotene (Targretin), which is an oral retinoid used in the treatment of mycosis fungoides and Sézary syndrome [108]. For cases with progressive disease that are unresponsive to immunosuppressive therapy or cases associated with HPS, multi-agent chemotherapy is recommended. Initial therapy with combined cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like combinations have been used most frequently with an overall response rate of 53% [105]. Other multi-agent regimens and hematopoietic stem cell transplantation have also been attempted with variable responses.

1.4.2 Primary Cutaneous Gamma–Delta T-Cell Lymphoma (PCGD-TCL)

The current WHO classification recognizes two main subtypes of gamma–delta T-cell lymphomas (hepatosplenic and primary cutaneous) [1]. Normally, gamma–delta T-cells constitute only a small proportion of peripheral blood T-cells but more prevalent at mucosal sites and have been considered part of the innate immune

system providing first-line defense. Primary cutaneous gamma–delta T-cell lymphomas (PCGD-TCL) are uncommon and were originally categorized with subcutaneous panniculitis-like T-cell lymphoma [109]. PCGD-TCL was later separated in the 2008 WHO classification due to the aggressive nature of this disease and gamma–delta phenotype [110–115]. With the recent advent in immunohistochemistry to detect either the lack of alpha–beta T-cell receptor (TCR) and/or staining with gamma–delta TCR, the diagnosis has been more achievable, but much is poorly understood about this disease due to its rarity.

PCGD-TCL is an uncommon and a highly aggressive skin lymphoma with a mature, cytotoxic, and activated gamma–delta phenotype. The median age is approximately 40–60 years with an equal male-to-female ratio [116, 117]. PCGD-TCL has a markedly poor prognosis and is generally not cured by standard chemotherapy regimens [116]. Typically, this disease presents with erythematous to violaceous patches, plaques, dermal, or subcutaneous nodules with superficial ulceration. These lesions can occur anywhere on the skin but have been reported to have a predilection for the lower extremities and buttocks. Patients usually have B-symptoms (fever, night sweats, weight loss, and malaise) with dissemination to mucosal sites being common. Typically, this lymphoma does not involve lymph node, spleen, or bone marrow [111, 118]; however, hemophagocytic syndrome is common but has not been associated with a poorer prognosis [111]. One study showed an association of autoimmune disorders with PCGD-TCL [117].

The typical pattern of infiltration for PCGD-TCL usually affects the epidermal, dermal, and subcutaneous compartments. Occasional cases may only have subcutaneous tissue involvement, and therefore it is important to sample the subcutaneous fat if the clinical suspicion is high for this disease [116, 119]. Superficial ulceration is common. Pautrier microabscesses are not seen. Angiocentricity or angiodestruction is a common finding. A prominent panniculitic pattern is common. The cytology of these lymphomas is typically monomorphous with predominantly medium-sized lymphocytes with irregular nuclear contours and coarse chromatin. Occasional cases may have larger cells. The distribution of these lymphocytes in the subcutaneous fat shows a prominent "rimming" around adipocytes, but the latter finding can also be seen in subcutaneous panniculitis-like T-cell lymphoma (SPTCL). Fat necrosis and karyorrhexis are common [111, 116, 117, 119]. PCGD-TCL typically involves more layers of the skin (e.g., subcutaneous, dermis, and epidermis) compared to SPTCL.

PCGD-TCL is an extremely aggressive disease with a median survival of approximately 15 months [103, 111]. Patients with subcutaneous involvement have a much worse prognosis compared to cases that are only involving the epidermis and dermis. Few effective treatments exist for this disease, and the lymphoma is highly resistant to chemotherapy and radiation [103, 116]. Some case reports have shown successful treatment after allogeneic stem cell transplantation [103, 117]. Rare cases have shown improvement of lesions with CD30 targeted monoclonal antibody–drug conjugate (Brentuximab vedotin) despite only a subset of the neoplastic cells being positive for CD30 [120, 121]. *STAT5B* mutation is also common.

1.4.3 Mycosis Fungoides

Mycosis fungoides is the most common type of cutaneous T-cell lymphoproliferative disorder accounting for close to 50% of all primary cutaneous lymphomas [107]. Most patients are older, and the male-to-female ratio is approximately 2:1 [122]. There are possible environmental cofactors in the pathogenesis of this disease and it has been associated with professions such as farming, textile industry, metal work, carpentry, woodworking, and painting [123]. The disease is usually limited to the skin but extracutaneous site such as lymph nodes can be involved in advanced stages.

MF typically has an indolent clinical course with slow disease progression over years to even decades. Histologically, early patch lesions show superficial band-like infiltrates of atypical small- to medium-sized cells with cerebriform nuclei with a linear distribution along the basal layer. Plaques have more prominent epidermotropism with intraepidermal collections of tumor cells called Pautrier microabscesses which is a highly characteristic feature but only seen in a minority of cases [107]. Progression to tumor stage shows a more diffuse dermal infiltrate and epidermotropism may be minimal. In this advanced stage, the cells are larger in size with pleomorphic or blastoid nuclei. Transformation is defined by the presence of greater than 25% large lymphoid cells and they may be positive for CD30.

Variants of mycosis fungoides include folliculotropic mycosis fungoides (F-MF), pagetoid reticulosis, and granulomatous slack skin. F-MF is characterized by involvement of the hair follicles with sparing of the epidermis [124]. Many of the cases show mucinous degeneration in these lesions and preferentially involve the head and neck areas which may be associated with alopecia. The survival is significantly worse compared to typical mycosis fungoides (5-year survival of approximately 70–80%) [125]. Pagetoid reticulosis is a localized disease with atypical medium to large cerebriform nuclei with a T-cell phenotype that is CD8 positive and often CD30 positive. Extracutaneous dissemination or disease-related deaths have not been reported. Lastly, granulomatous slack skin is characterized by bulky skin folds in the groin and axillae with a granulomatous infiltrate in the dermis and subcutaneous tissue with CD4-positive T-cells, abundant macrophages, and multinucleated giant cells. This disease is characterized by an indolent clinical course.

Classic MF typically has mostly intact pan-T-cell markers (e.g., CD2, CD3, and CD5) and expresses CD4 with alpha–beta phenotype. CD7 is typically lost. There are rare cases with a cytotoxic phenotype expressing CD8 and/or TCR gamma. T-cell gene rearrangements are usually positive and can be helpful when comparing multiple sites of involvement to rule out a reactive process.

Clinically, patients with limited disease have excellent prognosis, while patients with advanced stages have a poor prognosis. Other adverse prognostic features are increased number of large atypical cells seen with transformation (greater than 25%) [126, 127], elevated LDH, failure to achieve complete remission after first treatment, and age greater than 60 years old.

1.4.4 Sézary Syndrome

Sézary syndrome is defined by triad of erythroderma, generalized lymphadenopathy, and the presence of neoplastic T-cells in the skin, lymph node, and peripheral blood. Peripheral blood involvement requires demonstration of a clonal T-cell gene rearrangement in combination with a total Sézary cell count greater than 1000/μL, CD4 : CD8 ratio of greater than 10, or an expanded CD4+ T-cell population with abnormal phenotype which includes loss of CD7 or CD26. Staging is performed according to the International Society of Cutaneous Lymphomas [128]/European Organization for Research and Treatment of Cancer (EORTC).

Histologically, the tumor cells are similar to mycosis fungoides but epidermotropism may be absent. Lymph node involvement shows a dense monotonous infiltrate and effacement of the lymph node architecture. The neoplastic cells express CD3, CD4, PD1, and lack CD7, CD26, and CD8 [129]. T-cell R gene rearrangement is also clonal.

Sézary syndrome is an aggressive disease with a median survival of approximately 32 months. Most patients die due to infectious causes.

1.5 Adult T-Cell Leukemia/Lymphoma

Adult T-cell leukemia/lymphoma is a mature T-cell neoplasm which is caused by infection with the human retrovirus HTLV-1. Most patients with ATLL have widespread disease involving the lymph nodes and peripheral blood. Morphologically, the neoplastic cells are multilobulated with remarkable pleomorphism, so-called flower cells, and can often be seen in the peripheral blood. ATLL occurs in adults with a median age of 50 years and a male-to-female ratio of 1.5:1. Clinical variants of this disease have been described (acute, lymphomatous, chronic, and smoldering). The acute variant is the most common and characterized by leukemic involvement with an elevated white blood cell count, skin rash, generalized lymphadenopathy, and hypercalcemia. Patients with systemic disease usually have hepatosplenomegaly, constitutional symptoms, and an elevated LDH. The lymphomatous variant is characterized by prominent lymphadenopathy without blood involvement, and most patients do not have hypercalcemia. Cutaneous lesions are commonly seen and have a broad spectrum of appearance from erythematous rashes to large nodules which may be ulcerated. The skin lesions have epidermal infiltration with Pautrier-like microabscesses similar to mycosis fungoides. Dermal infiltration is mostly perivascular but tumor lesions can extend into the subcutaneous fat. Many cases of cutaneous involvement by ATLL may mimic mycosis fungoides. Therefore, patient demographic information is critical for this distinction, as well as serologic studies for this infection.

Phenotypically, the neoplastic cells express pan-T-cell antigens but usually lack CD7 and the majority of the cases are CD4-positive compared to CD8 [130]. CD25 is strongly expressed in nearly all cases and has been used as a target for therapy

[131]. The neoplastic cells are negative for ALK and cytotoxic markers. CD30 can be expressed, especially in the transformed cases. Because the neoplastic cells express FoxP3 and CD25, the postulated normal counterpart for ATLL is peripheral CD4-positive T-cells (T-regs). T-cell receptor genes are clonally rearranged.

The prognosis is highly dependent on the IPI and may range from 2 weeks to greater than 1 year. Because of the immunodeficiency associated with this disease, many patients die due to infectious complications. Chronic and smoldering forms may have a more prolonged survival, but can progress to more aggressive disease [132, 133].

1.6 Extranodal NK/T-Cell Lymphoma, Nasal Type (ENKTCL)

ENKTCL is a predominantly extranodal disorder characterized by vascular destruction, prominent necrosis, and infection of the neoplastic cells with EBV [134]. ENKTCL is seen mainly in Asia, Mexico, and South, and Central America, mostly in adults (median age of 44–54 years), and more often in males.

ENKTCL demonstrates an EBV latency type II pattern. Typically, patients have an elevated EBV viral load which can be correlated with the extent of disease, treatment response, and survival. Sites of involvement typically are in the upper aerodigestive tract, but can also be seen in the skin, soft tissue, GI tract, and testis. Patients often present with symptoms of nasal obstruction or epistaxis. The disease is usually limited to the upper aerodigestive tract at presentation but may disseminate to other sites. Some cases may develop hemophagocytic syndrome. Patients with lesions outside of the aerodigestive tract commonly have high stage of disease with multiple extranodal sites of involvement. Systemic symptoms such as malaise, fever, and weight loss may be present.

Histologically, there usually is extensive ulceration at mucosal sites with an angiocentric/angiodestructive growth pattern. The neoplastic cells have a broad cytologic spectrum ranging from small to large, or anaplastic, but the infiltrates are usually monomorphic. The cells may have irregular nuclear contours. ENKTCL with a small cell morphology can mimic a reactive/inflammatory process. Therefore, it is important to be aware of the clinical presentation and patient demographics. The cells of ENKTCL are positive for CD2, CD56, and CD43, but lack surface CD3 and CD5 [135–137]. Typically, cytoplasmic CD3 is present (cytoplasmic CD3-epsilon). Other T-cell markers are usually negative, such as CD4 and CD8. There is a small subset of cases that have a T-cell lineage and may express CD5, CD8, as well as T-cell receptors [138]. Cytotoxic markers are usually positive (granzyme B, TIA1, and perforin) and CD30 is positive in approximately 30% of cases. EBV is found by in situ hybridization (EBER) in all cases. However, EBV can be seen in other T-cell lymphomas and therefore, the presence of EBV does not equate to a diagnosis of ENKTCL. ENKTCL with an NK-cell lineage should be negative for T-cell gene rearrangements, while the T-cell lineage will have a clonal rearrangement.

The prognosis of ENKTCL is variable with patients responding well to therapy having disease localized to the nasal cavity [139]. However, the overall survival has generally been poor. Adverse prognostic factors include advanced age and a high IPI score. Cases with extra-nasal disease are usually very aggressive with poor response to therapy and short survival. Recent therapies with L-asparaginase and etoposide have improved outcomes (SMILE regimen) [139].

1.7 Conclusion

There have been significant recent advances in the classification and understanding of the biology of peripheral T-cell and NK-cell lymphomas, mainly the result of genomic studies evaluating the gene expression and mutational landscape of those lymphomas. These new insights have helped to differentiate and further classify these lymphomas. The new WHO classification has provided an update in the diagnostic categories of these neoplasms to facilitate research and advance the therapeutics in these diseases.

References

1. Swerdlow SH, Campo E, Harris NL et al (2017) WHO classification of tumours of haematopoietic and lymphoid tissues (ed revised 4th), International agency for research on cancer lyon
2. Hsi ED, Said J, Macon WR et al (2014) Diagnostic accuracy of a defined immunophenotypic and molecular genetic approach for peripheral T/NK-cell lymphomas. A North American PTCL study group project. Am J Surg Pathol 38(6):768–775
3. Iqbal J, Wright G, Wang C et al (2014) Gene expression signatures delineate biological and prognostic subgroups in peripheral T-cell lymphoma. Blood 123(19):2915–2923
4. Swerdlow SH, Campo E, Pileri SA et al (2016) The 2016 revision of the world health organization classification of lymphoid neoplasms. Blood 127(20):2375–2390
5. Vose J, Armitage J, Weisenburger D (2008) International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol 26(25):4124–4130
6. Wang SS, Vose JM (2013) Epidemiology and prognosis of T-cell lymphoma. In: Foss F (ed) T-cell lymphomas. Humana Press, Totowa, NJ, pp 25–39
7. Attygalle AD, Cabecadas J, Gaulard P et al (2014) Peripheral T-cell and NK-cell lymphomas and their mimics; taking a step forward—report on the lymphoma workshop of the XVIth meeting of the European association for haematopathology and the society for hematopathology. Histopathology 64(2):171–199
8. Huang Y, Moreau A, Dupuis J et al (2009) Peripheral T-cell lymphomas with a follicular growth pattern are derived from follicular helper T cells (TFH) and may show overlapping features with angioimmunoblastic T-cell lymphomas. Am J Surg Pathol 33(5):682–690
9. Rodriguez-Pinilla SM, Atienza L, Murillo C et al (2008) Peripheral T-cell lymphoma with follicular T-cell markers. Am J Surg Pathol 32(12):1787–1799
10. Hu S, Young KH, Konoplev SN, Medeiros LJ (2012) Follicular T-cell lymphoma: a member of an emerging family of follicular helper T-cell derived T-cell lymphomas. Hum Pathol 43(11):1789–1798

11. Odejide O, Weigert O, Lane AA et al (2014) A targeted mutational landscape of angioimmunoblastic T-cell lymphoma. Blood 123(9):1293–1296
12. Lemonnier F, Couronne L, Parrens M et al (2012) Recurrent TET2 mutations in peripheral T-cell lymphomas correlate with TFH-like features and adverse clinical parameters. Blood 120(7):1466–1469
13. Ondrejka SL, Grzywacz B, Bodo J et al (2016) Angioimmunoblastic T-cell Lymphomas With the RHOA p.Gly17Val mutation have classic clinical and pathologic features. Am J Surg Pathol 40(3):335–341
14. Jaffe ES, Nicolae A, Pittaluga S (2013) Peripheral T-cell and NK-cell lymphomas in the WHO classification: pearls and pitfalls. Mod Pathol 26(Suppl 1):S71–87
15. Attygalle AD, Kyriakou C, Dupuis J et al (2007) Histologic evolution of angioimmunoblastic T-cell lymphoma in consecutive biopsies: clinical correlation and insights into natural history and disease progression. Am J Surg Pathol 31(7):1077–1088
16. Rodriguez-Justo M, Attygalle AD, Munson P, Roncador G, Marafioti T, Piris MA (2009) Angioimmunoblastic T-cell lymphoma with hyperplastic germinal centres: a neoplasia with origin in the outer zone of the germinal centre? Clinicopathological and immunohistochemical study of 10 cases with follicular T-cell markers. Mod Pathol 22(6):753–761
17. Nicolae A, Pittaluga S, Venkataraman G et al (2013) Peripheral T-cell lymphomas of follicular T-helper cell derivation with Hodgkin/Reed-Sternberg cells of B-cell lineage: both EBV-positive and EBV-negative variants exist. Am J Surg Pathol 37(6):816–826
18. Zettl A, Lee S, Rudiger T et al (2002) Epstein-Barr virus-associated B-cell lymphoproliferative disorders in angioimmunoblastic T-cell lymphoma and peripheral T-cell lymphoma, unspecified. Am J Clin Pathol 117(3):368–379
19. Federico M, Rudiger T, Bellei M et al (2013) Clinicopathologic characteristics of angioimmunoblastic T-cell lymphoma: analysis of the international peripheral T-cell lymphoma project. J Clin Oncol 31(2):240–246
20. Agostinelli C, Hartmann S, Klapper W et al (2011) Peripheral T cell lymphomas with follicular T helper phenotype: a new basket or a distinct entity? Revising Karl Lennert's personal archive. Histopathology. 59(4):679–691
21. Moroch J, Copie-Bergman C, de Leval L et al (2012) Follicular peripheral T-cell lymphoma expands the spectrum of classical Hodgkin lymphoma mimics. Am J Surg Pathol 36 (11):1636–1646
22. de Leval L, Rickman DS, Thielen C et al (2007) The gene expression profile of nodal peripheral T-cell lymphoma demonstrates a molecular link between angioimmunoblastic T-cell lymphoma (AITL) and follicular helper T (TFH) cells. Blood 109(11):4952–4963
23. Dobay MP, Lemonnier F, Missiaglia E et al (2017) Integrative clinicopathological and molecular analyses of angioimmunoblastic T-cell lymphoma and other nodal lymphomas of follicular helper T-cell origin. Haematologica 102(4):e148–e151
24. Streubel B, Vinatzer U, Willheim M, Raderer M, Chott A (2006) Novel t(5;9)(q33;q22) fuses ITK to SYK in unspecified peripheral T-cell lymphoma. Leukemia 20(2):313–318
25. Dierks C, Adrian F, Fisch P et al (2010) The ITK-SYK fusion oncogene induces a T-cell lymphoproliferative disease in mice mimicking human disease. Cancer Res 70(15):6193–6204
26. Attygalle AD, Feldman AL, Dogan A (2013) ITK/SYK translocation in angioimmunoblastic T-cell lymphoma. Am J Surg Pathol 37(9):1456–1457
27. Rizvi MA, Evens AM, Tallman MS, Nelson BP, Rosen ST (2006) T-cell non-Hodgkin lymphoma. Blood 107(4):1255–1264
28. Menon MP, Nicolae A, Meeker H et al (2015) Primary CNS T-cell Lymphomas: a clinical, morphologic, immunophenotypic, and molecular analysis. Am J Surg Pathol 39(12): 1719–1729
29. Hayashi E, Takata K, Sato Y et al (2013) Distinct morphologic, phenotypic, and clinical-course characteristics of indolent peripheral T-cell lymphoma. Hum Pathol 44(9): 1927–1936

30. Bellei M, Sabattini E, Pesce EA et al (2016) Pitfalls and major issues in the histologic diagnosis of peripheral T-cell lymphomas: results of the central review of 573 cases from the T-Cell Project, an international, cooperative study. Hematol Oncol
31. Swerdlow SH, Jaffe ES, Brousset P et al (2014) Cytotoxic T-cell and NK-cell lymphomas: current questions and controversies. Am J Surg Pathol 38(10):e60–71
32. Went P, Agostinelli C, Gallamini A et al (2006) Marker expression in peripheral T-cell lymphoma: a proposed clinical-pathologic prognostic score. J Clin Oncol 24(16):2472–2479
33. Sabattini E, Pizzi M, Tabanelli V et al (2013) CD30 expression in peripheral T-cell lymphomas. Haematologica 98(8):e81–82
34. Barry TS, Jaffe ES, Sorbara L, Raffeld M, Pittaluga S (2003) Peripheral T-cell lymphomas expressing CD30 and CD15. Am J Surg Pathol 27(12):1513–1522
35. Geissinger E, Odenwald T, Lee SS et al (2004) Nodal peripheral T-cell lymphomas and in particular, their lymphoepithelioid (Lennert's) variant are often derived from CD8(+) cytotoxic T-cells. Virchows Arch 445(4):334–343
36. Hartmann S, Agostinelli C, Klapper W et al (2011) Revising the historical collection of epithelioid cell-rich lymphomas of the Kiel Lymph Node registry: what is Lennert's lymphoma nowadays? Histopathology 59(6):1173–1182
37. Ha SY, Sung J, Ju H et al (2013) Epstein-Barr virus-positive nodal peripheral T cell lymphomas: clinicopathologic and gene expression profiling study. Pathol Res Pract 209 (7):448–454
38. Swerdlow SH (2007) T-cell and NK-cell posttransplantation lymphoproliferative disorders. Am J Clin Pathol 127(6):887–895
39. Palomero T, Couronne L, Khiabanian H et al (2014) Recurrent mutations in epigenetic regulators, RHOA and FYN kinase in peripheral T cell lymphomas. Nat Genet 46(2): 166–170
40. Piccaluga PP, Fuligni F, De Leo A et al (2013) Molecular profiling improves classification and prognostication of nodal peripheral T-cell lymphomas: results of a phase III diagnostic accuracy study. J Clin Oncol 31(24):3019–3025
41. Laginestra MA, Piccaluga PP, Fuligni F et al (2014) Pathogenetic and diagnostic significance of microRNA deregulation in peripheral T-cell lymphoma not otherwise specified. Blood Cancer J 4:259
42. Liu C, Iqbal J, Teruya-Feldstein J et al (2013) MicroRNA expression profiling identifies molecular signatures associated with anaplastic large cell lymphoma. Blood 122(12):2083–2092
43. Piva R, Agnelli L, Pellegrino E et al (2010) Gene expression profiling uncovers molecular classifiers for the recognition of anaplastic large-cell lymphoma within peripheral T-cell neoplasms. J Clin Oncol 28(9):1583–1590
44. Wang T, Feldman AL, Wada DA et al (2014) GATA-3 expression identifies a high-risk subset of PTCL, NOS with distinct molecular and clinical features. Blood 123(19):3007–3015
45. Parrilla Castellar ER, Jaffe ES, Said JW et al (2014) ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes. Blood 124(9):1473–1480
46. Hapgood G, Savage KJ (2015) The biology and management of systemic anaplastic large cell lymphoma. Blood 126(1):17–25
47. Stein H, Foss HD, Durkop H et al (2000) CD30(+) anaplastic large cell lymphoma: a review of its histopathologic, genetic, and clinical features. Blood 96(12):3681–3695
48. Xing X, Feldman AL (2015) Anaplastic large cell lymphomas: ALK positive, ALK negative, and primary cutaneous. Adv Anat Pathol. 22(1):29–49
49. King RL, Dao LN, McPhail ED et al (2016) Morphologic features of ALK-negative anaplastic large cell lymphomas with DUSP22 rearrangements. Am J Surg Pathol 40(1): 36–43

50. Eberle FC, Song JY, Xi L et al (2012) Nodal involvement by cutaneous CD30-positive T-cell lymphoma mimicking classical Hodgkin lymphoma. Am J Surg Pathol 36(5):716–725
51. Wang X, Boddicker RL, Dasari S et al (2017) Expression of p63 protein in anaplastic large cell lymphoma: implications for genetic subtyping. Hum Pathol 64:19–27
52. Miranda RN, Aladily TN, Prince HM et al (2014) Breast implant-associated anaplastic large-cell lymphoma: long-term follow-up of 60 patients. J Clin Oncol 32(2):114–120
53. Brody GS, Deapen D, Taylor CR et al (2015) Anaplastic large cell lymphoma occurring in women with breast implants: analysis of 173 cases. Plast Reconstr Surg 135(3):695–705
54. de Jong D, Vasmel WL, de Boer JP et al (2008) Anaplastic large-cell lymphoma in women with breast implants. JAMA 300(17):2030–2035
55. Doren EL, Miranda RN, Selber JC et al (2017) U.S. epidemiology of breast implant-associated anaplastic large cell lymphoma. Plast Reconstr Surg 139(5):1042–1050
56. Largent J, Oefelein M, Kaplan HM, Okerson T, Boyle P (2012) Risk of lymphoma in women with breast implants: analysis of clinical studies. Eur J Cancer Prev 21(3):274–280
57. Roden AC, Macon WR, Keeney GL, Myers JL, Feldman AL, Dogan A (2008) Seroma-associated primary anaplastic large-cell lymphoma adjacent to breast implants: an indolent T-cell lymphoproliferative disorder. Mod Pathol 21(4):455–463
58. Taylor CR, Siddiqi IN, Brody GS (2013) Anaplastic large cell lymphoma occurring in association with breast implants: review of pathologic and immunohistochemical features in 103 cases. Appl Immunohistochem Mol Morphol 21(1):13–20
59. van Wijk F, Cheroutre H (2009) Intestinal T cells: facing the mucosal immune dilemma with synergy and diversity. Semin Immunol 21(3):130–138
60. Delabie J, Holte H, Vose JM et al (2011) Enteropathy-associated T-cell lymphoma: clinical and histological findings from the international peripheral T-cell lymphoma project. Blood 118(1):148–155
61. Tan SY, Chuang SS, Tang T et al (2013) Type II EATL (epitheliotropic intestinal T-cell lymphoma): a neoplasm of intra-epithelial T-cells with predominant CD8alphaalpha phenotype. Leukemia 27(8):1688–1696
62. Wilson AL, Swerdlow SH, Przybylski GK et al (2013) Intestinal gammadelta T-cell lymphomas are most frequently of type II enteropathy-associated T-cell type. Hum Pathol 44 (6):1131–1145
63. Chan JK, Chan AC, Cheuk W et al (2011) Type II enteropathy-associated T-cell lymphoma: a distinct aggressive lymphoma with frequent gammadelta T-cell receptor expression. Am J Surg Pathol 35(10):1557–1569
64. Kikuma K, Yamada K, Nakamura S et al (2014) Detailed clinicopathological characteristics and possible lymphomagenesis of type II intestinal enteropathy-associated T-cell lymphoma in Japan. Hum Pathol 45(6):1276–1284
65. Deleeuw RJ, Zettl A, Klinker E et al (2007) Whole-genome analysis and HLA genotyping of enteropathy-type T-cell lymphoma reveals 2 distinct lymphoma subtypes. Gastroenterology 132(5):1902–1911
66. Catassi C, Bearzi I, Holmes GK (2005) Association of celiac disease and intestinal lymphomas and other cancers. Gastroenterology 128(4 Suppl 1):S79–86
67. Sharaiha RZ, Lebwohl B, Reimers L, Bhagat G, Green PH, Neugut AI (2012) Increasing incidence of enteropathy-associated T-cell lymphoma in the United States, 1973-2008. Cancer 118(15):3786–3792
68. Malamut G, Chandesris O, Verkarre V et al (2013) Enteropathy associated T cell lymphoma in celiac disease: a large retrospective study. Dig Liver Dis 45(5):377–384
69. van de Water JM, Cillessen SA, Visser OJ, Verbeek WH, Meijer CJ, Mulder CJ (2010) Enteropathy associated T-cell lymphoma and its precursor lesions. Best Pract Res Clin Gastroenterol 24(1):43–56
70. Silano M, Volta U, Vincenzi AD, Dessi M, Vincenzi MD (2008) Collaborating centers of the italian registry of the complications of Coeliac D. effect of a gluten-free diet on the risk of enteropathy-associated T-cell lymphoma in celiac disease. Dig Dis Sci 53(4):972–976

71. Green PH, Cellier C (2007) Celiac disease. N Engl J Med 357(17):1731–1743
72. Megiorni F, Pizzuti A (2012) HLA-DQA1 and HLA-DQB1 in Celiac disease predisposition: practical implications of the HLA molecular typing. J Biomed Sci 19:88
73. Malamut G, Afchain P, Verkarre V et al (2009) Presentation and long-term follow-up of refractory celiac disease: comparison of type I with type II. Gastroenterology 136(1):81–90
74. Amiot A, Allez M, Treton X et al (2012) High frequency of fatal haemophagocytic lymphohistiocytosis syndrome in enteropathy-associated T cell lymphoma. Dig Liver Dis. 44(4):343–349
75. Berman EL, Zauber NP, Rickert RR, Diss TC, Isaacson PG (1998) Enteropathy-associated T cell lymphoma with brain involvement. J Clin Gastroenterol 26(4):337–341
76. Gobbi C, Buess M, Probst A et al (2003) Enteropathy-associated T-cell lymphoma with initial manifestation in the CNS. Neurology 60(10):1718–1719
77. Malamut G, Meresse B, Cellier C, Cerf-Bensussan N (2012) Refractory celiac disease: from bench to bedside. Semin Immunopathol. 34(4):601–613
78. de Mascarel A, Belleannee G, Stanislas S et al (2008) Mucosal intraepithelial T-lymphocytes in refractory celiac disease: a neoplastic population with a variable CD8 phenotype. Am J Surg Pathol 32(5):744–751
79. Farstad IN, Johansen FE, Vlatkovic L et al (2002) Heterogeneity of intraepithelial lymphocytes in refractory sprue: potential implications of CD30 expression. Gut 51(3):372–378
80. Tack GJ, van Wanrooij RL, Langerak AW et al (2012) Origin and immunophenotype of aberrant IEL in RCDII patients. Mol Immunol 50(4):262–270
81. Schmitz F, Tjon JM, Lai Y et al (2013) Identification of a potential physiological precursor of aberrant cells in refractory coeliac disease type II. Gut 62(4):509–519
82. Zettl A, Ott G, Makulik A et al (2002) Chromosomal gains at 9q characterize enteropathy-type T-cell lymphoma. Am J Pathol 161(5):1635–1645
83. Nicolae A, Xi L, Pham TH et al (2016) Mutations in the JAK/STAT and RAS signaling pathways are common in intestinal T-cell lymphomas. Leukemia 30(11):2245–2247
84. Kucuk C, Jiang B, Hu X et al (2015) Activating mutations of STAT5B and STAT3 in lymphomas derived from gammadelta-T or NK cells. Nat Commun 6:6025
85. Garcia-Herrera A, Song JY, Chuang SS et al (2011) Nonhepatosplenic gammadelta T-cell lymphomas represent a spectrum of aggressive cytotoxic T-cell lymphomas with a mainly extranodal presentation. Am J Surg Pathol 35(8):1214–1225
86. Tse E, Gill H, Loong F et al (2012) Type II enteropathy-associated T-cell lymphoma: a multicenter analysis from the Asia lymphoma study group. Am J Hematol 87(7):663–668
87. Tan SY, Ooi AS, Ang MK et al (2011) Nuclear expression of MATK is a novel marker of type II enteropathy-associated T-cell lymphoma. Leukemia 25(3):555–557
88. Chott A, Haedicke W, Mosberger I et al (1998) Most CD56+ intestinal lymphomas are CD8 + CD5-T-cell lymphomas of monomorphic small to medium size histology. Am J Pathol 153(5):1483–1490
89. Tomita S, Kikuti YY, Carreras J et al (2015) Genomic and immunohistochemical profiles of enteropathy-associated T-cell lymphoma in Japan. Mod Pathol 28(10):1286–1296
90. Sun J, Lu Z, Yang D, Chen J (2011) Primary intestinal T-cell and NK-cell lymphomas: a clinicopathological and molecular study from China focused on type II enteropathy-associated T-cell lymphoma and primary intestinal NK-cell lymphoma. Mod Pathol 24(7): 983–992
91. Nairismagi ML, Tan J, Lim JQ et al (2016) JAK-STAT and G-protein-coupled receptor signaling pathways are frequently altered in epitheliotropic intestinal T-cell lymphoma. Leukemia 30(6):1311–1319
92. Roberti A, Dobay MP, Bisig B et al (2016) Type II enteropathy-associated T-cell lymphoma features a unique genomic profile with highly recurrent SETD2 alterations. Nat Commun. 7:12602

93. Perry AM, Warnke RA, Hu Q et al (2013) Indolent T-cell lymphoproliferative disease of the gastrointestinal tract. Blood 122(22):3599–3606
94. Matnani R, Ganapathi KA, Lewis SK, Green PH, Alobeid B, Bhagat G (2017) Indolent T- and NK-cell lymphoproliferative disorders of the gastrointestinal tract: a review and update. Hematol Oncol 35(1):3–16
95. Margolskee E, Jobanputra V, Lewis SK, Alobeid B, Green PH, Bhagat G (2013) Indolent small intestinal CD4+ T-cell lymphoma is a distinct entity with unique biologic and clinical features. PLoS ONE 8(7):e68343
96. Belhadj K, Reyes F, Farcet JP et al (2003) Hepatosplenic gammadelta T-cell lymphoma is a rare clinicopathologic entity with poor outcome: report on a series of 21 patients. Blood 102(13):4261–4269
97. Falchook GS, Vega F, Dang NH et al (2009) Hepatosplenic gamma-delta T-cell lymphoma: clinicopathological features and treatment. Ann Oncol 20(6):1080–1085
98. Vega F, Medeiros LJ, Gaulard P (2007) Hepatosplenic and other gammadelta T-cell lymphomas. Am J Clin Pathol 127(6):869–880
99. Macon WR, Levy NB, Kurtin PJ et al (2001) Hepatosplenic alphabeta T-cell lymphomas: a report of 14 cases and comparison with hepatosplenic gammadelta T-cell lymphomas. Am J Surg Pathol 25(3):285–296
100. McKinney M, Moffitt AB, Gaulard P et al (2017) The genetic basis of hepatosplenic T-cell lymphoma. Cancer Discov 7(4):369–379
101. Yabe M, Medeiros LJ, Tang G et al (2016) Prognostic factors of hepatosplenic T-cell lymphoma: clinicopathologic study of 28 cases. Am J Surg Pathol 40(5):676–688
102. Kong YY, Dai B, Kong JC et al (2008) Subcutaneous panniculitis-like T-cell lymphoma: a clinicopathologic, immunophenotypic, and molecular study of 22 Asian cases according to WHO-EORTC classification. Am J Surg Pathol 32(10):1495–1502
103. Willemze R, Jansen PM, Cerroni L et al (2008) Subcutaneous panniculitis-like T-cell lymphoma: definition, classification, and prognostic factors: an EORTC cutaneous lymphoma group study of 83 cases. Blood 111(2):838–845
104. LeBlanc RE, Tavallaee M, Kim YH, Kim J (2016) Useful parameters for distinguishing subcutaneous panniculitis-like T-cell lymphoma from lupus erythematosus panniculitis. Am J Surg Pathol 40(6):745–754
105. Go RS, Wester SM (2004) Immunophenotypic and molecular features, clinical outcomes, treatments, and prognostic factors associated with subcutaneous panniculitis-like T-cell lymphoma: a systematic analysis of 156 patients reported in the literature. Cancer 101(6): 1404–1413
106. Janka GE, Lehmberg K (2014) Hemophagocytic syndromes—an update. Blood Rev 28(4): 135–142
107. Willemze R, Jaffe ES, Burg G et al (2005) WHO-EORTC classification for cutaneous lymphomas. Blood 105(10):3768–3785
108. Mehta N, Wayne AS, Kim YH et al (2012) Bexarotene is active against subcutaneous panniculitis-like T-cell lymphoma in adult and pediatric populations. Clin Lymph Myeloma Leuk 12(1):20–25
109. Jaffe ES, Organization WH (2001) Pathology and genetics of tumours of haematopoietic and lymphoid tissues, IARC Press
110. Toro JR, Beaty M, Sorbara L et al (2000) Gamma delta T-cell lymphoma of the skin: a clinical, microscopic, and molecular study. Arch Dermatol 136(8):1024–1032
111. Toro JR, Liewehr DJ, Pabby N et al (2003) Gamma-delta T-cell phenotype is associated with significantly decreased survival in cutaneous T-cell lymphoma. Blood 101(9):3407–3412
112. Swerdlow S, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW (2008) WHO classification of tumours of haematopoietic and lymphoid tissues. International Agency for Research on Cancer, Lyon, France
113. de Wolf-Peeters C, Achten R (2000) gammadelta T-cell lymphomas: a homogeneous entity? Histopathology 36(4):294–305

114. Arnulf B, Copie-Bergman C, Delfau-Larue MH et al (1998) Nonhepatosplenic gammadelta T-cell lymphoma: a subset of cytotoxic lymphomas with mucosal or skin localization. Blood 91(5):1723–1731
115. Emile JF, Boulland ML, Haioun C et al (1996) CD5-CD56+ T-cell receptor silent peripheral T-cell lymphomas are natural killer cell lymphomas. Blood 87(4):1466–1473
116. Tripodo C, Iannitto E, Florena AM et al (2009) Gamma-delta T-cell lymphomas. Nat Rev Clin Oncol 6(12):707–717
117. Guitart J, Weisenburger DD, Subtil A et al (2012) Cutaneous gammadelta T-cell lymphomas: a spectrum of presentations with overlap with other cytotoxic lymphomas. Am J Surg Pathol 36(11):1656–1665
118. Amado A, McDonnell JK, Somani N, Bunting ST, Winfield HL (2008) Cutaneous gamma-delta T-cell lymphoma. Leuk Lymph 49(10):2003–2005
119. Roullet M, Gheith SM, Mauger J, Junkins-Hopkins JM, Choi JK (2009) Percentage of {gamma}{delta} T cells in panniculitis by paraffin immunohistochemical analysis. Am J Clin Pathol 131(6):820–826
120. Rubio-Gonzalez B, Zain J, Garcia L, Rosen ST, Querfeld C (2016) Cutaneous gamma-delta T-cell lymphoma successfully treated with brentuximab vedotin. JAMA Dermatol 152(12): 1388–1390
121. Talpur R, Chockalingam R, Wang C, Tetzlaff MT, Duvic M (2016) A single-center experience with brentuximab vedotin in gamma delta T-cell lymphoma. Clin Lymph Myeloma Leuk 16(2):e15–19
122. Willemze R (2006) Primary cutaneous B-cell lymphoma: classification and treatment. Curr Opin Oncol 18(5):425–431
123. Aschebrook-Kilfoy B, Cocco P, La Vecchia C et al (2014) Medical history, lifestyle, family history, and occupational risk factors for mycosis fungoides and Sezary syndrome: the InterLymph non-Hodgkin lymphoma subtypes project. J Natl Cancer Inst Monogr 2014 (48):98–105
124. Cerroni L, Fink-Puches R, Back B, Kerl H (2002) Follicular mucinosis: a critical reappraisal of clinicopathologic features and association with mycosis fungoides and Sezary syndrome. Arch Dermatol 138(2):182–189
125. van Doorn R, Scheffer E, Willemze R (2002) Follicular mycosis fungoides, a distinct disease entity with or without associated follicular mucinosis: a clinicopathologic and follow-up study of 51 patients. Arch Dermatol 138(2):191–198
126. Arulogun SO, Prince HM, Ng J et al (2008) Long-term outcomes of patients with advanced-stage cutaneous T-cell lymphoma and large cell transformation. Blood 112(8): 3082–3087
127. Cerroni L, Rieger E, Hodl S, Kerl H (1992) Clinicopathologic and immunologic features associated with transformation of mycosis fungoides to large-cell lymphoma. Am J Surg Pathol 16(6):543–552
128. Olsen E, Vonderheid E, Pimpinelli N et al (2007) Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the international society for cutaneous lymphomas (ISCL) and the cutaneous lymphoma task force of the European organization of research and treatment of cancer (EORTC). Blood 110(6):1713–1722
129. Cetinozman F, Jansen PM, Vermeer MH, Willemze R (2012) Differential expression of programmed death-1 (PD-1) in Sezary syndrome and mycosis fungoides. Arch Dermatol 148 (12):1379–1385
130. Karube K, Ohshima K, Tsuchiya T et al (2004) Expression of FoxP3, a key molecule in CD4CD25 regulatory T cells, in adult T-cell leukaemia/lymphoma cells. Br J Haematol 126(1):81–84
131. Manoukian G, Hagemeister F (2009) Denileukin diftitox: a novel immunotoxin. Exp Opinion Biol Therapy 9(11):1445–1451
132. Ohshima K, Suzumiya J, Sato K et al (1999) Survival of patients with HTLV-I-associated lymph node lesions. J Pathol 189(4):539–545

133. Katsuya H, Ishitsuka K, Utsunomiya A et al (2015) Treatment and survival among 1594 patients with ATL. Blood 126(24):2570–2577
134. Jaffe ES (1995) Nasal and nasal-type T/NK cell lymphoma: a unique form of lymphoma associated with the Epstein-Barr virus. Histopathology 27(6):581–583
135. Tsang WY, Chan JK, Ng CS, Pau MY (1996) Utility of a paraffin section-reactive CD56 antibody (123C3) for characterization and diagnosis of lymphomas. Am J Surg Pathol 20(2): 202–210
136. Quintanilla-Martinez L, Franklin JL, Guerrero I et al (1999) Histological and immunophenotypic profile of nasal NK/T cell lymphomas from Peru: high prevalence of p53 overexpression. Hum Pathol 30(7):849–855
137. Chan JK, Tsang WY, Wong KF (1994) Classification of natural killer cell neoplasms. Am J Surg Pathol 18(11):1177–1179
138. Pongpruttipan T, Sukpanichnant S, Assanasen T et al (2012) Extranodal NK/T-cell lymphoma, nasal type, includes cases of natural killer cell and alphabeta, gammadelta, and alphabeta/gammadelta T-cell origin: a comprehensive clinicopathologic and phenotypic study. Am J Surg Pathol 36(4):481–499
139. Yamaguchi M, Kwong YL, Kim WS et al (2011) Phase II study of SMILE chemotherapy for newly diagnosed stage IV, relapsed, or refractory extranodal natural killer (NK)/T-cell lymphoma, nasal type: the NK-cell tumor study group study. J Clin Oncol 29(33): 4410–4416

Molecular and Genomic Landscape of Peripheral T-Cell Lymphoma

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Javeed Iqbal, Catalina Amador, Timothy W. McKeithan and Wing C. Chan

Abstract

Peripheral T-cell lymphoma (PTCL) is an uncommon group of lymphoma covering a diverse spectrum of entities. Little was known regarding the molecular and genomic landscapes of these diseases until recently but the knowledge is still quite spotty with many rarer types of PTCL remain largely unexplored. In this chapter, the recent findings from gene expression profiling (GEP) studies, including profiling data on microRNA, where available, will be presented with emphasis on the implication on molecular diagnosis, prognostication, and the identification of new entities (PTCL-GATA3 and PTCL-TBX21) in the PTCL-NOS group. Recent studies using next-generation sequencing have unraveled the mutational landscape in a number of PTCL entities leading to a marked improvement in the understanding of their pathogenesis and biology. While many mutations are shared among PTCL entities, the frequency varies and certain mutations are quite unique to a specific entity. For example, TET2 is often mutated but this is particularly frequent (70-80%) in angioimmunoblastic T-cell lymphoma (AITL) and IDH2 R172 mutations appear to be unique for AITL. In general, chromatin modifiers and molecular components in the CD28/T-cell receptor signaling pathways are frequently mutated. The major findings will be summarized in this chapter correlating with GEP data and clinical features where appropriate. The mutational landscape of cutaneous T-cell lymphoma, specifically on mycosis fungoides and Sezary syndrome, will also be discussed.

Keywords

Peripheral T-cell lymphoma · Gene expression profiling · Mutational landscape Pathogenesis · Biology · Mycosis fungoides · Sezary syndrome

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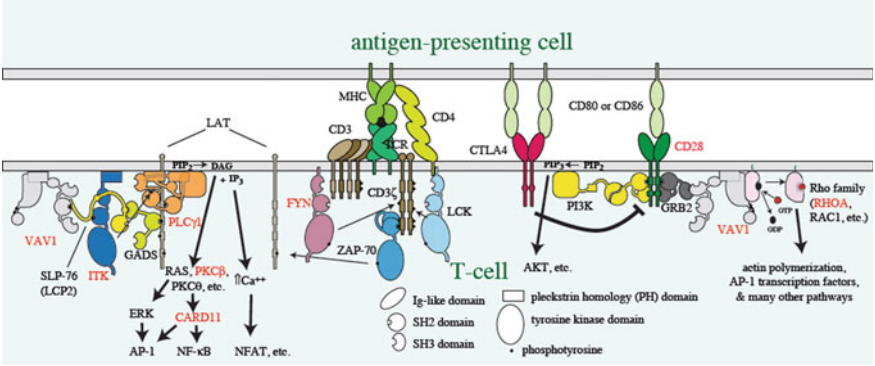

Fig. 2.1 Signaling through the T-cell receptor and co-stimulatory pathways: Upon binding of the TCR to pMHC, LCK, and FYN phosphorylate CD3 ITAMs, followed by recruitment and activation of ZAP70, which in turn phosphorylates LAT. A signalosome condenses on LAT clusters through binding to phosphotyrosines by SH2-containing proteins, which in turn are phosphorylated. Binding to proline-rich motifs through SH3 domains contributes to these recruitment steps. This leads to activation of PLCG1 and the subsequent generation of IP3 and DAG and activation of downstream pathways. PI3K is recruited and activated through several mechanisms, including CD28 activation, as shown. The resulting PIP3 contributes to the membrane recruitment and activation of AKT. Only a small fraction of the involved signaling molecules are shown. Proteins with frequent gain-of-function mutations or dominant-negative mutations (RHOA) in (PTCL are shown in red

2.1 Introduction

Peripheral T-cell lymphoma (PTCL) constitutes ~10–15% of all non-Hodgkin lymphomas (NHLs) in the western world [1–3] but may represent a higher proportion (~20–30%) of NHL in Asia and South America [1, 4, 5, 6]. The current World Health Organization (WHO) classification includes at least 27 subtypes of PTCL, whose incidence varies significantly among different geographic locations and different ethnic groups [7–9]. The differences could be due to genetic predisposition, a combination of genetic and environmental factors, or predominantly environmental factors. Despite a plateau observed in the incidence of B-cell lymphoma in the USA, an increase in the incidence of PTCL has been noted in recent studies [9, 10]. Whether this is due to improved diagnosis or due to epidemiological changes is not known. In general, NHL incidence increases with age and is higher in males than females, and the same pattern is also true in PTCL, with a few exceptions. Compared to B-cell lymphomas, T-cell malignancies more often relapse after chemotherapy and have shorter overall survival (OS) [11–13] (Fig. 2.1). The introduction of a number of novel therapies has done little to improve the long-term survival, as recent meta-analysis found no improvement in clinical outcome of AITL or PTCL patients in the last two decades [14–16].

The current updated edition of the WHO classification (2016 update) recognizes 7 more entities than the 2008 edition and 14 more than the 2001 edition, reflecting, in part, an improvement in the understanding of PTCL biology in the past 15 years [2, 3].

Although the major diagnostic criteria are the pathological and immunophenotypical characteristics, recent genetic studies have substantially improved the accuracy of classification, and additional molecular entities have been recognized as a result of genomic studies in T-cell and NK-cell neoplasms. The major PTCL entities presenting as nodal disease include angioimmunoblastic T-cell lymphoma (**AITL**), anaplastic large cell lymphoma (**ALCL**), and a large group of cases that cannot be specifically classified with current methods and are categorized as PTCL, not otherwise specified (**PTCL-NOS**) [7, 2, 3]. Adult T-cell leukemia/lymphoma (**ATLL**) and extranodal NK/T-cell lymphoma of nasal type (**ENKTCL**) [17] are primarily extranodal tumors that are common in specific geographical regions but rare elsewhere. Our subsequent discussions will be focused mainly on the above entities, as much of the recent progress has been in these diseases. There are other less frequent PTCL entities that are mostly extranodal tumors [17], and we will describe relevant findings where available. We will also describe and discuss the recent studies on cutaneous T-cell lymphoma (CTCL), focusing on mycosis fungoides (MF) and Sézary syndrome.

2.2 T-Cell Development and Activation: An Overview

Mature T-cells can broadly be separated into two categories based on the T-cell receptor (TCR) types expressed; [18] the α-chain always pairs with β chain to form a αβ receptor in αβ T-cells, which comprise approximately 98% of mature T-cells. The remaining 2% of T-cells express the γ and δ chains of the TCR and are abundant in mucosal surfaces. These frequencies are also reflected in the incidence of the T-cell lymphoma entities, as PTCLs expressing αβ TCR are far more frequent than γδ-PTCLs.

A brief overview of human normal T-lymphocyte differentiation and activation is presented in this subsection because it is crucial for the understanding of the heterogeneity associated with PTCL and because molecular abnormalities in PTCL frequently target genes encoding proteins with important roles in normal T-cell activation. The hematopoietic stem cell (HSC) in the bone marrow differentiates to a common lymphoid progenitor (CLP) from which the entire lymphoid lineage is derived. The CLP emigrates from the bone marrow to the thymus, where it undergoes further maturation [19] through the sequential generation of functional β and α TCR chains through recombination events. As the thymocyte progresses through well-defined developmental stages, a functional TCRβ-chain and a pre-α chain (non-recombined) are synthesized in the initial stages, to form a pre-TCR with CD3 subunits γ, δ, ε, and ζ, and subsequently a mature αβ-TCR, with the replacement of the pre-α chain with a mature α chain [18]. At the end of this developmental stage, the T-cells are single positive, expressing either CD4 or CD8, which allows them to interact with MHC II or MHC I, respectively. In the thymus, T-cells undergo both positive and negative selection based on the strength of the interaction of the TCR with self-peptides bound to MHC (pMHC), so that only cells whose TCRs have a modest affinity for self pMHC survive.

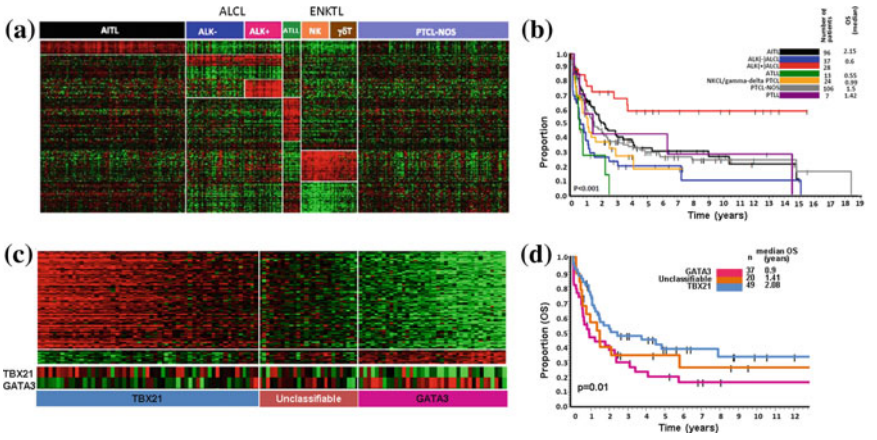

Fig. 2.2 **a** Unique gene expression signatures were identified for major Peripheral T-cell Lymphoma (PTCL) entities. Anaplastic large cell lymphoma (ALCL) and Extranodal natural killer/T-cell lymphoma (ENKTL), groups are further differentiated into ALK-positive ALCL and ALK-negative ALCL, and NK and γδ T-cell subgroups, respectively. **b** Overall survival (OS) in the different molecular PTCL subgroups. (C and D) GATA3 and TBX21 subgroups within PTCL-NOS with (C) biological and (D) overall survival differences. OS analysis of molecularly defined GATA3 and TBX21 subgroups showed a significant difference in clinical outcome (P = 0.01) (Adapted from Iqbal et al. Blood 2014)

Mature naïve αβ $CD4^+$ T-cells circulate throughout the body and enter secondary lymphoid organs—spleen, lymph nodes, and oral and gastrointestinal mucosa—to provide immunosurveillance. These quiescent T-cells express a mature TCR complex (αβ-chains, and CD3γ, δ, two ε and two ζ chains) that interacts with pMHC on antigen-presenting cells (APCs). When a T-cell finds an APC presenting a pMHC with which it can interact strongly, it is activated by recruiting a large array of signaling molecules to the T-cell-APC junction, the immunological synapse. This signaling is enhanced by ligation of co-stimulatory molecules, of which the most important in naïve T-cells is CD28. Strikingly, genes encoding many proteins important in TCR and CD28 signaling are mutated or affected by copy number abnormalities in PTCL, and, in this brief overview, we will put emphasis on these proteins (Fig. 2.2).

Upon ligation of the TCR with a cognate pMHC, the MHC II also interacts with CD4, which is constitutively associated with the tyrosine kinase LCK. LCK phosphorylates the immunoreceptor tyrosine-based activation motifs (ITAMs) on the CD3ζ chains (and to a lesser extent those on the other CD3 subunits), which allows binding by the kinase ζ-associated protein of 70 kilodaltons (ZAP-70), which is then phosphorylated and activated by LCK. Active ZAP-70 then phosphorylates linker of activated T-cells (LAT) on multiple tyrosines, allowing the recruitment of a large signaling complex that includes VAV1, ITK, SOS1 (an activator of the RAS-MEK-ERK pathway), and phospholipase Cγ1 (PLCγ1), among others. The tyrosine kinase ITK phosphorylates and activates PLCγ1, which then cleaves phosphatidylinositol (4, 5) bisphosphate to generate two important second messengers, inosine trisphosphate (IP_3) and diacylglycerol (DAG).

IP_3 binds to receptors on the endoplasmic reticulum (ER), leading to an initial phase of calcium release, which, after calcium depletion in the ER, is followed by further calcium flux due to activation of plasma membrane calcium release-activated channels (CRACs). Intracellular calcium activates several pathways; in T-cells, a particularly important effect is activation of the nuclear factor of activated T-cells (NFAT) family of transcription factors, whose targets include many important cytokines such as interleukin-2 (IL-2). DAG activates several important proteins. These include several isoforms of protein kinase C (PKC) and RASGRP1 and −2, which are responsible for an initial phase of RAS activation, which is sustained and amplified by SOS1 [20].

LCK also interacts with and phosphorylates FYN [21], the other Src family tyrosine kinase highly expressed in T-cells. FYN has important positive and negative effects on T-cell signaling. FYN-deficient mouse T-cells have severe defects in signaling induced by anti-CD3 antibodies [22], a condition in which LCK is poorly recruited to the TCR. In contrast, under normal antigenic stimulation, abnormalities in FYN-deficient T-cells are subtle. In addition to contributing to ITAM phosphorylation, the positive effects of FYN include enhancement of NF-κB activation [23] and cell adhesion to B-cells [24] through its interaction with SAP (SH3D1A) bound to SLAM family members [25], whereas it is also important in a negative feedback loop that inactivates both FYN and LCK [26].

Despite decades of experimentation, the pathways through which CD28 ligation leads to costimulation are still incompletely understood. LCK phosphorylates CD28, leading to recruitment of PI3 K, VAV1, and several other molecules, including PKCθ [27]. PI3 K is similarly recruited and activated by ligation of ICOS. In addition to stimulation of the AKT–mTOR pathway, the PIP_3 generated by PI3 K also contributes to membrane recruitment of several important proteins, including ITK, which activates PLCγ1, and PDK1, which activates not only AKT but also PKCθ, which in turn phosphorylates PDK1, increasing its stability [28]. PKCθ phosphorylates membrane-associated CARD11, which then assembles a complex with BCL10 and MALT1 (the CBM complex) [29], which, through several intermediate steps, activates nuclear factor κB (NF-κB). PKC-θ is also important in activating AP-1 [30] (heterodimers of the JUN and FOS family of transcription factors), which is essential for activating transcription of IL-2 and other genes required for T-cell proliferation.

2.3 TCR Rearrangement in the Diagnosis of PTCL

Assessment of T-cell clonality is a critical test in the diagnosis of PTCL. Each tumor arises from alterations in the progeny of a T-cell with uniquely rearranged TCR loci. Each rearrangement has distinctive *TCR* junctional regions, which can serve as a tumor-specific marker [31]. Although clonality is strongly supportive of the diagnosis of neoplasia, it is not sufficient to establish the diagnosis, which requires the integration of all relevant clinical, morphological, and immunophenotypic data. Clonal rearrangements of the *TCR* β and/or γ loci are detectable in > 90% of T-cell lymphomas [32, 33], even though some T-cell neoplasms lack

TCR expression, a common feature in ALCL. The newly defined mutations and structural abnormalities identified in PTCL (described below), can provide additional markers for the diagnosis.

2.4 Pathobiology of PTCL with Molecular Genomic Approaches

Global gene expression profiling using RNA-seq or microarray analysis has been extensively applied to lymphomas to define their oncogenic signatures as well as other characteristic features common to a group of tumors or unique to each tumor [34, 35]. More recently, additional global studies including miRNA profiling [36–38], mutation analysis, copy number alterations, and epigenetics analysis have been published [39–44]. We will discuss major findings from GEP studies of the more common PTCL entities and some rarer ones with sufficient data [11–13]. We will also discuss complementary studies that may validate or provide insight into the biological basis of these functional profiles as well as their likely impact on the diagnosis and management of PTCL patients.

2.5 Peripheral T-Cell Lymphoma, Not Otherwise Specified (PTCL-NOS)

PTCL-NOS represent the most common group of PTCL ($\sim$30%). By definition, it does not represent an entity, but a heterogeneous group of mainly nodal cases that cannot be specifically assigned to any known WHO classified entities[2, 3, 17]. Therefore, the morphologic and immunophenotypic spectrum of PTCL-NOS is broad. Some morphological variants such as lymphoepithelioid (Lennert) lymphoma have been described within PTCL-NOS, but whether these variants define unique biological entities is not clear. The diagnosis is challenging with a high frequency of discordant diagnosis among pathologists [45–47].

2.6 Gene Expression Profiling Revealed Biological Subgroups in PTCL-NOS

Major challenges in the initial GEP studies of PTCL-NOS were due to the limited number of cases studied and lack of a standardized platform [48–50]. Although several distinct clusters were identified in earlier studies, their biological significance was not clear and largely reflected characteristics of the tumor microenvironment [48–50]. These studies also reported that NF-κB activation was associated with a favorable clinical outcome and a high proliferation gene signature with a poor outcome [51, 52]

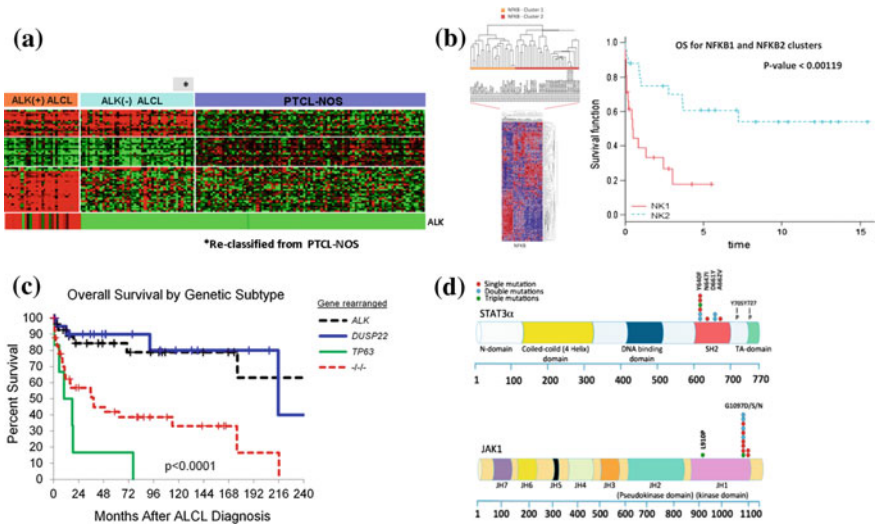

Fig. 2.3 **a** A unique gene expression signature for ALCL was identified, and then ALK-positive ALCL cases were separated from ALK-negative ALCL (reclassified PTCL-NOS cases are indicated at the top.) (Adapted from Iqbal et al. Blood 2014). **b** Unsupervised hierarchical clustering classifies ALCL into distinct groups which show significantly different overall survival (OS). (Adapted from Abate et al. Leukemia 2014) **c** OS of patients with ALCL, stratified by rearrangements of ALK, DUSP22, and TP63 and triple-negative cases (−/−/− ; lacking all 3 rearrangements) (Adapted from Parilla-Castellar et al. Blood 2014). **d** Recurrent mutations in the JAK-STAT3 pathway with JAK1 and STAT3 being the most common mutated genes (Adapted from Crescenzo et al. Cancer Cell 2015)

T_H1/T_H2-associated chemokine expression defined by immunohistochemistry was also found to be correlated with overall survival [36]. Additional studies showed an association of PTCL-NOS cases with activated $CD4^+$ or $CD8^+$ T-cells [50] and identified molecular classifiers in FFPE cases [53]. There was little consensus in these studies, which may be due to either platform differences, small sample size, or differences in the patient populations; nevertheless, overall they indicated the presence of multiple molecular subgroups within nodal PTCL-NOS [54].

Using GEP, we were able to define diagnostic molecular signatures for the major subgroups of PTCL, but about a third of the PTCL cases in this study remained uncharacterized, although a small subset of these cases showed features of αβ cytotoxic T-cells with poor clinical outcome [35, 11, 12, 13] (Fig. 2.3a, b). To further study PTCL-NOS, an international collaborative effort involving two major consortiums (LLMPP and I-PTCL) and a meta-analysis of two previously published series totaling 350 PTCL cases led to the identification of at least two novel biological subgroups. One subgroup (33% of PTCL-NOS) was characterized by high expression of GATA3 and its target genes (e.g., *CCR4*, *IL18RA*, *CXCR7*, *IK*), and the other subgroup by high expression of TBX21 and EOMES (49% of PTCL-NOS) and their known target genes (e.g., *CXCR3*, *IL2RB*, *CCL3*, *IFNγ*) (Fig. 2.3c, d). The "high GATA3" subgroup was associated with poor clinical

outcome and the lack of a prominent microenvironmental signature. It was associated with high MYC and proliferation signatures, whereas the NF-κB pathway was enriched in the TBX21 subgroup, which may likely explain the more favorable outcome associated with the NF-κB pathway activation reported in a previous study [52]. Our study also suggested that the TBX21 subgroup may contain a subset with high cytotoxic signature, which is associated with a poorer clinical outcome compared to the rest of the TBX21 subgroup. GATA3 and TBX21 are master regulators of T-cell differentiation (Th2 and Th1/cytotoxic T-cells, respectively) and may suggest the cell of origin in these subsets [11]. However, the data need to be interpreted cautiously due to the plasticity of the T-cell molded by the cytokine milieu [55]. The adverse outcome of the GATA3 subgroup is further supported by an independent study using immunohistochemistry for GATA3 expression [56]. Our study also identified a diagnostic signature that distinguishes ALK-negative ALCL from PTCL-NOS which is useful particularly in cases with high CD30 expression [11].

2.7 Genetic Studies Demonstrated Distinct Entities Within PTCL-NOS

We performed a high-resolution copy number analysis on the PTCL-GATA3 and PTCL-TBX21 subgroups, which revealed that these two subgroups showed significant differences in the profile of copy number aberrations (CNAs), and expectedly higher genomic complexity is associated with the PTCL-GATA3 subgroup. This preliminary analysis provided significant genetic evidence that these two subgroups represent distinct diseases that utilize different oncogenic pathways for tumorigenesis [57]. Efforts are being made to bring this information to clinical practice by translating the diagnostic signatures to platforms more amenable to routine clinical practice.

Scanty data are available so far regarding the mutational landscape of PTCL-NOS. Some mutations that are frequent in AITL (see below) are also detected in PTCL-NOS but at lower frequencies. A study using a limited capture panel of known mutated genes [58] reported frequent mutations in epigenetic regulators including MLL2, KDM6A, MLL, TET2, and DNMT3A. Cases showing alterations in histone methyltransferase genes (*MLL*, *MLL2*, or *KDM6A*) were associated with poor clinical outcome ($P = 0.0198$). Several recent studies have identified VAV1 fusion transcripts that have the common theme of deleting the terminal SH2 domain, thus eliminating an autoregulatory domain and possibly causing constitutive VAV1 activation [59, 60]. A small deletion affecting intron 25 extending to exon 26 of VAV1 is detected in number of PTCL cases resulting in the abnormal splicing of exon 26, again leading to a protein that is constitutively active. Thus, VAV1 activation could be a significant pathogenetic mechanism in this group of lymphomas.

2.8 Limited MicroRNA Profiling Studies in PTCL-NOS

One study [61] on microRNA profiling of 23 PTCL-NOS cases reported miRNAs that are differentially expressed compared to activated $CD4^+$ and $CD8^+$ T-lymphocytes. This study found that miR-132-3p may be an important modulator of the PTCL-NOS transcriptome, but this was a limited study, and a much more comprehensive international effort would be needed to characterize the miRNA transcriptome and understand its biological meaning.

2.9 Angioimmunoblastic T-Cell Lymphoma (AITL)

AITL represents the most common well-defined PTCL entity and accounts for about 30% of PTCL cases with unique clinical characteristics and pathological features[2, 3, 17]. Morphologically, it is characterized by a diffuse or T-zone expansion of $CD4^+$ T-cells accompanied by a proliferation of arborizing blood vessels with features of high endothelial venules. By immunohistochemistry, the majority of the neoplastic cells express two or more T-follicular helper (TFH) markers, such as PD-1, BCL6, CXCL13, CD10, ICOS, and CXCR5. Epstein–Barr virus (EBV)-infected B-cells are frequently present in the tumor microenvironment, and scattered patches of follicular dendritic cells are commonly found. There has been little clinical improvement in the past two decades, despite the introduction of novel therapies [14].

In the 2016 updated WHO classification, the subgroup of PTCL-NOS that expresses at least two T_{FH} markers, but without the typical morphology of AITL, is designated as nodal PTCL with T_{FH} phenotype [2, 17]. Moreover, a recent study suggested that this group shares not only phenotypic features with AITL, but also similar clinical features, genetic abnormalities, and molecular signatures, and based on these unifying features are likely part of the AITL spectrum [62]. It has been proposed to unify the entities of nodal PTCL with T_{FH} phenotype, follicular T-cell lymphoma, and AITL under the umbrella term of "nodal T-cell lymphomas with T-follicular helper phenotype" [2].

Cell of origin of AITL: We and others have now convincingly demonstrated that the follicular helper T-cell (T_{FH}) is the cell of origin of AITL [11, 12, 48, 63]. T_{FH} cells, located within germinal centers (GC) of lymph nodes, are essential for the development of high-affinity antibodies by driving cognate GC B-cells to proliferate and differentiate into plasma cells [64]. The GCs in AITL are often involuted or largely effaced; paradoxically, tumor cells do not show GC localization except in the rare follicular PTCL. Normal T_{FH} cells express a chemokine receptor (CXCR5) that drives their migration into B-cell follicles, bringing them into close proximity with B-cells. High affinity TCR epitopes are preferentially observed in T_{FH} populations compared to other $CD4^+$ T-cell subsets [65]. BCL6 has been identified as a master regulator of T_{FH} differentiation in murine models and has been shown to negatively regulate differentiation to other $CD4^+$ T-cell subsets [66]. It appears to also have a critical role in human

T_{FH} cells, but other transcription factors, such as MAF, are also important. Even though BCL6 and MAF are crucial for human T_{FH} development, BCL6 is infrequently detected in AITL tumor cells [67, 68], but MAF [69, 70] expression is noted in a substantial number of AITLs. The frequent lack of BCL6 expression is in contrast to the consistent expression of BCL6 in GC B-cells [71].

Initial GEP studies showed that the majority of AITLs clustered together and identified a molecular classifier for AITL, which was dominated by the tumor microenvironment, with the presence of B-cells and a complex cytokine profile in the tumor milieu. The molecular classifier also identified at least 18% of pathologically defined PTCL-NOS cases as AITL [37] (Fig. 2.3a, b). These studies also identified oncogenic pathways including the NF-κB pathway, IL-6 signaling, and the TGFβ pathway [48, 50, 72, 73] enriched in AITL. Recently, GEP on a much larger series refined the gene expression signatures for AITL [11] and reclassified 14% of PTCL-NOS cases as AITL, similar to the previous observation [37]. The validity of this reclassification was further supported by the analysis of IDH2 mutations ($R172^{K/S/T/G/M}$), which are frequent (∼33%) in molecularly defined AITL, but not in other PTCL entities [41]. In contrast, in a subset of pathologically defined AITL cases that were not classified by GEP as AITL, IDH2 mutation was infrequent (7%; 1/14) [11].

Genetic studies in AITL: Few molecular genetics studies have been reported in AITL [74], although a few cytogenetic studies [75–77] have shown recurrent trisomy-5, often co-occurring with trisomy 21. We recently performed a high-resolution aCGH study, which showed that AITL had the least abnormal genome (7%) compared to other major PTCL entities, with CN gains more frequent than CN losses. Chromosome 5 gain (15 of 38; 40%) and chromosome 21 gain (8 of 38; 21%) were the most frequent abnormalities and significantly co-occur ($p = 0.003$, Fisher's exact test). Losses were infrequent in AITL, and more focal than the pattern of the entire chromosome/arm abnormalities observed in gains [57]. Several small focal deletions showed enrichment in genes resulting in dysregulation of the PI3 K–AKT–mTOR pathway. Whether constitutive activation of this pathway is critical for maintenance of a malignant phenotype in T_{FH} cells will be crucial to determine in the future studies.

Mutation spectrum of AITL: TET2 inactivating missense or nonsense mutations or insertions/deletions (indels) have been found variably in up to 85% of AITL cases suggesting high selective pressure in AITLs for loss of TET2 function [78–80]. Mutations in other family members, TET1 and TET3, however, are not observed, despite their homology, similar functions, and the likely ability for TET2 to compensate for TET1 in knockout mice [81], even though Tet1/Tet2 double knockout mice display some defects in T_{H17} differentiation [82]. Loss-of-function TET2 mutations are expected to result in DNA hypermethylation (5mC) and a decrease in 5-hydroxymethylcytosine (5hmC) in regions of the chromosome. 5hmC may not be just a byproduct of oxidation of 5mC but may have physiological functions [83, 84]. Thus, it is important to determine the profiles of aberrant 5mC and 5hmC in AITL to gain further insight to the consequence of TET2 inactivation. TET2 protein may also recruit other proteins such as HDAC1/2 and hence may

perform functions unrelated to DNA demethylation which may also be affected by the loss of the TET protein.

IDH1 and *IDH2* encode cytosolic and mitochondrial forms of isocitrate dehydrogenase, respectively, that catalyze the interconversion of isocitrate and α-ketoglutarate (αKG). The mutations in IDH1 and IDH2 found in cancer confer a novel enzymatic activity with conversion of α-ketoglutarate to the (R)-enantiomer of 2-hydroxyglutarate ((R)-2-HG) [85, 86] with depletion of αKG and generation of a large quantity of 2-HG, which acts as an oncometabolite by competitively inhibiting α-KG-dependent dioxygenases such as histone lysine demethylases, prolyl hydroxylases, collagen prolyl-4-hydroxylases, several DNA repair and RNA modifying enzymes, and the TET family of 5-methylcytosine (5mC) hydroxylases [87]. $IDH1^{R132H}$, $IDH2^{R140Q}$, and $IDH2^{R172K}$ knock-in (KI) mouse models showed an increase in lineage-restricted hematopoietic progenitors, a decrease in BM cellularity, and extramedullary hematopoiesis, but no effect on HSC self-renewal or expansion [88–90]. As R-2-HG has a wide array of effects beyond the altering of DNA 5mC and 5hmC patterns through inhibition of TET family members [91], the functional role of these effects warrants further investigation.

There is a remarkable similarity in the mutations of epigenome modifiers (e.g., TET2, IDH2, and DNMT3A) between AITL and myeloid neoplasms [92–94]. There are, however, also striking differences in the pattern of mutations between the two diseases: (i) TET2 and IDH1 or IDH2 mutations are mutually exclusive in acute myeloid leukemia (AML) and chronic myelomonocytic leukemia (CMML) [95]; however, IDH2 mutations often co-occur with TET2 in AITL [96, 97]. (ii) IDH1 mutations are not observed in AITL [96]. Of the two recurrent IDH2 mutants ($IDH2^{R140}$ and $IDH2^{R172}$) in myeloid malignancies [85, 86, 91, 95], only $IDH2^{R172}$ is observed in AITL [98], suggesting that the more efficient production of the oncometabolite 2-HG [85, 86, 91] associated with $IDH2^{R172}$ may be crucial for T-cell transformation. (iii) There is insignificant or no overlap of $IDH2^{R172}$-related gene signatures in CMML and AITL [98]. (iv) Mutations in polycomb group (PcG) genes (e.g., EZH2) are rare in AITLs, unlike myeloid proliferative disorders.

The identification of an oncometabolite allows a new consideration in diagnosis, by a noninvasive serum test rather than by histology as recently shown in AML [99]. Recent studies have shown that specific inhibition of IDH2 mutants can reverse the abnormal production of 2-HG and has shown efficacy in preclinical and phase-1 clinical studies of AML. Interestingly, a recent case report showed the efficacy of a hypomethylating agent, 5-azacytidine, in an AITL patient with TET2 mutation [100]. Epigenetic therapies, as single agent therapy, have shown early promise with objective durable response in at least 15–30% of AITL [101]. It would be of interest to see if a combination of epigenetic and PI3 K–mTOR inhibitors could prove to be synergistic.

RHOA has a specific G17 V mutation in up to 70% of AITLs, which exclusively occurs in the background of TET2 mutations with or without IDH2 mutations [92–94]. RHOA, a small GTPase, has long been known to be necessary for T-cell development, activation, and polarization [102, 103]. However, mice with transgenic T-cell-specific expression of a bacterial toxin that inhibits RHOA function develop aggressive thymic

lymphomas [104]. A recent study has shown that $RhoA^{G17V}$ knock-in mice resulted in the spontaneous accumulation of Tfh cells in the absence of immunization, and expression of mutant $RHOA^{G17V}$ in hematopoietic progenitors from Tet2 knockout mice resulted in the specific development of AITL-like disease demonstrating an instrumental role for the $RHOA^{G17V}$ mutation in AITL transformation [105]. Unlike AITL, $RHOA^{G17V}$ mutations in ATLL do not co-occur with Tet2 mutation, suggesting a cooperative role of $RHOA^{G17V}$ and Tet2 in skewing differentiation [92]. The $RHOA^{G17V}$ mutant protein cannot bind GDP or GTP but binds strongly to guanine nucleotide exchange factors (GEFs), and the mutant acts as a dominant negative to block wild-type function, presumably by sequestering RHOA GEFs. RHOA mutant may also abnormally recruit VAV1 to the cell membrane where it may be activated. RHOA is involved in numerous intracellular processes, many through activation of two kinases, ROCK1 and −2. An important target of the ROCK kinases is PTEN [106], which is activated and, in turn, down-modulates PI3 K signaling and AKT activity. Consistent with this hypothesis, $RHOA^{G17V}$ mutation results in increased AKT activity [94].

2.10 Anaplastic Large Cell Lymphoma (ALCL)

This entity, initially called Ki-1 lymphoma, is characterized by clusters of large strongly CD30 (Ki-1)-positive anaplastic cells often involving lymph nodes. These lymphomas are predominately of T-cell lineage, but some cases with null cell phenotype and genotype have been described. Two distinct sub-entities differentiated by the expression of anaplastic lymphoma kinase (ALK) protein are recognized, which, except for the expression of ALK protein, have similar morphological and immunophenotypic features. ALK-positive ALCL has a disease-defining genetic translocation involving ALK [107] and most commonly *NPM*, generating a fusion gene encoding a chimeric protein with constitutive tyrosine kinase activity [108–110] Many additional fusion partners have since been identified, and a recent study identified a novel translocation resulting in the fusion of the *TRAF1* and *ALK* genes, and aggressive clinical course. Genomic studies identified TP53 and PRDM1 loss and the activation of NF-κB signaling in TRAF1-ALK-ALCL. ALK-positive ALCL is more common in children and young adults, accounting for 10–20% of childhood NHL and 3% of adult NHL. The 5-year OS of ALK-positive ALCL (70–86%) is superior to that of ALK-negative ALCL (30–49%). ALK-negative ALCL occurs in older patients, and, when ALCL patients are stratified according to age and/or stage, ALK-positive, and ALK-negative individuals have more similar prognosis. In the current 2016 WHO classification, ALK-negative ALCL is considered as a true entity distinct from PTCL-NOS [2], and other rarer ALCL entities including breast implant-associated ALCL and primary cutaneous ALCL are included in the new version.

GEP studies: Several genome-wide GEP studies definitively demonstrated that ALK-ALCL is a distinct molecular entity, and this lymphoma shows enrichment of a number of signatures including IRF4 and MYC signatures (also see below). Both

ALK+ and ALK-negative ALCL demonstrate low expression of genes associated with TCR signaling and high expression of *CD30* (*TNFRSF8*), *BATF3* and *TMOD1* [111].

In our initial GEP study [12] we identified an ALK + ALCL classifier including T_{H17} cell-associated molecules (IL-17A, IL-17F, and ROR-γ) and a small group of immunoregulatory cytokines/receptors regulating the STAT3 pathway [112]. These T_{H17} cell-associated molecules (IL-17F,−A, ROR-γ) were shown to be regulated by miR-135b [113]. In a subsequent larger study, we defined a signature that included all systemic ALCL; the new signature was able to identify 97% of pathologically defined ALCL cases irrespective of ALK status. The signature reclassified 11% (17 of 150) of PTCL-NOS as ALCL, which were all ALK-negative ALCL cases [111] (Fig. 2.4a). Moreover, distinct signatures distinguishing ALK-positive ALCL from ALK-negative ALCL were identified including enrichment of MYC and IRF4 target gene signatures as well proliferation and mTOR gene signatures in ALK-negative ALCL. Although ALK status is prognostic in ALCL, in a recent

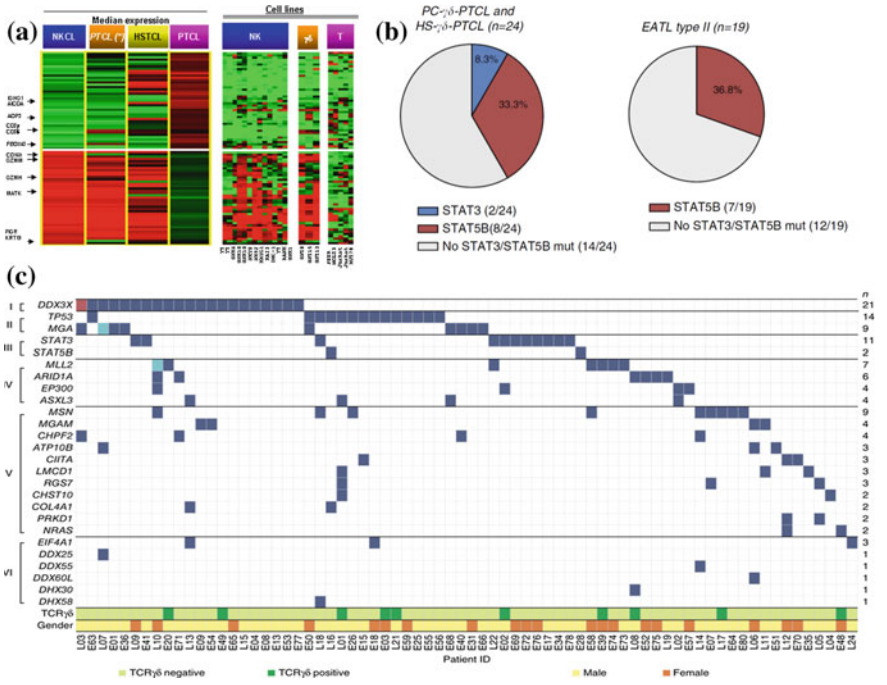

Fig. 2.4 **a** NKCLs have a gene expression signature similar to γδ-PTCLs, but distinct from cytotoxic (αβ)-PTCL and Hepatosplenic T-cell Lymphoma (HSTCL) (Adapted from Iqbal et al. Leukemia 2013). **b** STAT5B mutations are common in γδ T-cell lymphoma (Adapted from Kucuk et al. Nature Communications, 2015). **c** Whole-exome sequencing (WES) in 25 cases of NKCL and subsequent custom seq in a larger number of cases identified mutations in genes of several categories that include: an RNA helicase, DDX3X (I), tumor suppressors (II), JAK-STAT pathway (III), epigenetic modifiers (IV), other RNA helicases (VI) and other genes (V) (Adapted from Jiang et al. Nature Genetics 2015)

study, NF-κB signatures could also identify prognostic subgroups in ALCL irrespective of the ALK status [114] (Fig.2.4b).

Genetic studies in ALCL: Recent genomic studies have shown recurrent chromosomal rearrangements of genetic loci encoding *DUSP22* (30%) and *TP63 (8%)* in ALK-negative ALCLs, but not in ALK-positive ALCLs and demonstrated that ALK-negative ALCLs have more complex genomes than ALK-positive cases (Fig.2.4c). *DUSP22* and *TP63* rearrangements were mutually exclusive, and *DUSP22* rearranged cases appeared to have very favorable prognosis while *TP63* rearranged cases had a very poor outcome. Similarly, TP53 and PRDM1 losses are more common in ALK-negative than in ALK-positive ALCL and may be associated with a more aggressive course [115]. A recent comprehensive genomic study identified frequent activating, occasionally co-occurring mutations of *JAK1* and *STAT3* genes in ALK-negative ALCLs (38%), resulting in the constitutive activation of the JAK/STAT3 pathway [116]. There are more than 20 sporadic fusion transcripts with fusions involving *NFKB2* or *NCOR2* being the most common (Fig.2.4d). Some of the common mutations have been shown to activate STAT3. STAT3 activation is also central to ALK-positive ALCL where ALK kinase mediates the activation [117].

MiRNA studies in ALCL: Two studies that aimed to characterize the role of miRNA as downstream effectors of the ALK oncogenic pathway found members of the miR-17-92 clusters to be highly expressed in ALK-positive ALCL whereas miR-155 was expressed at higher levels in ALK-negative ALCL [38, 118]. Expression of the miRNA-17-92 cluster partially rescues STAT3 knockdown by sustaining proliferation and survival of ALK-positive cells. Liu et al. corroborated the high expression of the miR-17-92 cluster in primary ALK-positive ALCL and found a signature of 7 additional miRNAs that could help to distinguish ALK-positive from ALK-negative ALCL cases and an 11-miRNA signature that is useful in differentiating ALK-negative ALCL from other PTCLs. Another study showed that miR-155 was expressed more than tenfold higher in ALK-negative than ALK-positive ALCL, and miR-101 was downregulated in all ALCL model systems [119], but its forced expression attenuated cell proliferation only in ALK-positive but not in ALK-negative cell lines, suggesting different modes of ALK-dependent regulation of its target proteins.

2.11 Adult T-Cell Leukemia/Lymphoma (ATLL)

Adult T-cell leukemia/lymphoma (ATLL) is a rare mature T-cell lymphoma that is etiologically linked to infection with the human T-cell lymphotropic virus type 1 (HTLV-1). HTLV-1 infection is endemic in southwestern Japan, the Caribbean, Central and South America, the Middle East, and tropical Africa. Morphologically, ATLL is characterized by a wide spectrum of morphological appearances including variable patterns of infiltration and cell morphology. Usually, the neoplastic cells show marked nuclear pleomorphism with polylobation giving rise to the characteristic “flower cell” appearance. Clinically, the disease can be divided into the less

aggressive smoldering and chronic types and the aggressive acute and lymphomatous types. In Japan, the lifetime risk of ATLL among carriers is 6–7% for males and 2–3% for females, and malignancy typically develops many decades after infection. In addition to gag, pol, and env proteins expressed by other retroviruses, HTLV-1 encodes several other proteins, including Tax, which transcriptionally activates viral transcription and also activates several host signaling pathways, including NF-κB and AP-1 pathways, leading to T-cell proliferation. Tax has transforming activity for T-cells and can induce T-cell lymphomas in transgenic mice [120]. Despite its importance in initial immortalization of infected cells, its expression is almost completely lost in nearly all ATLL cases. The only viral protein that is always persistently expressed is a basic leucine zipper transcription factor, HBZ, encoded by a negative-strand transcript. Its transgenic expression can induce T-cell lymphomas resembling ATLL in mice. It also drives proliferation, inhibits apoptosis, and stimulates transcription of hTERT and several miRNAs such as miR-17 and miR-21 that act to disrupt genomic integrity [121]. It inhibits the acetyltransferase activity of two proteins: KAT7 (HBO1) and CREBBP (CBP) which in addition to modifying histones, also activates p53 by acetylation [122].

GEP studies: ATLL shows extensive abnormalities in gene expression, DNA methylation, and histone modifications and numerous mutations and copy number changes affecting key signaling pathways in T-cells. Gene expression studies have recently showed markedly increased expression of *t*umor suppressor in lung cancer 1 (TSLC1), CAV1, and prostaglandin D2 synthase [123]. Another study of uncultured lymphocytes from ATLL patients showed increased expression of genes linked to the cell cycle (*CDC2, cyclin B*), hypercalcemia (*RANKL, PTHLH*), tyrosine kinase signaling (*SYK, LYN*) pathways, and anti-apoptosis (*BIRC5*) [124] and identified BIRC5 as a rational clinical target in the treatment of ATLL. We also identified a unique signature for ATLL with many of the transcripts associated with the Tax viral oncoprotein [72] despite its frequent downregulation at this stage (see also below) or involved in TCR signaling but not an elaborate cytokine profile like AITL. Interestingly, CCR4 expression has been shown to be significantly associated with ATLL [11, 12], and recently, anti-CCR4 (mogamulizumab) was approved for the treatment of ATLL, PTCL-NOS, and CTCL [125, 126]. GSEA revealed the enrichment of TCR signaling genes, target genes of the transcription factor retinoic acid receptor-γ and mature $CD4^+$ T-cell signature but not Treg-related genes.

Genetic studies in ATLL: A recent large integrated study [127] involving 426 patients included mutations (2 whole genome sequencing (WGS), 35 whole-exomes sequencing (WES), 42 both; targeted sequencing, (370), copy number and structural abnormalities (426), DNA methylome (109), and transcriptome (57) analysis. An average of 7.1 mutations per Mb/sample (SNVs, insertions, or deletions) and ∼60 structural variants per case were found by WGS. Breakpoints tended to affect tumor suppressor genes and oncogenes relevant to ATLL but more frequently affected known fragile sites with multiple deletions of the *NRXN3* locus (14q31.1 fragile site) in 60% of cases. Significant focal CNAs included 26 gains, often high-level amplifications, and 50 losses, many homozygous. A total of

50 genes were found to be significantly mutated ($q < 0.1$), 13 of them in > 10% of cases. Notably, 13 of these 50 genes lie within the significant CNAs. Many of the significantly altered genes encode proteins in the Tax interactome ($p = 8 \times 10^{-18}$), suggesting that these alterations compensate for the loss of Tax expression during disease evolution.

Driver abnormalities are highly enriched in components of the TCR pathway, the most significantly affected ($p = 1.4 \times 10^{-12}$) and the NF-κB pathway. Known or suspected gain-of-function mutations or focal amplifications predominated in these pathways, the most common being in *PLCG1* (36%) and *PRKCB* (33%), which are the two most commonly mutated genes overall. *CARD11* was also frequently mutated (24%) or amplified (12%), and four cases (8% of WGS cases) had focal small internal deletion within the protein's autoinhibitory domain. Hotspot mutations of CARD11 or PRKCB enhance NF-κB activation, with even further activation when they are co-expressed, a possible explanation of the significant co-occurrence of the two mutations in ATLL. Other changes include hotspot mutations in VAV1 (18%), some of which are known to be activating by altering autoinhibitory domains and in FYN (4%), many in the C-terminal autoinhibitory region. IRF4, a transcription factor constitutively active in ATLL and a target of NF-κB, shows copy number gains in 25% of cases and is mutated (14%) at hotspots within the DNA-binding domain that are predicted to confer a gain of function. Signaling from CD28 is expected to be very frequently enhanced by several mechanisms, including focal gains (71%), which are often high-level amplifications (23%); mutations in hotspots that could increase activity; and tandem duplications leading to expression of CD28 sequences from the *CTLA4* or *ICOS* promoter and occasionally substituting the extracellular domain with that of ICOS or CTLA4; the latter binds CD80 and CD86 more strongly than CD28, resulting in stronger signaling from the retained CD28 intracellular domain.

G-protein-coupled receptors (GPCRs) involved in T-cell trafficking are also commonly mutated. Mutations in CCR4 (29%) and CCR7 (11%) almost always result in truncation of the intracellular C-terminal tail, which prevents internalization upon stimulation with ligand and thereby enhances chemotaxis. CCR4 is typically well expressed in ATLL [128, 129] and likely contributes to the frequent skin involvement in this disease [130].

Other common mutations promote evasion of immune surveillance. Over half (54%) have alterations (copy number losses or inactivating mutations) affecting MHC class I (B2 M and HLA-A and –B), cell adhesion (CD58), cell death (FAS), and immune checkpoint (PDCD1 [PD-1]). Several transcription factors with important roles in T-cells are frequently affected. Strikingly, IKZF2 (Helios) has internal deletions or inversions in 40% of cases analyzed by WGS that generate abnormal short isoforms, previously reported in ATLL [131] that can act in a dominant-negative fashion and can induce T-cell lymphoma in mice [132]. GATA3, a master regulator of T_{H2} cells, is also frequently deleted (14%) or mutated (15%), with many mutations clearly conferring loss of function. Other transcription factors commonly targeted include CEBFA, ETV6, BCL11B, and ZEB1. STAT3 is mutated in 21% of cases, and activating mutations in NOTCH1 are present in 15%

of cases. As in other cancers and PTCL subtypes, TP53 is commonly affected (18% mutation and 23% deletion), as is CDKN2A (2% mutation and 29% deletion). Alterations affecting DNA methylation (TET2, DNMT3A, and IDH2) occur, but at far lower frequencies than in AITL. Despite the low frequency of mutations in TET2 and IDH2 (8% and 1%), ATLL shows prominent CpG island (CGI) hypermethylation, and about 40% of cases showed extensive CGI hypermethylation (CpG island methylator phenotype; CIMP). The CIMP was associated with much poorer overall survival ($p = 0.002$) [127]. Among the 180 significantly hypermethylated and downregulated genes were HLA-A, −B, −C, and –E. Together with deletions and mutations, about 90% of ATLL cases had loss of MHC class I expression. Earlier studies had shown that DNA methylation, including at *CDKN2A*, was associated with disease progression, with CIMP most common in the lymphomatous type [133, 134].

Another striking global epigenetic abnormality in ATLL is enhanced Polycomb-dependent repression by trimethylation of histone3 lysine-27 (H3K27me3), affecting half of the genes in ATLL [135]. This is found even at early stages, and, in fact, lentiviral transduction of normal T-cells with Tax leads to enhanced H3K27me3 with 83% overlap between the induced peaks and the peaks found in ATLL in comparison to normal T-cells. EZH2 and other components of the Polycomb repressor complex 2 (PRC2) are considerably upregulated in ATLL, and pharmacological inhibition of EZH2 markedly induced apoptosis in ATLL cell lines [135]. Among the many downregulated genes with enhanced H3K27me3 were important tumor suppressor genes such as *BCL2L11* (BIM) and *CDKN1A* and other genes encoding proteins whose expression is characteristically lost in ATLL such as *CD7*. Notably, *KDM6B*, encoding one of the two proteins that reverse H3K27me3 modification, is itself downregulated in association with H3K27me3. This modification may help to lock in the global changes initiated by Tax, resulting in their persistence when Tax expression is lost during disease evolution [135].

2.12 Cutaneous T-Cell Lymphoma (CTCL)

CTCL is heterogeneous, and in this discussion, we will focus on mycosis fungoides (MF) and Sézary syndrome (SS), where recent studies have provided significantly more molecular data. MF is far more common than SS and primarily comprises $CD4^+$ skin-homing memory T-cells, typically with a T_{H2}-like phenotype. The disease can vary from limited cutaneous plaques and patches to skin tumors. MF with limited skin involvement has a generally favorable prognosis, but with skin tumors and high stage disease, median survival is approximately four years. SS, with generalized erythema, lymphadenopathy, and high blood tumor burden, has even worse survival. SS may develop as a progression from MF but usually arises de novo. Most molecular analyses of CTCL have been directed at advanced stages of MF and included SS.

A chronic inflammatory infiltrate appears to have an important pathogenetic role in CTCL, with malignant cells being stimulated through paracrine loops involving malignant cells, inflammatory cells, keratinocytes, and other normal constituents of the skin [136]. There is suggestive but not yet conclusive evidence that TCR stimulation by superantigens [137], in particular, from Staphylococcus aureus, is important in MF. MFs adverse effects on skin barrier function [138, 139] likely contribute to infections that result in exposure to superantigens. Autocrine and paracrine loops involving cytokines appear to be very important in CTCL, but their relative importance appears to vary with the stage of the disease. Even at early stages of MF, autocrine or paracrine IL-15 appears to be important in malignant cell proliferation and survival [140, 141] and may be responsible for constitutive STAT5 activation [142]. ZEB1 binding to sites in the promoter negatively regulates IL-15 transcription. Methylation of the region of the promoter containing these sites [143] may enhance IL-15 expression, as would the frequent deletion or mutation of ZEB1 found in CTCL (see below). Transgenic expression of IL-15 in T-cells in mice leads to a spontaneous CTCL resembling the human disease [143]. In SS, JAK1, JAK2, and STAT3 are consistently constitutively active [144], perhaps due to autocrine IL-21 secretion [145]. There is evidence that several other cytokines function as autocrine or paracrine growth factors in CTCL. These include TSLP [146, 147], IL-13 [148], IL-16 [147], and IL-32 [149, 150] Perhaps due to aberrant STAT5 activation, lymphotoxin-α (LTA) is expressed in CTCL [151] and acts as an autocrine factor through its receptor, TNF receptor 2, encoded by *TNFRSF1B*, which, as noted below, has gain-of-function mutations and focal copy gains in CTCL.

Gene expression studies in CTCL: Numerous studies have compared the gene expression profiles (GEPs) of various CTCL subtypes to those of normal T-cells, normal skin, and inflammatory skin conditions. SS cells commonly express several genes not normally expressed in T-cells, including *TWIST1*, *PLS3* (plastin 3), and two NK-cell markers, *NCR1* (NKp46) and *KIR3DL2* [152]. *TWIST1* is also expressed in many cases of MF, especially in advanced stages. Aberrant DNA hypomethylation appears to play a role in inappropriate TWIST1 and PLS3 expression. [153] A recent study using RNA-seq compared SS to normal $CD4^+$ T-cells and found a total of 345 transcripts to be significantly upregulated in SS. Gene set enrichment analysis showed the upregulated genes to be enriched in only a few canonical pathways, including cell cycle control, MYC transcriptional activation, immune system regulation, and chemokine signaling. Several genes with critical roles in TCR, cytokine, and chemokine signaling are strongly upregulated ($\geq$ 5x). These include *CD3G*, *RAC2*, *PRKCQ* (*PKCθ*), and *HRAS* (TCR signaling); chemokine receptors *CCR4* and *CCR8*; *IL6R*; and *IL2RG*. *IL2RG* encodes the IL-2 receptor common gamma chain, which is a subunit of six cytokine receptors including receptors for IL-15 and IL-21, which are important autocrine factors in CTCL, as described above. Among upregulated transcripts of transcription factors is *TOX* ($\sim$19-fold increase), which has been suggested as a specific biomarker for MF and SS. There is evidence for a pathogenic role for TOX in CTCL by downregulating cell cycle inhibitory proteins CDKN1B and –C [154], as well as RUNX [155], which may act as a tumor suppressor gene in CTCL [156].

Genetic abnormalities: Many early studies identified individual mutated genes and studied copy number abnormalities at low resolution or in a limited number of patients, and demonstrated that CNAs found in CTCL are shared with other PTCLs, especially adult T-cell leukemia/lymphoma (ATLL), which often also shows homing to the skin. In recent years, several studies have performed WES and high-resolution copy number analysis on large numbers of patients [157–160]. The frequencies of the various abnormalities varied among the studies, sometimes considerably, probably due to the considerable heterogeneity of the disease; nevertheless, most of their results were very similar. About three-quarters of single nucleotide variants (SNVs) in most SS cases are C-to-T transitions, which mainly fall into two mutations signatures—one from spontaneous deamination at CpG dinucleotides, associated with age, and a second associated with ultraviolet-B light exposure. The presence of the latter in SS suggests that the disease may originate in skin-resident memory T (T_{RM}) cells. In addition to SNVs, SS cases show large numbers of structural abnormalities. One study [159] of six SS cases by WGS found an average of 168 abnormal junctions per case due to structural alterations. Although no recurring abnormalities were found, 42 potential fusion genes were identified, several of which appeared likely to have a pathogenetic impact. Many of the genes most commonly found deleted or deleteriously mutated in SS are also commonly lost in many other tumors. Loss of 17p occurs in ~40% of cases, and, including small deletions at 17p13.1, *TP53* is deleted in 50% or more of SS cases. In addition, mutations are also common (24% in one report). Deletions at 9p21.3 that include *CDKN2A* occur in ~50% of cases and are often homozygous; mutations also occasionally occur. Loss of CDKN2A and TP53 are expected to confer resistance to apoptosis and cellular senescence and enhance proliferation and genomic instability. Other deletions that appear to be driven by the loss of cell cycle regulators include deletion at 13q14.2 (*RB1*) and 12p13.1 (*CDKN1B*). An apoptosis regulator that is commonly deleted or mutated is *FAS* (10q23.3, which also includes *PTEN*). Loss of FAS is expected to interfere with activation-induced cell death (AICD), an important homeostatic mechanism in T-cells.

Genes involved in chromatin remodeling are frequently affected. A focused deletion on 1p36.1 includes *ARID1A*, which also shows a mutation in ~10% of cases. Together, ~40–60% of cases have either deletion or mutation. ARID1A is a targeting subunit of SWI/SNF chromatin-remodeling complexes, which can move nucleosomes along DNA. ARID1A is deleted or mutated in many other tumor types. In a colon cancer model, loss of ARID1A led to lost or decreased H3K27 acetylation and loss of other SWI/SNF components at most enhancers, often with associated decreased expression of the associated genes [161]. Intermediate effects were seen with heterozygous loss. ARID1A also has a role in DNA repair, and its loss sensitizes cells to DNA damage [162], and in deleted cells, inhibitors of the DNA damage checkpoint kinase ATR are synthetically lethal [163]. *ARID5B* is also frequently (~40%) included in deletions within 10q and *ARID3A* in deletions of distal 19p [159]. Other SWI/SNF components are also frequently affected by deletions. In particular, *SMARCC1* at 3p21.31 was included in deletions of < 4 Mb

in 21% of tumors. Deletions or mutations affecting ARID1A, ARID5B, or SMARCC1 occurred in 61% of cases.

Other genes mutated in CTCL also have roles in enhancer function. For example, mutations in MLL2, MLL3, and MLL4 (KDM2D, −C, and B) occur in SS although the frequencies vary considerably among reports; for example, MLL3-mutant SS cases vary between 1 of 25 (4%) [158] to 39 of 66 (59%) [159]. The MLL family catalyzes mono-, di-, and trimethylation of histone H3 lysine 4 and seems to be particularly important in monomethylation at enhancers [164, 165], which is associated with enhancer activity. Other chromatin regulators mutated in SS include BRD9, CHD3, and CREBBP. Alterations affecting DNA methylation are also common in CTCL. Focal deletions at 2p23.3, sometimes homozygous, likely target de novo DNA methyltransferase DNMT3A in ∼20% of SS [158]; another report found 37.5% of cases with DNMT3A deletions in CTCL [157]. Deleterious mutations also occur. Mutations and deletions also occur in TET family genes, including TET2 [158].

Another commonly deleted gene with a broad effect on transcription is *NCOR1* on 17p, with deletions in almost half of SS cases. Although 17p also includes *TP53*, NCOR1 mutations, including nonsense and frameshift mutations, were found in 15% of SS cases, often together with deletion of the other allele, suggesting a pathogenetic role [159]. NCOR1 interacts with a large number of transcription factors and recruits histone deacetylases (HDACs) to repress transcription. Several transcription factors have either activating or inactivating alterations. In addition to *TP53*, one of the most commonly deleted genes is *ZEB1*, on 10p, which was reported to be deleted in 36% of SS cases and to have mutations in ∼10%, half of them frameshifts. ZEB1 is a candidate TSG in ATLL, and ZEB1 KO mice develop $CD4^+$ T-cell lymphoma [166]. ZEB1 is a transcription factor that usually represses, but can activate transcription, and binds to some E-box sites in competition with E2A (TCF3). Among the genes repressed by ZEB1 are *BCL6* [167], *IL2* [168], and *IL15*. [143] Gain-of-function mutations in STAT3 and STAT5B and JAK1 and JAK3 are found occasionally in SS, altogether occurring in ∼10% of cases. In addition, STAT3, −5A, and −5B are on chromosome 17q, which is very frequently gained in CTCL. Deletions in 10q frequently include *NFKB2*, which encodes the NF-κB inhibitory subunit p100. In the noncanonical pathway, the C-terminus of p100 is proteolytically removed, yielding a p52 subunit, which, as a heterodimer with RELB, activates a subset of NF-κB target genes. In one study, 10% of CTCLs had 10q deletions causing C-terminal truncation of NFKB2 [157], mimicking natural activation through the noncanonical pathway; such truncations in CTCL had been reported 20 years before [169, 170]. Several other mechanisms contribute to NF-κB activation in CTCL. TCR-induced NF-κB activation involves recruitment and phosphorylation of a CARD11-BCL10-MALT1 complex by PKCθ. Activating mutations in CARD11 are found in CTCL (6% in one study [159]). Focal gains of *PRKCQ*, encoding PKCθ, are also frequent. Focal deletions, sometimes homozygous, of the negative feedback regulator *TNFAIP3* are common [29, 157]. A recurrent point mutation in *TNFRSF1B*, encoding TNFR2, was identified in 5% of CTCL and SS cases [171]. This mutation was shown to result in enhanced

activation of the noncanonical NF-κB pathway. Focal copy gains of the gene also occur.

Other alterations that are expected to have broader effects on signaling pathways include point mutations in CD28 and occasional partial tandem duplications that result in CTLA4-CD28 fusion, resulting in enhanced co-stimulatory signaling. Mutations in *PLCG1*, encoding phospholipase C γ1, have been reported at various frequencies, often ∼10%. Some of the recurring abnormalities have been shown to confer a gain of function. PLCγ1 generates two critically important second messengers, inosine trisphosphate (IP3), which induces calcium release from the ER, and diacylglycerol (DAG), which activates several pathways in T-cells, including the RAS-ERK and NF-κB pathways (Fig. 2.1). Notably, the RAS-ERK pathway can also be activated by occasion gain-of-function mutations in NRAS and KRAS and MAPK1 (ERK2) in CTCL.

miRNA expression in CTCL: Several studies of miRNA expression in CTCL tumor cells from various stages of the disease have been reported [172–174]. Different stages appear to show different patterns of miRNA expression. In SS, the most strikingly upregulated miRNAs are miR-214 and miR-199a-5p and −3p (∼50, 40 and tenfold), generated from the same primary RNA, which is upregulated due to aberrant TWIST1 expression. The miRNA cluster has been shown to promote cell survival in CTCL cell lines [175]. MiR-155 is upregulated even in early-stage MF, and miR-21 is upregulated in more advanced stages [143]. Both miRNAs have clear oncogenic functions.

2.13 ENK/T-Cell Lymphomas

NK/T-cell lymphoma comprises 1–2% of all NHL and 10% of PTCL [7]. The vast majority of cases present as an extranodal lymphoma characterized by vascular damage and destruction, prominent necrosis, cytotoxic phenotype, and the consistent presence of the EBV genome in tumor cells. This lymphoma has a higher incidence in Asia [7] and Central and South America and there is an increased incidence in the US due to changes in the demographic of the population [176, 177]. Except for localized nasal or paranasal disease, the prognosis is unfavorable, and most patients succumb to their disease.

Although ENKTCL is strongly associated with EBV, the role of the virus in the etiology of the disease is unclear. In addition, rare cases and NK-cell lines without EBV have been reported [178–182]. The tumor cells typically show a viral latency II pattern with expression of LMP1, LMP2, EBERs, and EBNA1. The expression of LMP1 may be significant as it is the main transforming protein in B-lymphoblastoid cell lines [183] and can activate both the canonical and alternative NF-kB pathways. EBV has been reported to produce some microRNAs from two primary transcripts from the *BART* and the *BHRF1* loci [184, 185]. Only the BART locus associated miRNAs are expressed with type I or II latency, and there is evidence that at least some of these miRNAs promote transformation in

B-lymphocytes [186]. A recent report [187] suggests that miR-BART20-5p and miR-BART8 may repress the IFN-STAT1 pathway with decreased expression of TP53 in ENKTCL. The expression profile and implications of these miRNAs in ENKTCL pathogenesis warrant further investigation [188].

GEP studies on ENKTCL identified unique signatures with the majority contributed by the neoplastic cells, and a classifier has been derived (Fig. 2.5a). Interestingly, this classifier also identified a set of γδ-PTCLs both in the ENKTCL and in cases initially classified as PTCL-NOS. These γδ-PTCLs expressed transcripts associated with the T-cell receptor (TCR)/CD3 complex consistent with their T-cell lineage. They were very similar to NK-cell tumors by GEP but were distinct from cytotoxic (αβ)-PTCL indicating derivation from an ontogenically and functionally distinct subset of γδ T-cells (Fig. 2.5). The platelet-derived growth factor receptor (PDGFR) signaling pathway has been reported to be activated in ENKTCL, and the expression of phosphorylated PDGFRα has been confirmed by immunohistochemistry. If this is a clinically important pathway, it is possible that imatinib could be an effective treatment. GEP studies also revealed activation of the NOTCH pathway, and tumor cell lines with NOTCH pathway activation were highly sensitive to γ-secretase inhibitors (Fig. 2.6) [189, 190].Aurora kinase A (AURKA) is frequently upregulated in ENKTCL, and NK-cell lines are highly sensitive to AURKA inhibitors. In addition to being an important regulator of mitosis, AURKA also downregulates the TP53 pathway, with an increase in survivin (BIRC5) expression [13]. The frequent angiocentric and angiodestructive feature of the tumor is expected to produce hypoxia and thereby activation of hypoxia-induced factors (HIFs). Indeed, activation of the HIF1α pathway is observed in GEP studies and may promote tumorigenesis and angiogenesis. These findings provide a rationale for further study of inhibitors to all these pathways as novel therapeutic agents in NK-cell malignancies.

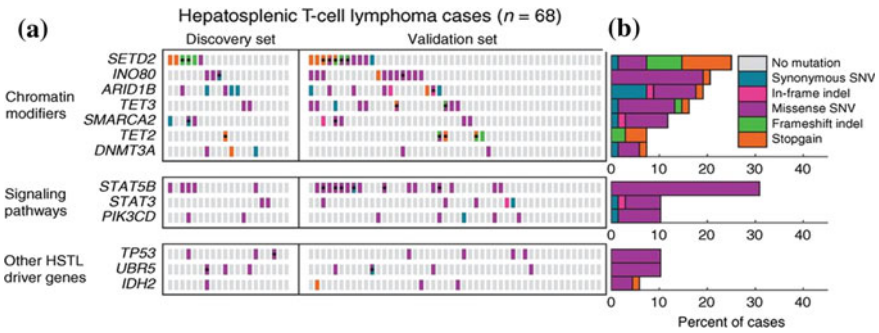

Fig. 2.5 Mutated genes in Hepatosplenic T-cell Lymphoma patients (**a**). Percentage of cases and types of mutations affected per gene (**b**). Every box represents the mutation status of a patient for a particular gene and black dots indicate more than one mutation in that gene, with boxes split to show the different types of mutations affecting that gene (Adapted from McKinney et al. Cancer Discovery 2017)

Fig. 2.6 Mutations in EATL patients (**a**) and percentage of cases and types of mutations affected per gene (**b**). Every box represents the mutation status of a patient for a particular gene and black dots indicate more than one mutation in that gene, with boxes split to show different types of mutations affecting that gene (Adapted from Moffitt et al. J Exp Med 2017)

Genetic studies in ENKTCL: Cytogenetic information on ENKTCL is limited, but some studies on chromosomal copy number changes and loss of heterozygosity (LOH) have been reported [189–194]. A number of frequent gains and losses including gains of 1q21-q44 and losses of 6q21 and 17p11-p13 were detected. The minimal common region of del 6q21 includes *PRDM1, ATG5, AIM1*, and *HACE1*. Additional studies have found inactivating mutations affecting PRDM1 in cell lines and infrequently in patient samples. In contrast, DNA methylation that inhibits the transcription of this gene is frequently detected. In vitro functional studies also indicate that *PRDM1* is a tumor suppressor gene in ENKTCL [195, 196]. There is also evidence implicating HACE [197]; an E3 ubiquitin ligase reported to be a tumor suppressor gene in other tumors [198]. The 17p deletion includes the *TP53* gene which has also been found to be frequently mutated in ENKTCL [199]. It is interesting that EBNA1 has been found to decrease TP53 expression, probably through the interruption of the interaction of USP7 (HAUSP) with TP53. These observations, together with the possibility of decreased TP53 expression due to miR-BART20-5p and 8, indicate that the TP53 pathway is likely to be impaired in most ENKTCL lymphomas through diverse mechanisms [200–202].

Several important genes have also been found to be frequently methylated such as *TP73* and *SHP1* [203, 204]. TP73 is a member of the TP53 family that may regulate a similar set of target genes as TP53, although it may also have functions other than that of a transactivator. [205, 206]. *SHP1* is one of the major negative regulators of NK-cell activation [207] through dephosphorylation of phosphotyrosines in activated receptor/adaptor. In addition, SHP1 also regulates STAT3 activation in several systems although the exact mechanism has not been elucidated [208–212]. Thus, SHP1 loss may contribute, similar to the loss of SOSC6 and other negative regulators, to the aberrant activation of the JAK/STAT3 pathway (see below). By genome-wide methylation analysis, we found frequent prominent global hypermethylation in ENKTCL and detected additional potentially important methylated loci, including some that have been previously reported to be methylated or inactivated by mutation in other tumors or are known tumor suppressor genes. These include BIM, a crucial pro-apoptotic BH3-only protein; SOCS6, an inhibitor of the JAK/STAT pathway; *DDX3X*; and *DAPK1* [43]. One interesting finding is the frequent methylation of *ASNS*, encoding asparagine synthetase. Its inactivation may explain the sensitivity of the tumor cells to asparaginase treatment [213].

FAS have been reported to be mutated or deleted in ENKTCL [214, 215] which may help to overcome the fratricidal function of NK-cells. Also, survivin (BIRC5), an inhibitor of apoptosis, has been reported to be overexpressed in ENKTCL, probably through TP53 inactivation. These changes, together with *BIM* methylation and upregulation of BCLXL and BCL2 through STAT3 or STAT5B activation, represent some of the mechanisms for ENKTCL to resist apoptosis.

The STAT3 pathway is frequently activated in ENKTCL. This may be achieved through autocrine/paracrine activation of STAT3 via cytokine receptors [216]. Inactivation of negative regulators may play a role as noted above; however, STAT3 mutations affecting the SH2 domain are one of the most frequent mutations (Fig. 2.5b) [213]. These mutations may prolong and enhance the activation of STAT3, which may be particularly relevant when cytokine concentrations are suboptimal [213]. These STAT3 mutants may also promote tumor development through the production of tumor-promoting inflammation and an immunosuppressive tumor microenvironment as a result of the production of cytokines such as VEGF and IL-10 [217–219]. There were two reports of frequent JAK3 mutations in ENKTCL [220, 221]. However, other studies failed to confirm such a high frequency [213, 222]. As STAT3 is activated by JAK kinases, JAK inhibitors are expected to suppress tumor proliferation/survival, and this is indeed observed both for wild-type and mutant cell lines [213].

A recent mutation analysis using whole exome sequencing and subsequently more focused sequencing has described the mutational landscape of ENKTCL [223] (Fig. 2.5c). Interestingly, the most frequent mutations involved *DDX3X,* an RNA helicase that has been found to be recurrently methylated as well [43]. The mutants have reduced RNA helicase activity, but the precise roles of DDX3X in the pathogenesis of ENKTCL need further investigation. This study also confirmed the frequent *TP53* and *STAT3* mutations and reported mutations affecting epigenetic

modifiers. Two other studies have reported frequent inactivating BCOR mutations [224, 225].

Hepatosplenic T-cell lymphoma (HSTL): HSTL is a rare entity mostly derived from γδ T-cells, and the disease is usually fatal. It occurs predominantly in young male adults and may arise in the setting of chronic immune suppression such as in solid organ transplant recipients or patients treated with azathioprine and infliximab for Crohn's disease. Morphologically, HSTL typically presents with intermediate-sized T-cells that preferentially infiltrate the liver, spleen, and bone marrow in a sinusoidal pattern. CD4 and CD8 are frequently absent in the gamma–delta expressing form of the tumor. GEP studies on HSTL demonstrated that irrespective of TCR cell lineage, these lymphomas share unique gene signatures and in general form a distinct hierarchical cluster, but with closer association with ENKTCL than other αβPTCLs (Fig.2.3) [13]. The differentially expressed transcripts reflected the characteristic anatomical (liver and spleen) distribution of the neoplastic cells, with high expression of metabolic and B-cell-related genes, mainly from stromal components. Overall, there were differences in the expression of cytotoxicity genes compared with NKCL and also other non-HS γδ PTCLs [226]. No significant differential expression of KIR or KLR family members was observed between HSTCL and other γδ-PTCL in this study. [226] Genomic profiles confirm frequent recurrent isochromosome 7q and trisomy 8 in HSTL [227]. Despite the rarity of this disease, a comprehensive genomic study of HSTL identified frequent mutations in chromatin-modifying genes (*SETD2*, *INO80*, and *ARID1B*) affecting 62% of cases, and also in *STAT5B* (31%), *STAT3* (9%), and *PIK3CD* (9%). This study also demonstrated that *SETD2* acts as a tumor suppressor gene in HSTCL [44] (Fig. 2.5).

Intestinal T-cell lymphoma: Enteropathy-associated T-cell lymphoma (EATL) defines a primary intestinal tumor derived from intestinal intraepithelial lymphocytes (IEL), with a variable abundance of large lymphoid cells. It accounts for approximately 5% of PTCL. The neoplastic cells express the mucosal homing receptor CD103 characteristic of IEL and are usually $CD3^+$ $CD5^-$ $CD4^-$ $CD8^-$ αβ T-cells with an activated cytotoxic profile and frequent co-expression of CD30. This tumor is associated with gluten sensitivity and enteropathy (celiac disease) and is, therefore, prevalent in people of Northern European descent. Type II EATL, characterized by a monomorphic proliferation of medium-sized cells, is more prevalent in Asia, and is not associated with celiac disease. The neoplastic cells are usually $CD3^+$ $CD5^-$ $CD7^+$ $CD4^-$, $CD8^+$ $CD56^+$, and more commonly $CD20^+$. The majority of the cases are of γδ origin and about a third of the cases have mutation of STAT5B similar to HSTCL [213]. Type II EATL has been reclassified as monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL). A recent genetic study identified *SETD2* as the most frequently (32%) mutated gene in EATL (32% of cases) and the JAK-STAT pathway as the most frequently mutated pathway, with frequent mutations in *STAT5B, JAK1*, *JAK3*, *STAT3*, and *SOCS1*. EATL and MEITL shared mutations in *KRAS*, *TP53*, and *TERT* and had overlapping genetic alterations indicating shared mechanisms underlying their pathogenesis [228] (Fig. 2.6).

2.14 The Expanding Scope of Genomics for Therapeutic Opportunities in PTCLs

Recent genomics studies have significantly improved our understanding of the pathogenesis and biology of the major PTCL entities and even some rare ones such as HSTCL and EATL [35]. More and more agents that specifically target biologic pathways are now becoming available for clinical studies. It is possible to rationally design clinical trials in which treatment cohorts are stratified according to molecular profiling defined criteria. This approach will test the feasibility of personalized treatment based on agents specifically targeting genetic abnormalities or oncogenic pathways found in the tumor.

GEP studies can help elucidate oncogenic pathways in different types of cancers [229, 230] which may suggest novel therapeutic targets. An example of this comes from the profiling studies of DLBCL, in which the ABC and PMBL subgroups of DLBCL showed an increased expression of target genes of the transcription factor NF-κB [229, 231, 232]. Davis et al. [229] demonstrated constitutive activation of NF-κB in ABC-derived cell lines, which underwent apoptosis when the NF-κB pathway was inhibited. Several NF-κB inhibitors are currently available and could be tested in clinical trials. Bortezomib (a proteasome inhibitor that also has NF-κB inhibitory activity) has demonstrated some early promise in the treatment of PTCL [233]. Another known drug for this pathway, CEP-18770, has a strong antiangiogenic activity and potently represses RANKL-induced osteoclastogenesis [234]. We have recently demonstrated differential NF-κB activation in T-cell lymphomas, particularly in AITL [72], and this class of drugs may be particularly effective in AITL. Since the microenvironment and angiogenesis are important particularly in AITL, lenalidomide, an angiogenesis inhibitor and immune modulator may be a potential agent for future trials. Clinical grade epigenetic modifiers are being tested in several diseases and could potentially prove synergistic with other drugs in AITL.

Another possible target is SYK, a receptor-associated tyrosine kinase which is expressed in 94% of all PTCL [235]. In vitro studies have demonstrated the efficacy of a small molecule SYK inhibitor (R402) in cell lines, which induced apoptosis and growth inhibition of the cells [236]. PDGFRA is a member of the vascular endothelial growth factor (VEGF) receptor family, and a recent study indicates a high level of PDGFR subunit expression in PTCL-NOS cases, including downstream activation of STAT1, STAT3, and STAT5 transcription factors in primary tumor samples [237]. Notably, PDGFR interacts with the CD3/TCR and CD28 signaling through SH2-binding proteins such as GRB2 and their downstream targets (reviewed in [238]).

The JAK/STAT3 or −5B pathways are often aberrantly activated in PTCL and ENKTCL and are a potential target for therapy. JAK1/2 and JAK3 inhibitors are already in the clinics for myeloid disorders and may be tested for their efficacy in diseases with JAK/STAT activation. Some of the mutations may aberrantly activate the TCR signaling pathway such as the frequent gain-of-function mutations in

PLCγ1, which is important for calcium flux and RAS pathway activation. Mutations or other changes affecting VAV1, CD28, PI3 K/AKT/mTOR, and occasionally the RAS pathway are also observed and potentially targetable. We are entering an exciting era with tremendous potential to improve the outcome of patients with T- and NK-cell lymphomas employing single agents or combinations of targeted agents. Further studies are needed to improve our understanding of these rather uncommon tumors so that even more effective and precise targets can be identified for future clinical trials. As these diseases are uncommon or even rare, national or international collaborative efforts are critical to advance our objectives.

References

1. Rudiger T, Weisenburger DD, Anderson JR et al (2002) Peripheral T-cell lymphoma (excluding anaplastic large-cell lymphoma): results from the Non-Hodgkin's Lymphoma Classification Project. Ann Oncol 13(1):140–149
2. Swerdlow SH, Campo E, Pileri SA et al (2016) The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 127(20):2375–2390
3. Swerdlow SH, Campo E, Harris NL et al (2008) WHO classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th edn
4. Bellei M, Chiattone CS, Luminari S et al (2012) T-cell lymphomas in South america and europe. Rev Bras Hematol Hemoter. 34(1):42–47
5. Arora N, Manipadam MT, Nair S (2013) Frequency and distribution of lymphoma types in a tertiary care hospital in South India: analysis of 5115 cases using the World Health Organization 2008 classification and comparison with world literature. Leuk Lymphoma 54 (5):1004–1011
6. Perry AM, Diebold J, Nathwani BN et al (2016) Non-Hodgkin lymphoma in the Far East: review of 730 cases from the international non-Hodgkin lymphoma classification project. Ann Hematol 95(2):245–251
7. International peripheral T-cell and natural killer/t-cell lymphoma study (2008) pathology findings and clinical outcomes. J Clin Oncol 26(25):4124–4130
8. Perry AM, Diebold J, Nathwani BN et al (2016) Non-Hodgkin lymphoma in the developing world: review of 4539 cases from the International Non-Hodgkin Lymphoma Classification Project. Haematologica 101(10):1244–1250
9. Adams SV, Newcomb PA, Shustov AR (2016) Racial Patterns of Peripheral T-Cell Lymphoma Incidence and Survival in the United States. J Clin Oncol 34(9):963–971
10. Wang. SS, Vose. JM (2103) Epidemiology and Prognosis of T-Cell Lymphoma. Springer Science, New York
11. Iqbal J, Wright G, Wang C et al (2014) Gene expression signatures delineate biological and prognostic subgroups in peripheral T-cell lymphoma. Blood 123(19):2915–2923
12. Iqbal J, Weisenburger DD, Greiner TC et al (2010) Molecular signatures to improve diagnosis in peripheral T-cell lymphoma and prognostication in angioimmunoblastic T-cell lymphoma. Blood 115(5):1026–1036
13. Iqbal J, Weisenburger DD, Chowdhury A et al (2011) Natural killer cell lymphoma shares strikingly similar molecular features with a group of non-hepatosplenic gammadelta T-cell lymphoma and is highly sensitive to a novel aurora kinase A inhibitor in vitro. Leukemia 25 (2):348–358
14. Xu B, Liu P (2014) No survival improvement for patients with angioimmunoblastic T-cell lymphoma over the past two decades: a population-based study of 1207 cases. PLoS ONE 9(3):e92585

15. Croziera JA,, Shera T, Yangb D et al (2015) Persistent disparities among patients with T-cell Non-Hodgkin Lymphomas and B-cell Diffuse Large Cell Lymphomas over 40 years: a seer database review. Clin Lymphoma Myeloma Leukemia
16. Briski R, Feldman AL, Bailey NG et al (2014) The role of front-line anthracycline-containing chemotherapy regimens in peripheral T-cell lymphomas. Blood Cancer J. 4:e214
17. Swerdlow SH, Elias Campo, Harris NL et al (2017) WHO classification of Tumours of the Haematopoitic and Lymphoid Tissues. Lyon, IARC Press, France
18. Germain RN (2002) T-cell development and the CD4-CD8 lineage decision. Nat Rev Immunol 2(5):309–322
19. Martin CH, Aifantis I, Scimone ML et al (2003) Efficient thymic immigration of $B220^+$ lymphoid-restricted bone marrow cells with T precursor potential. Nat Immunol 4 (9):866–873
20. Poltorak M, Meinert I, Stone JC, Schraven B, Simeoni L (2014) Sos1 regulates sustained TCR-mediated Erk activation. Eur J Immunol 44(5):1535–1540
21. Filipp D, Zhang J, Leung BL et al (2003) Regulation of Fyn through translocation of activated Lck into lipid rafts. J Exp Med 197(9):1221–1227
22. Sugie K, Jeon MS, Grey HM (2004) Activation of naive CD4 T cells by anti-CD3 reveals an important role for Fyn in Lck-mediated signaling. Proc Natl Acad Sci U S A. 101 (41):14859–14864
23. Cannons JL, Yu LJ, Hill B et al (2004) SAP regulates T(H)2 differentiation and PKC-theta-mediated activation of NF-kappaB1. Immunity 21(5):693–706
24. Cannons JL, Qi H, Lu KT et al (2010) Optimal germinal center responses require a multistage T cell: B cell adhesion process involving integrins, SLAM-associated protein, and CD84. Immunity 32(2):253–265
25. Latour S, Roncagalli R, Chen R et al (2003) Binding of SAP SH2 domain to FynT SH3 domain reveals a novel mechanism of receptor signalling in immune regulation. Nat Cell Biol 5(2):149–154
26. Yasuda K, Nagafuku M, Shima T et al (2002) Cutting edge: Fyn is essential for tyrosine phosphorylation of Csk-binding protein/phosphoprotein associated with glycolipid-enriched microdomains in lipid rafts in resting T cells. J Immunol. 169(6):2813–2817
27. Kong KF, Yokosuka T, Canonigo-Balancio AJ, Isakov N, Saito T, Altman A (2011) A motif in the V3 domain of the kinase PKC-theta determines its localization in the immunological synapse and functions in T cells via association with CD28. Nat Immunol 12(11):1105–1112
28. Kang JA, Choi H, Yang T, Cho SK, Park ZY, Park SG (2017) PKCtheta-Mediated PDK1 Phosphorylation Enhances T Cell Activation by Increasing PDK1 Stability. Mol Cells 40 (1):37–44
29. Qiao Q, Yang C, Zheng C et al (2013) Structural architecture of the CARMA1/Bcl10/MALT1 signalosome: nucleation-induced filamentous assembly. Mol Cell 51(6):766–779
30. Isakov N, Altman A (2002) Protein kinase C(theta) in T cell activation. Annu Rev Immunol 20:761–794
31. Gazzola A, Mannu C, Rossi M et al (2014) The evolution of clonality testing in the diagnosis and monitoring of hematological malignancies. Ther Adv Hematol. 5(2):35–47
32. van Dongen JJ, Langerak AW, Bruggemann M et al (2003) Design and standardization of PCR primers and protocols for detection of clonal immunoglobulin and T-cell receptor gene recombinations in suspect lymphoproliferations: report of the BIOMED-2 Concerted Action BMH4-CT98-3936. Leukemia 17(12):2257–2317
33. Szczepanski T, van der Velden VH, Raff T et al (2003) Comparative analysis of T-cell receptor gene rearrangements at diagnosis and relapse of T-cell acute lymphoblastic leukemia (T-ALL) shows high stability of clonal markers for monitoring of minimal residual disease and reveals the occurrence of second T-ALL. Leukemia 17(11):2149–2156
34. Iqbal J, Naushad H, Bi C et al (2016) Genomic signatures in B-cell lymphoma: How can these improve precision in diagnosis and inform prognosis? Blood Rev 30(2):73–88

35. Iqbal J, Wilcox R, Naushad H et al (2016) Genomic signatures in T-cell lymphoma: How can these improve precision in diagnosis and inform prognosis? Blood Rev 30(2):89–100
36. Iqbal J, Shen Y, Huang X et al (2015) Global microRNA expression profiling uncovers molecular markers for classification and prognosis in aggressive B-cell lymphoma. Blood 125(7):1137–1145
37. Iqbal J, Shen Y, Liu Y et al (2012) Genome-wide miRNA profiling of mantle cell lymphoma reveals a distinct subgroup with poor prognosis. Blood 119(21):4939–4948
38. Liu C, Iqbal J, Teruya-Feldstein J et al (2013) MicroRNA expression profiling identifies molecular signatures associated with anaplastic large cell lymphoma. Blood 122(12):2083–2092
39. Bouska A, McKeithan TW, Deffenbacher KE et al (2014) Genome-wide copy-number analyses reveal genomic abnormalities involved in transformation of follicular lymphoma. Blood 123(11):1681–1690
40. Bouska A, Zhang W, Gong Q et al (2017) Combined copy number and mutation analysis identifies oncogenic pathways associated with transformation of follicular lymphoma. Leukemia 31(1):83–91
41. Cairns RA, Iqbal J, Lemonnier F et al (2012) IDH2 mutations are frequent in angioimmunoblastic T-cell lymphoma. Blood 119(8):1901–1903
42. Guo S, Chan JK, Iqbal J et al (2014) EZH2 mutations in follicular lymphoma from different ethnic groups and associated gene expression alterations. Clin Cancer Res 20(12):3078–3086
43. Kucuk C, Hu X, Jiang B et al (2015) Global promoter methylation analysis reveals novel candidate tumor suppressor genes in natural killer cell lymphoma. Clin Cancer Res 21 (7):1699–1711
44. McKinney M, Moffitt AB, Gaulard P et al (2017) The Genetic Basis of Hepatosplenic T-cell Lymphoma. Cancer Discov 7(4):369–379
45. Laurent C et al (2017) J Clinic Oncol 35(18):2008–2017
46. Weisenburger et al (2011) Blood, 117:3402–3408
47. Bowen et al (2014) Bristish J Hematol 166:202–208
48. de Leval L, Rickman DS, Thielen C et al (2007) The gene expression profile of nodal peripheral T-cell lymphoma demonstrates a molecular link between angioimmunoblastic T-cell lymphoma (AITL) and follicular helper T (TFH) cells. Blood 109(11):4952–4963
49. Martinez-Delgado B (2006) Peripheral T-cell lymphoma gene expression profiles. Hematol Oncol 24(3):113–119
50. Piccaluga PP, Agostinelli C, Califano A et al (2007) Gene expression analysis of peripheral T cell lymphoma, unspecified, reveals distinct profiles and new potential therapeutic targets. J Clin Invest. 117(3):823–834
51. Cuadros M, Dave SS, Jaffe ES et al (2007) Identification of a proliferation signature related to survival in nodal peripheral T-cell lymphomas. J Clin Oncol 25(22):3321–3329
52. Martinez-Delgado B, Cuadros M, Honrado E et al (2005) Differential expression of NF-kappaB pathway genes among peripheral T-cell lymphomas. Leukemia 19(12):2254–2263
53. Piccaluga PP, Fuligni F, De Leo A et al (2013) Molecular profiling improves classification and prognostication of nodal peripheral T-cell lymphomas: results of a phase III diagnostic accuracy study. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 31(24):3019–3025
54. Ballester B, Ramuz O, Gisselbrecht C et al (2006) Gene expression profiling identifies molecular subgroups among nodal peripheral T-cell lymphomas. Oncogene 25(10):1560–1570
55. O'Shea JJ, Paul WE (2010) Mechanisms underlying lineage commitment and plasticity of helper $CD4^+$ T cells. Science 327(5969):1098–1102
56. Wang T, Feldman AL, Wada DA et al (2014) GATA-3 expression identifies a high-risk subset of PTCL, NOS with distinct molecular and clinical features. Blood 123(19):3007–3015

57. Heavican TB, Yu J, Bouska A, Greiner TC, Lachel CM, Wang C, Dave BJ, Amador CC, Fu K, Vose JM, Weisenburger DD, Gascoyne RD, Hartmann S, Pedersen MBJ, Wilcox R, Teh BT, Lim ST, Ong CK, Seto M, Berger F, Rosenwald A, Ott G, Campo E, Rimsza LM, Jaffe ES, Braziel RM, d'Amore FA, Inghirami G, Bertoni F, Staudt L, McKeithan TW, Pileri SA, Chan WC, Iqbal J (2016) Molecular subgroups of peripheral T-cell lymphoma evolve by distinct genetic pathways. In: 58th ASH Annual Meeting and Exposition, San Diego, CA
58. Schatz JH, Horwitz SM, Teruya-Feldstein J et al (2015) Targeted mutational profiling of peripheral T-cell lymphoma not otherwise specified highlights new mechanisms in a heterogeneous pathogenesis. Leukemia 29(1):237–241
59. Abate F, da Silva-Almeida AC, Zairis S et al (2017) Activating mutations and translocations in the guanine exchange factor VAV1 in peripheral T-cell lymphomas. Proc Natl Acad Sci U S A. 114(4):764–769
60. Yoo HY, Sung MK, Lee SH et al (2014) A recurrent inactivating mutation in RHOA GTPase in angioimmunoblastic T cell lymphoma. Nat Genet 46(4):371–375
61. Laginestra MA, Piccaluga PP, Fuligni F et al (2014) Pathogenetic and diagnostic significance of microRNA deregulation in peripheral T-cell lymphoma not otherwise specified. Blood Cancer J. 4:259
62. Dobay MP, Lemonnier F, Missiaglia E et al (2017) Integrative clinicopathological and molecular analyses of angioimmunoblastic T-cell lymphoma and other nodal lymphomas of follicular helper T-cell origin. Haematologica 102(4):e148–e151
63. Piccaluga et al (2007) Cancer Res 15, 67(22):10703–10710
64. CrottyS (2014) Immunity 41(4):529–542
65. Fazilleau N, McHeyzer-Williams LJ, Rosen H, McHeyzer-Williams MG (2009) The function of follicular helper T cells is regulated by the strength of T cell antigen receptor binding. Nat Immunol 10(4):375–384
66. Hatzi K, Nance JP, Kroenke MA et al (2015) BCL6 orchestrates Tfh cell differentiation via multiple distinct mechanisms. J Exp Med 212(4):539–553
67. Dupuis J, Boye K, Martin N et al (2006) Expression of CXCL13 by neoplastic cells in angioimmunoblastic T-cell lymphoma (AITL): a new diagnostic marker providing evidence that AITL derives from follicular helper T cells. Am J Surg Pathol 30(4):490–494
68. Miysohi et al (2012) Am J Clin Pathol 137(6):879–89
69. Bisig B, Thielen C, Herens C et al (2012) c-Maf expression in angioimmunoblastic T-cell lymphoma reflects follicular helper T-cell derivation rather than oncogenesis. Histopathology 60(2):371–376
70. Murakami YI, Yatabe Y, Sakaguchi T et al (2007) c-Maf expression in angioimmunoblastic T-cell lymphoma. Am J Surg Pathol 31(11):1695–1702
71. Iqbal J et al (2007) Leukemia 21(11):2332–2343
72. Iqbal J, Weisenburger DD, Greiner TC et al (2010) Molecular signatures to improve diagnosis in peripheral T-cell lymphoma and prognostication in angioimmunoblastic T-cell lymphoma. Blood 115(5):1026–1036
73. Grogg KL, Attygalle AD, Macon WR, Remstein ED, Kurtin PJ, Dogan A (2005) Angioimmunoblastic T-cell lymphoma: a neoplasm of germinal-center T-helper cells? Blood 106(4):1501–1502
74. Schlegelberger B, Himmler A, Godde E, Grote W, Feller AC, Lennert K (1994) Cytogenetic findings in peripheral T-cell lymphomas as a basis for distinguishing low-grade and high-grade lymphomas. Blood 83(2):505–511
75. Nelson M, Horsman DE, Weisenburger DD et al (2008) Cytogenetic abnormalities and clinical correlations in peripheral T-cell lymphoma. Br J Haematol 141(4):461–469
76. Lepretre S, Buchonnet G, Stamatoullas A et al (2000) Chromosome abnormalities in peripheral T-cell lymphoma. Cancer Genet Cytogenet 117(1):71–79
77. Lakkala-Paranko T, Franssila K, Lappalainen K et al (1987) Chromosome abnormalities in peripheral T-cell lymphoma. Br J Haematol 66(4):451–460

78. Lemonnier F, Couronne L, Parrens M et al (2012) Recurrent TET2 mutations in peripheral T-cell lymphomas correlate with TFH-like features and adverse clinical parameters. Blood 120(7):1466–1469
79. Sakata-Yanagimoto M, Enami T, Yoshida K et al (2014) Somatic RHOA mutation in angioimmunoblastic T cell lymphoma. Nat Genet 46(2):171–175
80. Odejide O, Weigert O, Lane AA et al (2014) A targeted mutational landscape of angioimmunoblastic T-cell lymphoma. Blood 123(9):1293–1296
81. Dawlaty MM, Ganz K, Powell BE, et al Tet1 is dispensable for maintaining pluripotency and its loss is compatible with embryonic and postnatal development. Cell Stem Cell 9 (2):166–175
82. Dawlaty MM, Breiling A, Le T, et al. Combined deficiency of Tet1 and Tet2 causes epigenetic abnormalities but is compatible with postnatal development. Dev Cell 24(3):310–323
83. Wu H, Zhang Y (2011) Mechanisms and functions of Tet protein-mediated 5-methylcytosine oxidation. Genes Dev 25(23):2436–2452
84. Hill PW, Amouroux R, Hajkova P (2014) DNA demethylation, Tet proteins and 5-hydroxymethylcytosine in epigenetic reprogramming: an emerging complex story. Genomics 104(5):324–333
85. Losman JA, Looper RE, Koivunen P et al (2013) (R)-2-hydroxyglutarate is sufficient to promote leukemogenesis and its effects are reversible. Science 339(6127):1621–1625
86. Koivunen P, Lee S, Duncan CG et al (2012) Transformation by the (R)-enantiomer of 2-hydroxyglutarate linked to EGLN activation. Nature 483(7390):484–488
87. Li Z, Cai X, Cai CL et al (2011) Deletion of Tet2 in mice leads to dysregulated hematopoietic stem cells and subsequent development of myeloid malignancies. Blood 118 (17):4509–4518
88. Sasaki M, Knobbe CB, Munger JC et al (2012) IDH1(R132H) mutation increases murine haematopoietic progenitors and alters epigenetics. Nature 488(7413):656–659
89. Akbay EA, Moslehi J, Christensen CL et al (2014) D-2-hydroxyglutarate produced by mutant IDH2 causes cardiomyopathy and neurodegeneration in mice. Genes Dev 28(5):479–490
90. Chen C, Liu Y, Lu C et al (2013) Cancer-associated IDH2 mutants drive an acute myeloid leukemia that is susceptible to Brd4 inhibition. Genes Dev 27(18):1974–1985
91. Xu W, Yang H, Liu Y et al Oncometabolite 2-hydroxyglutarate is a competitive inhibitor of alpha-ketoglutarate-dependent dioxygenases. Cancer Cell 19(1):17–30
92. Palomero T, Couronne L, Khiabanian H et al Recurrent mutations in epigenetic regulators, RHOA and FYN kinase in peripheral T cell lymphomas. Nature genetics 46(2):166–170
93. Nagata Y, Kontani K, Enami T et al (2016) Variegated RHOA mutations in adult T-cell leukemia/lymphoma. Blood 127(5):596–604
94. Yoo HY, Sung MK, Lee SH, et al A recurrent inactivating mutation in RHOA GTPase in angioimmunoblastic T cell lymphoma. Nature genetics 46(4):371–375
95. Abdel-Wahab O, Levine RL (2013) Mutations in epigenetic modifiers in the pathogenesis and therapy of acute myeloid leukemia. Blood 121(18):3563–3572
96. Rohr J, Guo S, Hu D et al (2014) CD28 Mutations in Peripheral T-Cell Lymphomagenesis and Progression. Blood 124(21):1681–1681
97. Rohr J, Guo S, Huo J et al (2015) Recurrent activating mutations of CD28 in peripheral T-cell lymphomas. Leukemia
98. Wang C, McKeithan TW, Gong Q et al (2015) IDH2R172 mutations define a unique subgroup of patients with angioimmunoblastic T-cell lymphoma. Blood 126(15):1741–1752
99. DiNardo CD, Propert KJ, Loren AW et al Serum 2-hydroxyglutarate levels predict isocitrate dehydrogenase mutations and clinical outcome in acute myeloid leukemia. Blood 121 (24):4917–4924
100. Cheminant M, Bruneau J, Kosmider O et al (2014) Efficacy of 5-Azacytidine in a TET2 mutated angioimmunoblastic T cell lymphoma. Br J Haematol

101. Pro B, Horwitz SM, Prince HM et al (2016) Romidepsin induces durable responses in patients with relapsed or refractory angioimmunoblastic T-cell lymphoma. Hematol Oncol
102. Borroto A, Gil D, Delgado P et al (2000) Rho regulates T cell receptor ITAM-induced lymphocyte spreading in an integrin-independent manner. Eur J Immunol 30(12):3403–3410
103. Rougerie P, Delon J Rho GTPases: masters of T lymphocyte migration and activation. Immunol Lett 142(1–2):1-13
104. Cleverley SC, Costello PS, Henning SW, Cantrell DA (2000) Loss of Rho function in the thymus is accompanied by the development of thymic lymphoma. Oncogene 19(1):13–20
105. Cortes JR, Ambesi-Impiombato A, Couronne L, Kim CS, West Z, Belver L, da Silva Almeida AC, Bhagat G, Bernard OA, Ferrando AA, PalomeroT (2016) Role and Mechanisms of Rhoa G17 V in the Pathogenesis of AITL. ASH Meeting, San Diego
106. Li Z, Dong X, Wang Z et al (2005) Regulation of PTEN by Rho small GTPases. Nat Cell Biol 7(4):399–404
107. Morris SW, Kirstein MN, Valentine MB et al (1995) Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma. Science 267(5196):316–317
108. Mason DY, Bastard C, Rimokh R et al (1990) CD30-positive large cell lymphomas ('Ki-1 lymphoma') are associated with a chromosomal translocation involving 5q35. Br J Haematol 74(2):161–168
109. Morris SW, Kirstein MN, Valentine MB et al (1994) Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma. Science 263(5151):1281–1284
110. Rimokh R, Magaud JP, Berger F et al (1989) A translocation involving a specific breakpoint (q35) on chromosome 5 is characteristic of anaplastic large cell lymphoma ('Ki-1 lymphoma'). Br J Haematol 71(1):31–36
111. Agnelli L, Mereu E, Pellegrino E et al (2012) Identification of a 3-gene model as a powerful diagnostic tool for the recognition of ALK-negative anaplastic large-cell lymphoma. Blood 120(6):1274–1281
112. Piva R, Pellegrino E, Mattioli M et al (2006) Functional validation of the anaplastic lymphoma kinase signature identifies CEBPB and BCL2A1 as critical target genes. J Clin Invest. 116(12):3171–3182
113. Matsuyama H, Suzuki HI, Nishimori H et al (2011) miR-135b mediates NPM-ALK-driven oncogenicity and renders IL-17-producing immunophenotype to anaplastic large cell lymphoma. Blood 118(26):6881–6892
114. Abate F, Todaro M, van der Krogt JA et al (2014) A novel patient-derived tumorgraft model with TRAF1-ALK anaplastic large-cell lymphoma translocation. Leukemia
115. Parrilla Castellar ER, Jaffe ES, Said JW et al (2014) ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes. Blood 124(9):1473–1480
116. Crescenzo R, Abate F, Lasorsa E et al (2015) Convergent mutations and kinase fusions lead to oncogenic STAT3 activation in anaplastic large cell lymphoma. Cancer Cell 27(4):516–532
117. Chiarle R, Voena C, Ambrogio C, Piva R, Inghirami G (2008) The anaplastic lymphoma kinase in the pathogenesis of cancer. Nat Rev Cancer 8(1):11–23
118. Spaccarotella E, Pellegrino E, Ferracin M et al (2014) STAT3-mediated activation of microRNA cluster 17–92 promotes proliferation and survival of ALK-positive anaplastic large cell lymphoma. Haematologica 99(1):116–124
119. Merkel O, Hamacher F, Laimer D et al (2010) Identification of differential and functionally active miRNAs in both anaplastic lymphoma kinase $(ALK)^+$ and ALK- anaplastic large-cell lymphoma. Proc Natl Acad Sci U S A. 107(37):16228–16233
120. Portis T, Grossman WJ, Harding JC, Hess JL, Ratner L (2001) Analysis of p53 inactivation in a human T-cell leukemia virus type 1 Tax transgenic mouse model. J Virol 75(5):2185–2193
121. Vernin C, Thenoz M, Pinatel C et al (2014) HTLV-1 bZIP factor HBZ promotes cell proliferation and genetic instability by activating OncomiRs. Cancer Res 74(21):6082–6093

122. Wright DG, Marchal C, Hoang K et al (2016) Human T-cell leukemia virus type-1-encoded protein HBZ represses p53 function by inhibiting the acetyltransferase activity of p300/CBP and HBO1. Oncotarget. 7(2):1687–1706
123. Sasaki H, Nishikata I, Shiraga T et al (2005) Overexpression of a cell adhesion molecule, TSLC1, as a possible molecular marker for acute-type adult T-cell leukemia. Blood 105 (3):1204–1213
124. Pise-Masison CA, Radonovich M, Dohoney K et al (2009) Gene expression profiling of ATL patients: compilation of disease related genes and evidence for TCF-4 involvement in BIRC5 gene expression and cell viability. Blood
125. Zinzani et al(2016) Haematologica 101(10):e407–410
126. Ogura M et al(2014) J Clin Oncol 10, 32(11):1157–1163
127. Kataoka K, Nagata Y, Kitanaka A et al (2015) Integrated molecular analysis of adult T cell leukemia/lymphoma. Nat Genet 47(11):1304–1315
128. Yoshie O, Fujisawa R, Nakayama T et al (2002) Frequent expression of CCR4 in adult T-cell leukemia and human T-cell leukemia virus type 1-transformed T cells. Blood 99 (5):1505–1511
129. Harasawa H, Yamada Y, Hieshima K et al (2006) Survey of chemokine receptor expression reveals frequent co-expression of skin-homing CCR4 and CCR10 in adult T-cell leukemia/lymphoma. Leuk Lymphoma 47(10):2163–2173
130. Li J, Lu E, Yi T, Cyster JG (2016) EBI2 augments Tfh cell fate by promoting interaction with IL-2-quenching dendritic cells. Nature 533(7601):110–114
131. Fujii K, Ishimaru F, Nakase K et al (2003) Over-expression of short isoforms of Helios in patients with adult T-cell leukaemia/lymphoma. Br J Haematol 120(6):986–989
132. Zhang Z, Swindle CS, Bates JT, Ko R, Cotta CV, Klug CA (2007) Expression of a non-DNA-binding isoform of Helios induces T-cell lymphoma in mice. Blood 109(5):2190–2197
133. Sato H, Oka T, Shinnou Y et al (2010) Multi-step aberrant CpG island hyper-methylation is associated with the progression of adult T-cell leukemia/lymphoma. Am J Pathol 176 (1):402–415
134. Nosaka K, Maeda M, Tamiya S, Sakai T, Mitsuya H, Matsuoka M (2000) Increasing methylation of the CDKN2A gene is associated with the progression of adult T-cell leukemia. Cancer Res 60(4):1043–1048
135. Fujikawa D, Nakagawa S, Hori M et al (2016) Polycomb-dependent epigenetic landscape in adult T-cell leukemia. Blood 127(14):1790–1802
136. Krejsgaard T, Lindahl LM, Mongan NP et al (2016) Malignant inflammation in cutaneous T-cell lymphoma—a hostile takeover. Seminars in immunopathology
137. Macias ES, Pereira FA, Rietkerk W, Safai B (2011) Superantigens in dermatology. J Am Acad Dermatol 64(3):455–472; Quiz 473–454
138. Suga H, Sugaya M, Miyagaki T et al (2014) Skin barrier dysfunction and low antimicrobial peptide expression in cutaneous T-cell lymphoma. Clin Cancer Res 20(16):4339–4348
139. Thode C, Woetmann A, Wandall HH et al (2015) Malignant T cells secrete galectins and induce epidermal hyperproliferation and disorganized stratification in a skin model of cutaneous T-cell lymphoma. J Invest Dermatol. 135(1):238–246
140. Dobbeling U, Dummer R, Laine E, Potoczna N, Qin JZ, Burg G (1998) Interleukin-15 is an autocrine/paracrine viability factor for cutaneous T-cell lymphoma cells. Blood 92(1):252–258
141. Leroy S, Dubois S, Tenaud I et al (2001) Interleukin-15 expression in cutaneous T-cell lymphoma (mycosis fungoides and Sezary syndrome). The British journal of dermatology. 144(5):1016–1023
142. Netchiporouk E, Litvinov IV, Moreau L, Gilbert M, Sasseville D, Duvic M (2014) Deregulation in STAT signaling is important for cutaneous T-cell lymphoma (CTCL) pathogenesis and cancer progression. Cell Cycle 13(21):3331–3335

143. Mishra A, La Perle K, Kwiatkowski S et al (2016) Mechanism, Consequences, and Therapeutic Targeting of Abnormal IL15 Signaling in Cutaneous T-cell Lymphoma. Cancer Discov 6(9):986–1005
144. McKenzie RC, Jones CL, Tosi I, Caesar JA, Whittaker SJ, Mitchell TJ (2012) Constitutive activation of STAT3 in Sezary syndrome is independent of SHP-1. Leukemia 26(2):323–331
145. van der Fits L, Out-Luiting JJ, van Leeuwen MA et al (2012) Autocrine IL-21 stimulation is involved in the maintenance of constitutive STAT3 activation in Sezary syndrome. J Invest Dermatol. 132(2):440–447
146. Takahashi N, Sugaya M, Suga H et al (2016) Thymic Stromal Chemokine TSLP Acts through Th2 Cytokine Production to Induce Cutaneous T-cell Lymphoma. Cancer Res 76 (21):6241–6252
147. Tuzova M, Richmond J, Wolpowitz D et al (2015) $CCR4^+$ T cell recruitment to the skin in mycosis fungoides: potential contributions by thymic stromal lymphopoietin and interleukin-16. Leuk Lymphoma 56(2):440–449
148. Geskin LJ, Viragova S, Stolz DB, Fuschiotti P (2015) Interleukin-13 is overexpressed in cutaneous T-cell lymphoma cells and regulates their proliferation. Blood 125(18):2798–2805
149. Ohmatsu H, Humme D, Gulati N et al (2014) IL32 is progressively expressed in mycosis fungoides independent of helper T-cell 2 and helper T-cell 9 polarization. Cancer Immunol Res 2(9):890–900
150. Suga H, Sugaya M, Miyagaki T et al (2014) The role of IL-32 in cutaneous T-cell lymphoma. J Invest Dermatol. 134(5):1428–1435
151. Lauenborg B, Christensen L, Ralfkiaer U et al (2015) Malignant T cells express lymphotoxin alpha and drive endothelial activation in cutaneous T cell lymphoma. Oncotarget. 6 (17):15235–15249
152. Michel L, Jean-Louis F, Begue E, Bensussan A, Bagot M (2013) Use of PLS3, Twist, CD158 k/KIR3DL2, and NKp46 gene expression combination for reliable Sezary syndrome diagnosis. Blood 121(8):1477–1478
153. Wong HK, Gibson H, Hake T et al (2015) Promoter-Specific Hypomethylation Is Associated with Overexpression of PLS3, GATA6, and TWIST1 in the Sezary Syndrome. J Invest Dermatol. 135(8):2084–2092
154. Huang Y, Su MW, Jiang X, Zhou Y (2015) Evidence of an oncogenic role of aberrant TOX activation in cutaneous T-cell lymphoma. Blood 125(9):1435–1443
155. Dulmage BO, Akilov O, Vu JR, Falo LD, Geskin LJ (2015) Dysregulation of the TOX-RUNX3 pathway in cutaneous T-cell lymphoma. Oncotarget
156. Haider A, Steininger A, Ullmann R et al (2016) Inactivation of RUNX3/p46 Promotes Cutaneous T-Cell Lymphoma. J Invest Dermatol. 136(11):2287–2296
157. Choi J, Goh G, Walradt T et al (2015) Genomic landscape of cutaneous T cell lymphoma. Nat Genet 47(9):1011–1019
158. da Silva Almeida AC, Abate F, Khiabanian H et al (2015) The mutational landscape of cutaneous T cell lymphoma and Sezary syndrome. Nat Genet 47(12):1465–1470
159. Kiel MJ, Sahasrabuddhe AA, Rolland DC et al (2015) Genomic analyses reveal recurrent mutations in epigenetic modifiers and the JAK-STAT pathway in Sezary syndrome. Nat Commun. 6:8470
160. Wang L, Ni X, Covington KR et al (2015) Genomic profiling of Sezary syndrome identifies alterations of key T cell signaling and differentiation genes. Nat Genet 47(12):1426–1434
161. Mathur R, Alver BH, San Roman AK et al (2017) ARID1A loss impairs enhancer-mediated gene regulation and drives colon cancer in mice. Nat Genet 49(2):296–302
162. Watanabe R, Ui A, Kanno S et al (2014) SWI/SNF factors required for cellular resistance to DNA damage include ARID1A and ARID1B and show interdependent protein stability. Cancer Res 74(9):2465–2475
163. Williamson CT, Miller R, Pemberton HN et al (2016) ATR inhibitors as a synthetic lethal therapy for tumours deficient in ARID1A. Nat Commun. 7:13837

164. Guo C, Chen LH, Huang Y et al (2013) KMT2D maintains neoplastic cell proliferation and global histone H3 lysine 4 monomethylation. Oncotarget. 4(11):2144–2153
165. Kaikkonen MU, Spann NJ, Heinz S et al (2013) Remodeling of the enhancer landscape during macrophage activation is coupled to enhancer transcription. Mol Cell 51(3):310–325
166. Hidaka T, Nakahata S, Hatakeyama K et al (2008) Down-regulation of TCF8 is involved in the leukemogenesis of adult T-cell leukemia/lymphoma. Blood 112(2):383–393
167. Papadopoulou V, Postigo A, Sanchez-Tillo E, Porter AC, Wagner SD (2010) ZEB1 and CtBP form a repressive complex at a distal promoter element of the BCL6 locus. Biochem J 427(3):541–550
168. Wang J, Lee S, Teh CE, Bunting K, Ma L, Shannon MF (2009) The transcription repressor, ZEB1, cooperates with CtBP2 and HDAC1 to suppress IL-2 gene activation in T cells. Int Immunol 21(3):227–235
169. Migliazza A, Lombardi L, Rocchi M et al (1994) Heterogeneous chromosomal aberrations generate 3' truncations of the NFKB2/lyt-10 gene in lymphoid malignancies. Blood 84 (11):3850–3860
170. Neri A, Fracchiolla NS, Migliazza A, Trecca D, Lombardi L (1996) The involvement of the candidate proto-oncogene NFKB2/lyt-10 in lymphoid malignancies. Leuk Lymphoma 23(1–2):43–48
171. Ungewickell A, Bhaduri A, Rios E et al (2015) Genomic analysis of mycosis fungoides and Sezary syndrome identifies recurrent alterations in TNFR2. Nat Genet 47(9):1056–1060
172. Ralfkiaer U, Hagedorn PH, Bangsgaard N et al (2011) Diagnostic microRNA profiling in cutaneous T-cell lymphoma (CTCL). Blood 118(22):5891–5900
173. Sandoval J, Diaz-Lagares A, Salgado R et al (2015) MicroRNA expression profiling and DNA methylation signature for deregulated microRNA in cutaneous T-cell lymphoma. J Invest Dermatol. 135(4):1128–1137
174. Ralfkiaer U, Lindahl LM, Litman T et al (2014) MicroRNA expression in early mycosis fungoides is distinctly different from atopic dermatitis and advanced cutaneous T-cell lymphoma. Anticancer Res 34(12):7207–7217
175. Narducci MG, Arcelli D, Picchio MC et al (2011) MicroRNA profiling reveals that miR-21, miR486 and miR-214 are upregulated and involved in cell survival in Sezary syndrome. Cell Death Dis 2:e151
176. Carreon JD, Morton LM, Devesa SS et al (2008) Incidence of lymphoid neoplasms by subtype among six Asian ethnic groups in the United States, 1996-2004. Cancer Causes Control 19(10):1171–1181
177. Morton LM, Wang SS, Devesa SS, Hartge P, Weisenburger DD, Linet MS (2006) Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. Blood 107 (1):265–276
178. Chan JK, Sin VC, Wong KF et al (1997) Nonnasal lymphoma expressing the natural killer cell marker CD56: a clinicopathologic study of 49 cases of an uncommon aggressive neoplasm. Blood 89(12):4501–4513
179. Matano S, Nakamura S, Nakamura S et al (1999) Monomorphic agranular natural killer cell lymphoma/leukemia with no Epstein-Barr virus association. Acta Haematol 101(4):206–208
180. Martin AR, Chan WC, Perry DA, Greiner TC, Weisenburger DD (1995) Aggressive natural killer cell lymphoma of the small intestine. Mod Pathol 8(5):467–472
181. Yagita M, Huang CL, Umehara H et al (2000) A novel natural killer cell line (KHYG-1) from a patient with aggressive natural killer cell leukemia carrying a p53 point mutation. Leukemia 14(5):922–930
182. Chen IM, Whalen M, Bankhurst A et al (2004) A new human natural killer leukemia cell line, IMC-1. A complex chromosomal rearrangement defined by spectral karyotyping: functional and cytogenetic characterization. Leuk Res 28(3):275–284
183. Kulwichit W, Edwards RH, Davenport EM, Baskar JF, Godfrey V, Raab-Traub N (1998) Expression of the Epstein-Barr virus latent membrane protein 1 induces B cell lymphoma in transgenic mice. Proc Natl Acad Sci U S A. 95(20):11963–11968

184. Pratt ZL, Kuzembayeva M, Sengupta S, Sugden B (2009) The microRNAs of Epstein-Barr Virus are expressed at dramatically differing levels among cell lines. Virology 386(2):387–397
185. Klinke O, Feederle R, Delecluse HJ (2014) Genetics of Epstein-Barr virus microRNAs. Semin Cancer Biol 26:52–59
186. Vereide DT, Seto E, Chiu YF et al (2014) Epstein-Barr virus maintains lymphomas via its miRNAs. Oncogene 33(10):1258–1264
187. Huang WT, Lin CW (2014) EBV-encoded miR-BART20-5p and miR-BART8 inhibit the IFN-gamma-STAT1 pathway associated with disease progression in nasal NK-cell lymphoma. Am J Pathol 184(4):1185–1197
188. Motsch N, Alles J, Imig J et al (2012) MicroRNA profiling of Epstein-Barr virus-associated NK/T-cell lymphomas by deep sequencing. PLoS ONE 7(8):e42193
189. Iqbal J, Kucuk C, Deleeuw RJ et al (2009) Genomic analyses reveal global functional alterations that promote tumor growth and novel tumor suppressor genes in natural killer-cell malignancies. Leukemia 23(6):1139–1151
190. Huang Y, de Reynies A, de Leval L et al (2010) Gene expression profiling identifies emerging oncogenic pathways operating in extranodal NK/T-cell lymphoma, nasal type. Blood 115(6):1226–1237
191. Nakashima Y, Tagawa H, Suzuki R et al (2005) Genome-wide array-based comparative genomic hybridization of natural killer cell lymphoma/leukemia: different genomic alteration patterns of aggressive NK-cell leukemia and extranodal Nk/T-cell lymphoma, nasal type. Genes Chromosomes Cancer 44(3):247–255
192. Siu LL, Chan V, Chan JK, Wong KF, Liang R, Kwong YL (2000) Consistent patterns of allelic loss in natural killer cell lymphoma. Am J Pathol 157(6):1803–1809
193. Siu LL, Wong KF, Chan JK, Kwong YL (1999) Comparative genomic hybridization analysis of natural killer cell lymphoma/leukemia. Recognition of consistent patterns of genetic alterations. Am J Pathol 155(5):1419–1425
194. Ko YH, Choi KE, Han JH, Kim JM, Ree HJ (2001) Comparative genomic hybridization study of nasal-type NK/T-cell lymphoma. Cytometry 46(2):85–91
195. Kucuk C, Iqbal J, Hu X et al (2011) PRDM1 is a tumor suppressor gene in natural killer cell malignancies. Proc Natl Acad Sci USA 108(50):20119–20124
196. Karube K, Nakagawa M, Tsuzuki S et al (2011) Identification of FOXO3 and PRDM1 as tumor-suppressor gene candidates in NK-cell neoplasms by genomic and functional analyses. Blood 118(12):3195–3204
197. Kucuk C, Hu X, Iqbal J et al (2013) HACE1 is a tumor suppressor gene candidate in natural killer cell neoplasms. Am J Pathol 182(1):49–55
198. Zhang L, Anglesio MS, O'Sullivan M et al (2007) The E3 ligase HACE1 is a critical chromosome 6q21 tumor suppressor involved in multiple cancers. Nat Med 13(9):1060–1069
199. Quintanilla-Martinez L, Kremer M, Keller G et al (2001) p53 Mutations in nasal natural killer/T-cell lymphoma from Mexico: association with large cell morphology and advanced disease. Am J Pathol 159(6):2095–2105
200. Frappier L (2012) Contributions of Epstein-Barr nuclear antigen 1 (EBNA1) to cell immortalization and survival. Viruses. 4(9):1537–1547
201. Li M, Chen D, Shiloh A et al (2002) Deubiquitination of p53 by HAUSP is an important pathway for p53 stabilization. Nature 416(6881):648–653
202. Saridakis V, Sheng Y, Sarkari F et al (2005) Structure of the p53 binding domain of HAUSP/USP7 bound to Epstein-Barr nuclear antigen 1 implications for EBV-mediated immortalization. Mol Cell 18(1):25–36
203. Oka T, Ouchida M, Koyama M et al (2002) Gene silencing of the tyrosine phosphatase SHP1 gene by aberrant methylation in leukemias/lymphomas. Cancer Res 62(22):6390–6394
204. Siu LL, Chan JK, Wong KF, Kwong YL (2002) Specific patterns of gene methylation in natural killer cell lymphomas: p73 is consistently involved. Am J Pathol 160(1):59–66

205. Deyoung MP, Ellisen LW (2007) p63 and p73 in human cancer: defining the network. Oncogene 26(36):5169–5183
206. Candi E, Agostini M, Melino G, Bernassola F (2014) How the TP53 family proteins TP63 and TP73 contribute to tumorigenesis: regulators and effectors. Hum Mutat 35(6):702–714
207. Lanier LL (2008) Up on the tightrope: natural killer cell activation and inhibition. Nat Immunol 9(5):495–502
208. Han Y, Amin HM, Frantz C et al (2006) Restoration of shp1 expression by 5-AZA-2'-deoxycytidine is associated with downregulation of JAK3/STAT3 signaling in ALK-positive anaplastic large cell lymphoma. Leukemia 20(9):1602–1609
209. Chim CS, Fung TK, Cheung WC, Liang R, Kwong YL (2004) SOCS1 and SHP1 hypermethylation in multiple myeloma: implications for epigenetic activation of the Jak/STAT pathway. Blood 103(12):4630–4635
210. Chen KF, Su JC, Liu CY et al (2012) A novel obatoclax derivative, SC-2001, induces apoptosis in hepatocellular carcinoma cells through SHP-1-dependent STAT3 inactivation. Cancer Lett 321(1):27–35
211. Kim DJ, Tremblay ML, Digiovanni J (2010) Protein tyrosine phosphatases, TC-PTP, SHP1, and SHP2, cooperate in rapid dephosphorylation of Stat3 in keratinocytes following UVB irradiation. PLoS ONE 5(4):e10290
212. Gupta SC, Phromnoi K, Aggarwal BB (2013) Morin inhibits STAT3 tyrosine 705 phosphorylation in tumor cells through activation of protein tyrosine phosphatase SHP1. Biochem Pharmacol 85(7):898–912
213. Kucuk C, Jiang B, Hu X et al (2015) Activating mutations of STAT5B and STAT3 in lymphomas derived from gammadelta-T or NK cells. Nat Commun. 6:6025
214. Takakuwa T, Dong Z, Nakatsuka S et al (2002) Frequent mutations of Fas gene in nasal NK/T cell lymphoma. Oncogene 21(30):4702–4705
215. Shen L, Liang AC, Lu L et al (2002) Frequent deletion of Fas gene sequences encoding death and transmembrane domains in nasal natural killer/T-cell lymphoma. Am J Pathol 161 (6):2123–2131
216. Coppo P, Gouilleux-Gruart V, Huang Y et al (2009) STAT3 transcription factor is constitutively activated and is oncogenic in nasal-type NK/T-cell lymphoma. Leukemia 23 (9):1667–1678
217. Yu H, Kortylewski M, Pardoll D (2007) Crosstalk between cancer and immune cells: role of STAT3 in the tumour microenvironment. Nat Rev Immunol 7(1):41–51
218. Yu H, Pardoll D, Jove R (2009) STATs in cancer inflammation and immunity: a leading role for STAT3. Nat Rev Cancer 9(11):798–809
219. Wang T, Niu G, Kortylewski M et al (2004) Regulation of the innate and adaptive immune responses by Stat-3 signaling in tumor cells. Nat Med 10(1):48–54
220. Koo GC, Tan SY, Tang T et al (2012) Janus kinase 3-activating mutations identified in natural killer/T-cell lymphoma. Cancer Discov 2(7):591–597
221. Bouchekioua A, Scourzic L, de Wever O et al (2014) JAK3 deregulation by activating mutations confers invasive growth advantage in extranodal nasal-type natural killer cell lymphoma. Leukemia 28(2):338–348
222. Kimura H, Karube K, Ito Y et al (2014) Rare occurrence of JAK3 mutations in natural killer cell neoplasms in Japan. Leuk Lymphoma 55(4):962–963
223. Jiang L, Gu ZH, Yan ZX, et al. Exome sequencing identifies somatic mutations of DDX3X in natural killer/T-cell lymphoma. *Nature genetics.* 2015:Epub ahead of print
224. Dobashi A, Tsuyama N, Asaka R et al (2016) Frequent BCOR aberrations in extranodal NK/T-Cell lymphoma, nasal type. Genes Chromosomes Cancer 55(5):460–471
225. Lee S, Park HY, Kang SY et al (2015) Genetic alterations of JAK/STAT cascade and histone modification in extranodal NK/T-cell lymphoma nasal type. Oncotarget. 6(19):17764–17776
226. Miyazaki K, Yamaguchi M, Imai H et al (2009) Gene expression profiling of peripheral T-cell lymphoma including gammadelta T-cell lymphoma. Blood 113(5):1071–1074

227. Travert M, Huang Y, de Leval L et al (2012) Molecular features of hepatosplenic T-cell lymphoma unravels potential novel therapeutic targets. Blood 119(24):5795–5806
228. Moffitt AB, Ondrejka SL, McKinney M et al (2017) Enteropathy-associated T cell lymphoma subtypes are characterized by loss of function of SETD2. J Exp Med
229. Davis RE, Brown KD, Siebenlist U, Staudt LM (2001) Constitutive nuclear factor kappaB activity is required for survival of activated B cell-like diffuse large B cell lymphoma cells. J Exp Med 194(12):1861–1874
230. Bild AH, Yao G, Chang JT et al (2006) Oncogenic pathway signatures in human cancers as a guide to targeted therapies. Nature 439(7074):353–357
231. Rosenwald A, Wright G, Leroy K et al (2003) Molecular diagnosis of primary mediastinal B cell lymphoma identifies a clinically favorable subgroup of diffuse large B cell lymphoma related to Hodgkin lymphoma. J Exp Med 198(6):851–862
232. Savage KJ, Monti S, Kutok JL et al (2003) The molecular signature of mediastinal large B-cell lymphoma differs from that of other diffuse large B-cell lymphomas and shares features with classical Hodgkin lymphoma. Blood 102(12):3871–3879
233. Zinzani PL, Tani M, Musuraca G et al (2006) Phase II study of proteasome inhibitor bortezomib (Velcade®) in patients with relapsed/refractory T-cell lymphoma: preliminary results. Blood 108a
234. Piva R, Ruggeri B, Williams M et al (2007) CEP-18770: a novel orally-active proteasome inhibitor with a tumor-selective pharmacological profile competitive with bortezomib. Blood
235. Feldman A, Sun D, Law M (2007) Syk Tyrosine Kinase is Overexpressed in the Majority of Peripheral T and NK-cell Lymphomas, and Re. Blood 110:690a
236. Wilcox RA, Sun DX, Novak A, Dogan A, Ansell SM, Feldman AL (2010) Inhibition of Syk protein tyrosine kinase induces apoptosis and blocks proliferation in T-cell non-Hodgkin's lymphoma cell lines. Leukemia 24(1):229–232
237. Piccaluga PP, Rossi M, Agostinelli C et al (2014) Platelet-derived growth factor alpha mediates the proliferation of peripheral T-cell lymphoma cells via an autocrine regulatory pathway. Leukemia 28(8):1687–1697
238. Andrae J, Gallini R, Betsholtz C (2008) Role of platelet-derived growth factors in physiology and medicine. Genes Dev 22(10):1276–1312
239. Perry AM, Molina-Kirsch H, Nathwani BN et al (2011) Classification of non-Hodgkin lymphomas in Guatemala according to the World Health Organization system. Leuk Lymphoma 52(9):1681–1688
240. Wang C, Collins M, Kuchroo VK (2015) Effector T cell differentiation: are master regulators of effector T cells still the masters? Curr Opin Immunol 37:6–10
241. Rudiger T, Weisenburger DD, Anderson JR et al (2002) Peripheral T-cell lymphoma (excluding anaplastic large-cell lymphoma): results from the Non-Hodgkin's Lymphoma Classification Project. Ann Oncol 13(1):140–149
242. Vose J, Armitage J, Weisenburger D, International TCLP (2008) International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol 26(25):4124–4130

Tumor Microenvironment in T-Cell Lymphomas

3

N. Nora Bennani and Stephen M. Ansell

Abstract

T-cell lymphomas (TCL) are uncommon non-Hodgkin lymphomas that often have an aggressive clinical course. Patients typically have limited treatment options upon relapse and a dismal prognosis after progression despite newly approved therapies. New therapeutic approaches for these orphan diseases are very much needed and a greater understanding of the role of nonmalignant immune cells in the tumor microenvironment may allow for an improved antitumor immune response. The tumor microenvironment is a key component in tumor evasion and typically results in an ineffective T-cell response to the tumor cells despite a significant inflammatory response. A better understanding of the tumor microenvironment therefore, in an effort to overcome the barriers to an effective immune response, would help in developing novel therapeutic approaches to treat and improve outcomes of these diseases. Immune checkpoint blockade to reinvigorate suppressed T-cell, or modulation of the CD47-SIRPalpha axis to promote macrophage phagocytosis, would be such targets. However, whether modulating the immune response using each pathway alone or whether a combination approach is necessary has yet to be determined.

Keywords

T-cell lymphoma · Tumor microenvironment · Regulatory T-cells
Helper T-cells · Immunotherapy · Checkpoint blockade · CD47-SIRPalpha axis

Abbreviations

AITL Angioimmunoblastic T-cell lymphoma

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ALCL	Anaplastic Large Cell Lymphoma
APC	Antigen-Presenting Cells
BV	Brentuximab Vedotin
CTCL	Cutaneous T-cell Lymphoma
CTL	Cytotoxic T Lymphocytes
FDA	Food and Drug Administration
Foxp3	Forkhead box P3
GC	Germinal Centers
MDSC	Myeloid-derived Suppressor Cells
MHC	Major Histocompatibility Complex
NHL	Non-Hodgkin lymphomas
NK	Natural Killer
NKTCL	NK/T-cell lymphomas
MMAE	Monomethyl Auristatin E
NOS	Not Otherwise Specified
PTCL	Peripheral T-cell Lymphomas
TAM	Tumor-associated Macrophages
TCL	T-cell lymphomas
TCR	T-cell Receptor
T_{FH}	T Follicular Helper cells
Th	Helper T-cells
TGF-β	Transforming growth factor-β
TME	Tumor microenvironment
Treg	Regulatory T-cells

3.1 Introduction

Despite significant progress made in the management of non-Hodgkin lymphomas (NHL), close to a third of the patients will die of their disease in the year 2017 [53]. Mortality from disease is particularly high in T-cell lymphomas (TCL). So far, our approach to the management of T-cell lymphomas has been an extrapolation of our experience in B-cell NHL. Despite an initial response of TCL to standard chemotherapy combinations, it is unfortunately short-lived. Though several new therapies were recently approved by the Food and Drug Administration (FDA) and are now commonly used in the relapsed/refractory setting, the overall responses remain low (in the 25–30% range) and are short-lived [44]. Novel therapeutic approaches are clearly needed in these orphan diseases.

One strategy to develop new therapies in TCL is to manipulate the tumor microenvironment (TME), which was shown to be profoundly immunosuppressive in peripheral T-cell lymphomas (PTCL). A better understanding of the TME in TCL would be key to improving outcomes in these diseases. In this chapter, we will summarize our knowledge to date of the TME in TCL and how we could potentially use this understanding to overcome the barriers to an effective immune response and use that to our advantage to develop novel therapeutic approaches to treat TCL.

3.2 Components of the Tumor Microenvironment in T-Cell Lymphomas

In lymphoid malignancies, the malignant clone represents only a proportion of the cells that constitute the tumor. For instance, in classic Hodgkin lymphoma, the malignant Reed–Sternberg cells are rare among a mixture of inflammatory and immune cells that are unable to produce an effective antitumor response. Similarly, angioimmunoblastic T-cell lymphoma (AITL) is known for its rich polymorphous TME with the neoplastic cells buried in a mixture inflammatory/reactive cells including eosinophils, plasma cells, large B-cell blasts, and macrophages (reviewed in [24]). A better understanding of the components of the TME and of the factors that influence it and lead to immune evasion will allow us to potentially manipulate the immune system to eradicate the tumor. Our knowledge of the TME in TCL is in its infancy, largely due to the relative scarcity of TCL. Most of the available data are described in B-cell NHL. In this section, we will describe the different components that constitute the TME in lymphomas and how these influence each other and the malignant processes. When available, data, as it relates to TCL will be emphasized.

3.2.1 Tumor-Infiltrating Lymphocytes

In both solid and hematologic malignancies, it is recognized that the number, type, and composition of tumor-infiltrating lymphocytes (TiLs) are linked to patients' outcomes [10, 11, 17]. T-lymphocytes predominate in these infiltrates. These cells are distinct from the lymphoid organ original cell populations. Based on the expression of CD4 or CD8 molecules, T-lymphocytes are typically divided into CD4+ T helper cells (Th) and CD8+ cytotoxic T-cells (CTLs). In the following sections, we will discuss how these infiltrating T-cell subsets influence the TME and how they affect outcomes in lymphomas. We will also discuss regulators of T-cell function and the contributing factors to T-cell exhaustion/suppression.

CD8+ T-cells. CD8+ T-cells function is to destroy any cells that are not recognized as self such as cells infected by viruses and malignant cells [12]. This is made possible by T-cell receptors (TCRs), in the form of two transmembrane molecules TCR-α and TCR-β on the cell surface that identify antigens presented by

the major histocompatibility complex I (MHC) molecules, present on all nucleated cells in our body. This recognition triggers transduction signaling through the TCR and subsequent secretion of perforin and granzyme B, leading to direct cell killing [2, 59]. It is, however, well recognized that CTL function as depicted above is quite intricate as the degree of CTL activation can vary under the influence of various factors. For both helper and cytotoxic T-cells, the cellular immune response goes through three phases: activation, clonal expansion, and differentiation. It is important to note that for each cell subtype, these phases are intertwined and can influence each other. Naïve T-cell activation into effector cells requires binding of TCR to an antigen, which then signals through co-stimulatory signals on the T-cell. Antigen-presenting cells (APC) and Th cells and various cytokines contribute to the strength of the signal and activation of CTL. B7-1 (CD80) and B7-2 (CD86) molecules on the APC or tumor cell surface interact with CD28 which is constitutively expressed on the T-cell surface. This interaction leads to activation of the naïve T-cell. To prevent uncontrolled immune activation, at the earlier stages of T-cell activation, CTL-associated antigen 4 (CTLA-4) or CD152, an inhibitory signal exclusively expressed on activated T-cells, has higher affinity for B7 molecules than CD28, hence hindering B7-CD28 interactions and thus leading swiftly to T-cell cycle arrest [1, 42, 60].

Similarly, PD-1 (CD279), another inhibitory pathway, is expressed on APCs and on activated T-cells and acts on the effector phase. Binding to one of its ligands, PD-L1 (CD274 or B7-H1) or PD-L2 (CD273), triggers an inhibitory kinase-mediated signaling pathway with subsequent T-cell function anergy [57], exhaustion [68], and apoptosis [19, 28]. PD-L1 expression is limited to the immune cells such as APC and activated T-cells [30] and can be induced on tumor cells leading to CTL inefficiency in tumor cell killing [57]. In various T-cell lymphoproliferative disorders, we have shown that PD-L1 was expressed by the tumor cells in 27% of cutaneous T-cell lymphoma (CTCL) biopsy specimens examined (n = 11), while only present in 15% of other types of TCL combined (n = 144), though a higher expression was seen in ALK+ anaplastic large cell lymphoma (ALCL) (33% of cases) [61]. This finding supported previous reports that the oncogenic ALK through STAT3 leads to PD-L1 upregulation [39]. Interestingly, PD-L1 expression was more prominent in the TME, seen in 73% of the CTCL cases and in 39% of other PTCL cases [61]. PD-L1 was also shown to be expressed with high frequency on the malignant cells in nasal NK/T-cell lymphomas (NKTCL) [43] and extra-nasal NKTCL [13]. In 43 cases of adult T-cell leukemia/lymphoma, 27% overexpressed PD-L1 with an underlying stable variation in the 3′ region of the PD-L1 gene, which was shown to promote further immune evasion [29].

CD4+ T-cells. CD4+ T-cells are crucial elements of the immune system. They contribute to several key aspects in regulating the immune response and preventing autoimmune disorders. Once in contact with an antigen-HLA class II complex presented by an APC, the naïve CD4+ T-cell is activated [54]. It is now recognized that once the CD4+ T-cells are activated, they form a pool of T-cell sub-populations with various immune functions [52]. Several types of Th cell subsets have been described. Each subset affects the function of other immune cells through secretion

of specific cytokines. For instance, Th1 cells, under the influence of IL-12, promote cytotoxic immune responses and lead to the formation of granulomas. These cells secrete INF-γ, TGF-β, and IL-2. IFN-γ appears to be a key element in this response, enhancing leukocyte activation and phagocytic cells killing capacity (reviewed in [3]). Though Th1 cells, by promoting cytotoxic T-cell killing, are mostly known for their antitumor effects, they were also shown to contribute to tumor resistance through INF-γ, which can lead to PD-L1 expression on cytotoxic T-cells and subsequent anergy and exhaustion of the latter (reviewed in [16]). Th2 cells, on the other hand, produce a different set of cytokines (IL-4, IL-5, and IL-6) and tend to modulate humoral immune responses. Depending on the clinical situation, the response may be more directed towards a Th1 response rather than Th2 and vice versa.

T follicular helper cells (T_{FH}), another subset of effector Th cells, are localized in the germinal centers (GC) and were shown to be key regulators of various stages of GC B-cell development (reviewed in [40]) CXCR5, the receptor of CXCL13 chemokine, is a distinctive surface marker of T_{FH} cells. It is crucial to both T_{FH} cell and B-cell localization in the GC. Other recognized markers include several co-stimulatory molecules such as PD1, ICOS, and CD200. The same markers are used in the diagnosis of AITL, which is recognized to be of T_{FH} cells origin [18, 46], and is the prototypic TCL where the TME is particularly prominent (reviewed in [24]). Indeed, the composition of the TME in AITL can in part be explained by its T_{FH} cell origin with the presence of polyclonal plasma cells, blastic B-cells, several chemokines, and immunoglobulins. CXCL13, IL-6, and IL-21, secreted by the neoplastic AITL T_{FH} cells, appear to play a major role in some of the associated manifestations seen in AITL [45, 50]. PTCL, not otherwise specified (NOS), follicular variant, and primary cutaneous CD4+ small/medium-sized T-cell lymphoma display similar pathologic and molecular characteristics as AITL and express many of the T_{FH} cell markers.

Regulatory T-cells (Treg) are a subset characterized by their ability to suppress and limit immune activation and autoimmunity. These cells are known to be CD4+CD25+ [48]. Forkhead box P3 (Foxp3), a forkhead/winged helix transcription factor, is recognized as a fundamental regulator of Treg cells. Presence of a mutant FOXP3 in a mouse model leads to a lethal lymphoproliferative disorder due to excessive activation of CD4+ T-cells and a syndrome similar to a cytokine storm [8]. The human counterpart of this observed syndrome seen in mice leads to the X-linked genetic disorder IPEX comprised of immune dysregulation, polyendocrinopathy, and enteropathy [5]. CD4+CD25+Foxp3+ Treg cells, not only suppress effector T-cells, but also suppress the function of B-cells, macrophages, dendritic, and natural killer (NK) cells (reviewed in [3]). Among the recognized mechanisms of Treg-mediated immune suppression, we cite the following: suppression of proliferation and cytokine production by Th cells, production of cytokines leading to immunosuppression, cytotoxic effector T-cell killing, and induction of negative regulators (reviewed in [49]). Treg cells could be distinguished into naïve and inducible Treg cells, the former are naturally present in the peripheral blood. The latter occur upon antigenic stimulation. IL-2 appears to be a

key regulator of Treg cell expansion, function, and survival. IL-2 affects not only CD4+ and CD8+ T-cells, but also B-cells, and NK-cells. There is an important negative feedback loop mediated by IL-2 itself with the goal to avoid excessive immune activation and autoimmunity. In follicular lymphoma, we have shown that soluble IL-2 Receptor α (sIL-2Rα) was elevated and was associated with worse outcomes [65]. sIL-2Rα/IL-2 complex favored T-cell differentiation to suppressive Treg cells by inducing Foxp3 expression in CD4+ T-cells. Similarly, in a study evaluating pretreatment cytokines level in 68 untreated patients with T-cell lymphomas, sIL-2Rα was associated with a significantly worse event-free survival (EFS) when compared to controls with a hazard ratio (HR) of 3.95; 95% confidence interval (CI) 1.61–8.38 [26].

TGF-β, produced by Th1 cells and by malignant lymphoma cells, is another crucial suppressive regulator of several elements in the TME including T-cell function. It favors an exhausted phenotype through several mechanisms and is shown to contribute to tumor evasion and metastasis in several tumor types (Reviewed in [23]). TGF-β can be found as a soluble cytokine or membrane-bound to the malignant lymphoma cells in B-NHL and in T-cell NHL [15, 66]. We have shown that one of the mechanisms by which TGF- β leads to T-cell exhaustion is through CD70 upregulation on effector T-cells and by inducing Foxp3 in naïve Treg cells leading to a more immunosuppressive TME [64]. Furthermore, TGF-β inhibited INF-ɣ and IL-17 production leading to Th cell suppression [66].

Infiltration by Treg cells in NHL tumors is fairly common [67]. The prognostic value of Treg cells is somewhat conflicting. For instance, in a study analyzing skin biopsies from 86 patients with mycosis fungoides (MF) and other cutaneous T-cell lymphoma (CTCL) unspecified for Foxp3 expression and tumor-infiltrating Tregs, it was noted that an increased number of Foxp3+ Treg cells was seen in earlier stages, with less large cell transformation and associated with an improved survival in both MF and CTCL unspecified cases [25]. Similar observations were reported in FL [10]. In other studies, the above observations were not reproduced [21, 55, 58]. It is believed that these inconsistencies could be related to patient population selection, nonuniform therapies and possibly the location and distribution in the tumor of the Foxp3+ Treg cells [34].

3.2.2 Intratumoral Macrophages

As part of the mononuclear phagocytic system, macrophages are an important component of the innate immune response and the TME and possibly play a role in tumorigenesis and tumor spread. Similar to Th cells, macrophages can be distinguished into two types with different functions: M1 and M2. M1, also known as pro-inflammatory macrophages, are activated through the classical pathway, i.e., liposaccharides and Th1-induced cytokines such as IFN-ɣ and TNF-α, and produce pro-inflammatory cytokines. M1 macrophages help in the fight against pathogens such as viruses and bacteria. M2 macrophages are the opposite. They are induced via the alternative pathway by Th2-produced cytokines such as IL-4 and are geared

towards anti-inflammatory functions, angiogenesis, and wound healing among others (reviewed in [51]). Similar to what we know about the Th1/Th2 distinction, the above-described macrophages classification may be overly simplistic and that the macrophages change characteristics and function based on various stimuli.

In the TME, M1-like macrophages predominate in early tumorigenesis. Through the excretion of pro-inflammatory cytokines and various chemokines, T-cells are differentiated. In more advanced tumors, M2-like macrophages are more commonly seen and are referred to as tumor-associated macrophages (TAM) [6]. It is not entirely clear what causes this differentiation. Several studies have looked into this question. A switch from a pro-inflammatory antitumor milieu to an anti-inflammatory/pro-tumor environment has been implicated. TAM in the TME promote tumor progression through several mechanisms including and not limited to: anti-inflammatory cytokines production such as IL-10 which was shown to limit antigen presentation, inhibit the production of inflammatory cytokines and reduce the antitumor immune response through effects on B and T-cells within the TME [37]; chemokines production such as CCL13, CCL18, and CCL22 which play a role in attracting Treg cells [38], other chemokines such as CCL2, CCL5, CXCL9, CXCL10, and CXCL16 contribute to tumor growth through angiogenesis and matrix remodeling [4, 7].

Clinically, there is some evidence that an increased number of TAM in various tumors is associated with worse outcomes (Reviewed in [6]). In follicular lymphoma, for example, tumors with a higher number of CD68+ lymphoma-associated macrophages (LAM) were associated with significantly worse overall survival independent of other known predictors [22]. Similar results were seen in a larger number of patients with FL, though the observed worse outcomes were negated in patients receiving the anti-CD20 monoclonal antibody rituximab [9].

Limited data are available about TAM in TCL. One study looked into CD68 + expressing TAM in 38 PTCL, NOS cases. Similar results were observed with worse overall survival in patients with higher TAM content [69]. In a mouse model of CTCL, M2-like TAM depletion delayed development of CTCL in immunocompromised mice [63]. Few PTCL entities can be distinguished from others based on their histiocytic and macrophage content and appear to have worse outcomes compared to their counterparts. For example, ALK+ ALCL, lymphohistiocytic variant, a relatively rare variant of the ALK+ ALCL, is associated with worse prognosis than typically seen in ALK+ ALCL [33]. Gene expression profiling done in extra-nodal NKTCL, nasal-type, and hepatosplenic lymphoma were shown to be associated with macrophage dominant gene signature and these are known to be associated with cytotoxic chemotherapy resistance and poor prognosis [27, 56].

Myeloid-derived Suppressor Cells (MDSC)—MDSC are immature myeloid cells that have not yet differentiated in monocytes, granulocytes or dendritic cells. Though extensively studied in animal models and shown to play an immunosuppressive role in favor of cancer progression and spread (reviewed in [41]), our knowledge of these immature cell populations in humans has lagged behind due to differences between animal models and humans, lack of reliable cell markers and differing data in different cancer type. In solid malignancies where most the studies

are reported, MDSC are distinguished into two populations: a $CD14^{+}/CD15^{-}$ or CD15 low, a more immature monocytic population; a $CD14^{-}/CD15^{+}$ granulocytic more mature population of cells. They were shown in various studies to contribute to immune evasion through various mechanisms including T-cell suppression via various cytokines, modulate Treg function, and leading to neoangiogenesis through the production of vascular growth factors, and granulocyte growth factors.

In hematologic malignancies, limited data are available. In B-cell NHL, a $CD14^{+}HLA\text{-}DR^{low/-}$ monocytic population lead to T-cell suppression which was reversible once the monocytes were removed and believed to be induced through production of arginine. Patients with a higher ratio of this population of monocytes had more advanced stages [36]. In T-cell lymphomas, monocytes, abundantly recruited to the TME, were shown to induce tumor cell growth and survival [62]. They were also unable to reach maturation, leading to suppressed antitumor immune response, suggestive of potential new ways to target the TME.

3.3 Clinical Implications

In the last several years, clear clinical activity was observed with the use of immunotherapy in solid malignancies, and many immunotherapy-related studies emerged in hematologic malignancies including non-Hodgkin lymphoma. By capitalizing on what we have learned from the solid tumor experience and with a better understanding of how modulation of tumor microenvironment (TME) can be used, we may be able to better treat patients with T-cell lymphoma. A comprehensive understanding of the tumor microenvironment allows for the development of therapeutic strategies that are both rational and potentially effective. Targeting macrophages, regulatory T-cells, or optimizing the efficacy of effector T-cells are a few of the potential opportunities to improve patient outcomes in T-cell lymphoma.

3.3.1 Therapeutic Targets

The use of brentuximab vedotin (BV) as a means to direct a chemotherapy agent to CD30 positive cells has proven to be an effective treatment in patients with TCL. While BV delivers chemotherapy to malignant cells, the monomethyl auristatin E (MMAE) payload also leaks out of the target cells and is scavenged by surrounding macrophages and monocytes. Indirectly this is a mechanism by which the pro-malignant cell effects of intratumoral macrophages may be suppressed. Clinical trials thus far have shown that the use of BV is effective in TCL. BV has been added to frontline chemotherapy for peripheral T-cell lymphoma and was shown to be safe and effective. Now with long-term follow up, the 5-year progression-free survival is 52% and the 5-year overall survival is 80% (Fanale MA [20]). In CTCL, a randomized trial comparing BV to physician's choice of methotrexate or

bexarotene showed a substantial improvement in the overall response rate as well as the progression-free survival for patients receiving BV [47].

Strategies to target intratumoral regulatory T-cells have included the use of mogamolizumab, a CCR4 targeting antibody, which targets malignant T-cells but also depletes regulatory T-cells that express CCR4. In a randomized comparison of mogamolizumab versus vorinostat in cutaneous T-cell lymphoma, patients receiving mogamolizumab had a median progression-free survival of 7.7 months compared to 3.1 months for vorinostat [32].

Immune checkpoint therapy has also proven to be effective in T-cell lymphoma. The use of pembrolizumab in patients with cutaneous T-cell lymphoma showed an overall response rate of 38% [31]. In patients with peripheral T-cell lymphoma treated with nivolumab in the initial phase 1 trial, responses were also seen although the number of patients was very small [35]. The use of anti-PD1 antibodies in TCL may, however, be challenging as both the infiltrating normal T-cells and the malignant T-cell may express PD1 on the cell surface. While blocking inhibitory signals may promote effector T-cell proliferation and function, there is a potential risk that PD-1 blockade may remove signals that inhibit the malignant clone and promote malignant cell growth and survival.

Finally, improving the phagocytic ability of intratumoral monocytes may be an additional strategy to utilize the tumor microenvironment in a positive fashion. Blockade of the CD47 "don't eat me signal" has proven promising in initial phase 1 trials. The use of SIRPalpha-Fc to optimize macrophage function in phase 1 trials in lymphoma has been shown to be well tolerated and clinical responses thus far appear promising including responses in CTCL [14].

Overall, a greater understanding of the TME will allow us to optimize therapies by utilizing the power of the intratumoral immune system. So far, early clinical trials suggest that responses are seen when effector T-cells are activated, regulatory T-cells are suppressed, or macrophages are stimulated to phagocytose malignant cells. Future directions will require combination approaches using all of these therapies to effectively modulate the TME and improve patient outcomes.

References

1. Alegre ML, Frauwirth KA, Thompson CB (2001) T-cell regulation by CD28 and CTLA-4. Nat Rev Immunol 1(3):220–228. https://doi.org/10.1038/35105024
2. Andersen MH, Schrama D, Thor Straten P, Becker JC (2006) Cytotoxic T cells. J Investig Dermatol 126(1):32–41. https://doi.org/10.1038/sj.jid.5700001
3. Ansell SM, Vonderheide RH (2013) Cellular composition of the tumor microenvironment. Am Soc Clin Oncol Educ Book. https://doi.org/10.1200/EdBook_AM.2013.33.e91
4. Balkwill F (2004) Cancer and the chemokine network. Nat Rev Cancer 4(7):540–550. https://doi.org/10.1038/nrc1388
5. Bennett CL, Christie J, Ramsdell F, Brunkow ME, Ferguson PJ, Whitesell L, Kelly TE, Saulsbury FT, Chance PF, Ochs HD (2001) The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. Nat Genet 27 (1):20–21. https://doi.org/10.1038/83713

6. Bingle L, Brown NJ, Lewis CE (2002) The role of tumour-associated macrophages in tumour progression: implications for new anticancer therapies. J Pathol 196(3):254–265. https://doi.org/10.1002/path.1027
7. Biswas SK, Gangi L, Paul S, Schioppa T, Saccani A, Sironi M, Bottazzi B, Doni A, Vincenzo B, Pasqualini F, Vago L, Nebuloni M, Mantovani A, Sica A (2006) A distinct and unique transcriptional program expressed by tumor-associated macrophages (defective NF-kappaB and enhanced IRF-3/STAT1 activation). Blood 107(5):2112–2122. https://doi.org/10.1182/blood-2005-01-0428
8. Brunkow ME, Jeffery EW, Hjerrild KA, Paeper B, Clark LB, Yasayko SA, Wilkinson JE, Galas D, Ziegler SF, Ramsdell F (2001) Disruption of a new forkhead/winged-helix protein, scurfin, results in the fatal lymphoproliferative disorder of the scurfy mouse. Nat Genet 27 (1):68–73. https://doi.org/10.1038/83784
9. Canioni D, Salles G, Mounier N, Brousse N, Keuppens M, Morchhauser F, Lamy T, Sonet A, Rousselet MC, Foussard C, Xerri L (2008) High numbers of tumor-associated macrophages have an adverse prognostic value that can be circumvented by rituximab in patients with follicular lymphoma enrolled onto the GELA-GOELAMS FL-2000 trial. J Clin Oncol 26 (3):440–446. https://doi.org/10.1200/jco.2007.12.8298
10. Carreras J, Lopez-Guillermo A, Fox BC, Colomo L, Martinez A, Roncador G, Montserrat E, Campo E, Banham AH (2006) High numbers of tumor-infiltrating FOXP3-positive regulatory T cells are associated with improved overall survival in follicular lymphoma. Blood 108 (9):2957–2964. https://doi.org/10.1182/blood-2006-04-018218
11. Carreras J, Lopez-Guillermo A, Roncador G, Villamor N, Colomo L, Martinez A, Hamoudi R, Howat WJ, Montserrat E, Campo E (2009) High numbers of tumor-infiltrating programmed cell death 1-positive regulatory lymphocytes are associated with improved overall survival in follicular lymphoma. J Clin Oncol 27(9):1470–1476. https://doi.org/10.1200/jco.2008.18.0513
12. Castelli C, Rivoltini L, Andreola G, Carrabba M, Renkvist N, Parmiani G (2000) T-cell recognition of melanoma-associated antigens. J Cell Physiol 182(3):323–331. https://doi.org/10.1002/(sici)1097-4652(200003)182:3%3c323:aid-jcp2%3e3.0.co;2-%23
13. Chen BJ, Chapuy B, Ouyang J, Sun HH, Roemer MG, Xu ML, Yu H, Fletcher CD, Freeman GJ, Shipp MA, Rodig SJ (2013) PD-L1 expression is characteristic of a subset of aggressive B-cell lymphomas and virus-associated malignancies. Clin Cancer Res 19 (13):3462–3473. https://doi.org/10.1158/1078-0432.ccr-13-0855
14. Querfeld C, Thompson J, Taylor M, Pillai R, Johnson LD, Catalano T, Petrova PS, Uger RA, Irwin M, Sievers EL, Akilov OE (2017) A single direct intratumoral injection of TTI-621 (SIRPαFc) Induces antitumor activity in patients with relapsed/refractory mycosis fungoides and sézary syndrome: preliminary findings employing an immune checkpoint inhibitor blocking the CD47 "Do Not Eat" Signal. In: Proceedings of ASH 2017; Abstract#4076
15. Chung JS, Shiue LH, Duvic M, Pandya A, Cruz PD Jr, Ariizumi K (2011) Sezary syndrome cells overexpress syndecan-4 bearing distinct heparan sulfate moieties that suppress T-cell activation by binding DC-HIL and trapping TGF-beta on the cell surface. Blood 117 (12):3382–3390. https://doi.org/10.1182/blood-2010-08-302034
16. Coussens LM, Zitvogel L, Palucka AK (2013) Neutralizing tumor-promoting chronic inflammation: a magic bullet? Science 339(6117):286–291. https://doi.org/10.1126/science.1232227
17. Dave SS, Wright G, Tan B, Rosenwald A, Gascoyne RD, Chan WC, Fisher RI, Braziel RM, Rimsza LM, Grogan TM, Miller TP, LeBlanc M, Greiner TC, Weisenburger DD, Lynch JC, Vose J, Armitage JO, Smeland EB, Kvaloy S, Holte H, Delabie J, Connors JM, Lansdorp PM, Ouyang Q, Lister TA, Davies AJ, Norton AJ, Muller-Hermelink HK, Ott G, Campo E, Montserrat E, Wilson WH, Jaffe ES, Simon R, Yang L, Powell J, Zhao H, Goldschmidt N, Chiorazzi M, Staudt LM (2004) Prediction of survival in follicular lymphoma based on molecular features of tumor-infiltrating immune cells. N Engl J Med 351(21):2159–2169. https://doi.org/10.1056/NEJMoa041869

18. de Leval L, Rickman DS, Thielen C, Reynies A, Huang YL, Delsol G, Lamant L, Leroy K, Briere J, Molina T, Berger F, Gisselbrecht C, Xerri L, Gaulard P (2007) The gene expression profile of nodal peripheral T-cell lymphoma demonstrates a molecular link between angioimmunoblastic T-cell lymphoma (AITL) and follicular helper T (TFH) cells. Blood 109 (11):4952–4963. https://doi.org/10.1182/blood-2006-10-055145
19. Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, Roche PC, Lu J, Zhu G, Tamada K, Lennon VA, Celis E, Chen L (2002) Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med 8(8):793–800. https://doi.org/10.1038/nm730
20. Fanale MA, Horwitz S, Forero-Torres A, Bartlett NL, Advani RH, Pro B, Chen RW, Davies A, Illidge TM, Uttarwar M, Huebner D, Ren H, Shustov AR (2017) Five-year survival results: frontline brentuximab vedotin in combination with CHP in patients with CD30-expressing peripheral T-Cell lymphomas. In: Proceedings of ASH 2017 Abstract#2790
21. Farinha P, Al-Tourah A, Gill K, Klasa R, Connors JM, Gascoyne RD (2010) The architectural pattern of FOXP3-positive T cells in follicular lymphoma is an independent predictor of survival and histologic transformation. Blood 115(2):289–295. https://doi.org/10.1182/blood-2009-07-235598
22. Farinha P, Masoudi H, Skinnider BF, Shumansky K, Spinelli JJ, Gill K, Klasa R, Voss N, Connors JM, Gascoyne RD (2005) Analysis of multiple biomarkers shows that lymphoma-associated macrophage (LAM) content is an independent predictor of survival in follicular lymphoma (FL). Blood 106(6):2169–2174. https://doi.org/10.1182/blood-2005-04-1565
23. Flavell RA, Sanjabi S, Wrzesinski SH, Licona-Limon P (2010) The polarization of immune cells in the tumour environment by TGFbeta. Nat Rev Immunol 10(8):554–567. https://doi.org/10.1038/nri2808
24. Gaulard P, de Leval L (2014) The microenvironment in T-cell lymphomas: emerging themes. Semin Cancer Biol 24:49–60. https://doi.org/10.1016/j.semcancer.2013.11.004
25. Gjerdrum LM, Woetmann A, Odum N, Burton CM, Rossen K, Skovgaard GL, Ryder LP, Ralfkiaer E (2007) FOXP3+ regulatory T cells in cutaneous T-cell lymphomas: association with disease stage and survival. Leukemia 21(12):2512–2518. https://doi.org/10.1038/sj.leu.2404913
26. Gupta M, Stenson M, O'Byrne M, Maurer MJ, Habermann T, Cerhan JR, Weiner GW, Witzig TE (2016) Comprehensive serum cytokine analysis identifies IL-1RA and soluble IL-2Ralpha as predictors of event-free survival in T-cell lymphoma. Ann Oncol 27(1):165–172. https://doi.org/10.1093/annonc/mdv486
27. Huang Y, de Reynies A, de Leval L, Ghazi B, Martin-Garcia N, Travert M, Bosq J, Briere J, Petit B, Thomas E, Coppo P, Marafioti T, Emile JF, Delfau-Larue MH, Schmitt C, Gaulard P (2010) Gene expression profiling identifies emerging oncogenic pathways operating in extranodal NK/T-cell lymphoma, nasal type. Blood 115(6):1226–1237. https://doi.org/10.1182/blood-2009-05-221275
28. Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N (2002) Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci USA 99(19):12293–12297. https://doi.org/10.1073/pnas.192461099
29. Kataoka K, Shiraishi Y, Takeda Y, Sakata S, Matsumoto M, Nagano S, Maeda T, Nagata Y, Kitanaka A, Mizuno S, Tanaka H, Chiba K, Ito S, Watatani Y, Kakiuchi N, Suzuki H, Yoshizato T, Yoshida K, Sanada M, Itonaga H, Imaizumi Y, Totoki Y, Munakata W, Nakamura H, Hama N, Shide K, Kubuki Y, Hidaka T, Kameda T, Masuda K, Minato N, Kashiwase K, Izutsu K, Takaori-Kondo A, Miyazaki Y, Takahashi S, Shibata T, Kawamoto H, Akatsuka Y, Shimoda K, Takeuchi K, Seya T, Miyano S, Ogawa S (2016) Aberrant PD-L1 expression through 3′-UTR disruption in multiple cancers. Nature 534 (7607):402–406. https://doi.org/10.1038/nature18294

30. Keir ME, Butte MJ, Freeman GJ, Sharpe AH (2008) PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 26:677–704. https://doi.org/10.1146/annurev.immunol.26.021607.090331
31. Khodadoust M, Rook A, Porcu P, Foss F, Moskowitz A, Shustov AR, Shanbhag S, Sokol L, Shine R, Fling SP, Li S, Rahbar Z, Kim J, Yang Y, Yearley J, Chartash EK, Townson SM, Subrahmanyam PB, Maecker H, Alizadeh AA, Dai J, Horwitz SM, Sharon E, Kohrt HE, Cheever MA, Kim YH (2016) Pembrolizumab for treatment of relapsed/refractory mycosis fungoides and sézary syndrome: clinical efficacy in a CITN multicenter phase 2 study. In: Proceedings of Third World Congress of Cutaneous Lymphoma
32. Kim YH, Bagot M, Pinter-Brown L, Rook AH, Porcu P, Horwitz SM, Whittaker S, Tokura Y, Vermeer M, Zinzani PL, Sokol L, Morris S, Kim E, Ortiz-Romero PL, Eradat H, Scarisbrick J, Tsianakas A, Elmets C, Dalle S, Fisher DC, Halwani AS, Poligone B, Greer JP, Fierro MT, Khot A, Moskowitz AJ, Dwyer K, Moriya J, Humphrey J, Hudgens S, Grebennik DO, Tobinai K, and Duvic M (2017) Anti-CCR4 monoclonal antibody, mogamulizumab, demonstrates significant improvement in PFS compared to vorinostat in patients with previously treated cutaneous T-cell lymphoma (CTCL): results from the phase III MAVORIC study clinically relevant abstract. In: Proceedings of ASH 2017 Abstract#817
33. Lamant L, McCarthy K, d'Amore E, Klapper W, Nakagawa A, Fraga M, Maldyk J, Simonitsch-Klupp I, Oschlies I, Delsol G, Mauguen A, Brugieres L, Le Deley MC (2011) Prognostic impact of morphologic and phenotypic features of childhood ALK-positive anaplastic large-cell lymphoma: results of the ALCL99 study. J Clin Oncol 29(35):4669–4676. https://doi.org/10.1200/jco.2011.36.5411
34. Lee AM, Clear AJ, Calaminici M, Davies AJ, Jordan S, MacDougall F, Matthews J, Norton AJ, Gribben JG, Lister TA, Goff LK (2006) Number of CD4+ cells and location of forkhead box protein P3-positive cells in diagnostic follicular lymphoma tissue microarrays correlates with outcome. J Clin Oncol 24(31):5052–5059. https://doi.org/10.1200/jco.2006.06.4642
35. Lesokhin AM, Ansell SM, Armand P, Scott EC, Halwani A, Gutierrez M, Millenson MM, Cohen AD, Schuster SJ, Lebovic D, Dhodapkar M, Avigan D, Chapuy B, Ligon AH, Freeman GJ, Rodig SJ, Cattry D, Zhu L, Grosso JF, Bradley Garelik MB, Shipp MA, Borrello I, Timmerman J (2016) Nivolumab in patients with relapsed or refractory hematologic malignancy: preliminary results of a phase Ib study. J Clin Oncol 34(23):2698–2704. https://doi.org/10.1200/jco.2015.65.9789
36. Lin Y, Gustafson MP, Bulur PA, Gastineau DA, Witzig TE, Dietz AB (2011) Immunosuppressive CD14+ HLA-DR(low)/-monocytes in B-cell non-Hodgkin lymphoma. Blood 117(3):872–881. https://doi.org/10.1182/blood-2010-05-283820
37. Mantovani A, Allavena P, Sozzani S, Vecchi A, Locati M, Sica A (2004) Chemokines in the recruitment and shaping of the leukocyte infiltrate of tumors. Semin Cancer Biol 14(3):155–160. https://doi.org/10.1016/j.semcancer.2003.10.001
38. Mantovani A, Sica A, Sozzani S, Allavena P, Vecchi A, Locati M (2004) The chemokine system in diverse forms of macrophage activation and polarization. Trends Immunol 25(12):677–686. https://doi.org/10.1016/j.it.2004.09.015
39. Marzec M, Zhang Q, Goradia A, Raghunath PN, Liu X, Paessler M, Wang HY, Wysocka M, Cheng M, Ruggeri BA, Wasik MA (2008) Oncogenic kinase NPM/ALK induces through STAT3 expression of immunosuppressive protein CD274 (PD-L1, B7-H1). Proc Natl Acad Sci USA 105(52):20852–20857. https://doi.org/10.1073/pnas.0810958105
40. McHeyzer-Williams LJ, Pelletier N, Mark L, Fazilleau N, McHeyzer-Williams MG (2009) Follicular helper T cells as cognate regulators of B cell immunity. Curr Opin Immunol 21(3):266–273. https://doi.org/10.1016/j.coi.2009.05.010
41. Montero AJ, Diaz-Montero CM, Kyriakopoulos CE, Bronte V, Mandruzzato S (2012) Myeloid-derived suppressor cells in cancer patients: a clinical perspective. J Immunother 35(2):107–115. https://doi.org/10.1097/cji.0b013e318242169f

42. Murakami N, Riella LV (2014) Co-inhibitory pathways and their importance in immune regulation. Transplantation 98(1):3–14. https://doi.org/10.1097/tp.0000000000000169
43. Nagato T, Ohkuri T, Ohara K, Hirata Y, Kishibe K, Komabayashi Y, Ueda S, Takahara M, Kumai T, Ishibashi K, Kosaka A, Aoki N, Oikawa K, Uno Y, Akiyama N, Sado M, Takei H, Celis E, Harabuchi Y, Kobayashi H (2017) Programmed death-ligand 1 and its soluble form are highly expressed in nasal natural killer/T-cell lymphoma: a potential rationale for immunotherapy. Cancer Immunol Immunother CII 66(7):877–890. https://doi.org/10.1007/s00262-017-1987-x
44. O'Connor OA, Bhagat G, Ganapathi K, Pedersen MB, D'Amore F, Radeski D, Bates SE (2014) Changing the paradigms of treatment in peripheral T-cell lymphoma: from biology to clinical practice. Clin Cancer Res 20(20):5240–5254. https://doi.org/10.1158/1078-0432.ccr-14-2020
45. Papadi B, Polski JM, Clarkson DR, Liu-Dumlao TO (2012) Atypical angioimmunoblastic T-cell lymphomas masquerading as systemic polyclonal B-immunoblastic proliferation. Virchows Archiv Int J Pathol 461(3):323–331. https://doi.org/10.1007/s00428-012-1280-5
46. Piccaluga PP, Agostinelli C, Califano A, Carbone A, Fantoni L, Ferrari S, Gazzola A, Gloghini A, Righi S, Rossi M, Tagliafico E, Zinzani PL, Zupo S, Baccarani M, Pileri SA (2007) Gene expression analysis of angioimmunoblastic lymphoma indicates derivation from T follicular helper cells and vascular endothelial growth factor deregulation. Cancer Res 67 (22):10703–10710. https://doi.org/10.1158/0008-5472.can-07-1708
47. Prince HM, Kim YH, Horwitz SM, Dummer R, Scarisbrick J, Quaglino P, Zinzani PL, Wolter P, Sanches JA, Ortiz-Romero PL, Akilov OE, Geskin L, Trotman J, Taylor K, Dalle S, Weichenthal M, Walewski J, Fisher D, Dreno B, Stadler R, Feldman T, Kuzel TM, Wang Y, Palanca-Wessels MC, Zagadailov E, Trepicchio WL, Zhang W, Lin HM, Liu Y, Huebner D, Little M, Whittaker S, Duvic M (2017) Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. Lancet 390(10094):555–566. https://doi.org/10.1016/s0140-6736(17)31266-7
48. Sakaguchi S, Sakaguchi N, Asano M, Itoh M, Toda M (1995) Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha-chains (CD25). Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases. J Immunol 155(3):1151–1164
49. Sakaguchi S, Yamaguchi T, Nomura T, Ono M (2008) Regulatory T cells and immune tolerance. Cell 133(5):775–787. https://doi.org/10.1016/j.cell.2008.05.009
50. Sato F, Ishida T, Ito A, Mori F, Masaki A, Takino H, Narita T, Ri M, Kusumoto S, Suzuki S, Komatsu H, Niimi A, Ueda R, Inagaki H, Iida S (2013) Angioimmunoblastic T-cell lymphoma mice model. Leuk Res 37(1):21–27. https://doi.org/10.1016/j.leukres.2012.09.009
51. Schmieder A, Michel J, Schonhaar K, Goerdt S, Schledzewski K (2012) Differentiation and gene expression profile of tumor-associated macrophages. Semin Cancer Biol 22(4):289–297. https://doi.org/10.1016/j.semcancer.2012.02.002
52. Seder RA, Paul WE (1994) Acquisition of lymphokine-producing phenotype by CD4+ T cells. Annu Rev Immunol 12:635–673. https://doi.org/10.1146/annurev.iy.12.040194.003223
53. Siegel RL, Miller KD (2017) Jemal A (2017) Cancer Statistics. CA Cancer J Clin 67(1):7–30. https://doi.org/10.3322/caac.21387
54. Stockwin LH, McGonagle D, Martin IG, Blair GE (2000) Dendritic cells: immunological sentinels with a central role in health and disease. Immunol Cell Biol 78(2):91–102. https://doi.org/10.1046/j.1440-1711.2000.00888.x
55. Sweetenham JW, Goldman B, LeBlanc ML, Cook JR, Tubbs RR, Press OW, Maloney DG, Fisher RI, Rimsza LM, Braziel RM, Hsi ED (2010) Prognostic value of regulatory T cells, lymphoma-associated macrophages, and MUM-1 expression in follicular lymphoma treated before and after the introduction of monoclonal antibody therapy: a southwest oncology group study. Ann Oncol 21(6):1196–1202. https://doi.org/10.1093/annonc/mdp460
56. Travert M, Huang Y, de Leval L, Martin-Garcia N, Delfau-Larue MH, Berger F, Bosq J, Briere J, Soulier J, Macintyre E, Marafioti T, de Reynies A, Gaulard P (2012) Molecular features of hepatosplenic T-cell lymphoma unravels potential novel therapeutic targets. Blood 119(24):5795–5806. https://doi.org/10.1182/blood-2011-12-396150

57. Tsushima F, Yao S, Shin T, Flies A, Flies S, Xu H, Tamada K, Pardoll DM, Chen L (2007) Interaction between B7-H1 and PD-1 determines initiation and reversal of T-cell anergy. Blood 110(1):180–185. https://doi.org/10.1182/blood-2006-11-060087
58. Tzankov A, Meier C, Hirschmann P, Went P, Pileri SA, Dirnhofer S (2008) Correlation of high numbers of intratumoral FOXP3+ regulatory T cells with improved survival in germinal center-like diffuse large B-cell lymphoma, follicular lymphoma and classical Hodgkin's lymphoma. Haematologica 93(2):193–200. https://doi.org/10.3324/haematol.11702
59. Varghese B, Widman A, Do J, Taidi B, Czerwinski DK, Timmerman J, Levy S, Levy R (2009) Generation of CD8+ T cell-mediated immunity against idiotype-negative lymphoma escapees. Blood 114(20):4477–4485. https://doi.org/10.1182/blood-2009-05-223263
60. Walunas TL, Lenschow DJ, Bakker CY, Linsley PS, Freeman GJ, Green JM, Thompson CB, Bluestone JA (1994) CTLA-4 can function as a negative regulator of T cell activation. Immunity 1(5):405–413
61. Wilcox RA, Feldman AL, Wada DA, Yang ZZ, Comfere NI, Dong H, Kwon ED, Novak AJ, Markovic SN, Pittelkow MR, Witzig TE, Ansell SM (2009) B7-H1 (PD-L1, CD274) suppresses host immunity in T-cell lymphoproliferative disorders. Blood 114(10):2149–2158. https://doi.org/10.1182/blood-2009-04-216671
62. Wilcox RA, Wada DA, Ziesmer SC, Elsawa SF, Comfere NI, Dietz AB, Novak AJ, Witzig TE, Feldman AL, Pittelkow MR, Ansell SM (2009) Monocytes promote tumor cell survival in T-cell lymphoproliferative disorders and are impaired in their ability to differentiate into mature dendritic cells. Blood 114(14):2936–2944. https://doi.org/10.1182/blood-2009-05-220111
63. Wu X, Schulte BC, Zhou Y, Haribhai D, Mackinnon AC, Plaza JA, Williams CB, Hwang ST (2014) Depletion of M2-like tumor-associated macrophages delays cutaneous T-cell lymphoma development in vivo. J Invest Dermatol 134(11):2814–2822. https://doi.org/10.1038/jid.2014.206
64. Yang ZZ, Grote DM, Xiu B, Ziesmer SC, Price-Troska TL, Hodge LS, Yates DM, Novak AJ, Ansell SM (2014) TGF-beta upregulates CD70 expression and induces exhaustion of effector memory T cells in B-cell non-Hodgkin's lymphoma. Leukemia 28(9):1872–1884. https://doi.org/10.1038/leu.2014.84
65. Yang ZZ, Grote DM, Ziesmer SC, Manske MK, Witzig TE, Novak AJ, Ansell SM (2011) Soluble IL-2Ralpha facilitates IL-2-mediated immune responses and predicts reduced survival in follicular B-cell non-Hodgkin lymphoma. Blood 118(10):2809–2820. https://doi.org/10.1182/blood-2011-03-340885
66. Yang ZZ, Grote DM, Ziesmer SC, Xiu B, Yates NR, Secreto FJ, Hodge LS, Witzig TE, Novak AJ, Ansell SM (2013) Soluble and membrane-bound TGF-beta-mediated regulation of intratumoral T cell differentiation and function in B-cell non-Hodgkin lymphoma. PLoS ONE 8(3):e59456. https://doi.org/10.1371/journal.pone.0059456
67. Yang ZZ, Novak AJ, Stenson MJ, Witzig TE, Ansell SM (2006) Intratumoral CD4+ CD25 + regulatory T-cell-mediated suppression of infiltrating CD4+ T cells in B-cell non-Hodgkin lymphoma. Blood 107(9):3639–3646. https://doi.org/10.1182/blood-2005-08-3376
68. Yao S, Chen L (2006) Reviving exhausted T lymphocytes during chronic virus infection by B7-H1 blockade. Trends in molecular medicine 12(6):244–246. https://doi.org/10.1016/j.molmed.2006.04.007
69. Zhang W, Wang L, Zhou D, Cui Q, Zhao D, Wu Y (2011) Expression of tumor-associated macrophages and vascular endothelial growth factor correlates with poor prognosis of peripheral T-cell lymphoma, not otherwise specified. Leuk Lymphoma 52(1):46–52. https://doi.org/10.3109/10428194.2010.529204

Peripheral T-Cell Lymphoma, not Otherwise Specified (PTCL-NOS)

4

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Abstract

Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) is a World Health Organization (WHO)-defined diagnostic category within the highly heterogeneous group of mature post-thymic T-cell neoplasms. It is the most common subtype of mature post-thymic T-cell neoplasms globally, accounting for up to 35% of PTCL cases in Europe and North America. PTCL-NOS is a diagnosis of exclusion, comprising several disease entities that differ in biology, clinical presentation, and outcome. The diagnosis of PTCL-NOS is made based on the presence of typical histopathological features of lymphoma, an aberrant T-cell immunophenotype, often with a loss of CD5 and CD7, and a clonal T-cell receptor (TCR) gene rearrangement, in the appropriate clinical context. Unlike other types of T-cell lymphoma, recurrent mutations to assist with the diagnosis have not been identified. Patients often present with advanced stage. Prognosis is poor, with a 5-year overall survival (OS) of 20-30%. Anthracycline-based combination

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chemotherapy remains the most frequently used frontline strategy, with overall response rates (ORR) of 50-60%, and complete response rates (CRR) of 20-30%. Prospective studies with intent-to-treat analyses have shown that consolidation with high-dose chemotherapy and autologous stem cell transplant (ASCT) results in progression-free survivals (PFS) that compare favorably with historical cohorts and may improve OS in selected patient populations. However, randomized data are still lacking. Over the past decade, therapeutic agents approved in the relapsed and refractory setting have produced response rates of up to 33% and median PFS up to 18 months. Overall, outcomes remain poor and there is a dire need for more effective treatments. This review discusses the latest information on the diagnosis and treatment of PTCL-NOS.

Keywords
Peripheral T-cell lymphoma · Gene expression profiling · Somatic mutations
Hematopoietic stem cell transplantation · Novel therapies

4.1 Introduction

Clinically and biologically, peripheral T-cell lymphomas (PTCLs) are a highly heterogeneous and incompletely characterized group of lymphoid malignancies that arise from the transformation of mature, post-thymic (hence "peripheral") T-cells. They account for approximately 10–12% of all non-Hodgkin lymphomas (NHLs) and for a significantly greater fraction of aggressive lymphomas. The World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues divides PTCLs into nodal, extranodal, and leukemic types, each with multiple disease entities. Those that are not further classifiable into any of the more distinct disease entities, are called PTCL not otherwise specified (PTCL-NOS) [1, 2]. This heterogeneous, so-called wastebasket, category of PTCL accounts for up to 30–35% of all PTCL cases in Europe and North America and represents the most common subtype globally, reflecting the fact that a large fraction of neoplasms within the spectrum of PTCL still need to be precisely characterized [1, 3]. PTCL-NOS are predominantly nodal lymphomas, although extranodal involvement at presentation or relapse is common. The most common extranodal sites are the skin and the gastrointestinal tract, but the bone marrow, lungs, and peripheral blood can also be involved. There is significant geographical variation in the reported frequency of PTCL-NOS, which is more common in North America and Europe and less common in Asia [1, 3, 4]. Advanced stage disease is the rule at presentation, with up to 60% of the patients presenting in stage IV and over half having an unfavorable risk by the International Prognostic Index (IPI) [5, 6].

PTCL-NOS are aggressive, chemoresistant neoplasms, with 5-year overall survival (OS) rates ranging from 11 to 58% depending on the stage, prognostic index score, and molecular profiling, and median survival at 5 years no greater than 30% [1, 3, 7]. Anthracycline-based combination chemotherapy with CHOP-like regimens remains the most frequently used front-line strategy for patients with PTCL-NOS, with overall response rates (ORR) of 50– 60%, and complete response rates (CRR) of 20– 30%. The importance of anthracyclines remains controversial and non-anthracycline-containing regimens are being investigated. Long-term survival remains poor (median OS at 3 years ~30%) [1, 5, 8]. Studies suggest that consolidation with high-dose chemotherapy and autologous stem cell transplantation (ASCT) improves progression-free survival (PFS) and may improve OS, but selection bias, lack of randomization, and high dropout rates in intent-to-treat studies prevent definitive conclusions about the value of this approach for most patients. Furthermore, the absence of robust risk stratification tools has made identifying the subset of patients who may benefit from ASCT consolidation challenging [7, 8]. This review discusses the latest information on the diagnosis and treatment of PTCL-NOS.

4.2 Epidemiology and Risk Factors

The report of the International Peripheral T-cell Lymphoma Project (IPTCLP), published in 2008, was the largest aggregate cohort of clinically annotated T-cell lymphomas cases ever reported. It included centrally reviewed PTCL cases from 22 academic institutions in North America, Europe, and Asia. Currently, two large registries prospectively enrolling PTCL patients include the T-cell Project (TCP) and the Comprehensive Oncology Measures for Peripheral T-cell Lymphoma Treatment (COMPLETE) registry. These registries, which are now mature, are starting to provide very valuable information on patient characteristics, clinicopathological features, prognosis, treatments, and outcomes [4, 9]. Data from these registries confirm PTCL-NOS as the most prevalent subtype of PTCL overall, with a global reported frequency ranging between 22 and 36%. The incidence is about 25–36% in North America and Europe where it is the most common type of PTCL. In Asia, adult T-cell lymphoma/leukemia (ATLL) was more common, at about 25%, with PTCL-NOS being the next most common T-cell lymphoma at 22% [4, 9, 10].

A study of racial patterns of the incidence of PTCL, analyzing data from the population-based US Surveillance, Epidemiology, and End Results (SEER) cancer registry, showed a higher incidence of PTCL-NOS in blacks compared to Hispanic and non-Hispanic whites, Asian/Pacific Islanders, American Indian, and Alaskan natives. The incidence rate ratio for PTCL-NOS for blacks compared to non-Hispanic whites was 1.67 (95%CI, 1.53–1.82). Compared to non-Hispanic whites, all the other races had lower incidence rate ratios. The higher rates of PTCLs seen in blacks have been found to be due to the higher rates of PTCL-NOS [11]. The median age at presentation is about 60 years with a male predominance of

about 1.9:1 [4, 11–13]. Reported risk factors include a history of celiac disease, psoriasis, and cigarette smoking for 40 or more years compared with nonsmokers and a family history of hematologic malignancies. Alcohol consumption of at least one alcoholic drink per month, sun exposure, and a history of allergies have been reported to be associated with a lower risk [14].

4.3 Pathological Classification, Gene Expression Profiling, and Mutational Landscape

A revision of the fourth edition of the WHO classification of lymphoid and myeloid neoplasms was published in 2016. This update incorporated new information from basic science and clinical research over the 8 years since the previous edition, published in 2008. The classification of PTCL-NOS in 2008 was based on its distinct clinical, morphologic, immunophenotypic, and cytogenetic features that distinguished it from other types of nodal T-cell lymphomas. The most recent revision incorporates information on recurrent mutations and gene expression profiles (GEPs) identified in molecular biology and genetic studies [10, 15–17]. This has allowed some of these diseases to be reclassified into new or previously defined entities that are clinically relevant for practice and research [15, 18].

Despite the use of these advanced diagnostic tools, PTCL-NOS remains a very heterogeneous disease, not in the least pathologically [10, 16]. The involved lymph node more often shows a diffuse pattern of involvement but can be interfollicular or paracortical with effacement of the normal architecture of the node. There are an increased number of high endothelial venules which can also be seen in angioimmunoblastic T-cell lymphoma (AITL) making the diagnosis challenging. Extensive immunophenotyping may be necessary to distinguish between the two [16, 19]. The 2008 WHO classification described three morphologic variants of PTCL-NOS. A lymphoepithelioid (Lennert) variant, a T-zone variant, and a follicular variant. Cases that do not fit into any of these three categories are described as unspecified PTCL [12, 16]. A report of 340 cases of PTCL-NOS from the International Peripheral T-cell Lymphoma Project classified 88.5% of the cases as unspecified PTCL, 8.2% as lymphoepithelioid (Lennert) PTCL, 1.8% as follicular PTCL, and 1.5% as T-zone PTCL [12].

The lymphoepithelioid variant (Lennert's type) is characterized by a rich infiltrate of reactive epithelioid histiocytes with scattered Reed–Sternberg (RS)-like cells sometimes positive for the Epstein–Barr virus (EBV), and small malignant cells in a diffuse interfollicular growth pattern derived predominately from CD8 positive cytotoxic cells [16, 20]. In the T-zone variant, small to medium sized lymphoid cells are described as being restricted to the paracortical areas of the involved lymph nodes. The follicular variant has been described as mimicking follicular lymphoma with neoplastic cells forming intrafollicular aggregates. It can also mimic nodular lymphocyte-predominant Hodgkin lymphoma with small nodular aggregates formed in settings of progressively transformed germinal

centers or mimic nodal marginal zone lymphoma with nodular aggregates and enlarged perifollicular zones surrounding hyperplastic follicles [10, 16, 19–21]. A rare and indolent form of PTCL-NOS has been reported in the patients with autoimmune thyroiditis. It involves the thyroid gland and may spontaneously regress without therapy. This variant is associated with CD3, CD4, and CXCR3 positivity [16, 22].

The cytology in PTCL-NOS is often pleomorphic, with most cases consisting of a mixed population of medium to large cells with a high proliferation rate. Clear cells are frequently present [16, 19]. The expression of pan T-cell antigens by the malignant cells in PTCL-NOS is highly variable, with reduced or absent expression of CD5 and CD7 in up to 80% of cases. Loss of expression of CD3 and CD2 are less common. The predominant immunophenotype in PTCL-NOS is CD3+ CD4+, without cytotoxic markers. A subset of PTCL-NOS, however, express CD8+ with cytotoxic markers (TIA1, Granzyme-B, and Perforin), and CD56. Yet another subset shows double positivity, or double negativity, for CD4 and CD8 [10, 12, 16, 19]. The expression of CD52 is highly variable, ranging from 35 to 100%. Flow cytometry is more sensitive than immunohistochemistry (IHC) in detecting CD52 expression and is also useful in quantification [21, 23, 24]. Quantification of surface CD52 expression has been suggested to be of utility in determining response to alemtuzumab, a humanized anti-CD52 monoclonal antibody [20, 21]. The expression of another well-defined target of therapy, CD30, has been reported in about 32–58% of PTCL-NOS cases, as opposed to 100% of ALK-negative anaplastic large cell lymphoma (ALCL) cases [12, 20, 25]. Although the pattern of CD30 positivity in PTCL-NOS is typically focal with variable staining intensity, distinguishing between the two entities can be challenging [16, 20]. Gene expression profiling (GEP) has suggested shared oncogenic pathways between PTCL-NOS and ALK-ALCL but the signatures are sufficiently different to distinguish them [10, 16, 21]. Given the overlap, an accurate diagnosis relies heavily on incorporating and thoroughly reviewing all of the clinical information and data from morphologic, immunophenotypic, cytogenetic and GEPs studies [10, 12, 16, 20, 21]. A study reporting how often experts agreed on a diagnosis in the cases of PTCL reports an agreement rate of 75% for PTCL-NOS, when all the available data was fully reviewed. The most challenging distinctions were between AITL (34%) and ALK-negative ALCL (13%) [12]. Other potentially targetable, aberrations in PTCL-NOS include the frequent overexpression of PDGFRA and the expression of activated NOTCH1 [20]. Clonal T-cell receptor (TCR) gene rearrangements are often present with >85% expressing TCR-αβ and fewer cases expressing TCR-γδ or being TCR-silent [16, 19].

The 2016 WHO updates to the classification of PTCL-NOS and AITL reflect an evolution in knowledge derived from genetic studies. Genetic analyses of PTCL have revealed recurrent somatic mutations that create a distinct genetic signature in AITL. These recurrent mutations were also found in many cases formally classified as PTCL-NOS that had a T follicular helper (T_{FH}) phenotype. They include well-known mutations in *TET2*, *IDH2*, *DNMT3A*, *RHOA*, *and CD28.* Recurrent gene fusions found include *ITK-SYK* and *CTLA4-CD28* [2, 17]. Cases of

PTCL-NOS with a T_{FH} phenotype expressing at least two or three T_{FH}-related antigens including *CD279/PD1*, *CD10*, *BCL6*, *CXCL 13*, *ICOS*, *SAP*, and *CCR5* were moved to one of the two new categories. The two new provisional entities, follicular T-cell lymphoma and nodal peripheral PTCL with T_{FH} phenotype, were added under AITL. One large study reported that 37% of PTCL-NOS cases were reclassified as AITL and about 22% of AITL cases were reclassified as PTCL-NOS based on GEP and genetic studies [1, 10, 15, 16, 20, 26].

Recent efforts to better characterize PTCL-NOS have led to the identification at two major prognostic subgroups. One subgroup was characterized by the overexpression of GATA-binding protein 3 (*GATA3*) and target genes (*CCR4*, *IL18RA*, *CXCR7*, *IK*) that play a key role in regulating T helper cell 2 (Th2) differentiation. The second is T-box 21 (*TBX21*) and eomesodermin (*EOMES*) and their target genes (*CXCR3*, *IL2RB*, *CCL3*, *IFNγ*) that regulate Th1 cell differentiation [15, 20, 26–28]. The *GATA3* signature subset is associated with a poorer prognosis compared to the subset with a *TBX21* signature (5 yr OS 19% vs. 38%) [29]. Some cases in the *TBX21* subset, expressing cytotoxic markers (*GNLY*, *PRF*, *GZM-K*, *-H-M*, *LYZ*) and specific cytokine transcripts (*CXCR3*, *CXCL12*, and *CCL-2*, *-3*, *-6*, *-11*), were associated with cytotoxic CD8+ T-cells and had a poorer overall survival than those that do not express these transcripts [1, 15, 16, 20]. Next-generation sequencing (NGS) is also revealing potential targetable mutations. These include epigenetic regulators (*KMT2D* [*MLL2*], *TET2*, *KDM6A*, *ARID1B*, *DNMT3A*, *CREBBP*, *MLL*, *and ARID2*), genes with roles in signaling pathways (*TNFAIP3*, *APC*, *CHD8*, *ZAP70*, *NF1*, *TNFRSF14*, *TRAF3*), and tumor suppressors genes (*TP53*, *FOXO1*, *BCORL1*, *ATM*) [15, 16, 19].

4.4 Clinical Presentation and Staging

The median age of patients with PTCL-NOS is ~60 years, with a slight male predominance (M:F ratio 1.5–1.9 to 1.0) [4, 5, 12, 16, 21, 30]. Most patients present with multifocal nodal disease, sometimes bulky. Up to 69% have advanced stage (III/IV) and 50–70% have high or high-intermediate International Prognostic Index (IPI) scores [4, 12]. Extranodal disease often coexists with nodal disease (49%) and can affect any site but usually affects the gastrointestinal tract, skin and bone marrow and less frequently, the lungs [4, 12, 16, 21]. B symptoms occur in up to 35% of patients; hemophagocytic syndrome can be observed. Common laboratory findings include anemia with or without hemolysis, thrombocytopenia, eosinophilia, elevated serum β_2-microglobulin, LDH and C-reactive protein, and hypercalcemia. Hypergammaglobulinemia, sometimes with a monoclonal spike, hypogammaglobulinemia, EBV and CMV reactivation, and circulating tumor cells can be observed [12, 21].

PTCL-NOS is a diagnosis made after other well-characterized types of PTCL have been excluded; even expert hematopathologists can reach a consensus about only ~75% of the time [4, 12]. Excisional biopsies of affected lymph nodes are required for diagnosis [19]. The evaluation of patients with PTCL-NOS involves a

thorough physical examination, with particular attention to the Waldeyer's ring, skin, and the presence of hepatosplenomegaly. Hematological and biochemical tests, computerized tomography (CT) of the chest, abdomen and pelvis and/or total body proton emission tomography (PET)/CT and bone marrow biopsy are useful in providing diagnostic, staging and prognostic information and also provide a reference point for monitoring therapy. Other investigations may include gastrointestinal endoscopy if gastrointestinal symptoms are present. When neurological symptoms are present, imaging of the central nervous system and cerebrospinal fluid analysis are required [21]. HTLV-1 status may be helpful in making a distinction between PTCL-NOS and adult T-cell lymphoma/leukemia (ATLL), particularly in patients who are at high risk for the disease, such as individuals from areas where HTLV-1 is endemic [12].

The Ann Arbor staging system is used in PTCL-NOS [21]. Staging is useful in some prognostic models but its utility in management is limited as there is currently no role for local therapy, even for patients with early stage, and systemic therapy is always required [19]. ^{18}F-fluorodeoxyglucose positron emission tomography (PET) has been shown to be more effective in estimating the extent of disease in PTCL for staging and monitoring. While computerized tomography is still used, clinicians need to be aware of the limitations in managing patients [31, 32].

4.5 Prognostic Factors and Risk Stratification

Four prognostic models have been published for use in patients with PTCL-NOS. The International Prognostic Index (IPI), the Prognostic Index for T-cell lymphoma (PIT), the modified PIT (m-PIT), and the International PTCL Project (IPTCLP). All four models have been reported to be useful in prognostication. In one retrospective study that compared all four models, the IPTCLP was the best score for OS in multivariate analysis [31]. These models incorporate varying combinations of clinical data including age, LDH, performance status, stage of disease, the presence of more than one extranodal site, bone marrow involvement, thrombocytopenia, and tumor Ki-67 index in estimating survival. With the exception of the m-PIT that has only three groups, the scores derived from these models classify patients into low (L), low-intermediate (L-I), intermediate-high (H-I), and high (H) risk groups [1, 30, 31]. The 5-year OS rates in patients with PTCL-NOS has been reported to range from about 28–35%, with a 5-year progression-free survival (PFS) of about 20% [16]. About 20% of patients may survive up to 10 years [12]. The 5-year OS rates for patients with IPI scores of 0/1 can be as high as 58%, but with IPI scores of 4/5 as low as 11% [4, 6, 12, 16, 30, 32]. The prognostic significance of IPI scores is also reflected in the 5-year PFS/failure-free survival (FFS) rates with scores of about 36% for low IPI scores, and scores as low as 9% for patients with high IPI scores [4, 12]. EBV positivity has been reported in up to 25–58% of cases of PTCL-NOS and in three retrospective studies was associated with inferior survival. In one study, EBV positivity affected outcomes only in patients younger than 60 years [21, 33,

34]. A high proliferative index (Ki-67 $\geq$ 80%) was found to be a strong predictor of survival but its use is limited due to poor reproducibility [21]. Other recently described prognostic factors include B symptoms, bulky disease ($\geq$10 cm), elevated serum C-reactive protein, the presence of circulating tumor cells, and hypogammaglobulinemia [12, 16]. Pathologic prognostic factors include the presence of cytotoxic markers (TIA1, GranB, and Perforin), CCR4, GATA3 and γδ T/NK-cell signatures. Expression of CD30 has been reported to be favorable in some studies, unfavorable in others [1, 16, 20].

4.6 Treatment Strategies

4.6.1 Front Line

In the absence of evidence suggesting an advantage for other regimens, four–six cycles of chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) are the most common first-line treatment of PTCL-NOS, and has been widely adopted as a standard of care [8, 12, 19, 21]. Overall response rates are acceptable (50–60%) but relapse rates are high, and long-term outcomes remain poor [1, 5]. CHOP, therefore, is significantly less effective in PTCL than in aggressive B-cell lymphomas, and the efficacy of this regimen in treating PTCL-NOS has been challenged by data that suggests that outcomes may be similar with or without anthracyclines [4, 8, 12]. One study suggested that anthracyclines may confer a benefit in high-risk patients with PTCL. Anthracycline-containing regimens were associated with significant improvements in PFS and OS when high-risk (IPI $\geq$ 3) patients were analyzed; with a median PFS and OS of 10 and 18 months respectively for anthracycline-treated patients, and both the median PFS and OS being 2 months in non-anthracycline-treated patients [35]. Studies investigating more intensive regimens have not demonstrated a significant improvement in OS [8, 12]. A subset analysis of patients with PTCL treated in a series of clinical trials conducted by the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL) compared outcomes following treatment with various permutations of CHOP versus CHOP with etoposide (CHOEP). This study showed that in patients younger than 60 years CHOEP may be superior to CHOP, with a 3-year EFS of 75.4% compared to 51.0% in patients that received CHOP [6, 12, 16, 19, 36, 37]. Other regimens that have been compared to CHOP without a clear improvement in outcomes include CHOP plus etoposide and gemcitabine (CHOP-EG); cisplatin, etoposide, gemcitabine, and methylprednisolone (PEGS); cyclophosphamide, etoposide, vincristine, and prednisone (CEOP) alternating with pralatrexate (P); etoposide, ifosfamide, cisplatin alternating with doxorubicin, bleomycin, vinblastine, dacarbazine (VIP-rABVD); and hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD) [16, 19, 38–42]. Based on the review of data available so far, the currently available

chemotherapy regimens that are more intensive than CHOP and the addition of etoposide do not improve outcomes in patients with PTCL-NOS [8, 12, 43].

4.6.2 High-Dose Chemotherapy (HDCT) and Autologous Hematopoietic Stem Cell Transplantation (ASCT)

As with front-line conventional-dose chemotherapy, PTCL-NOS has been shown to have significantly poorer post-ASCT outcomes compared to other subtypes. As such, results from studies should be interpreted carefully when limited or no subgroup analyses are reported [1, 8, 44, 45]. Given the high relapse rate with PTCL-NOS, there have been a number of investigations exploring the role of first-line consolidation with HDCT followed by ASCT in providing better long-term outcomes. Several studies report that a third of patients are not able to make it to transplant following chemotherapy and for those that are eligible, patient selection for upfront ASCT is challenging given the conflicting data. Patients with disease that is not chemosensitive do not appear to benefit from ASCT and have extremely poor outcomes with a median OS of about 6 months [8, 12]. Alternative therapeutic options should be pursued for these patients [19]. The Nordic Lymphoma Group study investigated 166 patients with PTCL, 62 with PTCL-NOS, all over 60 years. Patients who had achieved either complete response (CR) or partial response (PR) which resulted in 72% of enrolled patients proceeded to ASCT. Patients with PTCL-NOS had a 5-year OS of 47% and a PFS of 38% [46]. One challenge in interpreting the available data is that several of the studies were done in patients with different subtypes of PTCL and do not report a sub-analysis for PTCL-NOS [12, 16]. One other major limitation appears to be the number of patients with PTCL-NOS in these studies [12]. One study reports patients with PTCL-NOS as having significantly worse outcomes with an OS of 36% and a PFS of 36% at 3 years compared to an OS of 69% ($P = 0.013$) and a PFS of 61% ($P = 0.018$) when the other histological subclasses were grouped together [47]. The outcomes in PTCL-NOS were similar in another study with a reported OS of 33% and a PFS of 42% at 3 years [48]. Several studies report that patients treated with upfront ASCT who have chemosensitive disease, described as being in first CR (CR1) or PR at the time of SCT, and low prognostic index scores have significantly higher OS and PFS rates [8]. This, however, has raised the question about whether these patients would have done just as well without ASCT. One study in patients with PTCL-NOS receiving CHOP or CHOEP without any form of stem cell transplantation (SCT) reported an OS of 41% and a PFS of 54% at 3 years which are close to the rates reported following ASCT [37]. There is, however, no prospective trial comparing chemotherapy alone to upfront ASCT to date and with the evolution of novel targeted therapies, more studies investigating this are needed [1, 7, 16]. One study reported a 5-year OS of 80% in patients with PTCL transplanted after CR1 compared to 54% in patients who achieved CR with later lines of therapy [49, 50]. Another study reports 3-year OS rates of 71% in patients transplanted in second CR compared to 60% in patients transplanted in first CR/PR.

Higher 5-year OS rates have been reported in patients proceeding to ASCT in second CR than following first PR as a result, it is unclear how much the population in first PR influenced these results [49, 51]. At this time, patients with PTCL who achieve CR prior ASCT have been fairly consistently reported to have better outcomes. Achieving CR prior to ASCT appears to be a stronger predictor of a favorable outcome than whether ASCT is done in CR1 or CR2. Higher lines of therapy prior to transplant, however, have much poorer outcomes [7]. Favorable long-term survival rates of about 40–50% have been reported in young, medically fit patients with chemosensitive disease following ASCT in CR1 and as such, many experts favor upfront ASCT in younger patients. Given the lack of more suitable alternatives to therapy, many experts also recommend ASCT in patients with high-risk disease [1, 5–7, 16, 19].

4.7 Allogeneic Stem Cell Transplantation

Allogeneic stem cell transplantation (alloSCT) has been explored in the first-line setting. One study with eligible patients with PTCL who achieved CR or PR following chemotherapy with CHOP and with alemtuzumab (AL), and proceeded to ASCT or alloSCT, reported 4-year OS and PFS rates of 92% and 70% in the ASCT group compared to 69% and 69% in the alloSCT group, respectively. No significant difference was noted and at least 2 similar studies demonstrated similar outcomes with no significant difference in both groups [52–54]. One of them reported 4-year OS rates for patients in first CR of 84% and 83% following ASCT and alloSCT, respectively [54]. In the third study, an interim analysis showed a low probability of reaching the primary endpoint of a 25% improvement in EFS by alloSCT compared to ASCT. This led to an early termination of patient accrual. Higher transplant-related mortality (TRM) and non-relapse mortality (NRM) remain a significant concern in first-line alloSCT although lower toxicity rates are observed with experience [19, 52]. Given the higher chance of a cure with alloSCT, some may consider this option preferable over ASCT for young, fit patients with HLA-matched siblings [6].

4.8 Treatment of Relapsed or Refractory Patients

There is no established standard therapy for relapsed or refractory PTCL. For patients in CR2, high-dose chemotherapy and ASCT remains an option [7, 8, 19, 55]. Outcomes in patients with chemosensitive disease are much better than outcomes in refractory disease, but outcomes in all spectrums of PTCL-NOS are still very poor compared to other subtypes of PTCL and there is a dire need for the development of more effective treatment modalities for all of these patients [7, 8, 19, 21, 45, 56]. 3-year OS and PFS rates of 45 and 29% and NRM rates at 3 years of 15%

have been reported for ASCT in relapsed PTCL-NOS compared to 42 and 33% and 3-year NRM rates of 29% in alloSCT [45]. In another study, with PTCL-NOS and AITL as the predominant subtypes, 4-year OS and PFS rates of 59% were reported for patients in CR2 or CR3 compared to 53% in alloSCT. Patients in PR at the time of transplant had a 4-year OS of 55% compared to 22% in alloSCT. 4-year OS and PFS rates of 29 and 25% were reported for patients with chemorefractory disease [54]. The prognostic significance of CR compared to PR was also demonstrated in a study with PTCL-NOS patients reporting a 3-year OS rate for patients in CR2 of 71% compared to 50% for those in PR1 [51]. More effective therapies to help achieve CR prior to transplantation are needed to significantly improve outcomes and enrollment in a clinical trial is recommended [7, 8, 51].

In the front-line setting, outcomes in patients who proceed to ASCT appear to be better or at least similar to those who undergo allogenic stem cell transplantation (alloSCT) [16, 19, 43, 52]. With no clear advantage and the higher risk of transplant-related mortality (TRM) with alloSCT, ASCT is favored in the upfront setting [3, 6, 57]. In the relapsed and refractory setting, alloSCT is being considered more, as some studies report similar outcomes compared to ASCT with the potential benefit of a graft versus host effect and potentially, a greater chance of achieving a cure [1, 3, 45, 57]. About 25% of patients relapse following ASCT and a third of patients do not achieve remission with first-line chemotherapy but some may achieve a response with subsequent lines of therapy. In addition, some patients cannot mobilize stem cells following treatment with chemotherapy making them ineligible for ASCT. In patients with refractory PTCL treated with ASCT, dismal 5-year survival rates as low as 0% have been reported [8]. Eligibility for alloSCT should be considered in any of these patients as alloSCT has been reported to result in a cure in up to 50% of relapsed/refractory patients [1, 6, 7, 19, 49]. Outcomes are best when alloSCT is performed in patients with chemosensitive disease and few lines of therapy [1].

Both myeloablative and reduced intensity conditioning approaches have been investigated in patients with PTCL treated with alloSCT with similar outcomes [1, 45, 58]. As described with ASCT, outcomes were better in patients who achieved CR compared to patients in PR or less of a response prior to alloSCT with studies reporting 5-year OS rates of up to 69% compared to 29%. Outcomes were also better in patients who received fewer than two lines of therapy prior and 5-year OS rates of up to 73% compared to 39% have been reported. Rates of OS, event-free survival (EFS), TRM and non-relapse mortality (NRM) with both approaches were not significantly different. One study reported NRM rates at 100 days of 19% and 18% in myeloablative alloSCT and RIC alloSCT, respectively. The same study reported 1-year and 3-year non-relapse mortality rates of 3 and 15% for ASCT and 28 and 29% for alloSCT for PTCL-NOS. These NRM rates, however, were overall rates and do not represent sub-analyses by line of treatment, prior transplant, or type of response before transplant [45]. Benefits of the graft versus host effect conferred by alloSCT have been described and responses after donor lymphocyte infusions in patients with disease progression after allo-engraftment have also been reported with cure rates of up to 50% [8, 19]. One other reported advantage is the benefit

seen in patients with stable disease and early progression. Outcomes in haploidentical and matched unrelated donors appear to be similar [19].

4.8.1 Therapy in Transplant Ineligible Patients

After relapse, the median OS in patients with PTCL-NOS who do not proceed to transplant is reported to be around 6.5 months and enrollment in a clinical trial is recommended [59]. Chemotherapy does not appear to confer a significant survival benefit although newer therapies are emerging [59, 60]. Long-term survival remains dismal. Chemotherapy with single agents such as gemcitabine, etoposide, and alkylating agents has been used. Overall response rates (ORR) up to 55% and CR rates of up to 30% in PTCL-NOS has been reported with the use of single-agent gemcitabine which is often used in older, frail patients [61]. Combination chemotherapies used include gemcitabine-based combinations, ICE (ifosfamide, cisplatin, and etoposide), DA-EPOCH (dose-adjusted etoposide, prednisone, oncovin, cyclophosphamide, and doxorubicin), DHAP (dexamethasone, high-dose cytarabine and cisplatin), and ESHAP (etoposide, methylprednisolone, high-dose cytarabine and cisplatin) with response rates frequently less than 50% and a small number of patients achieving CR but a short PFS [62]. Monotherapy with corticosteroids has also been reported [7, 8, 19, 59].

In the last decade, four agents have been approved by the FDA for the treatment of relapsed and refractory PTCL. Pralatrexate, the histone deacetylase (HDAC) inhibitors romidepsin and belinostat, and the anti-CD30 antibody, brentuximab vedotin, are all currently approved for single-agent use but several trials investigating their efficacy in combination with other drugs are underway [1, 3]. While these agents have demonstrated responses in PTCL, they have not been shown to have a significant impact on survival and as such belinostat and brentuximab vedotin have received only limited approval in Europe [1, 60]. Chidamine is a HDAC inhibitor only approved in China [63].

Pralatrexate is a folate antagonist approved in 2009 and is a more potent analog of methotrexate with high affinity for the reduced folate carrier (RFC-1) via which they both cross cell membranes [1, 3, 60, 64, 65]. The mechanism of action of the HDAC inhibitors, romidespin and belinostat, is complex and not fully understood. One of the known mechanisms by which they act is by inducing the acetylation of histone and nonhistone proteins resulting in the upregulation of endogenous inhibitors of cell cycle progression such as tumor suppressor genes thus inhibiting tumor cell growth [1, 3, 66]. Brentuximab vedotin is anti-CD30 antibody-drug conjugate that binds to tumor cells expressing CD30 ultimately leading to cell cycle arrest and apoptosis following internalization. Up to 25% of PTCL-NOS patients express CD30 in up to 50% of tumor cells. Interestingly, the information on the correlation of CD30 expression with clinical response is inconsistent. One proposed reason is a limitation in the current techniques for evaluating CD30 expression leading a reporting of lower than actual levels. Another is that response may not be

entirely based on CD30 expression but other pathologic features of the tumor and other unidentified biomarkers [1, 3, 8, 10, 20, 60, 67].

In PTCL-NOS patients, overall response rates of 32%, 29%, 23%, and 33% have been reported for pralatrexate, romidepsin, belinostat, and brentuximab vedotin, respectively [1, 8, 57]. Although in all patients the median PFS and OS in these agents range from a few months to a little over 12 months, in patients who achieve a response, a median duration of response (DOR) of up to 17 months and more than 36 months has been reported for romidepsin and belinostat, respectively [8, 60].

4.8.2 Limited Stage and Role of Radiation

The role of radiation in consolidation has been explored in patients with limited stage disease in PTCL. No benefit in EFS or OS has been demonstrated with the combined modality of radiation and chemotherapy. Given the high relapse rate, including relapse occurring exclusively outside of the field of previous radiation, as described in one study, there is a need for more effective systemic therapy. Even in patients who present with limited stage disease, the aggressiveness of PTCL limits the use of radiation therapy [12, 16, 68].

4.8.3 CNS Involvement and Prophylaxis

The role of CNS prophylaxis in PTCL to prevent leptomeningeal or parenchymal relapse appears to be limited. A number of retrospective studies have looked at the incidence of CNS relapse in PTCL which is low and prophylaxis in all patients is not recommended [69, 70].

References

1. Broccoli A, Zinzani PL (2017) Peripheral T-cell lymphoma, not otherwise specified. Blood 129(9):1103–1112
2. Carson KR et al (2017) A prospective cohort study of patients with peripheral T-cell lymphoma in the United States. Cancer 123(7):1174–1183
3. Foss FM et al (2011) Peripheral T-cell lymphoma. Blood 117(25):6756–6767
4. Vose J et al (2008) International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol 26(25):4124–4130
5. Vose JM (2008) Peripheral T-cell non-Hodgkin's lymphoma. Hematol Oncol Clin North Am 22(5): 997–1005, x
6. Armitage JO (2015) The aggressive peripheral T-cell lymphomas: 2015. Am J Hematol 90 (7):665–673
7. Dhawale TM, Shustov AR (2017) Autologous and allogeneic hematopoietic cell transplantation in peripheral T/NK-cell lymphomas: a histology-specific review. Hematol Oncol Clin North Am 31(2):335–357
8. Horwitz SM et al (2016) NCCN guidelines insights: non-Hodgkin's lymphomas, version 3.2016. J Natl Compr Cancer Netw 14(9):1067–1079

9. Bellei M et al (2015) The value and relevance of the T cell lymphoma registries and international collaborations: the case of COMPLETE and the T-cell project. Curr Hematol Malig Rep 10(4):448–455
10. Hildyard C et al (2017) Toward a biology-driven treatment strategy for peripheral T-cell lymphoma. Clin Med Insights Blood Disord 10:1179545X17705863
11. Adams SV, Newcomb PA, Shustov AR (2016) Racial patterns of peripheral T-cell lymphoma incidence and survival in the United States. J Clin Oncol 34(9):963–971
12. Weisenburger DD et al (2011) Peripheral T-cell lymphoma, not otherwise specified: a report of 340 cases from the international peripheral T-cell lymphoma project. Blood 117(12):3402–3408
13. Phan A, Veldman R, Lechowicz MJ (2016) T-cell lymphoma epidemiology: the known and unknown. Curr Hematol Malig Rep 11(6):492–503
14. Wang SS et al (2014) Medical history, lifestyle, family history, and occupational risk factors for peripheral T-cell lymphomas: the InterLymph non-Hodgkin lymphoma subtypes project. J Natl Cancer Inst Monogr 2014(48):66–75
15. Swerdlow SH et al (2016) The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 127(20):2375–2390
16. Al-Zahrani M, Savage KJ (2017) Peripheral T-cell lymphoma, not otherwise specified: a review of current disease understanding and therapeutic approaches. Hematol Oncol Clin North Am 31(2):189–207
17. Casulo C et al (2017) T-cell lymphoma: recent advances in characterization and new opportunities for treatment. J Natl Cancer Inst 109(2)
18. Leonard JP, Martin P, Roboz GJ (2017) Practical implications of the 2016 revision of the World Health Organization classification of lymphoid and myeloid neoplasms and acute leukemia. J Clin Oncol 35(23):2708–2715
19. Schmitz N, de Leval L (2017) How I manage peripheral T-cell lymphoma, not otherwise specified and angioimmunoblastic T-cell lymphoma: current practice and a glimpse into the future. Br J Haematol 176(6):851–866
20. Maura F (2016) Biology of peripheral T cell lymphomas—not otherwise specified: is something finally happening? Pathogenesis 3(1):9–18
21. Savage KJ et al (2011) Peripheral T-cell lymphoma–not otherwise specified. Crit Rev Oncol Hematol 79(3):321–329
22. Yoshida N et al (2013) Primary peripheral T-cell lymphoma, not otherwise specified of the thyroid with autoimmune thyroiditis. Br J Haematol 161(2):214–223
23. Geissinger E et al (2009) CD52 expression in peripheral T-cell lymphomas determined by combined immunophenotyping using tumor cell specific T-cell receptor antibodies. Leuk Lymphoma 50(6):1010–1016
24. Jiang L et al (2009) Variable CD52 expression in mature T cell and NK cell malignancies: implications for alemtuzumab therapy. Br J Haematol 145(2):173–179
25. Hsi ED et al (2017) Analysis of peripheral T-cell lymphoma diagnostic workup in the United States. Clin Lymphoma Myeloma Leuk 17(4):193–200
26. Sakata-Yanagimoto M, Chiba S (2015) Molecular pathogenesis of peripheral T cell lymphoma. Curr Hematol Malig Rep 10(4):429–437
27. Iqbal J et al (2014) Gene expression signatures delineate biological and prognostic subgroups in peripheral T-cell lymphoma. Blood 123(19):2915–2923
28. de Leval L, Gaulard P (2014) Cellular origin of T-cell lymphomas. Blood 123(19):2909–2910
29. de Leval L et al (2007) The gene expression profile of nodal peripheral T-cell lymphoma demonstrates a molecular link between angioimmunoblastic T-cell lymphoma (AITL) and follicular helper T (TFH) cells. Blood 109(11):4952–4963
30. Xu P et al (2015) Analysis of prognostic factors and comparison of prognostic scores in peripheral T cell lymphoma, not otherwise specified: a single-institution study of 105 Chinese patients. Ann Hematol 94(2):239–247

31. Gutierrez-Garcia G et al (2011) Comparison of four prognostic scores in peripheral T-cell lymphoma. Ann Oncol 22(2):397–404
32. Ellin F et al (2014) Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the Swedish Lymphoma Registry. Blood 124(10):1570–1577
33. Haverkos BM et al (2017) Frequency and clinical correlates of elevated plasma Epstein-Barr virus DNA at diagnosis in peripheral T-cell lymphomas. Int J Cancer 140(8):1899–1906
34. Gru AA et al (2015) The Epstein-Barr Virus (EBV) in T cell and NK cell lymphomas: time for a reassessment. Curr Hematol Malig Rep 10(4):456–467
35. Briski R et al (2014) The role of front-line anthracycline-containing chemotherapy regimens in peripheral T-cell lymphomas. Blood Cancer J 4:e214
36. Abouyabis AN et al (2011) A systematic review and meta-analysis of front-line anthracycline-based chemotherapy regimens for peripheral T-cell lymphoma. ISRN Hematol 2011:623924
37. Schmitz N et al (2010) Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. Blood 116(18):3418–3425
38. Kim JG et al (2006) CHOP plus etoposide and gemcitabine (CHOP-EG) as front-line chemotherapy for patients with peripheral T cell lymphomas. Cancer Chemother Pharmacol 58(1):35–39
39. Mahadevan D et al (2013) Phase 2 trial of combined cisplatin, etoposide, gemcitabine, and methylprednisolone (PEGS) in peripheral T-cell non-Hodgkin lymphoma: Southwest Oncology Group Study S0350. Cancer 119(2):371–379
40. Advani RH et al (2016) A phase II study of cyclophosphamide, etoposide, vincristine and prednisone (CEOP) Alternating with Pralatrexate (P) as front line therapy for patients with peripheral T-cell lymphoma (PTCL): final results from the T-cell consortium trial. Br J Haematol 172(4):535–544
41. Simon A et al (2010) Upfront VIP-reinforced-ABVD (VIP-rABVD) is not superior to CHOP/21 in newly diagnosed peripheral T cell lymphoma. Results of the randomized phase III trial GOELAMS-LTP95. Br J Haematol 151(2):159–166
42. Escalon MP et al (2005) Prognostic factors and treatment of patients with T-cell non-Hodgkin lymphoma: the M. D. Anderson Cancer Center experience. Cancer 103(10):2091–2098
43. Mehta N et al (2013) A retrospective analysis of peripheral T-cell lymphoma treated with the intention to transplant in the first remission. Clin Lymphoma Myeloma Leuk 13(6):664–670
44. Beaven AW, Diehl LF (2015) Peripheral T-cell lymphoma, NOS, and anaplastic large cell lymphoma. Hematology Am Soc Hematol Educ Program 2015:550–558
45. Smith SM et al (2013) Hematopoietic cell transplantation for systemic mature T-cell non-Hodgkin lymphoma. J Clin Oncol 31(25):3100–3109
46. d'Amore F et al (2012) Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01. J Clin Oncol 30(25):3093–3099
47. Feyler S et al (2007) The role of high-dose therapy and stem cell rescue in the management of T-cell malignant lymphomas: a BSBMT and ABMTRR study. Bone Marrow Transpl 40 (5):443–450
48. Abramson JS et al (2014) Peripheral T-cell lymphomas in a large US multicenter cohort: prognostication in the modern era including impact of frontline therapy. Ann Oncol 25 (11):2211–2217
49. Rodriguez J et al (2003) High-dose chemotherapy and autologous stem cell transplantation in peripheral T-cell lymphoma: the GEL-TAMO experience. Ann Oncol 14(12):1768–1775
50. Rodriguez J et al (2003) High dose chemotherapy and autologous stem cell transplantation in patients with peripheral T-cell lymphoma not achieving complete response after induction chemotherapy. The GEL-TAMO experience. Haematologica 88(12):1372–1377
51. Yang DH et al (2009) Prognostic factors and clinical outcomes of high-dose chemotherapy followed by autologous stem cell transplantation in patients with peripheral T cell lymphoma, unspecified: complete remission at transplantation and the prognostic index of peripheral T

cell lymphoma are the major factors predictive of outcome. Biol Blood Marrow Transpl 15 (1):118–125
52. Corradini P et al (2014) Intensified chemo-immunotherapy with or without stem cell transplantation in newly diagnosed patients with peripheral T-cell lymphoma. Leukemia 28 (9):1885–1891
53. Schmitz N et al (2015) Allogeneic or autologous transplantation as first-line therapy for younger patients with peripheral T-cell lymphoma: results of the interim analysis of the AATT trial. J Clin Oncol 33(15): 8507
54. Beitinjaneh A et al (2015) Comparison of survival in patients with T cell lymphoma after autologous and allogeneic stem cell transplantation as a frontline strategy or in relapsed disease. Biol Blood Marrow Transpl 21(5):855–859
55. Hosing C, Champlin RE (2011) Stem-cell transplantation in T-cell non-Hodgkin's lymphomas. Ann Oncol 22(7):1471–1477
56. Song KW et al (2003) Autologous stem cell transplant for relapsed and refractory peripheral T-cell lymphoma: variable outcome according to pathological subtype. Br J Haematol 120 (6):978–985
57. Moskowitz AJ, Lunning MA, Horwitz SM (2014) How I treat the peripheral T-cell lymphomas. Blood 123(17):2636–2644
58. Corradini P et al (2004) Graft-versus-lymphoma effect in relapsed peripheral T-cell non-Hodgkin's lymphomas after reduced-intensity conditioning followed by allogeneic transplantation of hematopoietic cells. J Clin Oncol 22(11):2172–2176
59. Mak V et al (2013) Survival of patients with peripheral T-cell lymphoma after first relapse or progression: spectrum of disease and rare long-term survivors. J Clin Oncol 31(16):1970–1976
60. Marchi E, Raufi AG, O'Connor OA (2017) Novel agents in the treatment of relapsed or refractory peripheral T-cell lymphoma. Hematol Oncol Clin North Am 31(2):359–375
61. Zinzani PL et al (2010) Gemcitabine as single agent in pretreated T-cell lymphoma patients: evaluation of the long-term outcome. Ann Oncol 21(4):860–863
62. Dreyling M et al (2013) ESMO consensus conferences: guidelines on malignant lymphoma. part 2: marginal zone lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma. Ann Oncol 24(4):857–877
63. Shi Y et al (2015) Results from a multicenter, open-label, pivotal phase II study of chidamide in relapsed or refractory peripheral T-cell lymphoma. Ann Oncol 26(8):1766–1771
64. Marchi E, O'Connor OA (2012) Safety and efficacy of pralatrexate in the treatment of patients with relapsed or refractory peripheral T-cell lymphoma. Ther Adv Hematol 3(4):227–235
65. Wood GS, Wu J (2015) Methotrexate and pralatrexate. Dermatol Clin 33(4):747–755
66. Bose P, Dai Y, Grant S (2014) Histone deacetylase inhibitor (HDACI) mechanisms of action: emerging insights. Pharmacol Ther 143(3):323–336
67. van de Donk NW, Dhimolea E (2012) Brentuximab vedotin. MAbs 4(4):458–465
68. Briski R et al (2015) Survival in patients with limited-stage peripheral T-cell lymphomas. Leuk Lymphoma 56(6):1665–1670
69. Gurion R et al (2016) Central nervous system involvement in T-cell lymphoma: a single center experience. Acta Oncol 55(5):561–566
70. Pro B, Perini G (2010) Central nervous system prophylaxis in peripheral T-cell lymphoma. Blood 115(26):5427
71. Park HS et al (2017) T-cell non-Hodgkin lymphomas: spectrum of disease and the role of imaging in the management of common subtypes. Korean J Radiol 18(1):71–83

Angioimmunoblastic T-Cell Lymphoma

5

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Abstract

Angioimmunoblastic T-cell lymphoma (AITL) is one of the most common types of T-cell lymphoma, representing about 15–20% of cases of peripheral T-cell lymphoma (PTCL). It is characterized by a unique clinical presentation and distinct pathologic and molecular features. Classes of drugs particularly active in AITL are emerging; however, treatment of relapsed and refractory disease remains a challenge. This chapter reviews the epidemiology, clinical presentation, pathogenesis, diagnosis, and treatment of AITL.

Keywords

Angioimmunoblastic T-cell lymphoma · Follicular helper T-cell Pathology · Treatment

5.1 Historical Perspective

Angioimmunoblastic T-cell lymphoma (AITL) was originally recognized in the 1970s as a clinical syndrome characterized by generalized lymphadenopathy, hepatosplenomegaly, anemia, and hypergammaglobulinemia. The syndrome was described by different terms based on histology, including angioimmunoblastic

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lymphadenopathy with dysproteinemia (AILD) [1]; immunoblastic lymphadenopathy [2]; or lymphogranulomatosis X [3]. Among these, the term AILD became widely accepted. AILD was initially recognized as a premalignant non-neoplastic atypical lymphoid process, with a tendency to develop into a frank lymphoma. In the 1980s, the identification of clonal cytogenetic abnormalities and of clonal T-cell receptor (TCR) gene rearrangements established the neoplastic nature of the disease [4, 5]. Thereafter, this entity was recognized as angioimmunoblastic T-cell lymphoma in the REAL (revised European-American classification of lymphoid neoplasms) classification and WHO (World Health Organization) classifications of hematological malignancies [6, 7].

5.2 Epidemiology

AITL is one of the most common specific types of T-cell lymphoma in western nations, representing 15–20% of all cases of peripheral T-cell lymphoma (PTCL) worldwide [8]. This lymphoma is more common in Europe, comprising 28.7% of PTCL and natural killer/T-cell lymphoma (NKTCL) cases, and is less common in Asia (17.9%) and North America (16.0%); however, the results might be influenced by the overall low prevalence of T-cell neoplasms in European countries and a relatively high prevalence of other PTCL and NKTCL in Asia. It is unclear if true racial predisposition exists. No consistent risk factors or etiological agents have been identified in AITL. The relation to Epstein–Barr virus (EBV) is discussed below separately.

5.3 Clinical Presentation

The median age of the patients with AITL is in the sixth decade, ranging from 62 to 65, and there is no definite gender preference [8, 9]. AITL is commonly a systemic disease at its onset, characterized by immunodysregulation and immunodeficiency, and more than 80% of the patients present with higher stage disease (stage III/IV) at the time of diagnosis [8, 9]. Many patients have constitutional symptoms such as fever, chills, night sweats, malaise, weight loss, and arthralgias. B symptom is seen in more than 70% of patients [9]. Patients usually have peripheral lymphadenopathy, often generalized, and extranodal involvement is common including liver, spleen, skin, lungs, and bone marrow. A high proportion of patients have hepatosplenomegaly. Bone marrow involvement is observed in up to 70% of the patients and tends to correlate with a higher frequency of B-symptoms, hepatosplenomegaly, laboratory abnormalities and with the presence of circulating tumor cells [10, 11]. Various laboratory abnormalities are common including polyclonal hypergammaglobulinemia, anemia (often hemolytic with positive direct Coombs test), cold agglutinins, circulating immune complexes, cryoglobulins, antinuclear antibodies, eosinophilia, and elevated serum levels of LDH and

beta-2-microglobulin. Up to half of the patients show skin rash, and this will be discussed separately below. Other clinical signs and symptoms, such as arthralgias or arthritis, pleural effusions, ascites and/or edema, neurological manifestations, gastrointestinal symptoms, are also seen, but less common. Peripheral blood leukocytosis with lymphocytosis is rare; however, the presence of aberrant T-cells may be detected by flow cytometry [12].

Patients with AITL are at risk for developing B-cell lymphomas, particularly diffuse large B-cell lymphoma (DLBCL), and less frequently classical Hodgkin lymphoma or plasmacytoma [13]. Majority of cases of DLBCL and most classical Hodgkin lymphoma arising in this setting are positive for EBV. One possible explanation for this phenomenon is that EBV infection prolongs B-cell life span, increasing the likelihood of secondary molecular aberrations that result in lymphoma. In some patients, the diagnosis of DLBCL can be concurrent with or precede the diagnosis of AITL.

5.4 Pathogenesis

5.4.1 Cell of Origin

The cell of origin for AITL is the follicular helper T-cells (TFH), suggested by immunohistochemical studies, and gene expression profiling studies indicating the genetic similarity of TFH to AITL cells [14, 15]. The cellular derivation of AITL from these TFH provides a rational model to explain several characteristic pathological and biological features seen in this disease, such as immunodysregulation, expansion of B-cells, the intimate association with germinal centers in early-stage disease, and the prominent proliferation of follicular dendritic cell meshworks in advanced stage.

TFH were initially described as a CD4+ T-cell population characterized by high levels of expression of the chemokine receptor CXCR5 [16, 17]. Since then, TFH have emerged as a distinct subset of effector T helper cells with a characteristic gene expression signature and functionally separate from other known CD4+ T-cell subsets [18]. Normal TFH are located in the light zones of germinal centers and play an important role in germinal center B-cell differentiation and survival, and in the development of plasma cells and memory B-cells [19]. TFH differentiation is initiated by the activation of a naive CD4+ T lymphocyte by dendritic cells in the presence of IL-6, IL-12, and IL-21, which lead activation of JAK-STAT signaling [17, 19]. This interaction involves the activation of inducible T-cell co-stimulator (ICOS) in the T-cell, then activation of ICOS induces the upregulation of BCL6. Following ICOS activation and induction of BCL6 upregulation, these T-cells upregulate the expression of PD1 and CXCR5, and become TFH precursors, which migrate to the B-cell follicles to induce germinal center formation [20, 21]. As antigen stimulation builds up a germinal center reaction, these precursors complete maturation and acquire a definitive TFH phenotype characterized by expression of high levels of CXCR5, PD1,

Table 5.1 Frequently mutated or translocated genes in angioimmunoblastic T-cell lymphoma

		Epigenetic regulators			T-cell receptor pathway							
	RHOA	*TET2*	*IDH2*	*DNMT3A*	*CD28*	*CTLA4-CD28*	*FYN*	*PLCG1*	*CARD11*	*PI3K elements*	*CTNNB1*	*GTF2I*
AITL (%)	60–70	70–80	30–40	10–25	5–10	60	5–10	10–15	3–5	5–10	5–10	5–10

BCL6, MAF, and SAP. These TFH support B-cells and facilitate the generation of long-lived plasma cells and memory B-cells.

5.5 Genetics

Malignant transformation of TFH leads to the development of AITL. Recently, important discoveries of the genetic basis for development of AITL were made; mutations in the epigenetic regulators *TET2*, *DNMT3A*, and *IDH2*, TCR signaling pathway (e.g., *FYN* and *CD28*), and a loss-of-function mutation in the Ras homolog gene family member A (*RHOA*) (Table 5.1) [22–25]. These studies proposed that these mutations may be acquired in a multistep manner; the *RHOA*-mutated cases are *TET2*-mutated, and a subset of *IDH2*-mutated cases harbors both *TET2* and *RHOA* mutations, [24] although cases with *RHOA* mutation without *TET2* mutation are also reported [25]. Clonality and germline analysis of AITL supports a transformation model in which *TET2* and *DNMT3A* mutations constitute an initial or premalignant lesion in hematopoietic progenitors that could eventually lead to clonal expansion and malignant transformation both within the T-cell and myeloid lineages. Lineage specification into the TFH lineage, rather than myeloid malignancies, is guided by emergence of the *RHOA* G17V mutation and this is enhanced by hyperactivation of the TCR signaling pathway [24]. However, detailed mechanisms are still unknown.

5.6 *RHOA* G17V Mutation

RHOA is a small GTPase protein which regulates multiple biological processes, including cytoskeleton remodeling, cell adhesion, migration, proliferation, and survival [26]. It is known that RHOA has a critical regulatory role in thymus development, and inactivation of RHOA in the thymus has been linked to the development of T-cell lymphomas [27]. Moreover, altered Rho GTPase activity has been linked with the development of autoimmunity, one of the clinical characteristics of AITL [28]. A central role of RHOA in the pathogenesis of AITL is supported by the identification of recurrent, highly prevalent heterozygous missense mutations in the RHOA gene (*RHOA* G17 V) in about 70% of AITL cases. This missense mutation results in conversion of glycine to valine at amino acid 17, and biochemical analysis and cellular assays demonstrated that the *RHOA* G17V mutant

does not bind GTP and thus disrupts RHOA signaling [24, 25, 29]. Although *RHOA* G17V mutation is highly characteristic in AITL, this mutation has also been identified in adult T-cell leukemia–lymphoma (ATLL) samples [30]. The *RHOA* G17V mutation is also reported in about 25% of PTCL-NOS cases [25]. These cases most likely represent nodal PTCL with TFH phenotype, a provisional entity in WHO 2016 classification [31]; however, the criteria to define the borders between AITL and nodal PTCL with TFH phenotype remain unclear.

5.7 Mutations in Epigenetic Regulators

Mutations in *TET2*, *DNMT3A*, and *IDH2* are originally described in myeloid malignancies. Later, these mutations were also found in PTCL, with higher frequency in AITL and T-cell lymphomas with TFH phenotype [22, 32]. Mutations in these epigenetic regulators are strongly associated with the presence of the *RHOA* G17V mutation, which supports a multistep model of follicular T helper cell transformation in AITL.

5.7.1 *TET2* Mutation

TET2 is involved in the epigenetic control of gene expression through the oxidation of methylated cytosines and DNA demethylation by conversion of 5-methylcytosine to 5-hydroxymethylcytosine [33]. *TET2* was originally identified as a tumor suppressor in myeloid neoplasms [33, 34]. Later, high frequency of loss-of-function mutations in *TET2* was also found in PTCL-NOS and in AITL [22, 24]. Loss-of-function mutations in *TET2* are observed in about 70–80% of AITL cases [35]. The role of these mutations in AITL has been studied in mouse models. *TET2* knockdown mice develop T-cell lymphoma with TFH-like features after a long latency [36]. The current hypothesis is that hypermethylation of the first intron of the Bcl6 gene, which has been reported as an intronic silencer region (Bcl6 int1-S), possibly contributes to the upregulation of Bcl6 and outgrowth of TFH-like cell, and subsequent lymphomagenesis [36].

5.7.2 *IDH2* Mutation

IDH2 gene is mutated in about 30–40% of AITL cases [32, 35]. IDH1 and IDH2 are located in the cytoplasm and in the mitochondria, respectively. They encode metabolic mitochondrial enzymes that convert isocitrate to alpha-ketoglutarate. Although recurrent mutations in *IDH2* can be frequently identified in other types of cancer, including AML, AITL is the only PTCL subgroup where *IDH2* mutations are found [32]. In AITL cases, the mutations occur exclusively in position R172, and *IDH2* R140 or *IDH1* mutations seen in other malignancies are not seen in AITL

[35]. Notably, the *IDH2* R172 mutation confers a neomorphic enzymatic activity, catalyzing the conversion of alpha-ketoglutarate to 2-hydroxyglutarate (2-HG) [35]. 2-HG acts as a competitive antagonist of the alpha-ketoglutarate-dependent dioxygenases, including the TET family enzymes, leading to impairment of DNA and histone demethylation and abnormal regulation of gene transcription [35].

Of note, *IDH2* R172 mutation is associated with increased production of 2-HG compared with other *IDH2* mutant alleles [37]. The presence of *IDH2* mutations is associated with poor prognosis in a subset of AML patients [38], but there is no significant association of *IDH2* mutations with survival in AITL [32]. In contrast to AML, where *IDH2* and *TET2* mutations are mutually exclusive, AITL cases frequently present co-occurring mutations in these epigenetic regulators [35]. In one study, 68% of *IDH* mutant AITL cases also had *TET2* mutations [35]. Because mutant *IDH2* generates 2-HG and consequently can inhibit TET2 enzyme activity, *IDH2* mutation was not expected to co-occur with *TET2* mutation, however, gene expression profiling study for the comparison among *IDH2/TET2* double-mutant AITL cases and *TET2* single mutant AITL cases supported a cooperative effect of *IDH2* and *TET2* mutations on the upregulation of the TFH-associated genes, leading to a more TFH-like signature that was achieved by the presence of *TET2* mutations alone [35].

5.7.3 *DNMT3A* Mutation

DNMT3A gene encodes a methyltransferase involved in the epigenetic regulation of gene expression through methylation of cytosines in the DNA. Recurrent mutations in *DNMT3A* were originally described in myeloid neoplasms. Recurrent loss-of-function mutations in *DNMT3A* were identified in 10–25% of AITL samples [22, 24, 25]. Approximately, 80% of *DNMT3A* mutant AITL cases also have *TET2* mutations [35], and it is thought that these two mutations cooperate in the process of malignant transformation. One study with mice models showed a global increase in DNA methylation affecting tumor suppressor genes and local hypomethylation affecting genes involved in the Notch pathway in *TET2* and *DNMT3A* co-mutant mice [39].

5.8 Mutations in the T-cell Receptor Pathway

Genomic studies have detected the presence of recurrent genetic alterations affecting genes related to TCR signaling in AITL and other TFH-derived PTCL. Half of these patients carry virtually mutually exclusive mutations in TCR-related genes, including *CD28*, *FYN*, *PLCG1, CARD11, PI3K* elements, *CTNNB1,* and *GTF2I* [17, 25, 40, 41].

CD28 is a major co-stimulatory receptor in T-cells which, upon binding ligand, induces sustained T-cell proliferation and cytokine production when combined with T-cell receptor stimulation. Recurrent mutations in *CD28* have been recently

described in approximately 10% of AITL cases [40]. Interestingly, *CD28* mutation is not seen in other TFH-derived PTCL [41]. Mutations are seen in two residues, D124 and T195, and result in increased signaling via increased ligand–receptor interaction and signal transduction [40]. *CD28*-mutated AITL patients are reported to have inferior survival to non-mutated cases [40]. Recently, *CTLA4-CD28* gene fusion was detected in significant subset of AITL, up to 60% of cases [42]. CTLA4 and CD28 are co-regulatory receptors with opposite roles in T-cell signaling. The fusion gene, which codes for the extracellular domain of CTLA4 and the cytoplasmic region of CD28, is likely capable of transforming inhibitory signals into stimulatory signals for T-cell activation [42].

The FYN tyrosine kinase is an SRC family kinase found in T lymphocytes and plays an important role in T-cell activation upon TCR stimulation. Recurrent mutations of *FYN* are reported in PTCL-NOS and AITL cases, although rare [43]. These *FYN* mutations specifically disrupt the intramolecular inhibitory interaction of the *FYN* SH2 domain, resulting in increased tyrosine kinase signaling [25]. Also, t(5;9)(q33;q22), or *ITK-SYK* fusion transcript, which induce overexpression of *SYK*, has been reported in AITL [44].

Mutations in *PLCG1* and *CARD11* are previously reported in 15–20% of cutaneous T-cell lymphoma cases [45]. A recent study reveals that mutations in *PLCG1* are seen in 14% of AITL and other TFH-derived PTCL patients [41]. Mutations in *CARD11*, which encodes a scaffolding protein downstream of PLCG1 required for CD28/TCR-induced NF-κB activation, are also found in 3.5% of AITL and other TFH-derived PTCL patients [41]. These mutations are reported to functionally activate NF-κB/NFAT pathway by in vitro assays and could be targeted by the proteasome inhibitor bortezomib [41].

Mutations in PI3K genes encoding the regulatory subunits PIK3R1 and PIK3R5 are also reported in AITL and other TFH-derived PTCL patients in low frequency [41]. These mutations likely enhance the catalytic subunit activity or increase PIK3R1 binding to CD28. Mutations in PDPK1 (PDK1), a master serine/threonine kinase with multiple targets including AKT, are also seen in about 6% of AITL cases [41]. These mutations were found on or near its kinase domain, suggesting an activating effect. Mutations in *CTNNB1,* which encodes downstream protein of PI3 K, are seen in 6% of AITL and other TFH-derived PTCL patients [41]. These mutations have been previously reported in a variety of carcinomas and Wilms' tumors, and are characterized as activating or stabilizing variants that induce persistent signaling and increased proliferation [41].

Activating mutations in the MAPK pathway are also reported in AITL and other TFH-derived PTCL. *GTF2I* missense mutations are seen in 6% of AITL and other TFH-derived PTCL cases, and are likely activating as those reported in thymic epithelial tumors [41, 46]. Rare cases with *KRAS* or *STAT3* mutations are also reported in AITL [41].

5.9 Tumor Microenvironment

Upregulation of several angiogenic mediators has been demonstrated in AITL. Vascular endothelial growth factor (VEGF) is overexpressed in AITL and probably acts as a key mediator of the prominent vascularization observed in the disease [14, 47]. By immunostaining, neoplastic cells and endothelial cells are positive for both VEGF and its receptor, suggesting the possibility of some paracrine and/or autocrine loop [47, 48]. The angiopoietin system may also play an important role as angiopoietin 1 is expressed by AITL neoplastic cells and follicular dendritic cells [49]. Recent study with gene expression profiling of 114 AITL cases shows that the cytokine milieu in AITL includes potent interleukins that are angiogenic (IL8), proinflammatory (IL6, IL18), immunosuppressive (IL10), and proliferation-inducing (IL21), and have a vast repertoire of chemokines/receptors (e.g., CXCL-2,-9,-13, 14 and CXCR-4,-5,-6), thus indicating a complex immunologic network [50]. Deregulated expansion and/or function of TFH could induce the generation of cytokines (IL-4, IL-6, IL-21, and IL-10), which play a prominent role in the early stages of lymphoma progression and in setting the abundant inflammatory component of AITL tumor lesions. Of note, it also shows that AITL presents significant enrichment of the TFH gene signature as well as B-cell, follicular dendritic cell, and angiogenesis-related gene signatures from the microenvironment [50].

5.10 EBV

A significant subset of AITL patients presents with increased numbers of EBV-infected cells in lymph nodes compared with both normal lymph nodes and other peripheral T-cell lymphomas. In the past, a number of infectious diseases and agents had been reported to be associated with AITL, including EBV, human herpesvirus (HHV)-6, HHV-8, human immunodeficiency virus (HIV), and bacterial and fungal organisms [51–54]. Initial studies suggested the EBV-infected cells might be within both the T-cell and B-cell population [55]. Later, it was shown that virtually all cells infected by EBV are B-cells; thus EBV infection is unlikely to play a primary role in the lymphomagenesis of AITL [56, 57]. The presence of HHV-6B is also detected by PCR in almost half of the cases [57]. Now it is considered that these viral infections probably reflect the consequence of immune deregulation in AITL patients with underlying immunodeficiency with reduced cytotoxic activity. EBV and potentially also HHV-6B, may, through the modulation of cytokines, chemokines and membrane receptors, play a role in the development of the tumor microenvironment, ultimately favoring disease progression. Also, higher EBV viral loads in tissues have been found to correlate with progression of histological patterns and with B-cell clonality [57].

5.11 Diagnosis

5.11.1 Histologic Features

Malignant cells of AITL typically are small to intermediate-sized lymphocytes with clear cytoplasm (clear cells) and are present in a polymorphous inflammatory cell background composed of reactive lymphocytes, histiocytes, eosinophils, plasma cells, and immunoblasts, admixed with increased endothelial venules and follicular dendritic cells. In lymph nodes, AITL can show three general, often overlapping patterns designated as types I, II, and III (Fig. 5.1) [58, 59]. In the type I pattern, the architecture is partially preserved. Many hyperplastic lymphoid follicles with poorly developed mantle zones are present and show expanded paracortical area. In patterns II and III, there is progressive or complete replacement, respectively, of the lymph node architecture, and small and atrophic (so-called burned-out) germinal

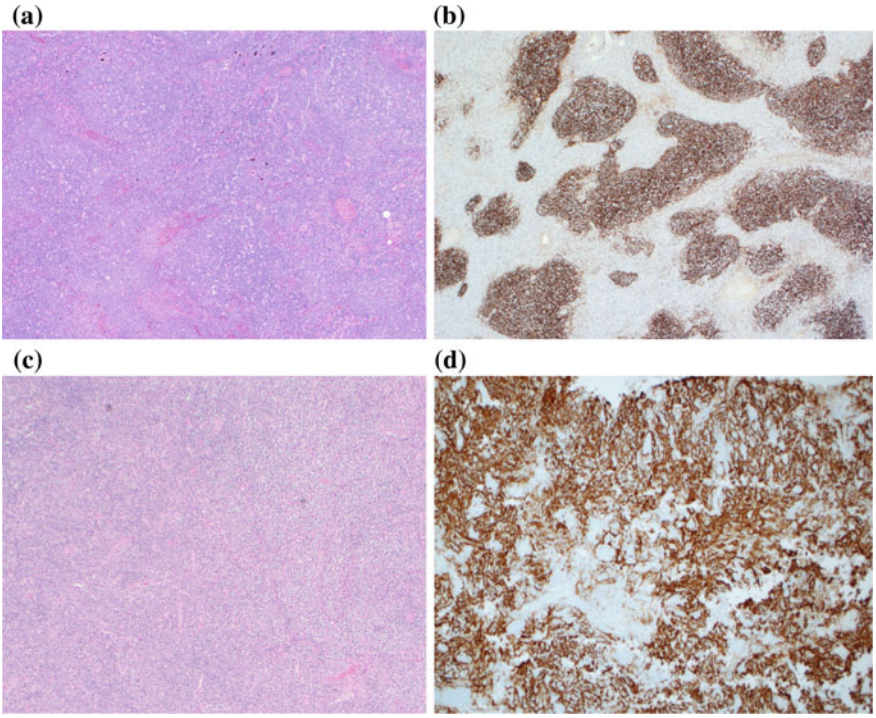

Fig. 5.1 Histologic features of angioimmunoblastic T-cell lymphoma (AITL). **a** Early involvement by AITL characterized by hyperplastic follicles and expansion of interfollicular region (pattern I). **b** Immunohistochemistry for follicular dendritic cell marker CD21 shows well-preserved follicular dendritic cell meshwork in pattern I AITL. **c** Nodal architecture is effaced, and prominent vascular proliferation is present in pattern III AITL. **d** Immunohistochemistry for follicular dendritic cell marker CD23 shows disrupted and expanded follicular dendritic cell meshwork in pattern III AITL (**a** hematoxylin and eosin, x 40; **b** CD21 immunohistochemistry, x40; **c** hematoxylin and eosin, x 40; **d** CD23 immunohistochemistry, x40)

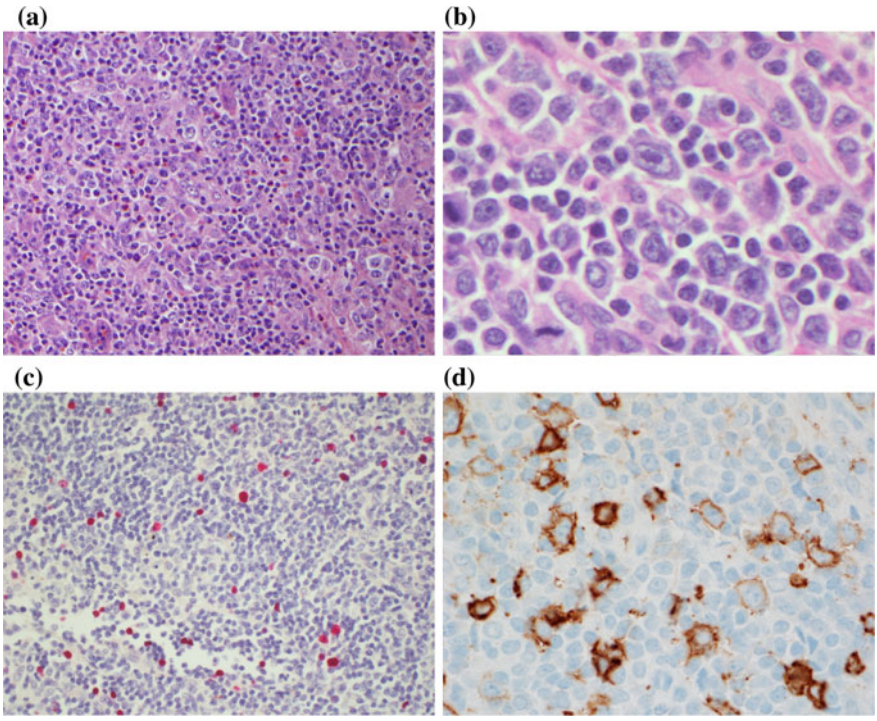

Fig. 5.2 Morphologic features of AITL. **a** Polymorphous infiltrate composed of a mixture of small and large lymphocytes, plasma cells, eosinophils, and prominent high endothelial venules are present in AITL. **b** Large atypical cells with prominent nucleoli resembling Hodgkin Reed-Sternberg cells are seen in some AITL cases. These cells are usually B-cells and commonly positive for EBV. **c** In situ hybridization of EBV encoded small RNA (EBER) shows that a subset of cells is positive in this case. **d** CD20 immunohistochemistry highlights large B-cells mimicking Hodgkin Reed-Sternberg cells (**a** hematoxylin and eosin, x 400; **b** hematoxylin and eosin, x 1000; **c** EBER, x400; **d** CD20 immunohistochemistry, x1000)

centers can be present. A mixture of patterns can occur at presentation, or patients may relapse with a different pattern [59]. The cytological features of AITL are broad, as there is usually an abundant and variable inflammatory infiltrate associated with the neoplastic cells (Figs. 5.2 and 5.3). In fact, in many cases of AITL, the neoplastic cells are a minor component in the biopsy specimen. As a result, the histologic appearance of AITL is polymorphous composed of neoplastic small and medium-sized lymphoid cells, often with clear cytoplasm, associated with reactive plasma cells, eosinophils, histiocytes, and B-immunoblasts. Large B-cells showing similar cytologic features with Hodgkin cells may be present, which are usually but not always infected by EBV [11]. Some cases of AITL can have numerous epithelioid histiocytes, mimicking lymphoepithelioid variant of PTCL, as well as plasma cells. These plasma cells can be cytologically atypical and show monoclonal IgH rearrangement [60]. Arborizing small blood vessels corresponding to

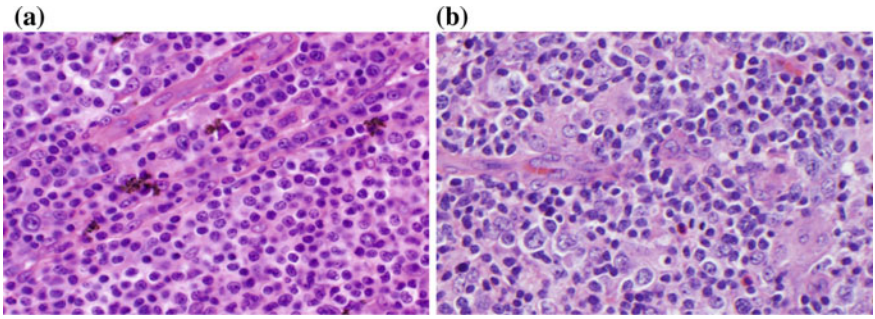

Fig. 5.3 Cytologic features of angioimmunoblastic T-cell lymphoma. **a** Lymphoma cells have intermediate-sized round nuclei and pale, abundant "monocytoid" cytoplasm. **b** The neoplastic cells are small to intermediate in size and locate adjacent to high endothelial venules (**a** hematoxylin and eosin, x 400; **b** hematoxylin and eosin, x 400)

epithelioid venules are present and usually numerous in AITL. In early cases (pattern I), the follicular dendritic cells proliferation can be minimal and limited to a few follicles. In more advanced cases (pattern II and III), the follicular dendritic cell extends into the interfollicular area and wrap around the arborizing vessels (Fig. 5.1).

5.12 Immunophenotype

Immunophenotypic studies of AITL have shown that these tumors are of mature T-cell lineage, expressing a variety of pan-T-cell antigens and negative for Ig and B-cell antigens. Lymphoma cells are of TFH origin; thus, cases of AITL have an immunophenotype closely akin to that of normal TFH [14]. Therefore, the neoplastic cells are CD4+ , CD8−, T-cell receptor (TCR) alpha/beta, and are often express CXCL13, CD10, BCL6, PD-1, ICOS, or CD200 (Fig. 5.4) [11, 61, 62]. Aberrant loss or reduced expression of surface CD3, CD5, and CD7 is frequently seen. CD10 expression is observed in 70–80% of the cases and is often heterogeneous, detected on a small subset and of variable intensity [9, 63]. CD30 expression is reported up to one-third of the cases, and the assessment for CD30 could be a potentially useful routine clinical tool for stratifying patients who might benefit from CD30-targeting treatment [64]. The immune dysregulation and immunodeficiency associated with AITL also may explain the common presence of EBV in nonneoplastic B-immunoblasts in many AITL specimens. EBV is positive in up to 80–90% of cases, and EBV viral load in tissue correlates with histologic evidence of progression [57]. The characteristic proliferation of follicular dendritic cells is highlighted by CD21 and CD23. In early cases (pattern I), the follicular dendritic cell proliferation can be minimal and limited to a few follicles. In more

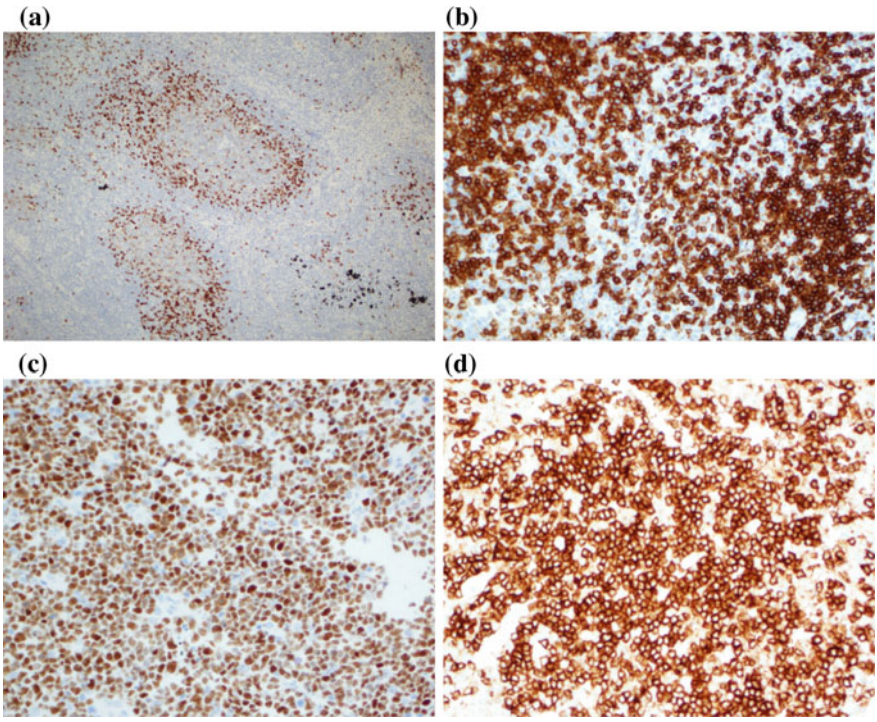

Fig. 5.4 Immunohistochemical findings seen in AITL. **a** CD10 immunostain highlights neoplastic T-cells surrounding the germinal centers. **b–d** The characteristic immunophenotype of tumor cells expressing CD3 (**b**), BCL6 (**c**), and PD-1 (**d**) (**a** CD10 immunohistochemistry, x100; **b** CD3 immunohistochemistry, x200; **c** BCL6 immunohistochemistry, x200; **d** PD-1 immunohistochemistry, x200)

advanced cases (pattern II and III), the follicular dendritic cell meshwork extends into the interfollicular area and wrap around the arborizing vessels.

The diagnosis of AITL can be challenging, especially in small needle core biopsy specimens, and a definitive diagnosis often requires a use of additional ancillary testing, such as flow cytometric immunophenotyping. Flow cytometric analysis for detecting aberrant T-cell population coexpressing PD-1 (CD279) and CD10 would be of help for the diagnosis of AITL (Fig. 5.5). In one study, CD10 expression by flow cytometric analysis has been suggested as a highly sensitive, but less specific marker when distinguishing AITL from other forms of PTCL [65]. Peripheral blood leucocytosis with lymphocytosis is rare in AITL; however, circulating sCD3−/CD4+ T-cells in peripheral blood have been described in the setting of AITL, with intracellular but no surface CD3 [66]. Following the recent advances of flow cytometry, nowadays it is reported that almost all cases of AITL present with a small, but distinct population of sCD3−/CD4+ T-cells with variable expression of CD10 in peripheral blood [12]. sCD3−/CD4+ T-cells have a high positive predictive value (94%) for the diagnosis of AITL, and flow cytometry is

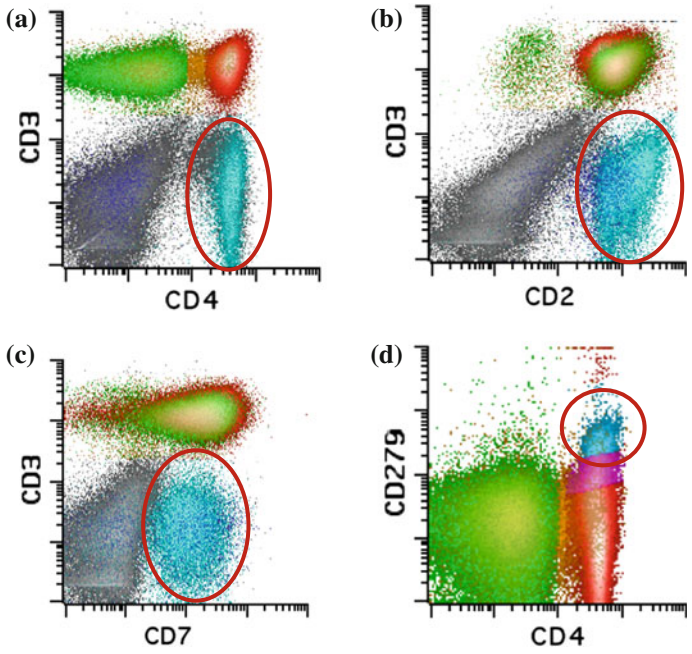

Fig. 5.5 **a–c** Flow cytometry of lymph node involved by AITL shows an abnormal CD4-positive T-cell population with aberrant loss of surface CD3 **a**, a bright expression of CD2 **b**, and dim expression of CD7 **c**. **d** This abnormal CD4-positive T-cell population expresses bright CD279 (PD-1). The findings are consistent with involvement by T-cell lymphoma with T follicle helper (TFH) cell immunophenotype

particularly useful in differentiating AITL from other CD4-positive T-cell lymphomas, including ATLL, anaplastic large cell lymphoma (ALCL), PTCL-NOS, T-cell prolymphocytic leukemia (T-PLL), and mycosis fungoides/Sezary syndrome, even if the aberrant T-cell population has a very low frequency [12].

5.13 Cytogenetics and Molecular Findings

Conventional cytogenetic studies have shown a wide variety of numerical and structural abnormalities in approximately 75% of cases of AITL. Trisomies of chromosomes 3, 5, 21, and X and loss of 6q are most common [67]. Comparative genomic hybridization studies have further increased the frequency of detection of chromosomal alterations, identified in up to 90% of AITL cases, and common alterations include gains of 22q, 19, and 11p11-q14, and losses of 13q [68]. Gene rearrangement studies have demonstrated that most AITL cases have *TCR* gene rearrangements. The *IGH* gene is rearranged in 10–20% of cases [61]. Recurrent genetic abnormalities seen in AITL cases include *RHOA, TET2, IDH2, DNMT3A*,

and genes related to TCR signaling, including *CD28*, *FYN*, *PLCG1, CARD11, PI3K* elements, *CTNNB1,* and *GTF2I*, as well as gene fusions such as *CTLA4-CD28* or *ITK-SYK*, as discussed earlier. However, these mutations are not specific for AITL; most specific to AITL is a *RHOA* G17V mutation; however, this is also detected in PTCL with a TFH immunophenotype.

5.14 Follicular T-Cell Lymphoma and Nodal PTCL with TFH Phenotype

Genetic studies have shown recurrent mutations that affect a significant proportion of cases of AITL. However, many of the same genetic alterations discussed above are also observed in cases of PTCL-NOS, and lymphoma cells in these cases show TFH immunophenotype, including expression of CD4, PD-1, CD10, BCL6, CXCL13, and ICOS [41]. From these observations, it is now recognized that a subset of PTCL-NOS cases has "TFH-like" features in the form of a molecular profile, the expression of TFH-associated molecules, and/or overlapping pathologic features with AITL. Thus, WHO 2016 classification now classifies follicular T-cell lymphoma (FTCL) and nodal PTCL with TFH phenotype as provisional entities, being unified under a common heading with AITL [31].

FTCL shows a prominent follicular growth pattern and lacks characteristic features of AITL, including proliferation of high endothelial venules, and expansion of follicular dendritic cell meshworks. Two distinct growth patterns are recognized; cases that mimic follicular lymphoma, and cases mimic progressive transformation of germinal centers (Fig. 5.6) [69]. Clinical features of FTCL resemble those of AITL; seen in middle-aged and elderly individuals, present with generalized lymphadenopathy, B-symptoms, splenomegaly, and hypergammaglobulinemia, however, patients with localized disease with fewer systemic symptoms are also reported [69–71].

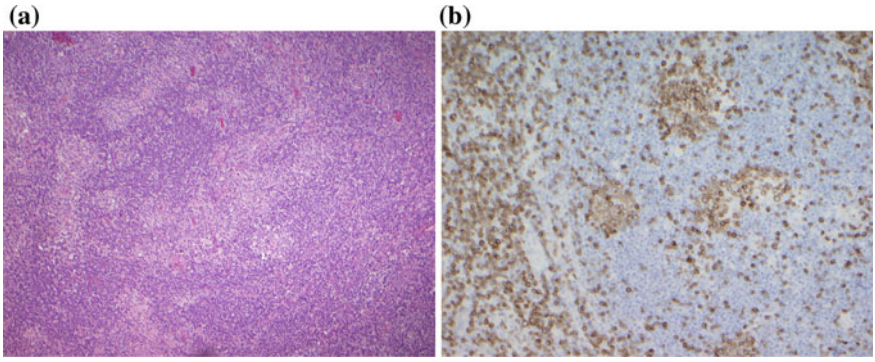

Fig. 5.6 Follicular T-cell lymphoma with a progressive transformation of germinal centers-like growth pattern. **a** Nests of neoplastic cells are present surrounded by mantle zone B-cells. **b** These nests of neoplastic cells are highlighted by CD3 (**a** hematoxylin and eosin, x100; **b** CD3, x200)

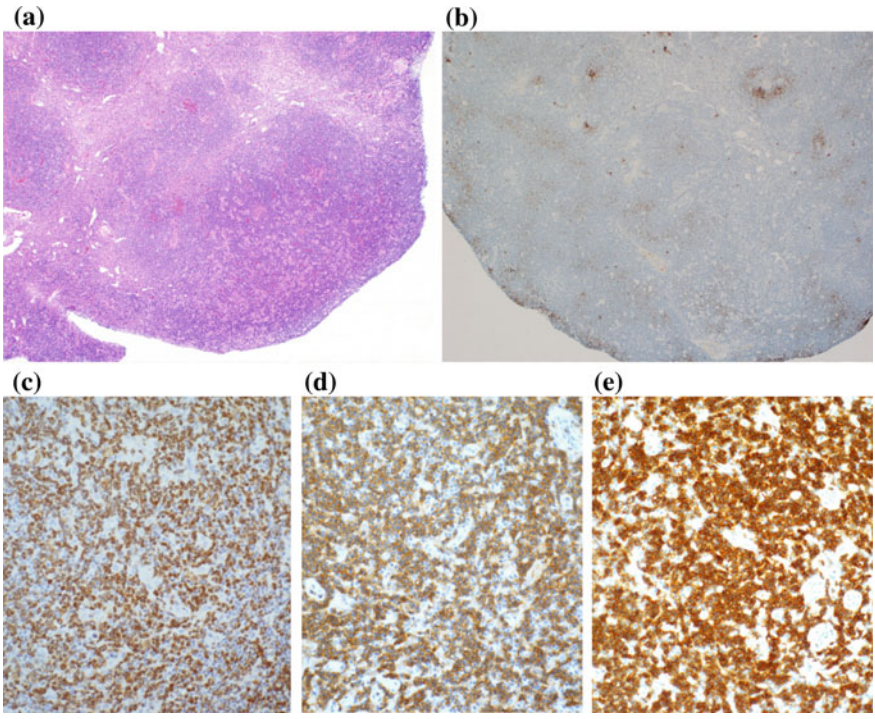

Fig. 5.7 Nodal peripheral T-cell lymphoma with T follicular helper phenotype. **a** Histologic section shows vaguely nodular to diffuse infiltration of lymphoma cells. **b** Expansion of follicular dendritic cell meshworks is not evident by CD23 immunostain. **c–e** Lymphoma cells express CD3 (C), CD4 (D), and PD-1 (E). CD10 and BCL6 are also expressed in this case (**a** hematoxylin and eosin, x40; **b** CD23 immunohistochemistry, x40; **c** CD3 immunohistochemistry, x400; **d** CD4 immunohistochemistry, x400; **e** PD-1 immunohistochemistry, x400)

The minimal criteria for assignment of TFH phenotype are not well established to make a diagnosis of nodal PTCL with TFH phenotype, but the detection of at least two of the TFH markers in addition to CD4 is suggested to assign a TFH phenotype to a nodal CD4+ T-cell lymphoma. This lymphoma often shows a diffuse infiltration pattern without a prominent polymorphic inflammatory background or expansion of follicular dendritic cell meshworks (Fig. 5.7).

5.15 Initial Treatment

Despite the unique pathologic and clinical features of AITL, the initial approach to treatment is currently similar to that used for the other nodal PTCLs, such as PTCL-NOS [72]. For most patients with AITL, the initial goal of treatment is curative and due to the rarity of these diseases, the best data available to guide

therapy comes from prospective phase II studies. CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) has been the backbone for the frontline treatment of AITL; however despite fairly high response rates to CHOP, long-term outcomes with CHOP alone are generally poor due to high relapse rates. The response rate to CHOP in AITL and other nodal PTCLs is best determined from prospective studies in which outcomes were assessed by intent-to-treat. In a phase II study evaluating CHOP induction therapy followed by ASCT for untreated PTCL, the ORR to CHOP was 79% with a CR rate of 39% [73]. Similarly, a small phase III study from the GOELAMS group of CHOP versus VIP-rABVD (etoposide, ifosfamide, cisplatin alternating with adriamycin, bleomycin, vinblastine, and dacarbazine) showed no difference in outcome for the two arms and resulted in an ORR of 70% and a CR rate of 35% with CHOP [74]. Long-term outcomes with CHOP are elucidated from retrospective series, such as the International T-cell lymphoma project (ITCP), in which 85% of patients received CHOP-based therapy, 18.5% had AITL, and the 5-year failure-free survival (FFS) for the AITL patients was only 18% [75]. Similar outcomes were observed in the British Columbia Cancer Agency (BCCA) series in which the 5-year progression-free survival (PFS) observed for AITL was only 13% [76].

Attempts to improve frontline therapy for nodal PTCLs have included adding additional active agents to the CHOP backbone and consolidating CHOP-based induction with autologous stem cell transplant (ASCT). For young, fit patients, CHOP plus etoposide (CHOEP) is often used as induction for nodal PTCLs. Support for this regimen comes from an analysis from the German high-grade non-Hodgkin lymphoma study group (DSHNHL) of PTCL patients treated on 7 different prospective phase II or phase III protocols comparing CHOP-based therapy to CHOP plus etoposide-based therapy [77]. Among the 320 patients with PTCL enrolled on these studies, the authors found that younger patients (<60 years old) with normal LDH, had a significant improvement in outcome if they received CHOP plus etoposide compared to CHOP alone with 3-year EFS of 75.4 versus 51%, although no difference in overall survival was observed. The benefits were greatest in the more favorable ALK-positive ALCL subtype but there was a trend toward improved EFS in favor of CHOP plus etoposide in the other subsets as well ($p = 0.057$). In elderly patients, the addition of etoposide added significant toxicity. Consistent with these findings, an analysis from the Swedish Lymphoma Registry of 252 PTCL patients (19% with AITL) treated with CHOP or CHOEP revealed a higher ORR with CHOEP (81 vs. 70%, $p = 0.052$) and improved PFS for patients less than 60 years of age treated with CHOEP (HR 0.49; 95% CI, 0.29–0.83; $p = 0.008$) [78].

To further improve upon the outcomes with CHOP-based therapy, many groups routinely offer consolidation with ASCT in first remission for patients with AITL, PTCL-NOS, ALK-negative ALCL, and higher risk ALK-positive ALCL. There are no randomized trials to support this treatment approach; however several prospective studies suggest benefit from up-front ASCT. The largest was the Nordic study by d'Amore and colleagues [79]. This study enrolled 160 patients with PTCL, including 39% with PTCL-NOS, 19% with ALK-negative ALCL, and 19% with

AITL and excluded ALK-positive ALCL. Most patients (81%) presented with advanced stage disease and 72% had international prognostic index (IPI) scores of 2 or more. Patients received CHOEP for 6 cycles (etoposide was omitted for patients >60 years of age) and those in CR or PR proceeded to high dose therapy with BEAM (carmustine, etoposide, cytarabine, and melphalan (or cyclophosphamide) and ASCT. 115 (71%) patients underwent ASCT. By intent-to-treat analysis, the 5-year OS and PFS were 51 and 44%. The patients with ALK-negative ALCL performed particularly well with 5-year OS and PFS of 70 and 61%. The 5-year OS and PFS for patients with PTCL-NOS were 47% and 38%, respectively, and for AITL, 52% and 49%, respectively. Reimer and colleagues conducted the second largest prospective study evaluating ASCT in first remission post CHOP, which enrolled 83 patients [73]. By intent-to-treat analysis, similar results were seen with 3-year OS rate at 48%. For those who were transplanted (66% of patients enrolled) outcomes were considerably more favorable with 3-year OS of 71%. Retrospective series evaluating up-front consolidation with ASCT closely mirror the experience in these prospective studies. In the Swedish Lymphoma Registry, intent to treat with ASCT in first remission was associated with 5-year overall survival (OS) of 48% compared to 26% ($p = 0.004$) for patients for whom up-front ASCT was not included in the treatment plan [78]. In addition, a retrospective series from Memorial Sloan Kettering Cancer Center (MSKCC) of 112 PTCL patients (49 with AITL) intended for treatment with CHOP-based chemotherapy followed by ASCT showed similar results with 4-year OS and PFS of 68% and 43%, respectively [80, 81].

Altogether, studies evaluating ASCT in first remission compare favorably to historical controls. The Nordic Study, which evaluated CHOEP followed by ASCT, demonstrated promising results in a large cohort of patients with PTCL; thus, outside of a clinical trial, induction with CHOEP followed by consolidation with ASCT is a reasonable approach for patients with PTCL, including AITL [79]. Given the lack of phase III data to support this approach, however, whenever possible, enrollment in clinical trials should be favored.

5.16 Relapsed/Refractory AITL

The approach to treatment of patients with relapsed or refractory AITL (as well as the other nodal PTCLs) depends upon the individuals' comorbidities, age, and overall goal of therapy [82]. For young, fit patients, allogeneic stem cell transplant (alloSCT) offers the chance of cure, and thus alloSCT is the goal of therapy for many patients, provided they can achieve good disease control prior to transplant. Support for the use of alloSCT in this setting comes from data reported from the French registry as well as single-center institutional data. In the French registry, 77 patients with PTCL underwent myeloablative (57) or reduced-intensity

(20) alloSCT and the 5-year OS and EFS were 57% and 53%, respectively. The 5-year OS was significantly higher for patients with complete or partial response prior to transplant (69% vs. 29%, p = 0.0003) and particularly favorable for the 11 patients with AITL (5-year OS 80%) [83]. Similar outcomes were reported in the MSKCC series that included 65 patients with PTCL undergoing alloSCT with 2-year OS and PFS of 59% and 48%, respectively [84]. These results are also consistent with a series from the Dana Farber Cancer Institute that included 52 PTCL patients treated with allogeneic stem cell transplant [85]. In contrast to data regarding alloSCT in the relapsed or refractory setting, our institutional data and others have shown that the use of autologous stem cell transplantation for relapsed PTCL, with a possible exception of ALCL, has rarely resulted in long-term disease control [86, 87]. Although a recent analysis from CIBMTR (Center for International Blood and Marrow Transplant Research) registry data points to better results with ASCT at relapse, this series is overrepresented by ALCL including many with ALK-positive ALCL. Therefore, with the exception of ALCL, ASCT is rarely considered in the relapsed or refractory setting for AITL and other PTCLs [88].

The choice of initial therapy for relapsed or refractory AITL depends upon whether alloSCT is being considered and whether a donor has already been identified. When an alloSCT is planned and a donor is already identified, reasonable treatment options include multi-agent chemotherapy, such as ICE (ifosfamide, carboplatin, etoposide) or DHAP (dexamethasone, cytarabine, cisplatin). Response rates up to 70% are observed with these regimens and therefore they can efficiently bridge patients to transplant; however, these regimens do not produce sustained disease control due to cumulative toxicity after three or four`` cycles [87]. When an alloSCT is either not part of the treatment plan (due to patient's age, comorbidities, or lack of donor) or the timing of alloSCT is unclear (due to unclear donor status or potential comorbidities that may disqualify the patient for transplant), multi-agent regimens such as ICE or DHAP are not typically beneficial because these patients need longer term disease control. The drugs recently FDA approved for relapsed or refractory PTCL, romidepsin, belinostat, and pralatrexate, are reasonable options in this setting because despite fairly low overall response rates (ranging from 25 to 29%), there is no significant cumulative toxicity and therefore responders can potentially achieve durable response with continuous treatment [89–91]. Table 5.2 summarizes the response rates associated with select active agents used for AITL. As shown in Table 5.2, histone deacetylase (HDAC) inhibitors appear to have preferential activity in AITL, likely related to the high frequency of mutations in epigenetic modifier genes seen in this disease. Accordingly, HDAC inhibitors, either alone or in combination with other agents (as part of clinical trials) are typically the first treatment choice for patients with relapsed or refractory AITL.

Table 5.2 Select active agents for angioimmunoblastic T-cell lymphoma and other peripheral T-cell lymphomas

Agents	AITL (n)	ORR/CR (AITL)	Total PTCL (n)	ORR/CR (all PTCL)	PFS (months)	DOR (months)
Romidepsin [89]	27	30%/19%	130	25%/15%	4	17
Belinostat [90, 97]	22	45%/18%	129	26%/10%	NA	8.3
5-azacytidine [98]	12	75%/42%	19	53%/26%	NA	NA
Pralatrexate [91]	13	8%/NR	111	29%/13%	3.5	10.5
Bendamustine [99]	32	NR	60	50%/28%	3.6	3.5
Brentuximab vedotin [94]	13	54%/38%	22	41%/24%	2.6	7.6
Gemcitabine [100]	NR	NR	20	55%/30%	NR	NR
lenalidomide [101]	7	29%/0	23	30%/0	3.2	5.7
Cyclosporine A [102]	12	67%/25%	NA	NA	NA	NA

Abbreviations: *ORR* overall response rate; *CR* complete response; *PFS* progression-free survival; *DOR* duration of response; *OS* overall survival; *NA* not applicable; *NR* not reported
Note PFS, DOR, and OS are all medians in months

5.17 Future Directions for Treatment of AITL

Given the signal of activity of HDAC inhibitors in AITL, regimens building upon these agents are likely to make a significant impact on treatment. In the frontline setting, the safety of adding romidepsin to CHOP (Ro-CHOP) has been established and this regimen is currently being evaluated in a phase III study comparing Ro-CHOP to CHOP (clinicaltrials.gov: NCT01796002) [92]. In the relapsed and refractory setting, romidepsin combinations were evaluated in two phase I studies at MSKCC, first in combination with lenalidomide and subsequently in combination with lenalidomide and carfilzomib. The two studies enrolled a total of 19 patients with PTCL, including 7 patients with AITL. The ORR and CR rates for the AITL patients (87 and 57%) were considerably higher than observed in the other PTCL patients (ORR 33%), further supporting the potential role of HDAC inhibitor-based therapy in AITL [84, 93].

Since up to one-third of AITL cases express CD30, brentuximab vedotin (BV), the anti-CD30 antibody–drug conjugate, is another promising agent for a subset of patients with AITL [64]. In a phase II study for relapsed or refractory CD30-positive PTCLs (other than ALCL), 35 patients were treated, including 13 patients with AITL. The ORR was 41%, however, AITL patients appeared to benefit more from treatment as the ORR and CR rates in this group were 54% and 38%, respectively [94]. In the frontline setting, another attempt to improve the CHOP regimen is the exchange of vincristine for BV for CD30 positive PTCLs. The BV plus CH-P regimen was initially studied in a phase I trial for patients with ALCL and other

CD30 positive PTCLs. The study enrolled 26 patients, including 19 with ALCL and 2 with AITL. Treatment was well tolerated; the ORR was 100% and CR rate 88% [95]. Building on this experience, BV plus CH-P is being compared to CHOP in a randomized, double-blind, phase III study for treatment-naïve patients with CD30-positive PTCL. This study, known as ECHELON-2, has finished accrual of about 300 patients and has the potential to meaningfully impact the management of AITL (www.clinicaltrials.gov: NCT01777152).

As mentioned above, TET2 is commonly mutated in AITL, thus suggesting a potential role for hypomethylating agents in this disease. A recent study evaluating 5-azacytidine in PTCLs that included 12 patients with AITL and 7 patients with other PTCLs, reported an ORR of 53%. Once again, preferential activity was observed in AITL with 9 of 12 (75%) achieving response and 5 of 12 (42%) achieving complete response [96]. Studies building upon this class in AITL are certainly warranted and are already underway (www.clinicaltrials.gov: NCT03161223 and NCT01998035).

5.18 Conclusion

While AITL has typically been grouped with the other T-cell lymphomas with regard to management, data is emerging regarding its unique sensitivity to certain classes of agents. This data will eventually lead to the development of regimens specific for AITL as well as potentially the new "TFH-like" provisional entities, follicular T-cell lymphoma and nodal PTCL with TFH phenotype. However, as described in this chapter, there is heterogeneity even among patients with AITL and therefore individualized treatment approaches are likely needed. Studies evaluating novel agents in AITL that include assessments aimed at identifying markers of response or resistance will aid in determining which drugs or regimens are most appropriate for individuals with AITL. At this time, although we currently have a "one size fits all" approach to the frontline treatment for AITL, there may come a time when molecular profiling allows for AITL patients to be stratified at diagnosis and treated according to likelihood of sensitivity to HDAC inhibitors, hypomethylating agents, anti-CD30 treatment, and other targeted agents. A more individualized frontline approach will undoubtedly lead to improved outcomes for patients with AITL.

References

1. Frizzera G, Moran EM, Rappaport H (1974) Angio-immunoblastic lymphadenopathy with dysproteinaemia. Lancet 1:1070–1073
2. Lukes RJ, Tindle BH (1975) Immunoblastic lymphadenopathy. A hyperimmune entity resembling Hodgkin's disease. New Engl J Med 292:1–8

3. Lennert K (1979) Nature, prognosis and nomenclature of angioimmunoblastic (lymphadenopathy (lymphogranulomatosis X or T-zone lymphoma). Deutsche medizinische Wochenschrift 104:1246–1247
4. Feller AC, Griesser H, Schilling CV, Wacker HH, Dallenbach F, Bartels H, Kuse R, Mak TW, Lennert K (1988) Clonal gene rearrangement patterns correlate with immunophenotype and clinical parameters in patients with angioimmunoblastic lymphadenopathy. Am J Pathol 133:549–556
5. Kaneko Y, Maseki N, Sakurai M, Takayama S, Nanba K, Kikuchi M, Frizzera G (1988) Characteristic karyotypic pattern in T-cell lymphoproliferative disorders with reactive "angioimmunoblastic lymphadenopathy with dysproteinemia-type" features. Blood 72:413–421
6. Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML, Delsol G, De Wolf-Peeters C, Falini B, Gatter KC et al (1994) A revised European-American classification of lymphoid neoplasms: a proposal from the international Lymphoma study group. Blood 84:1361–1392
7. Harris NL, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, Vardiman J (2000) Lymphoma classification—from controversy to consensus: the R.E.A.L. and WHO classification of lymphoid neoplasms. Ann Oncol 11(Suppl 1):3–10
8. Vose J, Armitage J, Weisenburger D (2008) International TCLP. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol 26:4124–4130
9. Mourad N, Mounier N, Briere J, Raffoux E, Delmer A, Feller A, Meijer CJ, Emile JF, Bouabdallah R, Bosly A, Diebold J, Haioun C, Coiffier B, Gisselbrecht C, Gaulard P (2008) Groupe d'Etude des Lymphomes de lA. Clinical, biologic, and pathologic features in 157 patients with angioimmunoblastic T-cell lymphoma treated within the Groupe d'Etude des Lymphomes de l'Adulte (GELA) trials. Blood 111:4463–4470
10. Cho YU, Chi HS, Park CJ, Jang S, Seo EJ, Huh J (2009) Distinct features of angioimmunoblastic T-cell lymphoma with bone marrow involvement. Am J Clin Pathol 131:640–646
11. de Leval L, Gisselbrecht C, Gaulard P (2010) Advances in the understanding and management of angioimmunoblastic T-cell lymphoma. Br J Haematol 148:673–689
12. Singh A, Schabath R, Ratei R, Stroux A, Klemke CD, Nebe T, Florcken A, van Lessen A, Anagnostopoulos I, Dorken B, Ludwig WD, Pezzutto A, Westermann J (2014) Peripheral blood sCD3(−) CD4(+) T cells: a useful diagnostic tool in angioimmunoblastic T cell lymphoma. Hematol Oncol 32:16–21
13. Willenbrock K, Brauninger A, Hansmann ML (2007) Frequent occurrence of B-cell lymphomas in angioimmunoblastic T-cell lymphoma and proliferation of Epstein-Barr virus-infected cells in early cases. Br J Haematol 138:733–739
14. de Leval L, Rickman DS, Thielen C, Reynies A, Huang YL, Delsol G, Lamant L, Leroy K, Briere J, Molina T, Berger F, Gisselbrecht C, Xerri L, Gaulard P (2007) The gene expression profile of nodal peripheral T-cell lymphoma demonstrates a molecular link between angioimmunoblastic T-cell lymphoma (AITL) and follicular helper T (TFH) cells. Blood 109:4952–4963
15. Grogg KL, Attygalle AD, Macon WR, Remstein ED, Kurtin PJ, Dogan A (2005) Angioimmunoblastic T-cell lymphoma: a neoplasm of germinal-center T-helper cells? Blood 106:1501–1502
16. Breitfeld D, Ohl L, Kremmer E, Ellwart J, Sallusto F, Lipp M, Forster R (2000) Follicular B helper T cells express CXC chemokine receptor 5, localize to B cell follicles, and support immunoglobulin production. J Exp Med 192:1545–1552
17. Cortes JR, Palomero T (2016) The curious origins of angioimmunoblastic T-cell lymphoma. Curr Opin Hematol 23:434–443
18. Ueno H, Banchereau J, Vinuesa CG (2015) Pathophysiology of T follicular helper cells in humans and mice. Nat Immunol 16:142–152

19. Vinuesa CG, Linterman MA, Yu D, MacLennan IC (2016) Follicular helper T cells. Annu Rev Immunol 34:335–368
20. Leavenworth JW, Verbinnen B, Yin J, Huang H, Cantor H (2015) A p85alpha-osteopontin axis couples the receptor ICOS to sustained Bcl-6 expression by follicular helper and regulatory T cells. Nat Immunol 16:96–106
21. Nurieva RI, Chung Y, Martinez GJ, Yang XO, Tanaka S, Matskevitch TD, Wang YH, Dong C (2009) Bcl6 mediates the development of T follicular helper cells. Science 325:1001–1005
22. Couronne L, Bastard C, Bernard OA (2012) TET2 and DNMT3A mutations in human T-cell lymphoma. New Engl J Med 366:95–96
23. Odejide O, Weigert O, Lane AA, Toscano D, Lunning MA, Kopp N, Kim S, van Bodegom D, Bolla S, Schatz JH, Teruya-Feldstein J, Hochberg E, Louissaint A, Dorfman D, Stevenson K, Rodig SJ, Piccaluga PP, Jacobsen E, Pileri SA, Harris NL, Ferrero S, Inghirami G, Horwitz SM, Weinstock DM (2014) A targeted mutational landscape of angioimmunoblastic T-cell lymphoma. Blood 123:1293–1296
24. Sakata-Yanagimoto M, Enami T, Yoshida K, Shiraishi Y, Ishii R, Miyake Y, Muto H, Tsuyama N, Sato-Otsubo A, Okuno Y, Sakata S, Kamada Y, Nakamoto-Matsubara R, Tran NB, Izutsu K, Sato Y, Ohta Y, Furuta J, Shimizu S, Komeno T, Sato Y, Ito T, Noguchi M, Noguchi E, Sanada M, Chiba K, Tanaka H, Suzukawa K, Nanmoku T, Hasegawa Y, Nureki O, Miyano S, Nakamura N, Takeuchi K, Ogawa S, Chiba S (2014) Somatic RHOA mutation in angioimmunoblastic T cell lymphoma. Nat Genet 46:171–175
25. Palomero T, Couronne L, Khiabanian H, Kim MY, Ambesi-Impiombato A, Perez-Garcia A, Carpenter Z, Abate F, Allegretta M, Haydu JE, Jiang X, Lossos IS, Nicolas C, Balbin M, Bastard C, Bhagat G, Piris MA, Campo E, Bernard OA, Rabadan R, Ferrando AA (2014) Recurrent mutations in epigenetic regulators, RHOA and FYN kinase in peripheral T cell lymphomas. Nat Genet 46:166–170
26. Jaffe AB, Hall A (2005) Rho GTPases: biochemistry and biology. Annu Rev Cell Dev Biol 21:247–269
27. Henning SW, Galandrini R, Hall A, Cantrell DA (1997) The GTPase Rho has a critical regulatory role in thymus development. EMBO J 16:2397–2407
28. Pernis AB (2009) Rho GTPase-mediated pathways in mature CD4+ T cells. Autoimmun Rev 8:199–203
29. Yoo HY, Sung MK, Lee SH, Kim S, Lee H, Park S, Kim SC, Lee B, Rho K, Lee JE, Cho KH, Kim W, Ju H, Kim J, Kim SJ, Kim WS, Lee S, Ko YH (2014) A recurrent inactivating mutation in RHOA GTPase in angioimmunoblastic T cell lymphoma. Nat Genet 46:371–375
30. Nagata Y, Kontani K, Enami T, Kataoka K, Ishii R, Totoki Y, Kataoka TR, Hirata M, Aoki K, Nakano K, Kitanaka A, Sakata-Yanagimoto M, Egami S, Shiraishi Y, Chiba K, Tanaka H, Shiozawa Y, Yoshizato T, Suzuki H, Kon A, Yoshida K, Sato Y, Sato-Otsubo A, Sanada M, Munakata W, Nakamura H, Hama N, Miyano S, Nureki O, Shibata T, Haga H, Shimoda K, Katada T, Chiba S, Watanabe T, Ogawa S (2016) Variegated RHOA mutations in adult T-cell leukemia/lymphoma. Blood 127:596–604
31. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, Advani R, Ghielmini M, Salles GA, Zelenetz AD, Jaffe ES (2016) The 2016 revision of the world health organization classification of lymphoid neoplasms. Blood 127:2375–2390
32. Cairns RA, Iqbal J, Lemonnier F, Kucuk C, de Leval L, Jais JP, Parrens M, Martin A, Xerri L, Brousset P, Chan LC, Chan WC, Gaulard P, Mak TW (2012) IDH2 mutations are frequent in angioimmunoblastic T-cell lymphoma. Blood 119:1901–1903
33. Ko M, Huang Y, Jankowska AM, Pape UJ, Tahiliani M, Bandukwala HS, An J, Lamperti ED, Koh KP, Ganetzky R, Liu XS, Aravind L, Agarwal S, Maciejewski JP, Rao A (2010) Impaired hydroxylation of 5-methylcytosine in myeloid cancers with mutant TET2. Nature 468:839–843

34. Abdel-Wahab O, Mullally A, Hedvat C, Garcia-Manero G, Patel J, Wadleigh M, Malinge S, Yao J, Kilpivaara O, Bhat R, Huberman K, Thomas S, Dolgalev I, Heguy A, Paietta E, Le Beau MM, Beran M, Tallman MS, Ebert BL, Kantarjian HM, Stone RM, Gilliland DG, Crispino JD, Levine RL (2009) Genetic characterization of TET1, TET2, and TET3 alterations in myeloid malignancies. Blood 114:144–147
35. Wang C, McKeithan TW, Gong Q, Zhang W, Bouska A, Rosenwald A, Gascoyne RD, Wu X, Wang J, Muhammad Z, Jiang B, Rohr J, Cannon A, Steidl C, Fu K, Li Y, Hung S, Weisenburger DD, Greiner TC, Smith L, Ott G, Rogan EG, Staudt LM, Vose J, Iqbal J, Chan WC (2015) IDH2R172 mutations define a unique subgroup of patients with angioimmunoblastic T-cell lymphoma. Blood 126:1741–1752
36. Muto H, Sakata-Yanagimoto M, Nagae G, Shiozawa Y, Miyake Y, Yoshida K, Enami T, Kamada Y, Kato T, Uchida K, Nanmoku T, Obara N, Suzukawa K, Sanada M, Nakamura N, Aburatani H, Ogawa S, Chiba S (2014) Reduced TET2 function leads to T-cell lymphoma with follicular helper T-cell-like features in mice. Blood Cancer J 4:e264
37. Ward PS, Lu C, Cross JR, Abdel-Wahab O, Levine RL, Schwartz GK, Thompson CB (2013) The potential for isocitrate dehydrogenase mutations to produce 2-hydroxyglutarate depends on allele specificity and subcellular compartmentalization. J Biol Chem 288:3804–3815
38. Paschka P, Schlenk RF, Gaidzik VI, Habdank M, Kronke J, Bullinger L, Spath D, Kayser S, Zucknick M, Gotze K, Horst HA, Germing U, Dohner H, Dohner K (2010) IDH1 and IDH2 mutations are frequent genetic alterations in acute myeloid leukemia and confer adverse prognosis in cytogenetically normal acute myeloid leukemia with NPM1 mutation without FLT3 internal tandem duplication. J Clin Oncol Official J Am Soc Clin Oncol 28:3636–3643
39. Scourzic L, Couronne L, Pedersen MT, Della Valle V, Diop M, Mylonas E, Calvo J, Mouly E, Lopez CK, Martin N, Fontenay M, Bender A, Guibert S, Dubreuil P, Dessen P, Droin N, Pflumio F, Weber M, Gaulard P, Helin K, Mercher T, Bernard OA (2016) DNMT3A(R882H) mutant and Tet2 inactivation cooperate in the deregulation of DNA methylation control to induce lymphoid malignancies in mice. Leukemia 30:1388–1398
40. Rohr J, Guo S, Huo J, Bouska A, Lachel C, Li Y, Simone PD, Zhang W, Gong Q, Wang C, Cannon A, Heavican T, Mottok A, Hung S, Rosenwald A, Gascoyne R, Fu K, Greiner TC, Weisenburger DD, Vose JM, Staudt LM, Xiao W, Borgstahl GE, Davis S, Steidl C, McKeithan T, Iqbal J, Chan WC (2016) Recurrent activating mutations of CD28 in peripheral T-cell lymphomas. Leukemia 30:1062–1070
41. Vallois D, Dobay MP, Morin RD, Lemonnier F, Missiaglia E, Juilland M, Iwaszkiewicz J, Fataccioli V, Bisig B, Roberti A, Grewal J, Bruneau J, Fabiani B, Martin A, Bonnet C, Michielin O, Jais JP, Figeac M, Bernard OA, Delorenzi M, Haioun C, Tournilhac O, Thome M, Gascoyne RD, Gaulard P, de Leval L (2016) Activating mutations in genes related to TCR signaling in angioimmunoblastic and other follicular helper T-cell-derived lymphomas. Blood 128:1490–1502
42. Yoo HY, Kim P, Kim WS, Lee SH, Kim S, Kang SY, Jang HY, Lee JE, Kim J, Kim SJ, Ko YH, Lee S (2016) Frequent CTLA4-CD28 gene fusion in diverse types of T-cell lymphoma. Haematologica 101:757–763
43. Palacios EH, Weiss A (2004) Function of the Src-family kinases, Lck and Fyn, in T-cell development and activation. Oncogene 23:7990–8000
44. Attygalle AD, Feldman AL, Dogan A (2013) ITK/SYK translocation in angioimmunoblastic T-cell lymphoma. Am J Surg Pathol 37:1456–1457
45. Vaque JP, Gomez-Lopez G, Monsalvez V, Varela I, Martinez N, Perez C, Dominguez O, Grana O, Rodriguez-Peralto JL, Rodriguez-Pinilla SM, Gonzalez-Vela C, Rubio-Camarillo M, Martin-Sanchez E, Pisano DG, Papadavid E, Papadaki T, Requena L, Garcia-Marco JA, Mendez M, Provencio M, Hospital M, Suarez-Massa D, Postigo C, San Segundo D, Lopez-Hoyos M, Ortiz-Romero PL, Piris MA, Sanchez-Beato M (2014) PLCG1 mutations in cutaneous T-cell lymphomas. Blood 123:2034–2043

46. Petrini I, Meltzer PS, Kim IK, Lucchi M, Park KS, Fontanini G, Gao J, Zucali PA, Calabrese F, Favaretto A, Rea F, Rodriguez-Canales J, Walker RL, Pineda M, Zhu YJ, Lau C, Killian KJ, Bilke S, Voeller D, Dakshanamurthy S, Wang Y, Giaccone G (2014) A specific missense mutation in GTF2I occurs at high frequency in thymic epithelial tumors. Nat Genet 46:844–849
47. Piccaluga PP, Agostinelli C, Califano A, Carbone A, Fantoni L, Ferrari S, Gazzola A, Gloghini A, Righi S, Rossi M, Tagliafico E, Zinzani PL, Zupo S, Baccarani M, Pileri SA (2007) Gene expression analysis of angioimmunoblastic lymphoma indicates derivation from T follicular helper cells and vascular endothelial growth factor deregulation. Can Res 67:10703–10710
48. Zhao WL, Mourah S, Mounier N, Leboeuf C, Daneshpouy ME, Legres L, Meignin V, Oksenhendler E, Maignin CL, Calvo F, Briere J, Gisselbrecht C, Janin A (2004) Vascular endothelial growth factor-A is expressed both on lymphoma cells and endothelial cells in angioimmunoblastic T-cell lymphoma and related to lymphoma progression. Lab Invest J Tech Methods Pathol 84:1512–1519
49. Konstantinou K, Yamamoto K, Ishibashi F, Mizoguchi Y, Kurata M, Nakagawa Y, Suzuki K, Sawabe M, Ohta M, Miyakoshi S, Crawley JT, Kitagawa M (2009) Angiogenic mediators of the angiopoietin system are highly expressed by CD10-positive lymphoma cells in angioimmunoblastic T-cell lymphoma. Br J Haematol 144:696–704
50. Iqbal J, Wright G, Wang C, Rosenwald A, Gascoyne RD, Weisenburger DD, Greiner TC, Smith L, Guo S, Wilcox RA, Teh BT, Lim ST, Tan SY, Rimsza LM, Jaffe ES, Campo E, Martinez A, Delabie J, Braziel RM, Cook JR, Tubbs RR, Ott G, Geissinger E, Gaulard P, Piccaluga PP, Pileri SA, Au WY, Nakamura S, Seto M, Berger F, de Leval L, Connors JM, Armitage J, Vose J, Chan WC, Staudt LM (2014) Lymphoma Leukemia molecular profiling P, the international peripheral TcLP. Gene expression signatures delineate biological and prognostic subgroups in peripheral T-cell lymphoma. Blood 123:2915–2923
51. Rho R, Laddis T, McQuain C, Selves J, Woda B, Knecht H (1996) Miliary tuberculosis in a patient with Epstein-Barr virus-associated angioimmunoblastic lymphadenopathy. Ann Hematol 72:333–335
52. Konig M, Grunder K, Nilles M, Schill WB (1991) Cutaneous cryptococcosis as the first symptom of a disseminated cryptococcosis in a patient with lymphogranulomatosis X. Mycoses 34:309–311
53. Luppi M, Torelli G (1996) The new lymphotropic herpesviruses (HHV-6, HHV-7, HHV-8) and hepatitis C virus (HCV) in human lymphoproliferative diseases: an overview. Haematologica 81:265–281
54. Helm TN, Steck WD, Proffitt MR, Bergfeld WF, Tubbs RR, Lo J (1990) Kaposi's sarcoma, angioimmunoblastic lymphadenopathy, and antibody to HIV-1 p24 antigen in a patient nonreactive for HIV-1 with use of ELISA. J Am Acad Dermatol 23:317–318
55. Anagnostopoulos I, Hummel M, Finn T, Tiemann M, Korbjuhn P, Dimmler C, Gatter K, Dallenbach F, Parwaresch MR, Stein H (1992) Heterogeneous Epstein-Barr virus infection patterns in peripheral T-cell lymphoma of angioimmunoblastic lymphadenopathy type. Blood 80:1804–1812
56. Brauninger A, Spieker T, Willenbrock K, Gaulard P, Wacker HH, Rajewsky K, Hansmann ML, Kuppers R (2001) Survival and clonal expansion of mutating "forbidden" (immunoglobulin receptor-deficient) epstein-barr virus-infected b cells in angioimmunoblastic t cell lymphoma. J Exp Med 194:927–940
57. Zhou Y, Attygalle AD, Chuang SS, Diss T, Ye H, Liu H, Hamoudi RA, Munson P, Bacon CM, Dogan A, Du MQ (2007) Angioimmunoblastic T-cell lymphoma: histological progression associates with EBV and HHV6B viral load. Br J Haematol 138:44–53
58. Dogan A, Attygalle AD, Kyriakou C (2003) Angioimmunoblastic T-cell lymphoma. Br J Haematol 121:681–691
59. Attygalle AD, Kyriakou C, Dupuis J, Grogg KL, Diss TC, Wotherspoon AC, Chuang SS, Cabecadas J, Isaacson PG, Du MQ, Gaulard P, Dogan A (2007) Histologic evolution of

angioimmunoblastic T-cell lymphoma in consecutive biopsies: clinical correlation and insights into natural history and disease progression. Am J Surg Pathol 31:1077–1088
60. Balague O, Martinez A, Colomo L, Rosello E, Garcia A, Martinez-Bernal M, Palacin A, Fu K, Weisenburger D, Colomer D, Burke JS, Warnke RA, Campo E (2007) Epstein-Barr virus negative clonal plasma cell proliferations and lymphomas in peripheral T-cell lymphomas: a phenomenon with distinctive clinicopathologic features. Am J Surg Pathol 31:1310–1322
61. Dogan A, Gaulard P, Jaffe ES, Ralfkiaer E, Müller-Hermelink HK (2008) Angioimmunoblastic T-cell Lymphoma. In: WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon, IARC, pp 309–311
62. Dorfman DM, Shahsafaei A (2011) CD200 (OX-2 membrane glycoprotein) is expressed by follicular T helper cells and in angioimmunoblastic T-cell lymphoma. Am J Surg Pathol 35:76–83
63. Attygalle A, Al-Jehani R, Diss TC, Munson P, Liu H, Du MQ, Isaacson PG, Dogan A (2002) Neoplastic T cells in angioimmunoblastic T-cell lymphoma express CD10. Blood 99:627–633
64. Sabattini E, Pizzi M, Tabanelli V, Baldin P, Sacchetti CS, Agostinelli C, Zinzani PL, Pileri SA (2013) CD30 expression in peripheral T-cell lymphomas. Haematologica 98:e81–2
65. Stacchini A, Demurtas A, Aliberti S, Francia di Celle P, Godio L, Palestro G, Novero D (2007) The usefulness of flow cytometric CD10 detection in the differential diagnosis of peripheral T-cell lymphomas. Am J Clin Pathol 128:854–864
66. Serke S, van Lessen A, Hummel M, Szczepek A, Huhn D, Stein H (2000) Circulating CD4 + T lymphocytes with intracellular but no surface CD3 antigen in five of seven patients consecutively diagnosed with angioimmunoblastic T-cell lymphoma. Cytometry 42:180–187
67. Schlegelberger B, Zhang Y, Weber-Matthiesen K, Grote W (1994) Detection of aberrant clones in nearly all cases of angioimmunoblastic lymphadenopathy with dysproteinemia-type T-cell lymphoma by combined interphase and metaphase cytogenetics. Blood 84:2640–2648
68. Thorns C, Bastian B, Pinkel D, Roydasgupta R, Fridlyand J, Merz H, Krokowski M, Bernd HW, Feller AC (2007) Chromosomal aberrations in angioimmunoblastic T-cell lymphoma and peripheral T-cell lymphoma unspecified: a matrix-based CGH approach. Genes Chromosom Cancer 46:37–44
69. Ruiz SJ, Cotta CV (2015) Follicular helper T-cell lymphoma: a B-cell-rich variant of T-cell lymphoma. Annals Diag Pathol 19:187–192
70. Hu S, Young KH, Konoplev SN, Medeiros LJ (2012) Follicular T-cell lymphoma: a member of an emerging family of follicular helper T-cell derived T-cell lymphomas. Hum Pathol 43:1789–1798
71. Huang Y, Moreau A, Dupuis J, Streubel B, Petit B, Le Gouill S, Martin-Garcia N, Copie-Bergman C, Gaillard F, Qubaja M, Fabiani B, Roncador G, Haioun C, Delfau-Larue MH, Marafioti T, Chott A, Gaulard P (2009) Peripheral T-cell lymphomas with a follicular growth pattern are derived from follicular helper T cells (TFH) and may show overlapping features with angioimmunoblastic T-cell lymphomas. Am J Surg Pathol 33:682–690
72. Moskowitz AJ, Lunning MA, Horwitz SM (2014) How I treat the peripheral T-cell lymphomas. Blood 123:2636–2644
73. Reimer P, Rudiger T, Geissinger E, Weissinger F, Nerl C, Schmitz N, Engert A, Einsele H, Muller-Hermelink HK, Wilhelm M (2009) Autologous stem-cell transplantation as first-line therapy in peripheral T-Cell Lymphomas: results of a prospective multicenter study. J Clin Oncol Official J Am Soc Clin Oncol 27:106–113
74. Simon A, Peoch M, Casassus P, Deconinck E, Colombat P, Desablens B, Tournilhac O, Eghbali H, Foussard C, Jaubert J, Vilque JP, Rossi JF, Lucas V, Delwail V, Thyss A, Maloisel F, Milpied N, le Gouill S, Lamy T, Gressin R. Upfront VIP-reinforced-ABVD (VIP-rABVD) is not superior to CHOP/21 in newly diagnosed peripheral T cell lymphoma.

Results of the randomized phase III trial GOELAMS-LTP95. Br J Haematol 2010;151:159-66
75. International T-Cell Lymphoma Project (2008) International peripheral T-Cell and natural killer/T-Cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol 26:4124–4130
76. Savage KJ, Chhanabhai M, Gascoyne RD, Connors JM (2004) Characterization of peripheral T-cell lymphomas in a single North American institution by the WHO classification. Ann Oncol 15:1467–1475
77. Schmitz N, Trumper L, Ziepert M, Nickelsen M, Ho AD, Metzner B, Peter N, Loeffler M, Rosenwald A, Pfreundschuh M (2010) Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma study group. Blood 116:3418–3425
78. Ellin F, Landstrom J, Jerkeman M, Relander T (2014) Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the Swedish Lymphoma registry. Blood 124:1570–1577
79. d'Amore F, Relander T, Lauritzsen GF, Jantunen E, Hagberg H, Anderson H, Holte H, Osterborg A, Merup M, Brown P, Kuittinen O, Erlanson M, Ostenstad B, Fagerli UM, Gadeberg OV, Sundstrom C, Delabie J, Ralfkiaer E, Vornanen M, Toldbod HE (2012) Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01. J Clin Oncol Official J Am Soc Clin Oncol 30:3093–3099
80. Mehta N, Maragulia JC, Moskowitz A, Hamlin PA, Lunning MA, Moskowitz CH, Zelenetz A, Matasar MJ, Sauter C, Goldberg J, Horwitz SM (2013) A retrospective analysis of peripheral T-cell lymphoma treated with the intention to transplant in the first remission. Clin Lymphoma Myeloma Leuk 13:664–670
81. Mehta-Shah N, Ito K, Bantilan KS, Moskowitz AJ, Sauter CS, Horwitz SM, Schoder H (2016) Interim PET evaluation by deauville criteria is an effective risk stratification tool in PTCL. Blood 128:186
82. Lunning MA, Moskowitz AJ, Horwitz S (2013) Strategies for relapsed peripheral T-cell lymphoma: the tail that wags the curve. J Clin Oncol 31:1922–1927
83. Le Gouill S, Milpied N, Buzyn A, De Latour RP, Vernant JP, Mohty M, Moles MP, Bouabdallah K, Bulabois CE, Dupuis J, Rio B, Gratecos N, Yakoub-Agha I, Attal M, Tournilhac O, Decaudin D, Bourhis JH, Blaise D, Volteau C, Michallet M (2008) Societe Francaise de Greffe de Moelle et de Therapie C. Graft-versus-lymphoma effect for aggressive T-cell lymphomas in adults: a study by the Societe Francaise de Greffe de Moelle et de Therapie Cellulaire. J Clin Oncol 26:2264–2271
84. Mehta-Shah N, Lunning MA, Ruan J, Nair S, Boruchov AM, Moskowitz AJ, Gerecitano JF, Hamlin PA, Leonard JP, Lynch P, Matasar MJ, Moskowitz C, Portlock C, Younes A, Myskowski P, Nolan P, Palomba ML, Vredenburgh J, Querfeld C, Straus DJ, Zelenetz A, Schroder H, Rademaker J, Schaffer W, Horwitz SM (2015) A phase I/II trial of the combination of romidepsin and lenalidomide in patients with relapsed/refractory lymphoma and myeloma. Hematol Oncol 33 (Supplement 1)
85. Jacobsen ED, Kim HT, Ho VT, Cutler CS, Koreth J, Fisher DC, Armand P, Alyea EP, Freedman AS, Soiffer RJ, Antin JH (2011) A large single-center experience with allogeneic stem-cell transplantation for peripheral T-cell non-Hodgkin lymphoma and advanced mycosis fungoides/Sezary syndrome. Ann Oncol 22:1608–1613
86. Smith SD, Bolwell BJ, Rybicki LA, Brown S, Dean R, Kalaycio M, Sobecks R, Andresen S, Hsi ED, Pohlman B, Sweetenham JW (2007) Autologous hematopoietic stem cell transplantation in peripheral T-cell lymphoma using a uniform high-dose regimen. Bone Marrow Transp 40:239–243
87. Horwitz SMC, Kewalramani T, Hamlin P, Straus D, O'Connor O, Noy A, Portlock C, Nimer S, Palomba L, Zelenetz A (2005) Second-line therapy with ICE followed by high dose therapy and autologous stem cell transplantation for relapsed/refractory peripheral

T-cell lymphomas: minimal benefit when analyzed by intent to treat. Blood (ASH Annual Meeting Abstracts) 106, abstract 2679
88. Smith SM, Burns LJ, van Besien K, Lerademacher J, He W, Fenske TS, Suzuki R, Hsu JW, Schouten HC, Hale GA, Holmberg LA, Sureda A, Freytes CO, Maziarz RT, Inwards DJ, Gale RP, Gross TG, Cairo MS, Costa LJ, Lazarus HM, Wiernik PH, Maharaj D, Laport GG, Montoto S, Hari PN (2013) Hematopoietic cell transplantation for systemic mature T-cell non-hodgkin lymphoma. J Clin Oncol Official J Am Soc Clin Oncol 31:3100–3109
89. Coiffier B, Pro B, Prince HM, Foss F, Sokol L, Greenwood M, Caballero D, Borchmann P, Morschhauser F, Wilhelm M, Pinter-Brown L, Padmanabhan S, Shustov A, Nichols J, Carroll S, Balser J, Balser B, Horwitz S (2012) Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. J Clin Oncol 30:631–636
90. O'Connor OA, Horwitz S, Masszi T, Van Hoof A, Brown P, Doorduijn J, Hess G, Jurczak W, Knoblauch P, Chawla S, Bhat G, Choi MR, Walewski J, Savage K, Foss F, Allen LF, Shustov A (2015) Belinostat in patients with relapsed or refractory peripheral T-Cell Lymphoma: results of the pivotal phase II BELIEF (CLN-19) study. J Clin Oncol 33:2492–2499
91. O'Connor OA, Pro B, Pinter-Brown L, Bartlett N, Popplewell L, Coiffier B, Lechowicz MJ, Savage KJ, Shustov AR, Gisselbrecht C, Jacobsen E, Zinzani PL, Furman R, Goy A, Haioun C, Crump M, Zain JM, Hsi E, Boyd A, Horwitz S (2011) Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. J Clin Oncol 29:1182–1189
92. Dupuis J, Morschhauser F, Ghesquieres H, Tilly H, Casasnovas O, Amorim S, Ribrag V, Coiffier B (2014) Final Analysis of the RO-CHOP Phase Ib/II Study: romidepsin in association with CHOP in patients with peripheral T-Cell Lymphoma (PTCL). Blood (ASH Annual Meeting Abstracts) 124:504
93. Mehta-Shah N, Moskowitz AJ, Lunning M, Lynch P, Scheuerman M, Kumar A, Gerecitano JF, Zelenetz AD, Hamlin PA, Noy A, Matasar MJ, Palomba ML, Younes A, Schaffer W, Grewal R, Rademaker J, Sauter CS, Dahi PB, Myskowski P, Kheterpal M, Dogan A, Pulitzer M, Tang L, Ni A, Horwitz SM (2016) A phase Ib/IIa trial of the combination of romidepsin, lenalidomide and carfilzomib in patients with relapsed/refractory lymphoma shows complete responses in relapsed and refractory T-Cell lymphomas. Blood (ASH Annual Meeting Abstracts) 128:2991
94. Horwitz SM, Advani RH, Bartlett NL, Jacobsen ED, Sharman JP, O'Connor OA, Siddiqi T, Kennedy DA, Oki Y (2014) Objective responses in relapsed T-cell lymphomas with single-agent brentuximab vedotin. Blood 123:3095–3100
95. Fanale MA, Horwitz SM, Forero-Torres A, Bartlett NL, Advani RH, Pro B, Chen RW, Davies A, Illidge T, Huebner D, Kennedy DA, Shustov AR (2014) Brentuximab vedotin in the front-line treatment of patients with CD30+ peripheral T-cell lymphomas: results of a phase I study. J Clin Oncol 32:3137–3143
96. Delarue R, Dupuis J, Sujobert P, Barbieux S, Marçais A, Tournilhac O, Lachenal F, Cheminant M, Sarkozy C, Fataccioli V, Morschhauser F, Hermine O, Haioun C, Gaulard P, Lemonnier F (2016) Treatment with hypomethylating agent 5-Azacytidine induces sustained response in angioimmunoblastic T Cell lymphomas. Blood (ASH Annual Meeting Abstracts) 128:4164
97. Horwitz S, O'Connor O, Jurczak W, Van Hoof A, Hess G, Gasztonyi Z, Doorduijn J, Walewski J, Brown P, Vranovsky A, Sissolak G, Aurer I, Nacinovic A, Shustov A, Chawla S, Knoblauch P, Wulf G, Visser O, Zinzani P, Masszi T (2013) Belinostat in relapsed or refractory peripheral T-cell lymphoma subtype angioimmunoblastic T-cell lymphoma: results from the pivotal BELIEF trial. Hematol Oncol 31(Suppl. 1):147
98. Delarue R, Dupuis J, Sujobert P, Barbieux S, Marçais A, Tournilhac O, Lachenal F, Cheminant M, Sarkozy C, Fataccioli V, Morschhauser F, Hermine O, Haioun C, Gaulard P,

Lemonnier F (2016) Treatment with hypomethylating agent 5-azacytidine induces sustained response in angioimmunoblastic T cell lymphomas
99. Damaj G, Gressin R, Bouabdallah K, Cartron G, Choufi B, Gyan E, Banos A, Jaccard A, Park S, Tournilhac O, Schiano-de Collela JM, Voillat L, Joly B, Le Gouill S, Saad A, Cony-Makhoul P, Vilque JP, Sanhes L, Schmidt-Tanguy A, Bubenheim M, Houot R, Diouf M, Marolleau JP, Bene MC, Martin A, Lamy T (2013) Results from a prospective, open-label, phase II trial of bendamustine in refractory or relapsed T-cell lymphomas: the BENTLY trial. J Clin Oncol Official J Am Soc Clin Oncol 31:104–110
100. Zinzani PL, Venturini F, Stefoni V, Fina M, Pellegrini C, Derenzini E, Gandolfi L, Broccoli A, Argnani L, Quirini F, Pileri S, Baccarani M (2010) Gemcitabine as single agent in pretreated T-cell lymphoma patients: evaluation of the long-term outcome. Ann Oncol 21:860–863
101. Dueck G, Chua N, Prasad A, Finch D, Stewart D, White D, van der Jagt R, Johnston J, Belch A, Reiman T (2010) Interim report of a phase 2 clinical trial of lenalidomide for T-cell non-Hodgkin lymphoma. Cancer 116:4541–4548
102. Advani R, Horwitz S, Zelenetz A, Horning SJ (2007) Angioimmunoblastic T cell lymphoma: treatment experience with cyclosporine. Leukemia Lymp 48:521–525

Anaplastic Large Cell Lymphoma: Contemporary Concepts and Optimal Management

6

Andrei Shustov and Lorinda Soma

Abstract

Anaplastic Large Cell Lymphomas (ALCL) are clinically aggressive and pathologically distinct lymphoid neoplasms that originate from a mature post-thymic T-cell. The contemporary World Health Organization (WHO) Classification of Haematologic Malignancies recognizes two distinct subtypes of systemic ALCL: Anaplastic Lymphoma Kinase (ALK)-negative, and ALK-positive. An additional unique subtype of ALCL is known to arise after prolonged exposure to breast implants, known as Breast Implant Associated ALCL (BIALCL). While histologic features of ALCL subtypes have significant overlap, genomic studies suggest the unique pathophysiology and molecular events of tumorigenesis. As a group, ALCLs are rare among non-Hodgkin lymphomas comprising 1–3% overall. There seems to be age and geographic predilection with ALK-positive ALCL affecting younger individuals and being diagnosed more frequently in North America than Europe. Both subtypes are quite uncommon in Hispanic and Asian populations. ALK-positive ALCL patients have a better overall prognosis than those with ALK-negative ALCL, and clinical features at presentation (i.e., International Prognostic Index, IPI) define the outcome in both subtypes. Molecular events affecting *DUSP22* and *TP63* have been reported to predict survival outcomes as well, with former being favorable, and the latter an unfavorable prognostic marker. Multiagent CHOP-like chemotherapy remains a standard of care for newly diagnosed ALCL patients treated with curative intent

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and provide a chance of cure for the majority of ALK-positive ALCL patients, and at least half of the ALK-negative ALCL patients. The role of consolidative high-dose therapy and autologous hematopoietic stem cell transplantation remains unclear. Novel targeted agents are actively being investigated for their role in initial therapy. New immunoconjugates, targeted kinase inhibitors, and transgenic autologous T-cells are being studied in patients with relapsed and refractory disease. This review will discuss contemporary concepts in pathogenesis and management of systemic ALCL. The biology and management of primary cutaneous ALCL will be discussed elsewhere.

Keywords
Anaplastic large cell lymphoma · Chemotherapy · Stem cell transplantation
Brentuximab vedotin · ALK-inhibitors

6.1 Introduction

Anaplastic large cell lymphomas comprise approximately 15% of all peripheral T-cell lymphoma diagnoses globally, equally represented by ALK-positive and ALK-negative subtypes (~7.5% each) [1]. This accounts for 3–5% of all non-Hodgkin lymphomas with the annual incidence in the United States of approximately 0.2–0.25 per 100,000 person-years [2, 3]. Recent population-based and registry studies have identified epidemiologic patterns for ALCL and subtypes. ALK-positive ALCL appears to affect younger individuals (median age: 30–35 years vs. 50–60 years) and is diagnosed more frequently in North America than Europe [4]. Both subtypes are quite uncommon in Asian/Pacific Islanders and are diagnosed more frequently in Blacks than non-Hispanic Whites (incidence rate ratios: 0.59, 95% Confidence Interval [CI]: 0.49–0.70; and 1.17, CI: 1.03–1.32, respectively) [3]. Breast implant associated ALCL (BIALCL), first described in 1997, now represents a distinct clinicopathologic entity (provisional status) in the most recent WHO classification and might have an association with specific bacterial pathogens [5]. It appears to be associated almost exclusively with fibrous, rather than smooth implants. The incidence of developing BIALCL among patients with breast implants is low and estimated by one study to be 1 in 500,000 women who received breast implants. Whether genetic factors predispose humans to development of any ALCL subtypes is unknown.

6.2 Diagnosis and Pathology

Anaplastic large cell lymphomas (ALCL) are two separate diagnostic entities in the 2017 WHO Classification, ALK+ ALCL and ALK− ALCL, with implant-associated ALCL (BIALCL) designated as a provisional entity. Although

separate entities, the morphology will be described together as there is much overlap, with the differences being noted where appropriate. Implant-associated ALCL has a phenotype similar to ALK− ALCL, although the morphologic pattern will be discussed separately.

The most common morphologic pattern in ALCL is a diffuse proliferation of large, markedly atypical, neoplastic cells diffusely effacing normal nodal architecture, with variable sinus involvement (on occasion mimicking metastatic carcinoma given the cohesive appearance of the cells) (Fig. 6.1). The neoplastic cells are typically large, malignant appearing (anaplastic) cells with abundant cytoplasm, vesicular chromatin, and variably prominent nucleoli. Some of the neoplastic cells will show a characteristic kidney bean or horseshoe-shaped nucleus, termed "hallmark" cells. "Wreath" cells may also be seen, with multiple nuclei forming a peripheral, wreathlike configuration along the cytoplasmic membrane. On occasion, the markedly atypical malignant cells may resemble Reed–Sternberg cells. Nuclear pseudoinclusions (cytoplasmic invagination) are also a feature in a subset of the-neoplastic cells in some cases, termed "doughnut" cells. These features can be seen in both ALK+ and ALK− ALCL (more prominent "doughnut" cells are noted in *DUSP22-IRF4* rearranged ALK− ALCL).

Additional patterns, besides the common pattern, can be seen in ALK+ ALCL, including the small cell pattern (5–10%), lymphohistiocytic pattern (10%) and Hodgkin like pattern (<5%). A combination of the morphologic patterns may also

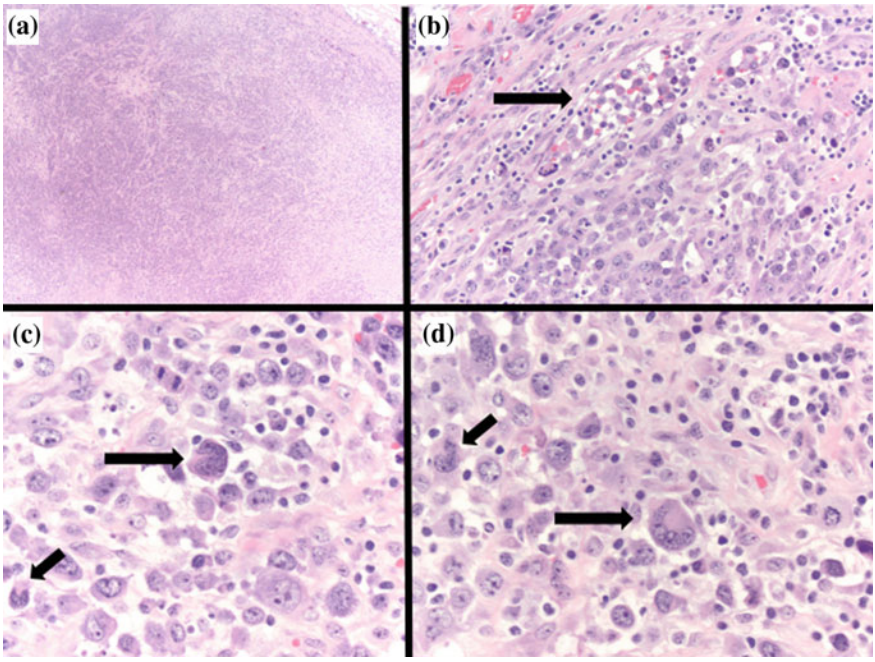

Fig. 6.1 Hematoxylin and Eosin staining of ALCL. (**a**) Low power view (2x) of ALCL, common pattern, showing diffuse effacement of the lymph node. (**b**) Higher power view (20x) showing the subcapsular sinus involvement (arrow). (**c**) and (**d**) Higher power view (40x) showing hallmark cells (short arrows) and wreath cells (long arrow)

be present. As indicated by the pattern name, the morphologic features in small cell pattern include small to intermediate sized cells (often in a perivascular location); numerous admixed histiocytes in the lymphohistiocytic pattern; and a nodular, sclerosing background in the Hodgkin like pattern. Regardless of what pattern type, the neoplastic cells express CD30 and ALK. Often a subset of "Hallmark" cells can be identified, typically noted around vessels in the small cell and lymphohistiocytic variant. ALK− ALCL does not show variant patterns (only the common pattern) and the neoplastic cells are often larger with more atypia than ALK+ ALCL (although Hallmark cells are still present).

ALCL is typified by CD30 expression which is strong and robust (membrane and Golgi), particularly in the larger cells; although smaller neoplastic cell may show more variable expression (i.e., small cell and lymphohistiocytic patterns) (Fig. 6.2). ALCL is a CD4 positive, T/Null cell lymphoma which variably expresses T-cell-associated antigens. The T-cell markers CD2, CD3, CD5, CD7 and CD45RO will show significant variability from case to case, with some showing a variably positive T-cell phenotype and others lacking all lineage-associated markers. ALK+ ALCL most commonly expresses CD2 and CD5 and ALK− ALCL most commonly CD2 and CD3 [6]. EMA and leukocyte common antigen (CD45) are variably expressed (with more expression seen in ALK+ ALCL). Cytotoxic markers (TIA1, granzyme B, and perforin), and CD43 are expressed in the majority of cases (ALK+ and ALK− ALCL); although it has been shown that ALK− ALCL with *DUSP22-IRF4* rearrangement often lack cytotoxic marker expression [6, 7]. MUM1 is consistently expressed and clusterin is often positive (cytoplasmic, dot-like) in both ALK+ and ALK− ALCL (possibly being useful in differentiating from PTCL). Expression of ALK in ALK+ ALCL can be nuclear, cytoplasmic or both. Most commonly, ALK-expression is nuclear and cytoplasmic, this pattern being characteristic of the most common translocation, *NPM1-ALK* (>80% of cases). The next most common ALK staining pattern is diffuse cytoplasmic expression with peripheral prominence (*TPM3-ALK*; >10% of cases). ALCL almost always expresses CD4, although rare CD8-positive cases exist. ALCLs are negative for PAX5, EBV, CD56, and CD15 (although some cases with variable CD15 and CD56 expression have been reported).

Breast implant associated ALCL (BIALCL) is defined as the presence of neoplastic cells in aspirated capsular fluid or in capsulectomy specimens (Fig. 6.3). The cells have similar cytologic and immunophenotypic features to ALK− ALCL. Capsulectomy specimens will demonstrate neoplastic cells lining the capsule wall, with variable capsular infiltration. If the neoplastic cells are present only in the fluid, or lining the capsule with no/minimal invasion, some have used the term "in situ" BIALCL [8, 9]. Alternatively, if the neoplastic cells should extend significantly beyond the capsule, inciting a host immune or stromal response, show tumoral necrosis or form a clinically or grossly identifiable mass lesion, the term "infiltrating" ALCL has been suggested [7, 8, 9].

Depending on the morphologic features, immunophenotype, and clinical setting, the differential diagnosis can be broad; however, the most common differential diagnostic considerations are Classic Hodgkin Lymphoma (CHL) and Peripheral

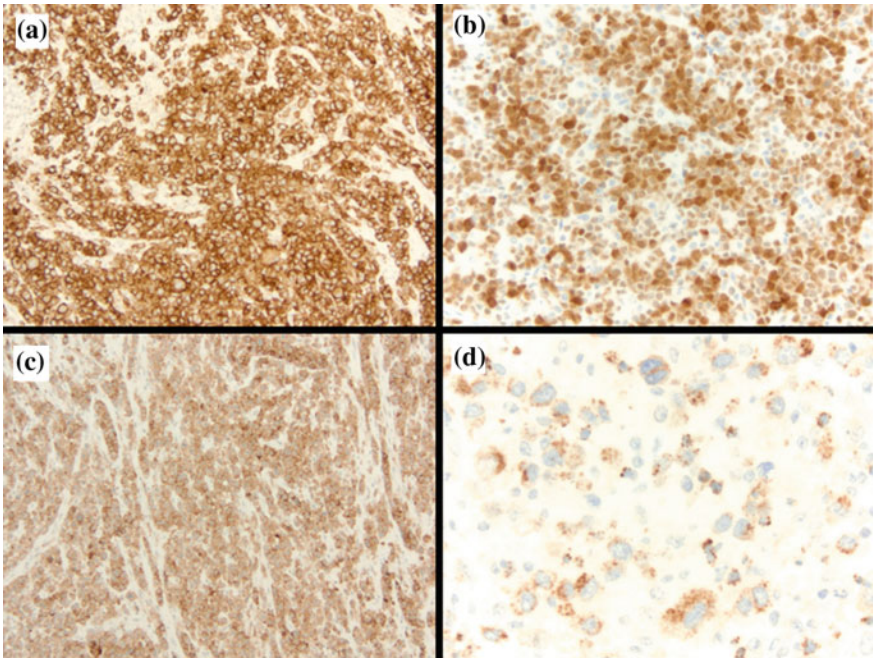

Fig. 6.2 Representative immunohistochemical stains in ALCL. (**a**) CD30 (10x), (**b**) ALK (20x), (**c**) CD4 (10x), (**d**) TIA1 (40x)

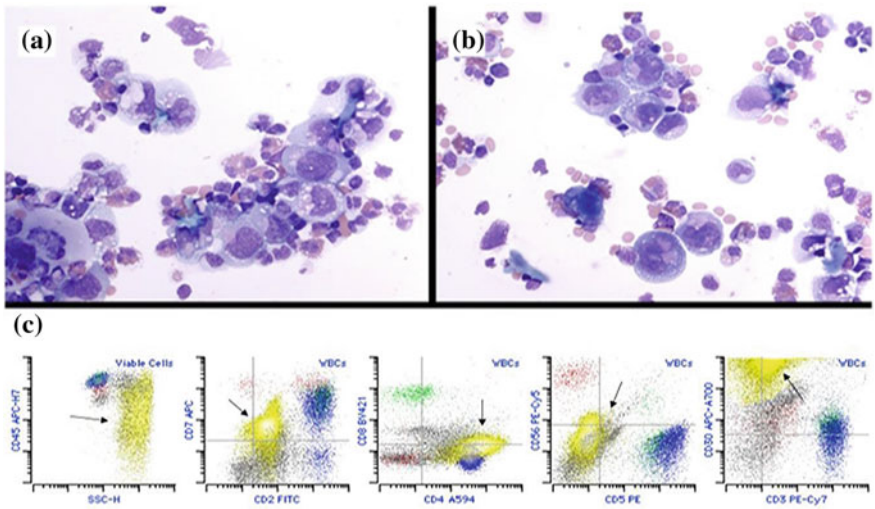

Fig. 6.3 Breast implant associated ALCL, capsular fluid. (**a**) and (**b**) Wright stained cytospin preparations showing large, bizarre, neoplastic cells (40x) (**c**) Flow cytometric evaluation of the capsule fluid showing a neoplastic population highlighted in yellow and also with arrows (dot plots discussed from left to right). The neoplastic population shows increased side scatter (SSC-H) and variable CD45 expression, is low to negative for CD2 and CD7, expresses CD4 without CD8, lacks CD5 and CD56 and shows bright CD30 (going off-scale) without CD3. Normal T-cells are highlighted in blue and green, natural killer cells in red

T-cell lymphoma, not otherwise specified (PTCL, NOS). Although both CHL and ALCL are CD30-positive, CHL classically expresses CD15 and PAX5 (weak) and is negative for T-cell associated antigens, and ALK. CHL additionally is associated with a mixed population of lymphocytes and inflammatory cells, often with fibrosclerosis, background findings uncommon in ALCL. PTCL, NOS can also express CD30, although usually not as robust as ALCL. Additionally, PTCL that express cytotoxic markers are typically positive for CD8, not CD4, and of course, are ALK-negative. However, it should be noted that differentiating between ALK− ALCL and PTCL, NOS may not always be possible [6, 10].

6.3 Clinical Characteristics and Prognosis

6.3.1 ALK+ Anaplastic Large Cell Lymphoma

Patients with ALK+ ALCL are generally younger with slight male predominance and median age at diagnosis in the third decade of life [3, 4]. It is the most common aggressive lymphoma diagnosed in pediatric population. Advanced stage disease (stage III–IV) is present in the majority of patients (appr. 60%) at the time of diagnosis and extranodal involvement is common. The most commonly involved extranodal sites include intestinal tract, lung parenchyma, axial skeleton, skin, and liver. Central nervous system and testicular involvement are rare. Constitutional symptoms are common at the time of diagnosis, especially recurrent fever, and paraneoplastic phenomena can be observed (migratory rash, pruritus, arthralgias, lymph node, and skeletal pain). The latter is likely due to cytokine production by malignant lymphocytes rather than tumor infiltration. Despite predominance of advanced stage at diagnosis, low or intermediate low International Prognostic Index (IPI) score is found in most of the patients at least partially responsible for favorable outcomes in this histology.

The prognosis in patients with ALK+ ALCL appears to be superior to any other subtypes of systemic PTCLs after appropriate frontline therapy [4, 10]. Anthracycline-based multiagent chemotherapy regimens are expected to produce an overall response (OR) in 80–85% of patients with majority of treated individuals attaining a complete remission (CR). CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) remains the most commonly used initial therapy, and the bulk of reported outcomes is attributed to the use of this well-known regimen. The addition of etoposide to CHOP (also known as CHOEP) has improved outcomes for younger patients with ALK+ ALCL (especially those with normal LDH value at diagnosis) in a large retrospective meta-analysis ($P < 0.04$), however, the regimen was too toxic for older patients [11]. Infusional dose-adjusted EPOCH protocol has produced very encouraging outcomes in a single institution long-term prospective study that enrolled patients with high-risk disease based on the IPI score. Overall, approximately three-quarters of adult ALK+ ALCL patients are expected to be cured after a full course (6–8 cycles) of multiagent chemotherapy [12].

International Prognostic Index has been validated for ALK+ ALCL in retrospective analyses [4]. Despite overall favorable outcomes, patients who present with intermediate-high and high IPI score have a guarded prognosis and should be considered for specialized approaches beyond initial CHOP therapy. Alternatively, patients presenting with low IPI score have excellent survival outcomes (5-year OS $\geq$ 90%), and avoidance of excessive toxicity should be exercised. Interestingly, at least in one analysis, patients with ALK+ ALCL aged $\geq$ 45 years had similarly poor outcomes to ALK− ALCL, but age impact was not validated in the prospective studies.

Histologic and laboratory features have been explored as prognostic markers in ALCL, including ALK+ ALCL. In the meta-analysis of three prospective trials by *Groupe d'Etude des Lymphomes de l'Adulte*, elevated β2-microglobulin and age > 45 years, but not ALK-status, were predictive of survival in ALCL patients in multivariate analysis, stratifying patients into four distinct groups with 8-year survival rates ranging from 22 to 84% [10]. A study by the Japan Lymphoma Group implicated CD56 expression on malignant T-cells to affect ALCL prognosis independent of ALK-expression. Among 83 ALK+ ALCL patients, 5-year OS rates in patients with CD56+ and CD56− tumors were 43% and 76%, respectively, in multivariate analysis [13]. This observation was not further validated in prospective clinical trials.

Owing to a recurrent genetic alteration, t(2;5)(p23;q35) a unique molecular fusion product emerges that consists of nucleophosmin 1 (NPM1) and ALK-kinase (present in 80–85% of cases) [14]. A unique exploitation of this genetic event was described by Damm-Welk et al. in pediatric patients [15]. The researchers used *NPM1-ALK-specific* primers and RT-PCR methodology to determine presence or absence of "minimal disseminated disease" (MDD) at diagnosis, and minimal residual disease (MRD) after initial therapy and their impact on outcomes in children with ALK+ ALCL. Notably, patients who were MDD+ at the time of diagnosis had significantly inferior 5-year PFS compared to MDD− patients (78% vs. 23%, $p \leq 0.01$). Even more intriguing was the impact of MRD+ versus MRD− status after two cycles of therapy on 5-year PFS (69% vs. 19%, $p = 0.0002$). These important findings make a strong case for further development of molecular MRD detection to guide therapy in ALK+ ALCL patients.

6.3.2 ALK− Anaplastic Large Cell Lymphoma

In contrast to ALK+ counterpart, ALK− ALCL patients are generally older with median age at diagnosis in the sixth decade of life, and this entity is very rarely found in children [3, 4, 16].

Clinical features of ALK− ALCL at diagnosis are similar to those of ALK + ALCL and presentation is usually with rapidly progressing lymphadenopathy and frequent constitutional symptoms. Once again, central nervous system, testicular, and bone marrow involvement are uncommon. Majority of patients will be diagnosed with advanced stage and intermediate-high or high IPI score [4].

The prognosis in patients with ALK− ALCL was historically considered poor and similar to other nodal types of PTCL. However, the International T-cell Lymphoma Study, the largest retrospective cohort study to date, reported survival outcomes in ALK− ALCL as intermediate between ALK+ ALCL and PTCL-NOS, with 5-year OS rates of 55% [4]. Similar outcomes were reported by few other large retrospective studies and meta-analyses [10]. Overall, approximately half of the patients are expected to be cured after frontline aggressive multiagent chemotherapy regimens. Previously mentioned study of dose-adjusted EPOCH that enrolled high-risk patients with ALK+ and ALK− ALCL reported 12-year OS of $\geq$70% regardless of ALK-status [12].

International Prognostic Index appears to have an impact on survival in ALK− ALCL with $\geq$70% of low-risk patients expected to be cured after frontline therapies, while survival rates for high-risk patients was $\leq$30%. The validation of these finding from a recently completed large prospective T-cell Project registry study is eagerly awaited.

Similar to ALK+ ALCL, one meta-analysis risk-stratified ALK− ALCL into four outcome groups based on age and β2-microglobulin value (see above) [10]. Further, CD56 surface marker expression had prognostic impact with 5-year OS rates of 48% and 18% for CD56− and CD56+ cases, respectively, in the above-mentioned study [13].

Recent reports also identified *DUSP22* and *TP63* molecular markers to be strongly associated with prognosis in ALK− ALCL [6, 17]. These appear to be mutually exclusive and found in 30% and 8% of patients' biopsies, respectively. *DUSP22-IRF4* chromosomal rearrangement, t(6:7) portends excellent prognosis regardless of other markers with 5-year overall survival rates approaching 90%. On the contrary, *TP63* overexpression, that results from either chromosomal aberration, inv(3), or cryptic gene mutation, predicts very poor outcomes with 5-year survival rate of only 17%, in a retrospective study. While testing for these chromosomal or genetic events is available, the implication on initial therapy is unclear at this time.

Continuous stream of new genomic discoveries will very likely redefine prognostic stratification for both ALK+ and ALK− ALCL in the near future [18]. Similarly, rapid development of new targeted and immunologic therapies discussed below will likely have a significant impact on future prognostic models.

6.4 Principles of Clinical Management

6.4.1 ALK+ Anaplastic Large Cell Lymphoma

The contemporary questions that a clinician would raise when evaluating a newly diagnosed or relapsed/refractory patient with ALK+ ALCL are those related to best frontline or salvage therapy, need for consolidative strategies, incorporation of novel immunoconjugates and ALK-kinase inhibitors into treatment paradigms, and

timing and the best use of hematopoietic stem cell or chimeric antigen receptor (CAR) T-cell therapies.

Initial ALK+ ALCL therapy. Multiagent anthracycline-containing regimens remain a standard-of-care approach for treatment of newly diagnosed patients. CHOP is the most widely used protocol and is expected to produce overall and complete response in ~90% and ~70% of patients, respectively [4, 10]. The 5-year rates of overall and progression-free survival (PFS) in multiple studies range from 70–80%, and 60–70%, respectively. The addition of etoposide to CHOP, typically in the form of CHOEP (etoposide, 100 mg/sqm on days 1, 2, and 3), has been studied by the German High-Grade non-Hodgkin Lymphoma Study Group (*Deutsche Studiengruppe Hochmaligne Non-Hodgkin Lymphome*) in a large meta-analysis of several prospective studies. The results on 320 PTCL patients were reported in a separate analysis [11]. The study found that the addition of etoposide to CHOP(-like) regimens improved overall response rates and provided superior event-free survival (EFS) in younger ALK+ ALCL patients (N = 78) with normal LDH at the time of diagnosis (3-year EFS of 91% vs. 57% in CHOEP vs. CHOP treated patients, respectively). The report from the *Swedish Lymphoma Registry* confirmed that the addition of etoposide to CHOP produced superior PFS in younger PTCL patients (age $\leq$ 60 years) [19]. 68 out of 755 PTCL patients had ALK+ ALCL; histology-specific analysis was not performed. The use of continuous infusion of chemotherapeutic agents might improve outcomes in highly proliferative malignancies. Dose-adjusted EPOCH (etoposide, cyclophosphamide, doxorubicin, vincristine, and prednisone) has been evaluated in ALCL patients with high-risk features. After a median follow-up of more than 12 years, median survival for both ALK+ , and ALK− patients was not reached with a 10-year OS rate of ~75% [12].

Based on these reports, CHOEP should be considered in younger patients with ALK+ ALCL for initial therapy, while CHOP and da-EPOCH should be reserved for older or less fit patients. ***At our institution, majority of ALK + ALCL patients are treated with dose-adjusted EPOCH protocol as initial therapy, regardless of age.***

Therapy of relapsed and refractory ALK+ ALCL. While the majority of ALK + ALCL patients are expected to be cured with frontline chemotherapy outlined above, relapses occur in up to 30–40% of patients. Interestingly, relapsed disease maintains chemotherapy sensitivity in significant proportion of patients, and intensive salvage regimens might transition patients to consolidative hematopoietic stem cell transplantation procedures with curative intent.

Commonly used combinations are ICE (ifosfamide, etoposide, carboplatin), [20] DHAP (dexamethasone, cisplatin, high-dose cytarabine), ESHAP (etoposide, solumedrol, high-dose cytarabine, carboplatin), [21] GemOx (gemcitabine, oxaliplatin), [22], and GDP (gemcitabine, dexamethasone, cisplatin) [23] that are expected to induce complete remission in up to 50% of relapsed patients. However, recent approval of a highly active immunoconjugate, brentuximab vedotin (see below) might have challenged traditional paradigms of management.

In patients with chemotherapy-sensitive disease, consolidative high-dose therapy with autologous hematopoietic cell transplantation is advisable and expected to

produce cure or long-term remission in up to 50% of patients [24–26]. Those with chemotherapy-refractory disease should be referred for participation in clinical trials or treated with novel agents if available (see below). In patients in whom very good partial or complete remission is obtained, allogeneic hematopoietic cell transplantation should be considered if feasible [27, 28].

Special considerations. Two classes of novel agents have recently emerged, that demonstrated high level of activity in ALK+ ALCL. Brentuximab vedotin (BV), a CD30-targeting immunoconjugate carrying potent anti-tubulin agent, monomethylauristatin E (MMAE), [29] has demonstrated high rate of overall and complete responses (86% and 57%, respectively) in both, ALK + and ALK− relapsed/refractory ALCL patients [30]. Responses were durable and facilitated transition to consolidative hematopoietic cell transplantation in significant proportion of eligible patients. In a recent update of the pivotal trial results, after median observation period of approximately 6 years, median PFS and OS were not reached, and, patients who achieved CR with brentuximab vedotin had OS and PFS rates of 79% and 57%, respectively, at 5 years [31]. Recent phase I trial evaluated feasibility of combining BV with frontline CHP (cyclophosphamide, doxorubicin, and prednisone) chemotherapy. In the initial report, BV-CHP combination was well tolerated and highly active in ALCL patients (as well as CD30-positive non-ALCL patients), with an overall and complete response rates of 100% and 84%, respectively [32]. In an updated analysis, estimated 5-year progression-free and overall survival rates after BV-CHP therapy were 52% and 80%, respectively [33]. 18 out of 19 patients (95%) with treatment-emergent peripheral sensory neuropathy reported resolution or improvement of symptoms. Based on the results of this study, a phase III randomized double-blinded controlled ECHELON-2 clinical trial has recently completed accrual, and results are eagerly awaited (NCT01777152). Further, ongoing studies are evaluating the feasibility of combining BV with salvage chemotherapy platforms (i.e. BV-ICE), and preliminary results appear promising with increasing CR rates in relapsed and refractory patients with CD30+ malignancies. The use of such combinations should be restricted to participation in open clinical trials at this time. ***At our institution, brentuximab vedotin is preferred for first and subsequent salvages in relapsed and refractory ALK+ ALCL patients over multiagent intensive chemotherapy combinations with CR patients proceeding to consolidative autologous HCT***. The use of BV-CHP combination in frontline setting will be considered upon release of the ECHELON-2 trial results.

Anaplastic lymphoma kinase (ALK) perpetual activation and downstream events play a cardinal role in pathogenesis and progression of ALK+ ALCL. It is, therefore, highly intriguing to study the use of specific ALK-kinase inhibitors in both, frontline and relapsed/refractory patients. Crizotinib demonstrated significant activity in pediatric population with ALK-positive malignancies [34]. Nine ALK + ALCL patients were enrolled in a large prospective study of ALK+ malignancies. Eight out of nine patients with refractory disease responded (ORR 88%), with 7 patients achieving complete remission (CR 78%). Responses were durable and crizotinib was well tolerated with prolonged continuous therapy. Crizotinib was also given to adult patients with ALK+ ALCL as a compassionate use in

chemotherapy-resistant disease; reported complete remission rate of 100%. Clearly, further evaluation of ALK-inhibitors in both frontline, and relapsed/refractory setting is highly warranted.

Despite high curability of ALK+ ALCL with CHOP-like combinations, novel treatment platforms that would maintain at least current cure rates but significantly reduce early and late sequalae of aggressive regimens are highly desirable. One such trial is currently evaluating the feasibility of ALK-inhibitor (ceritinib) and brentuximab vedotin combination in patients with newly diagnosed ALK+ ALCL. If successful, these "chemotherapy-free" platforms might become a new or alternative standard employing biology-driven approach.

6.4.2 ALK− Anaplastic Large Cell Lymphoma

Current challenges in management of patients with ALK− ALCL are similar to those listed above for ALK+ ALCL. Given higher relapse rate in this subtype, the need to improve frontline and salvage protocols, and define the role of consolidative approaches is even more acute. Furthermore, clinical utilization of molecular prognostic markers should drive treatment decisions and clinical research in the near future.

Initial ALK− ALCL therapy. While CHOP remains the most widely used regimen, it produces dissatisfactory results. While the overall and complete remission rates are ~70–80% and 50%, respectively, the 5-year progression-free survival rates are in the range of 30–55% [3, 4]. Similar to ALK+ counterpart, the addition of etoposide to frontline regimens might produce superior outcomes, however, this strategy has not been validated in prospective randomized trials. In the aforementioned retrospective study by the German High-Grade non-Hodgkin Lymphoma Study Group, patients with non-ALK+ ALCL, including 113 patients with ALK− ALCL who were treated with addition of etoposide had 3-year EFS of 61% versus 48% in those treated without etoposide [35]. Also, the aforementioned study by Ellin et al. showed superior outcomes with addition of etoposide to CHOP in PTCLs without histolog-specific analysis [19]. Dose-adjusted EPOCH produced promising results in both ALK+ and ALK− ALCL in prospective phase II trial reported by the NCI investigators. Long-term progression-free survival of 72% was the highest reported in any prospective studies of ALCL [12].

More intensive regimens were also explored to treat PTCLs in the frontline setting. MD Anderson Cancer Center (MDACC) reported results of the phase II trial evaluating an aggressive hyperCVIDD/MA (hyper-fractionated cyclophosphamide, pegylated doxorubicin, vincristine, dexamethasone alternating with high-dose methotrexate and cytarabine) [36]. Despite a high CR rate of 83% with this regimen, the median progression-free survival was only 7.5 months and 3-year PFS was 43% in ALK− ALCL patients, which was not significantly different from historical results with CHOP(-like) regimens. Similarly, GELA group retrospectively analyzed outcomes in ALK− ALCL patients treated on three prospective randomized trials with intensive chemotherapy protocols (most patients received a

combination of doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone). The use of intensified regimens did not produce superior results to CHOP treated patients [10].

Given the poor outcomes in ALK− ALCL patients with frontline therapies and high rates of relapses even in patients achieving initial response to therapy, consolidative approach in the form of high-dose therapy and autologous hematopoietic stem cell transplantation was evaluated in several non-randomized prospective and retrospective studies [24, 37, 38]. In the largest prospective phase II study reported by *Nordic Lymphoma Group*, 144 patients, including 31 ALK− ALCL patients, were treated with six cycles of dose-dense CHOEP-14 combination, followed by myeloablative BEAM-therapy and autologous stem cell rescue. 5-year OS and PFS rates in ALK− ALCL patients were 70% and 61%, respectively. Interestingly, treatment-related mortality (TRM) rate was unusually high at 4% [39]. While these results appear slightly superior to historical controls, they should be taken with caution given inherent selection bias in transplantation trials, and improved outcomes reported in studies using etoposide-containing protocols, as well as promising early results in brentuximab vedotin/chemotherapy combination trials, described above in this chapter. Short of prospective randomized trials, consolidative treatments should be considered with caution in ALK− ALCL patients preferably after evaluation at centers specializing in treating patients with PTCL and with expertise in stem cell transplantation. ***At our institution, majority of ALK− ALCL patients are treated with dose-adjusted EPOCH or CHOEP protocols as initial therapy, regardless of age***.

Therapy of relapsed and refractory ALK− ALCL. Management of relapsed and refractory ALK− ALCL is not dissimilar to described paradigms for ALK + counterpart. Historically, aggressive salvage protocols are employed to induce complete or very good partial remission that would facilitate consolidative high-dose therapy and autologous hematopoietic cell transplantation (if not performed in the first remission) for chemotherapy-sensitive disease. ICE [20], DHAP [21] and ESHAP are most commonly used in the United States and Europe. Patients with chemotherapy-refractory disease should be considered for participation in clinical trials and/or treated with novel approved agents (see below). If complete or very good partial remission is achieved in refractory patients, consolidative allogeneic hematopoietic cell transplantation is a preferred approach in patients pursuing curative intent management.

Special considerations. Development of molecular and/or genetic prognostic markers to identify high-risk or favorable-prognosis patients might refine individual treatment selection process. *TP63* and *DUSP22-IRF4* genetic alterations have been identified as poor and favorable prognosis correlates, respectively in recent reports [6, 17, 40]. At the time of this publication, it is difficult to recommend routine testing of all ALK− ALCL patients for presence of these chromosomal aberrations given lack of evidence that such information can facilitate management decisions (i.e., it is unclear whether intensification of therapy would improve outcomes in *TP63*-mutated cases). These markers should preferably be further evaluated in contemporary prospective trials. Also, see *Special considerations* described for ALK+ ALCL above.

6.4.3 Novel Agents

Several novel agents with unique mechanisms of action were recently developed and approved in the United States and abroad for treatment of relapsed and refractory PTCL patients, including with ALCL subtypes. Brentuximab vedotin was approved for treatment of relapsed and refractory ALCL patients only at the time of this publication and was discussed in detail previously.

Pralatrexate, an inhibitor of dihydrofolate reductase (DHFR), demonstrated approximately 12-fold higher affinity for reduced folate carrier and DHFR in preclinical assays that translated into impressive clinical activity in human cancers. [41, 42] In a pivotal phase II prospective study (PROPEL trial), 17 out of 115 enrolled patients had ALK− ALCL. The ORR for ALCL patients was 35% (95% CI: 14–62%); PFS in responding PTCL patients was 10.1 months [43]. Treatment was well tolerated with mucositis being most prominent toxicity leading to dose delays and reductions. Pralatrexate became an attractive treatment options for all relapsed/refractory PTCL patients, including ALCL, especially those pursuing palliative intent management. Combinations of pralatrexate with other agents are being actively explored.

Histone deacetylase (HDAC) inhibitors are epigenetic modifiers that also produced promising results in registrational trials for relapsed/refractory PTCL. Romidepsin and belinostat are two FDA approved HDAC inhibitors in the United States. In a prospective phase II registrational trial that enrolled 130 patients, including 21 with ALK− ALCL, ORR was 24%, with 19% of patients achieving a CR [44]. It should be noted that responses were durable (especially those in CR), with a median duration of response of 28 months. Common adverse events were thrombocytopenia, nausea, and dysgeusia. Belinostat demonstrated an ORR of 26%, with CR rate of 11% in a large (N = 129) prospective phase II international study (BELIEF trial) [45]. Among ALK− ALCL patients (N = 13) the ORR was 15% (95% CI: 2–45%). The median duration of response was 8.3 months. Treatment was well tolerated with most common grade three-fourths toxicities being thrombocytopenia (13%), neutropenia (13%), and anemia (10%). Both described HDAC inhibitors are actively investigated in combination clinical trials [46].

At our institution, we consider the use of approved novel agents in relapsed/refractory ALCL patients after failure of or intolerance to brentuximab vedotin treatment.

6.4.4 Special Considerations

Management of elderly patients with hematologic malignancies is an area of current research and public healthcare interest. Given curative potential of frontline therapies for both ALK+ and ALK− ALCL, serious consideration should be given to treat older adults with curative intent therapies as outlined above in this chapter, unless absolutely prohibitive. In newly diagnosed patients with significant comorbidities and at the extremes of age, the use of novel highly active agents can

be considered with intent to avoid excessive morbidities and mortality of multiagent protocols. Brentuximab vedotin as a single agent is a preferred consideration for both ALK+ and ALK− patients, while ALK-inhibitors (i.e., crizotinib, ceritinib, alectinib, and brigatinib) should be considered in ALK+ patients only. It should be noted that at the time of this publication these agents are not currently approved for use in frontline ALCL patients by the United States Food and Drug Administration.

Recent retrospective studies reported on low incidence of central nervous system involvement in PTCL patients, ranging from 4 to 7% [47, 48]. Given such a low frequency and lack of evidence for therapeutic prevention, ***at our institution, we do not employ routine chemotherapy prophylaxis or interventional evaluation (lumbar puncture) for asymptomatic PTCL patients***.

Emergence of chimeric antigen receptor (CAR) T-cell technologies and its rapid entry into clinical use for hematologic malignancies and solid tumors is reshaping current treatment paradigms in increasing number of disease groups. Clinical trial assessing the safety and efficacy of CD30-targeting CAR-T (NCT02274584) in CD30 + malignancies is ongoing and currently enrolled few patients with ALCL; the results are eagerly awaited. Development of β-TCR targeting CAR-T cell therapy is also underway and might bring this promising technology to multiple histologies of PTCL [49].

6.4.5 Breast Implant Associated ALCL (BIALCL)

Multidisciplinary approach, preferably within centers having experience with BIALCL, that involves qualified surgical personnel, medical oncology, radiation oncology, and hematopathology teams, provides the best management for this rare but well-recognized entity. High level of awareness and (high-volume) aspiration of all suspicious effusions is imperative for early detection of BIALCL. Systemic staging, preferably with PET-CT scan, will help differentiate localized and advanced disease.

Management of BIALCL differs significantly from systemic ALCLs that stems from the unique pathophysiology, clinical characteristics, and overall prognosis. The majority of women with an isolated capsular involvement undergo capsulectomy that ensures a cure for the majority of patients [5, 50, 51]. This procedure should preferably be performed by a qualified surgeon with experience in treating patients with BIALCL. The expected 5-year OS and PFS rates in patients with no associated mass are both 100%. In patients with associated mass lesion, the 3-year and 5-year OS rates were 82% and 75%, respectively in a recent retrospective case series analysis. The optimal management of patients with associated mass and/or regional lymph node involvement is unknown. Adjuvant chemotherapy, radiation therapy or both (combined modality) are widely used, but systematic trials of specific treatment protocols are lacking due to very low frequency of this entity. ***At our institution, patients with extensive but localized extracapsular involvement are treated with three to 4 cycles of CHO(E)P adjuvant therapy with/without external beam radiotherapy (XRT); patients with limited extracapsular***

involvement are treated with adjuvant XRT alone; single agent brentuximab vedotin is considered on individual basis with careful assessment of risks/benefits. Patients with regional or distant nodal involvement are managed similar to systemic ALK− ALCL. Given the paucity of strong evidence, treatment decisions in BIALCL are highly individualized and based on multidisciplinary assessment.

6.4.6 Final Remarks

ALCL encompasses several distinct clinicopathologic entities with unique genomic underprinting. Among systemic types, ALK+ ALCL, ALK− ALCL, and breast implant associated ALCL are recognized; primary cutaneous ALCL is a distinct cutaneous subtype discussed elsewhere in these series. Multiagent chemotherapy remains a standard frontline approach in the majority of systemic (nodal) ALCL patients treated with curative intent. The role of consolidative stem cell transplantation and incorporation of novel agents into frontline protocols is being investigated. Salvage therapy options for the relapsed and refractory disease should be stratified into curative or palliative intent. Patients with curative intent should be treated with aggressive regimens or single agent brentuximab vedotin followed by consolidative stem cell transplantation (autologous or allogeneic) if complete remission or very good partial remission is achieved. Brentuximab vedotin emerged as preferred single-agent therapy in palliative intent patients and those who can not pursue intensive frontline treatments due to comorbidities or extreme age. HDAC inhibitors (romidepsin and belinostat), novel antifolate (pralatrexate) were recently approved for subsequent lines of therapy and present other options for patients with relapsed and refractory disease. CAR-T cell therapy targeting CD30 is under investigation and might in the near future reshape the landscape for these patients.

References

1. Armitage J, Vose J, Weisenburger D (2008) International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol 26 (25):4124–4130. https://doi.org/10.1200/JCO.2008.16.4558
2. Morton LM, Wang SS, Devesa SS, Hartge P, Weisenburger DD, Linet MS (2006) Lymphoma incidence patterns by WHO subtype in the united states, 1992–2001. Blood 107(1):265–276
3. Adams SV, Newcomb PA, Shustov AR (2016) Racial patterns of peripheral T-cell lymphoma incidence and survival in the united states. J Clin Oncol
4. Savage KJ, Harris NL, Vose JM et al (2008) ALK− anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the international peripheral T-cell lymphoma project. Blood 111(12):5496–5504
5. Miranda RN, Aladily TN, Prince HM et al (2014) Breast implant-associated anaplastic large-cell lymphoma: Long-term follow-up of 60 patients. J Clin Oncol 32(2):114–120. https://doi.org/10.1200/JCO.2013.52.7911
6. Swerdlow SH, Campo E, Harris NL et al (2017) WHO classification of tumours of haematopoietic and lymphoid tissues

7. King RL, Dao LN, McPhail ED et al (2016) Morphologic features of ALK-negative anaplastic large cell lymphomas with DUSP22 rearrangements. Am J Surg Pathol 40(1):36–43. https://doi.org/10.1097/PAS.0000000000000500
8. Laurent C, Delas A, Gaulard P et al (2016) Breast implant-associated anaplastic large cell lymphoma: two distinct clinicopathological variants with different outcomes. Ann Oncol 27 (2):306–314. https://doi.org/10.1093/annonc/mdv575
9. Ganapathi KA, Pittaluga S, Odejide OO, Freedman AS, Jaffe ES (2014) Early lymphoid lesions: conceptual, diagnostic and clinical challenges. Haematologica 99(9):1421–1432. https://doi.org/10.3324/haematol.2014.107938
10. Medeiros LJ, Elenitoba-Johnson KS (2007) Anaplastic large cell lymphoma. Am J Clin Pathol 127(5):707–722
11. Sibon D, Fournier M, Briere J et al (2012) Long-term outcome of adults with systemic anaplastic large-cell lymphoma treated within the groupe d'etude des lymphomes de l'adulte trials. J Clin Oncol 30(32):3939–3946. https://doi.org/10.1200/JCO.2012.42.2345
12. Schmitz N, Trumper L, Ziepert M et al (2010) Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the german high-grade non-hodgkin lymphoma study group. Blood 116(18):3418–3425
13. Dunleavy K, Pittaluga S, Shovlin M et al (2016) Phase II trial of dose-adjusted EPOCH in untreated systemic anaplastic large cell lymphoma. Haematologica 101(1):e27–9. https://doi.org/10.3324/haematol.2015.131151
14. Suzuki R, Kagami Y, Takeuchi K et al (2000) Prognostic significance of CD56 expression for ALK-positive and ALK-negative anaplastic large-cell lymphoma of T/null cell phenotype. Blood 96(9):2993–3000
15. Duyster J, Bai RY, Morris SW (2001) Translocations involving anaplastic lymphoma kinase (ALK). Oncogene 20(40):5623–5637. https://doi.org/10.1038/sj.onc.1204594
16. Damm-Welk C, Mussolin L, Zimmermann M et al (2014) Early assessment of minimal residual disease identifies patients at very high relapse risk in NPM-ALK-positive anaplastic large-cell lymphoma. Blood 123(3):334–337
17. Savage KJ, Chhanabhai M, Gascoyne RD, Connors JM (2004) Characterization of peripheral T-cell lymphomas in a single north american institution by the WHO classification. Ann Oncol 15(10):1467–1475
18. Parrilla Castellar ER, Jaffe ES, Said JW et al (2014) ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes. Blood 124(9):1473–1480. https://doi.org/10.1182/blood-2014-04-571091
19. Piccaluga PP, Fuligni F, De Leo A et al (2013) Molecular profiling improves classification and prognostication of nodal peripheral T-cell lymphomas: results of a phase III diagnostic accuracy study. J Clin Oncol 31(24):3019–3025. https://doi.org/10.1200/JCO.2012.42.5611
20. Ellin F, Landstrom J, Jerkeman M, Relander T (2014) Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the swedish lymphoma registry. Blood 124(10):1570–1577. https://doi.org/10.1182/blood-2014-04-573089
21. Moskowitz CH, Bertino JR, Glassman JR et al (1999) Ifosfamide, carboplatin, and etoposide: a highly effective cytoreduction and peripheral-blood progenitor-cell mobilization regimen for transplant-eligible patients with non-hodgkin's lymphoma. J Clin Oncol 17(12):3776–3785. https://doi.org/10.1200/JCO.1999.17.12.3776
22. Press OW, Livingston R, Mortimer J, Collins C, Appelbaum F (1991) Treatment of relapsed non-hodgkin's lymphomas with dexamethasone, high-dose cytarabine, and cisplatin before marrow transplantation. J Clin Oncol 9(3):423–431. https://doi.org/10.1200/JCO.1991.9.3.423
23. Yao YY, Tang Y, Zhu Q et al (2013) Gemcitabine, oxaliplatin and dexamethasone as salvage treatment for elderly patients with refractory and relapsed peripheral T-cell lymphoma. Leuk Lymphoma 54(6):1194–1200. https://doi.org/10.3109/10428194.2012.739286

24. Emmanouilides C, Colovos C, Pinter-Brown L et al (2004) Pilot study of fixed-infusion rate gemcitabine with cisplatin and dexamethasone in patients with relapsed or refractory lymphoma. Clin Lymphoma 5(1):45–49. S1526-9655(11)70055-0 [pii]
25. Dhawale TM, Shustov AR (2017) Autologous and allogeneic hematopoietic cell transplantation in peripheral T/NK-cell lymphomas: a histology-specific review. Hematol Oncol Clin North Am 31(2):335–357. S0889-8588(16)30171-X [pii]
26. Fanin R, Ruiz de Elvira MC, Sperotto A, Baccarani M, Goldstone A (1999) Autologous stem cell transplantation for T and null cell CD30-positive anaplastic large cell lymphoma: analysis of 64 adult and paediatric cases reported to the european group for blood and marrow transplantation (EBMT). Bone Marrow Transp 23(5):437–442
27. Smith SM, Burns LJ, van Besien K et al (2013) Hematopoietic cell transplantation for systemic mature T-cell non-hodgkin lymphoma. J Clin Oncol 31(25):3100–3109. https://doi.org/10.1200/JCO.2012.46.0188
28. Le Gouill S, Milpied N, Buzyn A et al (2008) Graft-versus-lymphoma effect for aggressive T-cell lymphomas in adults: a study by the societe francaise de greffe de moelle et de therapie cellulaire. J Clin Oncol 26(14):2264–2271
29. Shustov AR, Gooley TA, Sandmaier BM et al (2010) Allogeneic haematopoietic cell transplantation after nonmyeloablative conditioning in patients with T-cell and natural killer-cell lymphomas. Br J Haematol 150(2):170–178
30. Sutherland MS, Sanderson RJ, Gordon KA et al (2006) Lysosomal trafficking and cysteine protease metabolism confer target-specific cytotoxicity by peptide-linked anti-CD30-auristatin conjugates. J Biol Chem 281(15):10540–10547. M510026200 [pii]
31. Pro B, Advani R, Brice P et al (2012) Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. J Clin Oncol 30(18):2190–2196
32. Pro B, Advani R, Brice P et al (2017) Five-year results of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma. Blood 130(25):2709–2717. https://doi.org/10.1182/blood-2017-05-780049
33. Fanale MA, Horwitz SM, Forero-Torres A et al (2014) Brentuximab vedotin in the front-line treatment of patients with CD30+ peripheral T-cell lymphomas: results of a phase I study. J Clin Oncol 32(28):3137–3143
34. Fanale MA, Horwitz SM, Forero-Torres A et al (2018) Five-year outcomes for frontline brentuximab vedotin with CHP for CD30-expressing peripheral T-cell lymphomas. Blood 131(19):2120–2124. https://doi.org/10.1182/blood-2017-12-821009
35. Mosse YP, Lim MS, Voss SD et al (2013) Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: a children's oncology group phase 1 consortium study. Lancet Oncol 14(6):472–480
36. Kyriakou C, Canals C, Goldstone A et al (2008) High-dose therapy and autologous stem-cell transplantation in angioimmunoblastic lymphoma: complete remission at transplantation is the major determinant of outcome-lymphoma working party of the european group for blood and marrow transplantation. J Clin Oncol 26(2):218–224
37. Chihara D, Pro B, Loghavi S et al (2015) Phase II study of HCVIDD/MA in patients with newly diagnosed peripheral T-cell lymphoma. Br J Haematol 171(4):509–516. https://doi.org/10.1111/bjh.13628
38. d'Amore F, Jantunen E, Relander T (2009) Hemopoietic stem cell transplantation in T-cell malignancies: who, when, and how? Curr Hematol Malig Rep 4(4):236–244
39. Reimer P, Rudiger T, Geissinger E et al (2009) Autologous stem-cell transplantation as first-line therapy in peripheral T-cell lymphomas: results of a prospective multicenter study. J Clin Oncol 27(1):106–113
40. d'Amore F, Relander T, Lauritzsen GF et al (2012) Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01. J Clin Oncol 30(25):3093–3099
41. Iqbal J, Wright G, Wang C et al (2014) Gene expression signatures delineate biological and prognostic subgroups in peripheral T-cell lymphoma. Blood 123(19):2915–2923

42. Sirotnak FM, DeGraw JI, Colwell WT, Piper JR (1998) A new analogue of 10-deazaaminopterin with markedly enhanced curative effects against human tumor xenografts in mice. Cancer Chemother Pharmacol 42(4):313–318
43. Sirotnak FM, DeGraw JI, Schmid FA, Goutas LJ, Moccio DM (1984) New folate analogs of the 10-deaza-aminopterin series. further evidence for markedly increased antitumor efficacy compared with methotrexate in ascitic and solid murine tumor models. Cancer Chemother Pharmacol 12(1):26–30
44. O'Connor OA, Pro B, Pinter-Brown L et al (2011) Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. J Clin Oncol 29(9):1182–1189
45. Coiffier B, Pro B, Prince HM et al (2012) Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. J Clin Oncol 30(6):631–636
46. O'Connor OA, Horwitz S, Masszi T et al (2015) Belinostat in patients with relapsed or refractory peripheral T-cell lymphoma: results of the pivotal phase II BELIEF (CLN-19) study. J Clin Oncol 33(23):2492–2499. https://doi.org/10.1200/JCO.2014.59.2782
47. Strati P, Chihara D, Oki Y et al (2018) A phase I study of romidepsin and ifosfamide, carboplatin, etoposide for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma. Haematologica. haematol.2018.187617 [pii]
48. Ellin F, Landstrom J, Jerkeman M, Relander T (2015) Central nervous system relapse in peripheral T-cell lymphomas: a Swedish lymphoma registry study. Blood 126(1):36–41. https://doi.org/10.1182/blood-2014-12-616961
49. Gurion R, Mehta N, Migliacci JC et al (2016) Central nervous system involvement in T-cell lymphoma: a single center experience. Acta Oncol 55(5):561–566. https://doi.org/10.3109/0284186X.2015.1118656
50. Maciocia PM, Wawrzyniecka PA, Philip B et al (2017) Targeting the T cell receptor beta-chain constant region for immunotherapy of T cell malignancies. Nat Med 23(12):1416–1423. https://doi.org/10.1038/nm.4444
51. Clemens MW, Medeiros LJ, Butler CE et al (2016) Complete surgical excision is essential for the management of patients with breast implant-associated anaplastic large-cell lymphoma. J Clin Oncol 34(2):160–168. https://doi.org/10.1200/JCO.2015.63.3412

Adult T-Cell Leukemia-Lymphoma

7

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Abstract

Adult T-cell leukemia-lymphoma (ATL) is a peripheral T-lymphocyte malignancy caused by an RNA retrovirus, human T-cell leukemia virus type 1. ATL is clinically classified into four disease subtypes. The acute, lymphoma type, and cases of the chronic type involving unfavorable prognostic factors are regarded as aggressive ATL subtypes that require immediate treatment. Dose-intensified chemotherapy, such as the VCAP-AMP-VECP regimen, is considered to be the most recommended treatment for aggressive ATL. However, ATL remains difficult to cure and has an extremely poor prognosis, even when such chemotherapy is employed. Allogeneic stem cell transplantation is the only known curative therapy and is recommended for younger patients with aggressive ATL. However, because of the increasing age at the onset of ATL, only a small fraction of patients with ATL can benefit from such transplants; therefore, there is an unmet medical need for novel drugs. Mogamulizumab, a defucosylated, humanized anti-C-C motif chemokine receptor 4 (CCR4) monoclonal antibody, was developed using a novel glycoengineering technique. Mogamulizumab monotherapy achieved clinically meaningful effects in patients with relapsed aggressive ATL and has exhibited acceptable toxicity profiles both inside and outside of Japan. In addition, lenalidomide has shown promising

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antitumor activity in patients with ATL. Furthermore, based on the results of translational research, several promising novel agents are currently being investigated and might contribute to improving the prognosis of ATL.

Keywords
Adult T-cell leukemia-lymphoma · ATL · CCR4 · Mogamulizumab
Lenalidomide

7.1 Introduction

Adult T-cell leukemia-lymphoma (ATL) is a distinct subtype of peripheral T-cell lymphoma (PTCL) caused by human T-cell leukemia virus type 1 (HTLV-1) [1], and compared with those of other types of non-Hodgkin lymphoma its prognosis is extremely poor. ATL is relatively common in southwestern Japan, West Africa, the Caribbean islands, and Brazil, which are HTLV-1-endemic areas [2, 3]. Approximately 1.08 million individuals are carriers of HTLV-1 in Japan [4], and the total number of HTLV-1 carriers globally is estimated to be between 5 and 20 million [5]; however, the latter figure is probably an underestimate because of lack of epidemiological information for developing countries. Epidemiological studies have suggested that HTLV-1 is primarily transmitted by breastfeeding, although its spread via blood transfusions and sexual intercourse have also been reported. The lifetime risk of ATL developing in HLTV-1 carriers is only 3–5% in Japan. The reported risk factors for the development of ATL among HTLV-1 carriers include HTLV-1 infection early in life, an increased age, male sex, and a higher proviral load [6]. The mean age at ATL onset differs among geographic areas: the mean age at diagnosis was reported to be ∼40 years in Central and South America [7, 8], which was lower than that seen in Japan (over 60 years). The differences in the age at ATL onset between different areas of the world suggest that environmental and genetic factors are involved in the onset of the disease. Due to lack of large-scale studies, the mechanism responsible for ATL onset remains to be elucidated.

The HTLV-1 gene encodes three structural proteins: Gag, Pol, Env, and complex regulatory proteins such as Tax, which not only activate viral replication, but also induce the expression of several cellular genes that are important for promoting the proliferation and preventing the apoptosis of ATL cells, including nuclear factor (NF)-κB [9]. The expression of these cellular proteins might enhance the multistep carcinogenic process involved in ATL, whereas the expression of the abovementioned viral proteins in vivo is suppressed by cytotoxic T-cells. HTLV-1 basic Zip factor (HBZ), which is encoded by a minus strand of mRNA, might play a role in viral replication and T-cell proliferation because it is steadily expressed in most HTLV-1-infected cells and primary ATL cells whereas Tax is not [10]. The polycomb-mediated epigenetic silencing of miR31 was reported to be implicated in the aberrant and constitutive activation of NF-κB signaling in ATL cells [11]. An

integrated genomic analysis of ATL revealed that genomic alterations are highly concentrated in genes associated with T-cell receptor-NF-kB signaling, such as phospholipase C gamma 1 (*PLCG1*), protein kinase C (*PRKCB*), and caspase recruitment domain family member 11 (*CARD11*), and gain-of-function mutations were found in C-C motif chemokine receptor 4 (*CCR4*) and *CCR7* [12]. Furthermore, a study investigating structural variations (SV) revealed that the 3' region of the programmed cell death 1 ligand (*PD-L1*) gene was disrupted by SV in 27% of ATL cases [13]. These SV invariably led to a markedly elevated number of aberrant *PD-L1* transcripts, which were stabilized by the truncation of the 3'-untranslated region. This is a unique genetic mechanism of immune escape caused by SV. In addition, according to a recent comprehensive study of the polycomb-dependent epigenetic landscape of ATL cells, high levels of enhancer zeste homolog 2 (EZH2) expression were observed in HTLV-1-infected cells as well as in ATL cells [14]. A compensatory mechanism involving EZH1 and EZH2 that contributes to the oncogenesis and progression of ATL might exist. These results, which were obtained via basic research, might contribute to the further development of novel agents against ATL.

7.2 Clinical Features of ATL

The clinical features of ATL include generalized lymphadenopathy; skin lesions, hepatosplenomegaly; leukocytosis involving increased numbers of abnormal lymphocytes exhibiting cerebriform or flower-like nuclei, or increased numbers of neutrophils; hypercalcemia; and frequent opportunistic infections due to *Pneumocystis jiroveci*, *Candida spp.*, or cytomegalovirus. ATL cells characteristically express CD3, CD4, CD25, CCR4, and forkhead box P3 (FOXP3) on their surfaces, and the monoclonal integration of HTLV-1 proviral DNA is detectable by Southern blotting.

The clinical course of ATL is very heterogeneous. Most cases of ATL are resistant to conventional chemotherapeutic agents, and treatment options are limited. ATL is clinically classified into four disease subtypes (the acute, lymphoma, chronic, and smoldering subtypes), based on its clinical features, including the presence/absence of leukemic changes, high lactate dehydrogenase (LDH) levels, hypercalcemia, and organ infiltration [15]. Chronic-type ATL can be further divided into favorable and unfavorable types based on the presence/absence of LDH, blood urea nitrogen concentrations that are greater than the upper limits of normal, or an albumin concentration that is lower than the lower limit of normal. This system; the Shimoyama classification, is widely used to establish therapeutic strategies for ATL (Fig. 7.1). It was reported that the median survival time of ATL varies according to the disease type: acute type—6 months; lymphoma type—10 months; chronic type—24 months; and smoldering type—3 years or more. It is recommended that the treatment strategy for ATL should be selected according to the disease subtype. In Japan, the acute type, lymphoma type, and cases of the chronic type involving

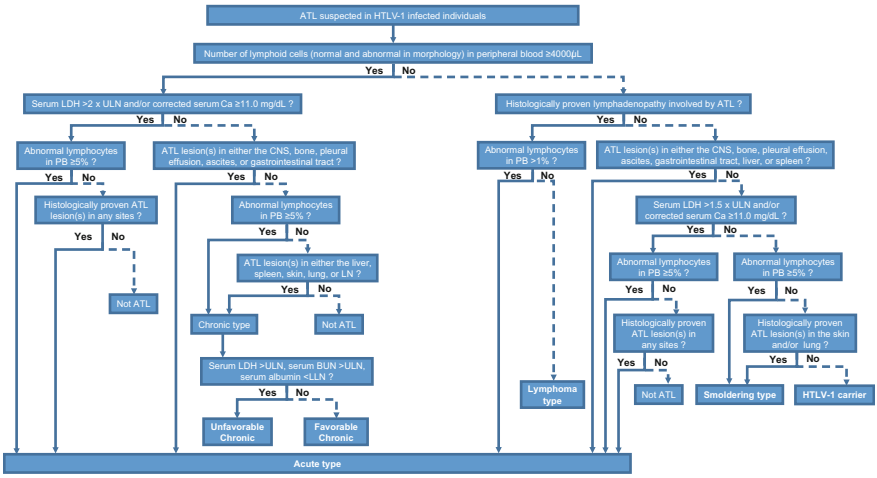

Fig. 7.1 ATL subtypes according to Shimoyama classification. *Abbreviations ATL* adult T-cell leukemia-lymphoma; *PB* peripheral blood; *ULN* upper limit of normal; *LLN* lower limit of normal; *LN* lympho node

unfavorable prognostic factors are regarded as aggressive ATL subtypes that require immediate treatment. On the other hand, chronic type cases that do not involve unfavorable prognostic factors and the smoldering type are considered to be indolent ATL subtypes. Among the various major subtypes of PTCL, cases of ATL involving the aggressive subtypes have the worst prognosis, with 5-year overall survival (OS) and failure-free survival rates of 14% and 12%, respectively [16].

7.3 CCR4 and ATL

Chemokines, which are a small family of cytokines, act as signaling molecules during the migration and tissue homing of various leukocytes. Among them, thymus and activation-regulated chemokine (TARC) and monocyte-derived chemokine (MDC) induce the selective recruitment of distinct subsets of T-cells by triggering the chemokine receptor CCR4. CCR4 is a seven-transmembrane G-protein-coupled receptor that is used as a marker of type 2 helper T-cells (Th2) and regulatory T-cells (Tregs) [17, 18]. Although the expression of CCR4 on normal cells, such as Th2 cells, is partly regulated by its ligands [19], especially MDC, the mechanism involved in ligand-based regulation of CCR expression in tumor cells has not yet been fully elucidated. Ishida et al. examined ATL cells obtained from 103 patients and found that the tumor cells from approximately 90% of patients were positive for CCR4 [20]. They also showed that patients with CCR4-positive ATL were more likely to experience skin infiltration and worse outcomes than those with CCR4-negative ATL, which indicated that CCR4 plays an important pathogenetic role in ATL. CCR4 is also expressed on tumor cells in

approximately 30–65% of patients with other types of PTCL [21, 22]. An analysis of 50 patients with PTCL-not otherwise specified (NOS) revealed that CCR4-positive patients had significantly shorter survival times than CCR4-negative patients. Furthermore, CCR4 expression increased with advancing disease stage in patients with mycosis fungoides (MF) or Sézary syndrome [23]. Gain-of-function mutations in *CCR4* are frequently observed in ATL patients, as mentioned above [12]. Such mutations lead to increased cell surface expression of CCR4 and could result in enhanced ligand-induced chemotaxis and activation of the phosphatidylinositol-4, 5-bisphosphate 3-kinase (PI3K) pathway [12, 24]. Although the roles of CCR4 in the tumorigenesis and progression of ATL and PTCL have not been fully elucidated, CCR4 appears to be a promising target molecule for treatments against ATL and PTCL.

7.4 Treatment of Aggressive ATL

The treatments for aggressive ATL are summarized in Tables 7.1 and 7.2.

7.4.1 Chemotherapy and Hematopoietic Stem-Cell Transplantation

The Lymphoma Study Group of the Japan Clinical Oncology Group (JCOG-LSG) conducted consecutive clinical trials of treatments for aggressive ATL. In the 1990s, a phase II trial (JCOG9303) was performed to investigate a multi-agent chemotherapeutic regimen (LSG15; VCAP-AMP-VECP) consisting of vincristine, cyclophosphamide, doxorubicin, and prednisone (VCAP); doxorubicin, ranimustine, and prednisone (AMP); and vindesine, etoposide, carboplatin, and prednisone (VECP), combined with the prophylactic use of granulocyte-colony stimulating factor [25]. Since central nervous system involvement occurs in 10–20% of patients with ATL, intrathecal prophylaxis was incorporated into the treatment strategy for ATL. Among 93 evaluable patients, 75 responded (81%; 95% confidence interval [CI], 71.1–88.1%), and 33 patients achieved a complete remission (CR, 35.5%). The median OS time and OS rate at 2 years were 13 months and 31%, respectively. Despite considerable hematological toxicities, the LSG15 showed promising response and survival rates. Subsequently, a phase III study comparing modified VCAP-AMP-VECP (m-LSG15) with CHOP-14 in patients with previously untreated aggressive ATL (the acute, lymphoma, or unfavorable chronic type) was performed [26]. The median OS time and OS rate at 3 years were 12.7 months and 24%, respectively, in the VCAP-AMP-VECP arm and 10.9 months and 13%, respectively, in the CHOP-14 arm. VCAP-AMP-VECP achieved higher CR rates (40% vs. 25%) than CHOP-14. These results suggested that VCAP-AMP-VECP is a more effective treatment regimen, but causes greater toxicity, providing a basis for future investigations of the treatment of aggressive ATL.

Compared with those of patients with other types of PTCL, the outcomes of ATL patients that are treated with VCAP-AMP-VECP remain unfavorable.

Table 7.1 Prospective clinical trials for aggressive ATL

Disease	Reference	Treatment	Study design	No. of patients	CR rate	ORR	MST (months)
Untreated aggressive ATL	25	VCAP-AMP-VECP	Phase II	96	35.50%	81%	13
	26	CHOP-14 versus VCAP-AMP-VECP	Phase III	61	25%	66%	10.9
				57	40%	72%	12.7
	43	VCAP-AMP-VECP versus VCAP-AMP-VECP + Mogamulizumab	Randomized phase II	24	33%	75%	NR
				29	52%	86%	NR
Relapsed aggressive ATL	41	Mogamulizumab	Phase II	26	31%	50%	13.7
	42	Investigator's choice versus Mogamulizumab	Randomized phase II	24	NA	0%	6.87
				47	NA	34%	4.9
	47	Lenalidomide	Phase II	26	15	42	20.3

Abbreviations ATL adult T-cell leukemia-lymphoma; *CR* complete remission; *ORR* overall response rate; *MST* median survival time; *NA* not applicable; *VCAP* vincristine, cyclophosphamide, doxorubicin, and prednisone; *AMP* doxorubicin, ranimustine, and prednisone; *VECP* vindesine, etoposide, carboplatin, and prednisone; *CHOP* cyclophosphamide, doxorubicin, vincristine, and prednisolone; *NR* not reached

Table 7.2 Meta-analysis of IFN-alpha + zidovudine for ATL

Subtype	Treatment	No. of patients	MST	5-year OS (%)
Acute type	IFN-α/AZT	45	9 months	28
	Chemotherapy	53	6 months	10
Lymphoma type	IFN-α/AZT	13	7 months	0
	Chemotherapy	71	16 months	18
Chronic/smoldering type	IFN-α/AZT	17	NR	100
	Chemotherapy	6	60 months	42

Abbreviations ATL adult T-cell leukemia-lymphoma; *MST* median survival time; *OS* overall survival; *IFN-α* interferon alpha; *AZT* zidovudine

Allogeneic hematopoietic stem-cell transplantation (allogeneic HSCT) is recommended for younger patients with aggressive ATL, based on the results of several registry studies [27, 28], although robust evidence based on prospective studies is lacking. However, only a small fraction of patients with ATL can benefit from such transplants. A nationwide retrospective study analyzed the cases of 586 patients who underwent allogeneic HSCT involving bone marrow or peripheral blood stem cells between 1992 and 2009 [29]. The median OS time and 3-year OS rate were 9.9 months (95% CI, 7.4–13.2 months) and 36% (95% CI, 32–41%), respectively. The median OS time of patients who received myeloablative conditioning (MAC) did not differ significantly from that of patients that were treated with a reduced-intensity conditioning (RIC) regimen (9.5 months [95% CI, 6.7–18.0 months] versus 10.0 months [95% CI, 7.2–14.0 months]). RIC was found to be significantly associated with ATL-related mortality compared with MAC; however, there was a trend indicating that RIC contributed to better OS in older patients. The cumulative incidence of ATL-related mortality 1 year after transplantation was 18.5% (95% CI, 14.1–23.4) for MAC and 25.0% (95% CI, 20.1–30.1) for RIC recipients and was 22.5% (95% CI, 17.5–27.9) and 33.2% (95% CI, 27.6–38.9), respectively, at 3 years. When the hazard ratio (HR) for death of MAC recipients of a younger age (15–55 years) was determined as 1.000, the HRs of MAC recipients in the older age group (56–72 years) and RIC recipients in the younger and older age groups were 1.884, 1.239, and 1.443, respectively.

7.4.2 Interferon-α and Antiretroviral Agents

Combination therapy involving interferon-α (IFN-α) and the antiretroviral agent zidovudine (AZT) has been reported to be effective against aggressive ATL in several small phase II studies [30–32]. The therapeutic effects of IFN-α/AZT are not considered to be attributable to their direct cytotoxic effects on tumor cells. Regarding the mechanism responsible for the effects of this combination therapy, AZT treatment induces telomere attrition in ATL cell lines, resulting in the cells undergoing p53-dependent senescence, and IFN-α alone suppresses the expression

of HTLV-1 and cell cycling, whereas IFN-α/AZT combination treatment induced p53 signaling and apoptosis in HTLV-1 infected cells [33, 34]. A meta-analysis showed that first-line treatment involving IFN-α in combination with AZT was significantly more effective than chemotherapy in patients with acute type ATL [35].

On the other hand, chemotherapy was more effective than IFN-α/AZT against lymphoma-type ATL. The median OS of patients with acute-type ATL who were given chemotherapy was worse than that reported in Japanese studies. Although IFN-α/AZT appears promising, careful attention is required to avoid selection bias in this type of retrospective study, and further prospective evaluations are needed before this treatment can be widely applied.

7.4.3 Anti-CCR4 Antibody: Mogamulizumab

Mogamulizumab, KW-0761, is a humanized anti-CCR4 monoclonal antibody that recognizes the N-terminal region of human CCR4 [36]. It has a defucosylated Fc region, which markedly enhances antibody-dependent cell-mediated cytotoxicity (ADCC) by increasing the binding affinity of the Fcγ receptor on effector cells [37]. An in vitro ADCC assay and in vivo studies involving a humanized mouse model showed that mogamulizumab exhibited potent antitumor activity against ATL and PTCL cells [36, 38, 39].

7.4.3.1 Mogamulizumab Monotherapy

A phase I study involving patients with relapsed ATL or CCR4-positive PTCL was conducted in Japan [40]. Sixteen patients were enrolled, 13 of whom had ATL (acute type, 11; lymphoma type, 2), 1 had tumor stage MF, and 2 had PTCL-NOS. All 16 patients were included in the safety and efficacy analyses. No dose-limiting toxicities (DLT) were observed in any of the 13 patients who received mogamulizumab at doses of 0.01–1.0 mg/kg, and the maximum tolerated dose (MTD) was not reached. An additional 3 patients were enrolled to receive the highest dose (1.0 mg/kg). The objective response rate (ORR) for all 16 patients was 31% (5/16 patients; of these 5 patients, 2 achieved CR and 3 demonstrated partial responses [PR]), and the ORR of the ATL patients was also 31% (4/13 patients; of these 4 patients, 2 achieved CR and another 2 displayed PR). These results suggested that mogamulizumab might be effective against relapsed ATL.

Subsequently, a multicenter phase II study of mogamulizumab involving 28 patients with relapsed CCR4-positive ATL was carried out in Japan [41]. Of the 27 patients who received mogamulizumab, 14, 6, and 7 patients had the acute type, the lymphoma type, and the chronic type with unfavorable prognostic factors, respectively. The ORR was 50% (13/26 patients; 95% CI, 30–70%), and 8 patients achieved CR; thus, confirming the efficacy of mogamulizumab. The responses seen at each disease site were as follows: peripheral blood, 100% (13/13 patients, all achieved CR); the skin, 63% (5/8 patients, 3 CR, and 2 PR); and nodal and extranodal lesions, 25% (3/12 patients, 3 CR/CR unconfirmed). The median progression-free survival (PFS) and OS times were 5.2 and 13.7 months,

respectively. The most common adverse events experienced by the 27 ATL patients were lymphopenia (96%), neutropenia (52%), and thrombocytopenia (52%) as hematological toxicities, and acute infusion reactions (89%), pyrexia (82%), and skin eruptions (63%; 22% for grade 3/4 toxicities) as non-hematological toxicities. One patient developed Stevens–Johnson syndrome (SJS), which might have been related to the use of mogamulizumab, although they also received trimethoprim/sulfamethoxazole, fluconazole, and acyclovir to prevent infections. These adverse events were manageable with supportive measures, including corticosteroids or other drugs, in all patients.

Based on the results of this phase II study, mogamulizumab was approved as a treatment for relapsed ATL by the Japanese Pharmaceuticals and Medical Devices Agency (PMDA). However, post-marketing surveillance in Japan revealed that skin-related severe adverse events occurred in a fraction of ATL patients. During the first 4 months after mogamulizumab was approved by the PMDA, 9 skin-related severe adverse events, including 4 cases of SJS/toxic epidermal necrolysis (TEN), were reported. One of these 9 patients died. Therefore, close and careful follow-up of adverse events is necessary in such cases, and the prompt use of 0.5–1.0 mg/kg prednisolone is recommended for grade 2–4 skin disorders. If SJS or TEN is suspected, methylprednisolone pulse therapy should be considered.

Another randomized phase II study compared mogamulizumab with the investigator's regimen of choice (IC) in patients with relapsed or refractory ATL from the USA, EU, and Latin America [42]. The patients were randomized to the mogamulizumab or IC regimen arm at a ratio of 2:1. A total of 71 patients were enrolled and randomized (47 to the mogamulizumab arm, 24 to the IC arm). The ORR was 34% (16/47) in the mogamulizumab arm and 0% (0/24) in the IC arm. The median duration of the response to mogamulizumab was 5.65 months (95% CI, 3.63 to not reached). 18 IC patients crossed over to the mogamulizumab arm, and 3 of these patients (17%, 3/18) exhibited a response to mogamulizumab. The safety profile of mogamulizumab was similar to those seen in previous Japanese studies. These results supported the view that mogamulizumab has therapeutic potential for patients with relapsed or refractory ATL outside of Japan.

7.4.3.2 Mogamulizumab with Dose-Intensified Chemotherapy

A multicenter, randomized phase II study was performed to examine the efficacy of combined treatment with mogamulizumab and a dose-intensified multidrug regimen, mLSG15, for newly diagnosed aggressive ATL in Japan [43]. In this study, patients with newly diagnosed CCR4-positive aggressive ATL were randomly assigned to receive mLSG15 plus mogamulizumab (arm A) or mLSG15 alone (arm B) at a 1:1 ratio. The primary endpoint was the CR rate (%CR), and the secondary endpoints included the ORR, PFS, OS, and safety. The patients received 4 cycles of mLSG15, with or without a total of 8 cycles of mogamulizumab once every 2 weeks for 16 weeks at a dose of 1.0 mg/kg. Of the 54 randomized patients, 29 were treated in arm A, and 24 were treated in arm B. The %CR and ORR in arms A and B were 52% (15/29, 95% CI, 33–71%) versus 33% (8/24, 95% CI, 16–55%) and 86% (25/29, 95% CI, 68–96%) versus 75% (18/24, 95% CI, 53–90%),

respectively. The %CR for each disease site in arms A and B were 100% (14/14) and 43% (3/7) for the peripheral blood, 92% (24/26) and 73% (16/22) for nodal and extranodal lesions, and 50% (4/8) and 60% (3/5) for skin lesions, respectively. The median PFS times in arms A and B were 8.5 months and 6.3 months, respectively. The median OS time was not reached in either arm. The most common adverse events (of any grade) in each arm were neutropenia (arm A: 100%, arm B: 96%), thrombocytopenia (arm A: 100%, arm B: 96%), leukopenia (arm A: 100%, arm B: 92%), lymphopenia (arm A: 97%, arm B: 96%), anemia (arm A: 97%, arm B: 92%), and febrile neutropenia (arm A: 90%, arm B: 88%). Papular rashes (21%), hyperglycemia (14%), pyrexia (14%), interstitial lung disease (10%), erythematous rashes (7%), cytomegalovirus infections (7%), cytomegalovirus pneumonia (7%), and reductions in oxygen saturation (7%) occurred in arm A. Although mLSG15 plus mogamulizumab was found to be associated with substantial toxicities, particularly infectious and skin-related adverse events, the majority of the adverse events were manageable. These results suggested that combined treatment with mogamulizumab and mLSG15 might be a reasonable treatment option for managing patients with newly diagnosed aggressive ATL. However, further clinical trials are needed to confirm these results, mainly because of the small number of patients in this randomized phase II study.

7.4.3.3 Mogamulizumab for Transplant-Eligible Patients

A reduction in the frequency of the Treg subset is commonly observed in ATL patients receiving mogamulizumab and might contribute to skin disorders associated with mogamulizumab treatment [44]. Recently, it has been proposed that the reduction in the frequency of Tregs caused by the administration of mogamulizumab might exacerbate graft-versus-host disease (GVHD) after allogeneic HSCT. To clarify this issue, a retrospective analysis was conducted using a database that was created during a nationwide survey of aggressive ATL in Japan [45]. Pre-transplantation mogamulizumab was found to be associated with an increased risk of grade 3/4 acute GVHD (relative risk, 1.80; $P < 0.01$) and refractoriness to systemic corticosteroid treatment for acute GVHD (relative risk, 2.09; $P < 0.01$). The 1-year cumulative incidence of non-relapse mortality was significantly higher among the patients who received pre-transplantation mogamulizumab than among those who did not (43.7% vs. 25.1%; $P < 0.01$). The 1-year OS of patients who received pre-transplantation mogamulizumab was also significantly inferior to that of patients who did not receive pre-transplantation mogamulizumab (32.3% vs. 49.4%; $P < 0.01$). Therefore, mogamulizumab should be used cautiously in transplant-eligible ATL patients.

7.4.4 Lenalidomide

Lenalidomide is an immunomodulatory drug that was created by altering the structure of thalidomide. It was shown to be very effective against multiple myeloma when used as a monotherapy or in combination with other agents.

Furthermore, lenalidomide exhibits clinically meaningful efficacy in patients with several types of B-cell or T-cell non-Hodgkin lymphoma.

A phase I study involving patients with relapsed ATL or PTCL was carried out in Japan to assess the safety, MTD, pharmacokinetic profile, and efficacy of lenalidomide [46]. Dose escalation was conducted according to the conventional 3 + 3 design. The patients in cohort 1 received 25 mg oral lenalidomide daily on days 1–21 of each 28-day cycle. The patients in cohorts 2 and 3 received 25 mg and 35 mg, respectively, on each day of a 28-day cycle. The treatment was continued until the development of unacceptable toxicity or disease progression.

Thirteen patients, 9 and 4 of whom had ATL and PTCL, respectively, were enrolled in this phase I study: 3 in cohort 1, 6 in cohort 2, and 4 in cohort 3. The 3 patients in cohort 1 received lenalidomide until disease progression without any DLT. In cohort 2, 1 patient experienced a DLT (thrombocytopenia, platelet count: <10,000/μL). In cohort 3, 2 patients suffered from DLT (thrombocytopenia, platelet count: <10,000/μL in 1 patient, and grade 3 prolongation of the QTc interval in 1 patient). Based on these results, 25 mg daily per 28-day cycle was regarded as the MTD in patients with ATL or PTCL. Among the 9 ATL patients, 3 achieved PR with hematological CR seen in 2 patients, including the disappearance of skin lesions in 1 patient. These responses occurred after between 54 and 57 days' treatment and lasted for 92, 279+ and 505 days. On the other hand, among the 4 patients with PTCL, 1 achieved a PR. Therefore, 25 mg lenalidomide daily on each day of a 28-day cycle was recommended for the subsequent phase II study. These results suggested that lenalidomide displays promising antitumor activity in ATL and PTCL patients.

Based on the encouraging results of this phase I study, a phase II study was performed to evaluate the efficacy of lenalidomide in patients with relapsed ATL in Japan [47]. A total of 26 patients with relapsed or recurrent ATL were enrolled, of whom 15 had the acute type, 7 had the lymphoma type, and 4 had the chronic type with unfavorable prognostic factors. The ORR was 42% (11/26, 95% CI, 23–63%), and CR were seen in 4 cases. The median PFS and OS times were 3.8 months (95% CI, 1.9 months to not estimable [NE]) and 20.3 months (95% CI, 9.1 months to NE), respectively. The most common grade 3 or worse adverse events were neutropenia (65%), leukopenia (38%), lymphopenia (38%), and thrombocytopenia (23%), which were all manageable and reversible. Lenalidomide demonstrated clinically meaningful antitumor activity and an acceptable toxicity profile in patients with relapsed or recurrent aggressive ATL. Based on the results of this phase II study, lenalidomide was approved for use in Japan during the treatment of relapsed ATL by the PMDA in 2017.

7.4.5 Other Novel Agents for ATL

Several novel agents have recently been developed for the treatment of PTCL (mainly for patients with relapsed or refractory disease). These agents have various mechanisms of action, including a proteasome inhibitor (bortezomib); histone

deacetylase inhibitors (vorinostat, romidepsin, belinostat, and chidamide); antifolate (pralatrexate); and biologics, including antibodies, antibody-toxin conjugates, and antibody-drug conjugates (alemtuzumab, denileukin diftitox, and brentuximab vedotin). However, the clinical data on these novel agents are mainly derived from patients with PTCL, rather than from ATL patients. Furthermore, based on the results of basic research, early phase clinical studies of nivolumab, an immune checkpoint inhibitor, and DS-3201b, an EZH1/2 dual inhibitor, as treatments for non-Hodgkin lymphoma, including ATL, are also ongoing in Japan.

7.5 Treatment of Indolent ATL

The treatments for indolent ATL are summarized in Table 7.2.

The international consensus guidelines on the treatment of indolent ATL recommend the use of INF-α/AZT or a watchful waiting strategy until disease progression for symptomatic patients, and a watchful waiting strategy for asymptomatic patients [48]. However, these recommendations are not based on the results of prospective clinical trials. In clinical practice, some patients with indolent ATL develop skin lesions, which can be treated with skin-directed therapy by dermatologists. On the other hand, a Japanese retrospective analysis showed that conventional chemotherapy did not improve the prognosis of indolent ATL. Furthermore, another Japanese retrospective study demonstrated that the prognosis of the chronic and smoldering types of ATL was worse than expected when a watchful waiting strategy was employed (the median OS time was 4.1 years, and the OS curve did not plateau) [49]. A retrospective meta-analysis of the use of IFN-α/AZT for patients with indolent type ATL showed that 100% of the patients treated with IFN-α/AZT survived for 5 years, but only 42% of those who received chemotherapy survived for 5 years [35]. Although IFN-α/AZT appears to be a promising treatment for indolent type ATL, careful attention is required to avoid selection bias in this type of retrospective study, as mentioned above. To evaluate the efficacy of this combination therapy in a more scientific manner, a randomized phase III study comparing IFN-α/AZT with observation in patients with untreated indolent ATL is currently being performed in Japan (JCOG1111, UMIN000011805).

7.6 Prognosis and Prognostic Index of ATL

In a recent retrospective analysis of 1,594 ATL patients who were diagnosed and treated in Japan between 2000 and 2009, the median OS time of each disease subtype was as follows: acute type—8.3 months (95% CI, 7.5–8.9 months); lymphoma type—10.6 months (95% CI, 9.3–11.9 months); chronic type—31.5 months (95% CI, 25.9–41.1); and smoldering type–55.0 months (95% CI, 36.6–90.4 months) [50]. This study revealed that the survival improvement seen in

patients with the acute or lymphoma type was limited to a particular proportion of patients who were saved by induction chemotherapy, despite the recent progress in treatment modalities. On the other hand, the survival outcomes of patients with acute or lymphoma type ATL vary markedly. A prognostic index for acute and lymphoma-type ATL was developed via a retrospective analysis of 807 newly diagnosed patients in Japan [51]. The Ann Arbor stage (I and II vs. III and IV), performance status (PS) (0–1 vs. 2–4), age (>70 years), and the serum levels of albumin (<3.5 g/dL) and soluble interleukin-2 receptor (SIL-2R, >20,000 U/mL) were identified as independent prognostic factors. Then, a simplified ATL prognostic index was established as follows: prognostic score = 2 (if stage is III or IV) + 1 (if PS is >1) + 1 (if aged >70 years) + 1 (if serum albumin level is <3.5 g/dL) + 1 (if serum sIL-2R level is >20,000 U/mL). Scores of 0–2, 3–4, and 5–6 were categorized as low risk, intermediate risk, and high risk, respectively. The median OS times were 4.6 (95% CI, 2.6–5.4), 7.0 (95% CI, 6.3–8.6), and 16.2 (95% CI, 13.4–23.2) months, and the 2-year OS rates were 6% (95% CI, 2–12%), 17% (95% CI, 12–23%), and 37% (95% CI, 25–49%) for patients at high, intermediate, and low risk, respectively. The ATL prognostic index was found to be a better predictor of risk than the International Prognostic Index. On the other hand, the JCOG-LSG performed a combined analysis of all of the ATL patients enrolled in the previous JCOG studies to develop a new prognostic index for the disease [52]. As a result, the corrected calcium level ($\geq$ 2.75 mmol/L) and PS (2–4) were identified as independent prognostic factors. The median OS time and 5-year OS rate were 14 months and 18% in the moderate-risk group (a calcium level of <2.75 mmol/L and a PS of 0 or 1), and 8 months and 4% in the high-risk group (calcium level of $\geq$ 2.75 mmol/L and/or a PS of 2–4). This prognostic index was shown to be valuable for identifying patients with extremely poor prognoses.

7.7 Conclusions

In this chapter, we discussed the treatment strategies and novel agents for ATL, as well as the epidemiology and biology of ATL. ATL is clinically classified into four disease subtypes (the acute, lymphoma, chronic, and smoldering subtypes), and the acute type, lymphoma type, and cases of the chronic type involving unfavorable prognostic factors are regarded as aggressive ATL subtypes that require immediate treatment. On the other hand, cases of the chronic type without unfavorable prognostic factors and the smoldering type are considered to be indolent ATL subtypes.

Dose-intensified chemotherapy, such as the VCAP-AMP-VECP regimen, is the recommended treatment for aggressive ATL. However, ATL remains difficult to cure and has an extremely poor prognosis, even when such intensive chemotherapy is employed. To cure ATL, allogeneic HSCT is recommended for younger patients with aggressive ATL. However, mainly because of the increasing age at onset of ATL, only a small fraction of patients with ATL can benefit from allogeneic HSCT; therefore, there is an unmet medical need for novel drugs. Mogamulizumab, an

anti-CCR4 antibody, was shown to be highly effective for aggressive ATL in several clinical trials and this is an epoch-defining agent in ATL treatment. However, for those who plan to undergo allogeneic HSCT, the decision regarding whether to add mogamulizumab requires careful consideration due to the increased risk of acute GVHD and transplant-related mortality. On the other hand, a watchful waiting strategy is regarded as the standard management strategy for indolent ATL; however, a recent retrospective analysis revealed that the prognosis of indolent ATL patients that were subjected to a watchful waiting strategy was worse than expected. A randomized phase III study comparing IFN-α/AZT with observation for patients with untreated indolent ATL is underway (JCOG1111, UMIN000011805). Based on the results of this study, early interventions against indolent ATL might be considered in the near future. Furthermore, there have been marked advances in our knowledge about the biology of ATL, as well as its molecular characteristics. Recent scientific studies have revealed a lot of the genetic and molecular mechanisms by which ATL arises from HTLV-1-infected cells. Such translational research might contribute to the further development of novel agents against ATL and the improvement of the disease's prognosis.

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References

1. Swerdlow SH, Campo E, Pileri SA et al (2016) The 2016 revision of the world health organization classification of lymphoid neoplasms. Blood 127:2375–2390
2. Proietti FA, Carneiro-Proietti AB, Catalan-Soares BC et al (2005) Global epidemiology of HTLV-I infection and associated diseases. Oncogene 24:6058–6068
3. Sonoda S, Li HC, Tajima K (2011) Ethnoepidemiology of HTLV-1 related diseases: ethnic determinants of HTLV-1 susceptibility and its worldwide dispersal. Cancer Sci 102:295–301
4. Satake M, Yamaguchi K, Tadokoro K (2012) Current prevalence of HTLV-1 in Japan as determined by screening of blood donors. J Med Virol 84:327–335
5. Gessain A, Cassar O (2012) Epidemiological aspects and world distribution of HTLV-1 infection. Front Microbiol 3:388
6. Iwanaga M, Watanabe T, Utsunomiya A et al (2010) Human T-cell leukemia virus type I (HTLV-1) proviral load and disease progression in asymptomatic HTLV-1 carriers: a nationwide prospective study in Japan. Blood 116:1211–1219
7. Hanchard B (1996) Adult T-cell leukemia/lymphoma in Jamaica: 1986–1995. J Acquir Immune Defic Syndr Hum Retrovirol 13(Suppl 1):S20–S25
8. Pombo de Oliveira MS, Matutes E, Schulz T et al (1995) T-cell malignancies in Brazil. Clinico-pathological and molecular studies of HTLV-I-positive and -negative cases. Int J Cancer 60:823–827
9. Tsukasaki K, Tobinai K (2014) Human T-cell lymphotropic virus type I-associated adult T-cell leukemia-lymphoma: new directions in clinical research. Clin Cancer Res 20:5217–5225
10. Satou Y, Yasunaga J, Yoshida M et al (2006) HTLV-I basic leucine zipper factor gene mRNA supports proliferation of adult T cell leukemia cells. Proc Natl Acad Sci USA 103:720–725

11. Yamagishi M, Nakano K, Miyake A et al (2012) Polycomb-mediated loss of miR-31 activates NIK-dependent NF-kappaB pathway in adult T cell leukemia and other cancers. Cancer Cell 21:121–135
12. Kataoka K, Nagata Y, Kitanaka A et al (2015) Integrated molecular analysis of adult T cell leukemia/lymphoma. Nat Genet 47:1304–1315
13. Kataoka K, Shiraishi Y, Takeda Y et al (2016) Aberrant PD-L1 expression through 3'-UTR disruption in multiple cancers. Nature 534:402–406
14. Fujikawa D, Nakagawa S, Hori M et al (2016) Polycomb-dependent epigenetic landscape in adult T-cell leukemia. Blood 127:1790–1802
15. Shimoyama M (1991) Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma. A report from the lymphoma study group (1984–87). Br J Haematol 79:428–437
16. Vose J, Armitage J, Weisenburger D et al (2008) International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol 26:4124–4130
17. Iellem A, Mariani M, Lang R et al (2001) Unique chemotactic response profile and specific expression of chemokine receptors CCR4 and CCR8 by CD4(+)CD25(+) regulatory T cells. J Exp Med 194:847–853
18. D'Ambrosio D, Iellem A, Bonecchi R et al (1998) Selective up-regulation of chemokine receptors CCR4 and CCR8 upon activation of polarized human type 2 Th cells. J Immunol 161:5111–5115
19. Mariani M, Lang R, Binda E et al (2004) Dominance of CCL22 over CCL17 in induction of chemokine receptor CCR4 desensitization and internalization on human Th2 cells. Eur J Immunol 34:231–240
20. Ishida T, Utsunomiya A, Iida S et al (2003) Clinical significance of CCR4 expression in adult T-cell leukemia/lymphoma: its close association with skin involvement and unfavorable outcome. Clin Cancer Res 9:3625–3634
21. Jones D, O'Hara C, Kraus MD et al (2000) Expression pattern of T-cell-associated chemokine receptors and their chemokines correlates with specific subtypes of T-cell non-Hodgkin lymphoma. Blood 96:685–690
22. Ishida T, Inagaki H, Utsunomiya A et al (2004) CXC chemokine receptor 3 and CC chemokine receptor 4 expression in T-cell and NK-cell lymphomas with special reference to clinicopathological significance for peripheral T-cell lymphoma, unspecified. Clin Cancer Res 10:5494–5500
23. Yagi H, Seo N, Ohshima A et al (2006) Chemokine receptor expression in cutaneous T cell and NK/T-cell lymphomas: immunohistochemical staining and in vitro chemotactic assay. Am J Surg Pathol 30:1111–1119
24. Nakagawa M, Schmitz R, Xiao W et al (2014) Gain-of-function CCR4 mutations in adult T cell leukemia/lymphoma. J Exp Med 211:2497–2505
25. Yamada Y, Tomonaga M, Fukuda H et al (2001) A new G-CSF-supported combination chemotherapy, LSG15, for adult T-cell leukaemia-lymphoma: Japan Clinical oncology group study 9303. Br J Haematol 113:375–382
26. Tsukasaki K, Utsunomiya A, Fukuda H et al (2007) VCAP-AMP-VECP compared with biweekly CHOP for adult T-cell leukemia-lymphoma: Japan clinical oncology group study JCOG9801. J Clin Oncol 25:5458–5464
27. Hishizawa M, Kanda J, Utsunomiya A et al (2010) Transplantation of allogeneic hematopoietic stem cells for adult T-cell leukemia: a nationwide retrospective study. Blood 116:1369–1376
28. Choi I, Tanosaki R, Uike N et al (2011) Long-term outcomes after hematopoietic SCT for adult T-cell leukemia/lymphoma: results of prospective trials. Bone Marrow Transpl 46:116–118

29. Ishida T, Hishizawa M, Kato K et al (2012) Allogeneic hematopoietic stem cell transplantation for adult T-cell leukemia-lymphoma with special emphasis on preconditioning regimen: a nationwide retrospective study. Blood 120:1734–1741
30. Hodson A, Crichton S, Montoto S et al (2011) Use of zidovudine and interferon alfa with chemotherapy improves survival in both acute and lymphoma subtypes of adult T-cell leukemia/lymphoma. J Clin Oncol 29:4696–4701
31. Gill PS, Harrington W Jr, Kaplan MH et al (1995) Treatment of adult T-cell leukemia-lymphoma with a combination of interferon alfa and zidovudine. N Engl J Med 332:1744–1748
32. Hermine O, Bouscary D, Gessain A et al (1995) Brief report: treatment of adult T-cell leukemia-lymphoma with zidovudine and interferon alfa. N Engl J Med 332:1749–1751
33. Datta A, Bellon M, Sinha-Datta U et al (2006) Persistent inhibition of telomerase reprograms adult T-cell leukemia to p53-dependent senescence. Blood 108:1021–1029
34. Kinpara S, Kijiyama M, Takamori A et al (2013) Interferon-alpha (IFN-alpha) suppresses HTLV-1 gene expression and cell cycling, while IFN-alpha combined with zidovudine induces p53 signaling and apoptosis in HTLV-1-infected cells. Retrovirology 10:52
35. Bazarbachi A, Plumelle Y, Carlos Ramos J et al (2010) Meta-analysis on the use of zidovudine and interferon-alfa in adult T-cell leukemia/lymphoma showing improved survival in the leukemic subtypes. J Clin Oncol 28:4177–4183
36. Ishii T, Ishida T, Utsunomiya A et al (2010) Defucosylated humanized anti-CCR4 monoclonal antibody KW-0761 as a novel immunotherapeutic agent for adult T-cell leukemia/lymphoma. Clin Cancer Res 16:1520–1531
37. Shinkawa T, Nakamura K, Yamane N et al (2003) The absence of fucose but not the presence of galactose or bisecting N-acetylglucosamine of human IgG1 complex-type oligosaccharides shows the critical role of enhancing antibody-dependent cellular cytotoxicity. J Biol Chem 278:3466–3473
38. Niwa R, Shoji-Hosaka E, Sakurada M et al (2004) Defucosylated chimeric anti-CC chemokine receptor 4 IgG1 with enhanced antibody-dependent cellular cytotoxicity shows potent therapeutic activity to T-cell leukemia and lymphoma. Cancer Res 64:2127–2133
39. Niwa R, Sakurada M, Kobayashi Y et al (2005) Enhanced natural killer cell binding and activation by low-fucose IgG1 antibody results in potent antibody-dependent cellular cytotoxicity induction at lower antigen density. Clin Cancer Res 11:2327–2336
40. Yamamoto K, Utsunomiya A, Tobinai K et al (2010) Phase I study of KW-0761, a defucosylated humanized anti-CCR4 antibody, in relapsed patients with adult T-cell leukemia-lymphoma and peripheral T-cell lymphoma. J Clin Oncol 28:1591–1598
41. Ishida T, Joh T, Uike N et al (2012) Defucosylated anti-CCR4 monoclonal antibody (KW-0761) for relapsed adult T-cell leukemia-lymphoma: a multicenter phase II study. J Clin Oncol 30:837–842
42. Phillips AA, Fields P, Hermine O et al (2016) A prospective, multicenter, randomized study of anti-CCR4 monoclonal antibody mogamulizumab versus investigator's choice in the treatment of patients with relapsed/refractory adult T-cell leukemia-lymphoma. J Clin Oncol 34. abstrct 7501
43. Ishida T, Jo T, Takemoto S et al (2015) Dose-intensified chemotherapy alone or in combination with mogamulizumab in newly diagnosed aggressive adult T-cell leukaemia-lymphoma: a randomized phase II study. Br J Haematol 169:672–682
44. Ishida T, Ito A, Sato F et al (2013) Stevens-Johnson Syndrome associated with mogamulizumab treatment of adult T-cell leukemia/lymphoma. Cancer Sci 104:647–650
45. Fuji S, Inoue Y, Utsunomiya A et al (2016) Pretransplantation anti-CCR4 antibody mogamulizumab against adult T-Cell leukemia/lymphoma is associated with significantly increased risks of severe and corticosteroid-refractory graft-versus-host disease, nonrelapse mortality, and overall mortality. J Clin Oncol 34:3426–3433

46. Ogura M, Imaizumi Y, Uike N et al (2016) Lenalidomide in relapsed adult T-cell leukaemia-lymphoma or peripheral T-cell lymphoma (ATLL-001): a phase 1, multicentre, dose-escalation study. Lancet Haematol 3:e107–e118
47. Ishida T, Fujiwara H, Nosaka K et al (2016) Multicenter phase ii study of lenalidomide in relapsed or recurrent adult T-Cell leukemia/lymphoma: ATLL-002. J Clin Oncol 34:4086–4093
48. Tsukasaki K, Hermine O, Bazarbachi A et al (2009) Definition, prognostic factors, treatment, and response criteria of adult T-cell leukemia-lymphoma: a proposal from an international consensus meeting. J Clin Oncol 27:453–459
49. Takasaki Y, Iwanaga M, Imaizumi Y et al (2010) Long-term study of indolent adult T-cell leukemia-lymphoma. Blood 115:4337–4343
50. Katsuya H, Ishitsuka K, Utsunomiya A et al (2015) Treatment and survival among 1594 patients with ATL. Blood 126:2570–2577
51. Katsuya H, Yamanaka T, Ishitsuka K et al (2012) Prognostic index for acute- and lymphoma-type adult T-cell leukemia/lymphoma. J Clin Oncol 30:1635–1640
52. Fukushima T, Nomura S, Shimoyama M et al (2014) Japan clinical oncology group (JCOG) prognostic index and characterization of long-term survivors of aggressive adult T-cell leukaemia-lymphoma (JCOG0902A). Br J Haematol 166:739–748

NK-Cell Lymphomas

8

Dai Chihara and Yasuhiro Oki

Abstract

NK-cell malignancies are rare aggressive diseases associated with poor clinical outcome. There is a significant geographic variation in their incidence. At least a part of the reason for that is the fact that Epstein–Barr virus plays an important role in pathogenesis, and importantly, the plasma viral titer reflects disease burden and response to therapy. Extranodal NK/T-cell lymphoma, nasal type (ENKL), is the most common disease subtype in NK-cell malignancies. Conventional anthracycline-based chemotherapy was historically used for ENKL, only to produce dismal outcome. More recently, concurrent chemoradiation therapy for early-stage disease and non-anthracycline-based L-asparaginase containing chemotherapy have been studied, showing improved clinical response and survival, with long-term survival rates of 60–70% and 50–60%, respectively. Stem cell transplant can provide long-term disease control in recurrent or refractory disease settings, but the role of frontline use of such approach is yet to be determined. Several novel therapeutic approaches have shown promising results, and enrollment to clinical trials is the essential key to improve the treatment outcome in the future.

Keywords

NK-cell lymphoma · Treatment · Concurrent chemoradiotherapy
L-asparaginase · Stem cell transplant · Review

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8.1 Introduction

NK-cell malignancies are rare aggressive disease associated with poor clinical outcome. Currently, there are three types of NK-cell malignancies in World Health Organization (WHO) classification of mature T/NK neoplasm: extranodal NK/T-cell lymphoma, nasal type (ENKL), aggressive NK-cell leukemia (ANKL), and chronic lymphoproliferative disorder of NK-cells (CLPD-NK) [1]. While ENKL is an extremely rare disease entity representing less than 1% of all lymphoma [2], it is most common among three NK-cell malignancies. There is a difference in incidence by race in NK-cell malignancies, and ENKL is twice to four times more prevalent in Asians and Hispanic white than non-Hispanic white [2, 3]. The age-adjusted incidence rate of ENKL was 0.04 and 0.1 per 100,000 in the US and Japan, respectively [2]. ANKL and chronic lymphoproliferative disorder of NK-cells are even much less common than ENKL, and the actual incidence of these diseases is unclear.

There have been new findings on prognostication of NK-cell neoplasms, as well as improved treatment approaches for the disease. Here, we will review characteristics of this disease and recent advance in the treatment.

8.2 Patient and Disease Characteristics

ENKL occurs predominantly at upper aerodigestive tract area (nasal cavity, nasopharynx, paranasal sinuses, and palate) and less commonly in extranasal sites [4]. Patients most commonly present with nasal obstruction and/or epistaxis, usually with good performance status (PS) without B symptoms. Approximately, 70–75% of patients are diagnosed at limited stage (stage I and II) and it is uncommon to have bone marrow involvement [4, 5]. Median age at diagnosis is early 50s, and 70–80% of patients are in low-risk group according to international prognostic index (IPI) [4–6]. The disease can progress to a locally advanced disease, marked by the tumor eroding the palate and bone, causing pain, fistula, and frequent infection. Advanced stage disease is often associated with systemic symptoms such as fever, hemophagocytic lymphohistiocytosis, and disseminated intravascular coagulation. Skin/soft tissue, liver, and gastrointestinal tract are the common sites of involvement in extranasal ENKL. Extranasal ENKL is more frequently diagnosed at advanced stage disease compared to nasal ENKL, and the survival outcome of extranasal ENKL is similar to ANKL and worse than that of nasal ENKL [4, 7]. In the era of CHOP-based chemotherapeutic treatment and/or radiation therapy, 5-year overall survival (OS) rate of patients with ENKL was 30–50% [4, 5, 8].

ANKL is a rare leukemic form of NK-cell neoplasm, commonly affecting younger patients, with median age of early 40s [4, 9]. Patients most frequently present with systemic symptoms such as fever and night sweats. By physical examination, hepatosplenomegaly is commonly seen. Patients sometimes show hypersensitivity to mosquito bites or chronic active EBV infection which is shared features with Epstein–Barr virus (EBV)+ T-cell lymphoproliferative disorders of

childhood. It also can mimic systemic disease of ENKL; however, ANKL is a distinct subtype with significant difference in genomics compared to ENKL shown by array-based comparative genomic hybridization (CGH) [10]. Expression of CD16 characterizes ANKL and is a hallmark differentiating ANKL from ENKL. Prognosis is extremely poor with median OS of less than 2 months [4, 9].

CLPD-NK is characterized by a chronic increase in peripheral blood NK-cell with unknown etiology. It seems to be more common in male, and majority of patients are asymptomatic [11–13]. Some patients may have underlying medical conditions that can potentially cause NK-cell activation. It is commonly a very indolent disease with limited clinically significant symptoms, even with a possibility of spontaneous complete remission (CR) [11, 13]. However, few cases of transformation to ANKL were seen with additional genetic abnormality. These patients therefore need close monitoring for signs of aggressive transformation [14, 15].

Thought not defined as a distinct disease entity in WHO classification of lymphoid neoplasm 2016, there is another emerging disease entity called lymphomatoid gastropathy, which is an unusual NK-cell proliferative disorder in the stomach. [16]. In the original report, 10 patients with this condition are described. They were found to have ulcerative or erosive elevated lesion in stomach by surveillance gastric endoscopy (i.e., no symptoms). Biopsy of the lesion showed CD56 positive atypical lymphoid cell proliferation. Staging evaluation revealed localized disease in stomach. Interestingly, EBER was negative in all cases. Due to inconclusive pathologic diagnosis of lymphoma, all patients were carefully followed without chemotherapy, with favorable clinical course. Some patients experienced spontaneous disease regression and none of them required treatments (range: 12–145 months). Later, similar condition was reported in eight patients with other gastrointestinal tract involvement [17]. It is still unclear whether this is a malignant or pre-malignant status, but it seems clear that the course is indolent and conservative approach without aggressive therapy is reasonable.

8.3 Pathology and Pathogenesis of NK-Cell Lymphoma

Histologically, ENKL shows a diffuse proliferation of lymphoid neoplasm, often with an angiocentric or angiodestructive growth pattern, associated with a mixture of reactive lymphocytes and histiocytes. Fibrinoid change can be seen in the blood vessels. Granulocytes are rarely seen except for the areas of necrosis. Lymphoma cells express NK-cell markers marked by CD56, CD2, and cytoplasmic CD3 and are negative for surface CD3, CD5, and T-cell receptor (TCR) [18, 19]. Cytotoxic molecules such as TIA-1, granzyme B, and perforin are also positive [20, 21]. Deletion of chromosome 6 is the most frequent cytogenetic aberration [22, 23], and 6q21 region is the most frequently deleted (36%) by oligo-array CGH [24]. PRDM1 and FOXO3 are two genes on 6q21, and re-expression of FOXO3 and PRDM1 suppressed NK-cell proliferation suggesting that FOXO3 and PRDM1 are lymphoma-suppressing genes and indicates their important role in NK-cell lymphomagenesis [24, 25].

One of the most important driving factors in NK-cell malignancies is EBV infection, which is almost universally seen in ENKL and 50–90% of ANKL [1, 9, 26]. The EBV infection can be detected by Epstein–Barr encoding protein (EBER) in situ hybridization or Southern blotting using pathological specimen, and used as a hallmark of diagnosis for ENKL. High EBV-DNA load in plasma at the time of diagnosis is associated with lower response rate to chemotherapy and worse outcome, and well correlated with disease behavior after initiation of treatment [27, 28].

EBV is a commonly disseminated herpesvirus, and humans are the major reservoir of the virus. EBV acquired during childhood is mostly subclinical, but the symptomatic infection becomes as common as 10% when infection occurs in adolescent or adult. About 90–95% of adults are eventually EBV seropositive. The underlying pathogenesis of EBV infection in T/NK-cell lymphomas is very complex and is not fully understood, but studies have shown PI3 K/Akt, NF-κB, and JAK/STAT pathway activation and cytokines overproduction by oncogenic protein EBV latent membrane protein −1 (LMP-1) overexpression and those mechanisms have an important role in lymphomagenesis [29].

8.4 Treatment

Historically, the most commonly used chemotherapy for lymphoma has been CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). The outcome after CHOP in ENKL, however, was unsatisfactory. More than a decade ago, Korean group summarized survival outcomes of 17 patients with limited stage (stage I–II) ENKL who received CHOP followed by involved field radiation (IFRT) [8]. Overall, response rate (ORR) to CHOP was 53%, and only 35% of patients received planned IFRT due to progression during CHOP. The poor response to chemotherapy is believed at least in part due to the high expression of P-glycoprotein in NK neoplasm, leading to multidrug resistance [30–32].

Therefore, the idea of up-front radiation therapy has become important for limited disease of ENKL. In fact, several earlier studies have shown somewhat better outcome when radiation therapy was given as a primary therapy. Japanese group retrospectively analyzed 55 patients with stage I ENKL and found that CR rate of primary chemotherapy was 65%, compared to 80% in patients who received radiation therapy (RT) first [4]. Consistent with these results, several retrospective studies showed that "up-front" RT improves the ORR and OS [33, 34]. You JY and colleagues retrospectively compared RT and chemotherapy as an initial treatment for localized ENKL and showed that OS is significantly longer in patients who received primary RT than primary chemotherapy (5-year OS: 83.3% vs. 28.6%), and survival benefit of RT compared to chemotherapy alone was also confirmed with salvage treatment in patients who experienced relapse (5-year OS: 42.2% vs. 20.0%) [34]. In another study, Li YX and colleagues analyzed 105 patients (83 stage IE, 22 stage IIE) with ENKL who received RT and/or chemotherapy [33]. CR rate was significantly higher in patients who received RT as initial treatment than in those receiving

primary chemotherapy (83% vs. 20%). Five-year OS and PFS in patients who received RT alone was 66% and 61%, respectively, and adding chemotherapy followed by RT did not significantly improve survival outcome (76 and 61%). There is an inverse association with dose of RT and risk of local recurrence, disease progression, and mortality until RT dose of 50 to 52 Gy, and therefore optimal dose of RT is suggested to be $\geq$50 Gy is used as a single modality [35].

Above studies have once placed primary radiation therapy as a standard of care for limited stage ENKL, primarily owing to the better local disease control. However, RT therapy as a single modality was associated with relapsed disease outside RT field [36, 37]. With an intention to enhance the radiation efficacy, as well as to reduce the risk of disease progression outside of radiation field, combined chemoradiation therapy was evaluated for early-stage disease. Also, the newer generation of combination chemotherapy was developed, avoiding agents that are considered significantly affected by P-glycoprotein. Multiple different studies have been conducted for limited stage and also advanced stage ENKL, and are summarized below (Table 8.1).

8.4.1 Limited Stage, First-Line Treatment

- ***RT-2/3DeVIC therapy***

Japanese Clinical Oncology Group studied concurrent RT (50 Gy) and three courses of dexamethasone, etoposide, ifosfamide, and carboplatin (DeVIC) in 33 patients with localized disease (stage I–II) of ENKL [38]. The study was phase I/II trial, and the dose of DeVIC was reduced to two-third during phase I portion of this study due to dose-limiting hematologic toxicity. Detailed doses and schedule are summarized in Fig. 8.1. With this treatment, ORR was 78% with CR rate of 75% (95%CI: 57–89%). Grade 3–4 hematological toxicities, predominantly leukopenia, were observed in all patients. Febrile neutropenia occurred in 15% of patients and was manageable. Mucositis and dysphagia were the common grade 3–4 non-hematological toxicities and occurred in up to 30% of patients. All patients were able to complete RT. With a long-term follow-up of 67 months, 5-year progression-free survival (PFS) and OS were 63% (95%CI: 42–78%) and 70% (95%CI: 49–84%), respectively [39]. No relapses were seen beyond 3 years and overall, 60–70% of patients with localized disease were considered cured with this approach.

- ***RT–cisplatin followed by VIPD***

Korean group studied different concurrent treatment regimens [40]. Cisplatin single agent was given weekly during RT (median dose 40 Gy) followed by three cycles of etoposide, ifosfamide, cisplatin, and dexamethasone (VIPD), starting after 3–5

Table 8.1 Summary of treatments

	Number of patients	ORR (%)	CR (%)	PFS	OS	Grade 3/4 hematological toxicity	References
Limited stage, first-line treatment							
RT + 2/3DeVIC	33	78	75	5-yr: 63%	5-yr: 70%	Neutropenia: 91% Thrombocytopenia: 18% Anemia: 24%	[39]
CCRT +VIPD	30	100	80	3-yr: 85%	3-yr: 86%	Leukopenia: 47% Thrombocytopenia: 23% Anemia: 27%	[40]
CCRT +VIDL	30	90	87	5-yr: 60%	5-yr: 73%	Leukopenia: 80% Thrombocytopenia: 13% Anemia: 10%	[41]
CCRT +MIDLE	28	86	82	3-yr: 74%	3-yr: 82%	Neutropenia: 91% Thrombocytopenia: 13% Anemia: 9%	[42]
GELOX+RT	27	96	74	2-yr: 86%	2-yr: 86%	Leukopenia: 33% Thrombocytopenia: 30% Anemia: 7%	[43]
LVP+RT	26	89	81	2-yr: 81%	2-yr: 89%	Leukopenia: 8% Thrombocytopenia: 0% Anemia: 0%	[44]
Advanced stage, relapsed/refractory disease							

(continued)

Table 8.1 (continued)

	Number of patients	ORR (%)	CR (%)	PFS	OS	Grade 3/4 hematological toxicity	References
SMILE	38 87	80–84 (newly diagnosed) 77–93 (relapsed disease)	40–65 (newly diagnosed) 64–66% (relapsed disease)	4-yr DFS: 60 (newly diagnosed) 4-yr DFS: 68% (relapsed disease)	5-yr: 47% (newly diagnosed) 5-yr: 52% (relapsed disease)	Neutropenia: 67-100% Thrombocytopenia: 42–64% Anemia: 50%	[45, 46]
AspaMetDex	19	78	61	Median: 12.2 months	Median: 12.2 months	Neutropenia: 42% Thrombocytopenia: 5% Anemia: 21%	[49]
DDGP	21	95	71	1-yr: 86%	2-yr: 74%	Neutropenia: 71% Thrombocytopenia: 62% Anemia: 52%	[51]

Abbreviation: *ORR* overall response rate; *CR* complete response; *PFS* progression-free survival; *OS* overall survival; *DFS* disease-free survival

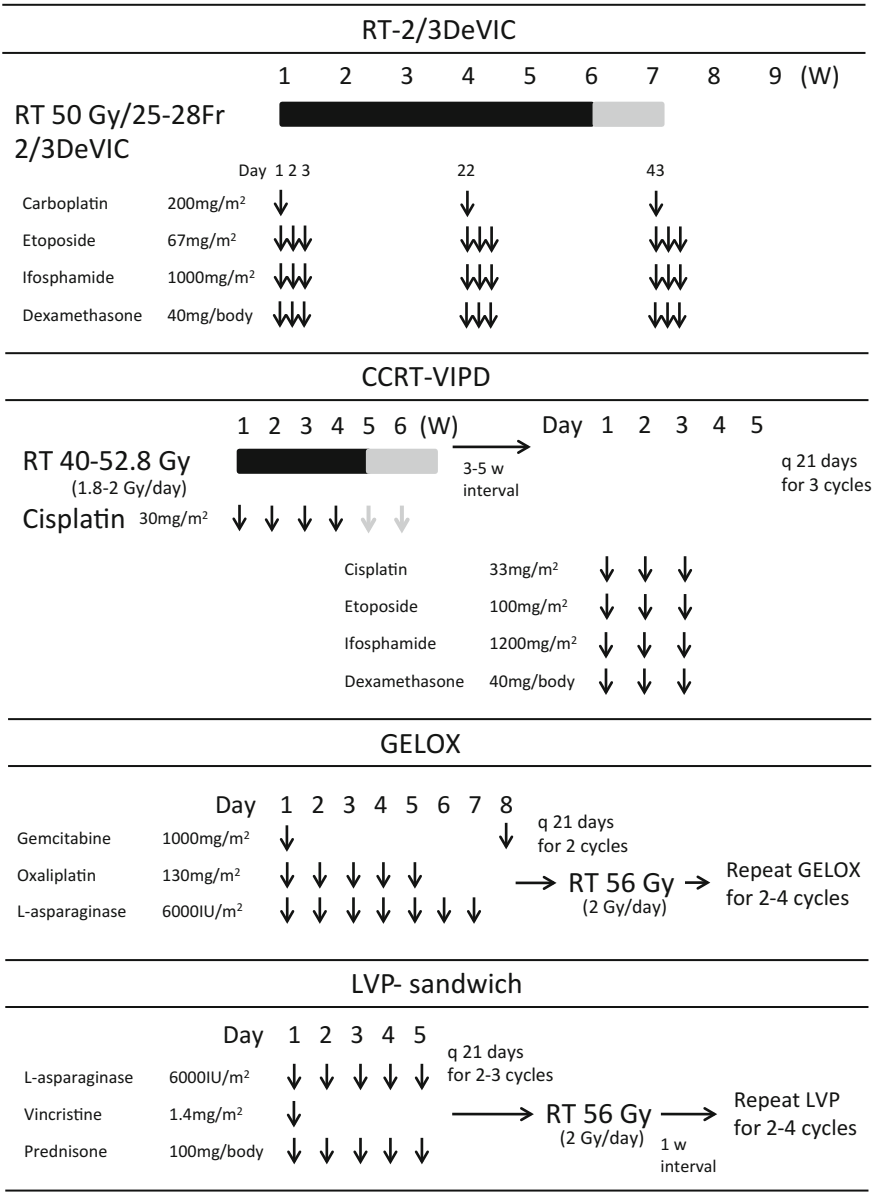

Fig. 8.1 Treatment schema for radiation containing regimens

weeks after completion of RT (Fig. 8.1). Thirty patients were enrolled in the study. ORR after initial concurrent chemoradiotherapy was 100% with CR rate of 73% (95%CI: 57–89%), and CR rate became 80% (95%CI: 66–94%) after three cycles of VIPD chemotherapy. Grade 3–4 hematological was observed in about 50% of

patients in VIPD chemotherapy phase, and non-hematological toxicities were uncommon. Although with short follow-up duration, estimated 3-year PFS and OS were 85% and 86%, respectively.

- ***RT–cisplatin followed by VIDL***

A similar approach with L-asparaginase containing regimen was tested also by Korean group [41]. L-asparaginase is an anti-metabolite agent which would not be affected by P-glycoprotein and has shown activity against NK neoplasm, as shown later in the part of advanced stage disease. First part of the treatment was similar, consisting of RT (40–44 Gy) and cisplatin. Then after RT, patients received etoposide, ifosfamide, cisplatin, dexamethasone, and L-asparaginase (VIDL). Thirty patients were enrolled in the study, and CR rate after concurrent chemoradiotherapy was 67% (95%CI: 47–83%). At the end of the entire regimen, CR rate increased to 87% (95%CI: 69–96%). The treatment was generally well tolerated, although with higher number of patients experienced, Grade 3–4 leukopenia compared to VIPD. With a median follow-up of 44 months, estimated 5-year PFS and OS were 60% and 73%, respectively.

- ***RT–cisplatin plus L-asparaginase followed by MIDLE***

In the more recent study, Korean group further upgraded the abovementioned concurrent chemoradiotherapy [42]. In this trial, L-asparaginase was added to cisplatin during concurrent chemoradiotherapy, and after RT, methotrexate, etoposide, Ifosfamide, dexamethasone, and L-asparaginase (MIDLE) were given every 28 days for two cycles. Twenty-eight patients were included in the study. CR rate after concurrent chemoradiotherapy was 57% (95%CI: 37–76%), and after MIDLE, CR rate increased to 82% (95%CI: 63–94%). This treatment approach, however, seems to be associated with more toxicity compared to former regimens and required delay, modification, or termination of treatment regimen (two during concurrent chemoradiotherapy and four during MIDLE) due to toxicity. During MIDLE, 91% of patients experienced Grade 3–4 neutropenia and 44% developed febrile neutropenia, and only 20 patients were able to complete two cycles of MIDLE. There was one treatment-related death due to pneumonia complicated by sepsis and acute kidney injury. With a median follow-up duration of 46 months, 3-year PFS and OS were 74% and 82%, respectively, which seems not too impressive compared to earlier studies from the same team.

- ***GELOX followed by IFRT***

Chinese group evaluated sequential chemotherapy followed by RT in patients with limited stage ENKL. Gemcitabine, oxaliplatin, and L-asparaginase (GELOX) were given every 21 days for at least 2 cycles followed by 56 Gy of RT [43]. One week after the completion of RT, GELOX was repeated for 2–4 cycles (Fig. 8.1).

Twenty-seven patients were included in the study; ORR and CR rates after first two cycles of GELOX were 93% and 56%, respectively. After RT, CR rate increases to 67% (95%CI: 46–83%). Toxicities were well tolerable with Grade 3–4 leukopenia and thrombocytopenia observed in 33% and 30%, respectively, and 11% of patients experienced a delay in chemotherapy for abnormal liver function test. With a median follow-up of 27 months, 2-year PFS and OS were both 86%.

- ***LVP-RT sandwich protocol***

Another Chinese group evaluated an RT "sandwich" treatment with two cycles of lead-in chemotherapy (L-asparaginase, vincristine, and prednisone: LVP) followed by RT (56 Gy) and two to four cycles of further consolidative LVP, starting 1 week after the completion of RT (Fig. 8.1) [44]. Twenty-six patients were enrolled, and all patients completed RT. ORR for whole treatment was 89% with CR rate of 81% (95%CI: 65–96%). Chemotherapy was very well tolerated without significant Grade 3–4 hematologic toxicity. Grade 3 mucositis occurred in 23% of patients during RT. With a median follow-up duration of 27 months, 2-year PFS and OS were 81 and 89%.

At this point, no randomized trials have been performed, comparing above concurrent chemoradiotherapy or sequential RT and thus, all treatments are considered as one of the standard treatments for limited stage ENKL. In addition, National Comprehensive Cancer Network (NCCN) clinical practice guideline suggests SMILE regimen followed by RT as a sequential chemoradiation option for limited stage ENKL. However, it should be noted that there has been no prospective study evaluating this treatment in localized stage ENKL and SMILE regimen is associated with high toxicity.

8.4.2 Advanced Stage, Relapsed/Refractory Disease

- ***SMILE***

Japanese NK-cell Tumor Study group evaluated chemotherapy consists of steroid (dexamethasone), methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) in patients with newly diagnosed stage IV and relapsed/refractory ENKL [45]. SMILE was repeated every 28 days, and two cycles were planned as the protocol treatment but additional cycles were allowed (Fig. 8.2). Granulocyte colony-stimulating factor (G-CSF) was mandatory from day 6 and discontinued when WBC count exceeded 5×10^9/L. The trial required good performance status, normal neutrophil count, normal platelet counts, adequate lymphocyte count, and normal liver and renal functions. Thirty-nine patients were enrolled, and 20 of them had newly diagnosed stage IV ENKL. Twenty-eight patients (74%) completed at least two cycles. ORR and CR rates were 80 and 40% (95%CI: 19–64%) in newly diagnosed patients. The response was also seen in patients with first recurrence,

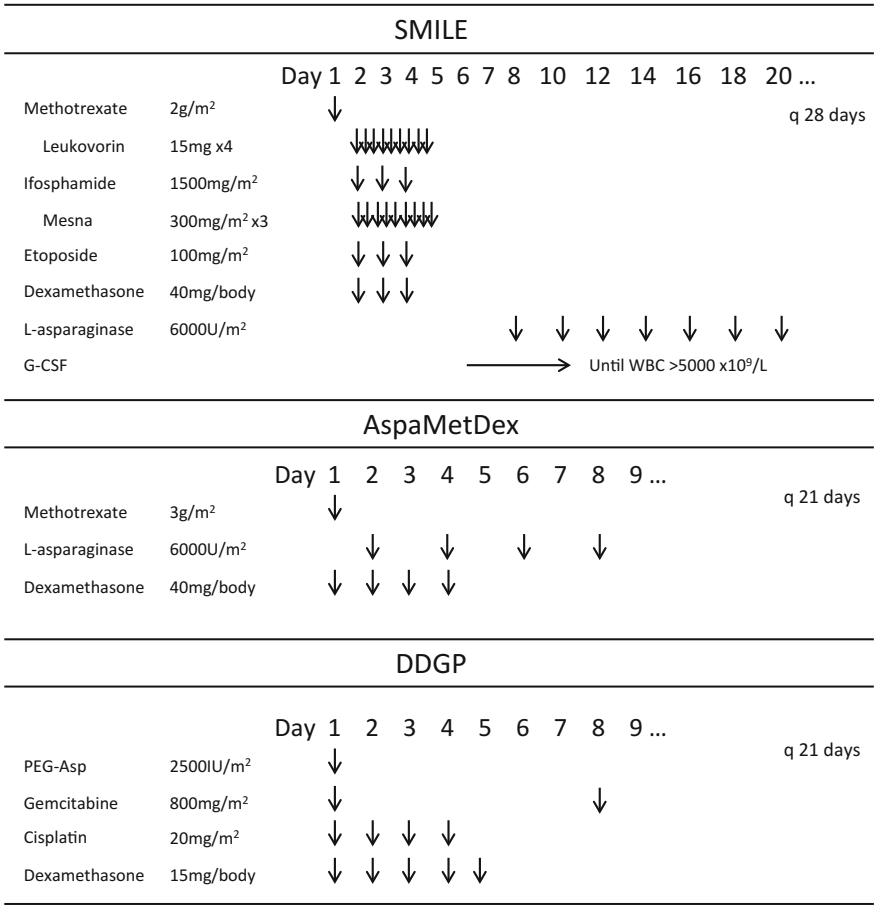

Fig. 8.2 Treatment schema for non-radiation containing regimens

with ORR 93% and CR rate 64% (95%CI: 35–87%). No CR was seen in patients who received SMILE in refractory disease. A total of 21 patients underwent stem cell transplant following the protocol treatment, including 4 patients for autologous (auto-SCT) and 17 for allogeneic stem cell transplant (allo-SCT). With a median follow-up of 24 months, 1-year PFS and OS rate for all patients were 53% (95%CI: 36–67%) and 55% (95%CI: 38–69%), respectively. There was no significant difference in survival outcome between patients who received auto-SCT and allo-SCT. SMILE was associated with 100% chance of Grade 3–4 neutropenia (92% Grade 4), despite mandatory growth factor use. Allergic reactions due to L-asparaginase of any grade were observed in five patients, and four patients discontinued L-asparaginase.

Multicenter study was conducted in Asia Lymphoma Study Group to validate efficacy of SMILE in patients with newly diagnosed advanced stage and relapsed/refractory ENKL with less stringent eligibility criteria [46]. Eighty-seven

patients were included in the study, and 43 patients had newly diagnosed advanced stage disease. Eighty-one patients (93%) received two or more cycles of SMILE, and the median number of cycles given was three (range: 0–6). Ten and 14 patients underwent allo-SCT and auto-SCT, respectively. ORR and CR rates were 84% and 65% (95%CI: 49–79%) in newly diagnosed patients, 77 and 66% (95%CI: 50–80%) in patients with relapsed/refractory disease. With a median follow-up duration of 31 months, 4-year disease-free survival and 5-year OS were 60% and 47% in newly diagnosed patients, 68% and 52% in relapsed/refractory patients. This study confirmed efficacy of SMILE in patients with ENKL, as well as significant toxicities. Grade 3–4 neutropenia occurred in 67% of patients despite with routine G-CSF administration and 31% patients developed life-threatening infection. Treatment-related death occurred in six patients (7%), five from infection and one from acute renal failure. Other significant toxicities included transaminitis (Grade 3–4: 7%), neurotoxicity, and allergic reaction (Grade 3–4: 1%) to L-asparaginase, making it difficult especially for elderly patients to complete treatment [47]. SMILE should be performed at well-trained advanced cancer center with an adequate supportive care planning [48].

- ***AspaMetDex***

French group studied a regimen named AspaMetDex (L-asparaginase, methotrexate, and dexamethasone) in patients with relapsed/refractory ENKL [49]. AspaMetDex was repeated every 21 days for three cycles (Fig. 8.2). After three cycles, patients with localized disease without prior radiation received RT. Responding patients received either auto-SCT or additional cycles of AspaMetDex up to total of six cycles. Nineteen patients were enrolled, 12 patients had limited stage disease, and eight patients had refractory disease to last treatment. ORR was 78% with CR rate of 61% (95%CI: 36–83%). Treatment was well tolerated; 42% and 16% of patients developed Grade 3–4 neutropenia and transaminitis (Grade 3–4: 16%), respectively. Five patients received auto-SCT after AspaMetDex. With a median follow-up duration of 26.2 months, both median PFS and OS were 12.2 months. During the treatment, 50% of patients developed anti-asparaginase antibody (four with anaphylactic reactions) and patients who developed antibody had significantly shorter survival than patients who did not.

- ***DDGP***

Recently, Chinese group evaluated a regimen consisting of peg-asparaginase, gemcitabine, cisplatin, and dexamethasone (DDGP). First, they retrospectively analyzed 17 patients with relapsed/refractory ENKL who received DDGP [50]. DDGP was repeated every 21 days for two to six cycles (Fig. 8.2). ORR was 88% with CR rate of 53% (95%CI: 28–77%). Treatment was well tolerated, Grade 3–4 neutropenia and infection occurred in 53% and 35%, respectively. With a median follow-up of 17 months, 1-year PFS and OS were 65% and 84%, respectively. No

patients underwent SCT after DDGP. Substantial number of patients relapsed around 1 year, and 2-year PFS was about 35%.

Then they evaluated DDGP in prospective trial in comparison to modified SMILE in patients with advanced stage ENKL [51]. Forty-two patients were enrolled and 21 patients each were randomly assigned to SMILE or DDGP. In this trial, they found significantly higher ORR and CR rates in DDGP (ORR 95% vs. 67%, P = 0.018 and CR rate 71% vs. 29%, P = 0.005), as well as significantly longer survival in DDGP (1-year PFS 86% vs. 38%, P = 0.006; 2-year OS 74% vs. 45%, P = 0.027) compared to SMILE. This study showed some value of DDGP regimen. However, caution is needed to interpret these results. First, this study used somewhat unusual staging system. This trial defined disease in paranasal sinus area with cervical lymph-node involvement as stage III disease and included in the study (14 in DDGP arm, 12 in SMILE arm). But, this extent of the disease is considered stage II by Ann Arbor staging definition, which is the universally applied system in essentially all studies mentioned above. Second, the study used modified SMILE regimen, in which L-asparaginase was given on days 3–9 (original every other day on day 8, 10, 12, 14, 16, 18, 20), and cycles were repeated every 21 days (original 28 days), which resulted in increased toxicity. In fact, two patients died in SMILE arm from methotrexate-related mucositis, which was uncommon in other reports of SMILE. Four patients (19%) did not complete a single cycle due to myelosuppression and mucositis; only 57% received four or more cycles in SMILE arm. In contrast, 95% of patients in the DDGP arm received four or more cycles. The ORR and CR rates reported for SMILE regimen are significantly lower compared to prior studies [52]. Third, the number of patients evaluated in this study is rather small as a randomized phase III study.

There is very limited data available for treatment of ANKL. Patients with ANKL commonly present with poor performance status and poor organ function. Toxic regimen such as SMILE is often not feasible. Dose-reduced SMILE or single-agent L-asparaginase could be considered for first-line treatment [53, 54].

8.4.3 Prognostic Factors

The most important prognostic factor upon diagnosis is clinical stage, which also defines treatment strategy [4, 5]. IPI for all aggressive lymphoma discriminates survival outcome of ENKL well; however, 70–80% of newly diagnosed patients are in low or low intermediate-risk group mainly due to predominantly localized disease, good PS, and relatively young age [4, 5, 28]. To develop better prognostic model specifically designed for ENKL, Korean group performed large retrospective analysis with 262 patients [5]. With a median follow-up of 51.2 months, 5-year OS was 49.5% in the entire cohort. Multivariate analysis revealed that the presence of B symptoms, advanced stage (stage III/IV), elevated LDH, and involvement of regional lymph nodes were independently associated with shorter survival. Using these four factors, new prognostic model was proposed for ENKL (Korean prognostic index: group 1, no adverse factors; group 2, one factor; group 3, two factors;

and group 4, three or four factors). This model separated patients well to four different groups compared to IPI (group 1, 27%; group 2, 31%; group 3, 20%; group 4, 22%), and discriminated survival well with 5-year OS for group 1–4 ranging from 81 to 7%.

Earlier retrospective studies from Japan and Korea included patients who received anthracycline-based treatment in the analysis [4, 5]. Given the development of newer approaches, including concurrent chemoradiotherapy and non-anthracycline-based chemotherapy, newer prognostic models became necessary. Recently, large multicenter retrospective analysis was conducted to better characterize patient outcomes who received non-anthracycline-based treatment. Thirty-eight hospitals in 11 countries mainly from Asia but including US and Europe contributed to the study [55]. Overall, 527 patients were included in training cohort, including 344 patients with limited stage disease and 183 patients with advanced stage disease. Among various non-anthracycline-based chemotherapies, 134 patients received SMILE, which was the most frequently used regimen. With a median follow-up of 44.9 months, 3-year PFS and OS were 48% (95%CI: 44–53%) and 59% (95%CI: 55–64%), respectively. Multivariate analysis showed that age greater than 60 years, advanced stage disease (stage III/IV), distant lymph-node involvement, non-nasal type disease, decreased platelet count, and low serum albumin level were independently associated with significantly shorter OS and PFS. Prognostic index for NK-cell lymphoma (PINK) was developed using four factors (age, stage, non-nasal type, and distant lymph-node involvement). Using PINK model, 3-year OS were 81% (95%CI: 75–86%), 62% (95%CI: 55–70%), and 25% (95%CI: 20–34%) in low-risk (no risk factors), intermediate-risk (one risk factor), or high-risk (two or more risk factors) groups, respectively. PINK model was validated in an independent cohort of 243 patients collected from different hospitals from Asia, confirming that the model discriminates survival well in patients with ENKL.

Japanese group conducted a multicenter study for patients with ENKL diagnosed between 2000 and 2013 [56]. Overall, 358 patients were analyzed, including 257 with localized disease and 101 with advanced stage disease. Among patients with localized disease, 169 patients received RT-2/3DeVIC. Five-year OS for localized and advanced ENKL were 68% and 24%, respectively. OS was better in patients with localized disease who were diagnosed between 2010 and 2013 than in those diagnosed between 2000 and 2010. They found that elevated soluble interleukin-2 receptor (sIL-2R) is significantly associated with shorter PFS and OS in patients who received RT-2/3DeVIC for localized disease.

Extensive research has been performed to evaluate the association between EBV-DNA viral load and survival outcome in patients with ENKL. EBV-DNA can be detected by polymerase chain reaction (PCR) using peripheral blood sample (plasma or whole blood), and the copy number is associated with tumor volume [57, 58]. Higher EBV-DNA titer in blood at the time of diagnosis was associated with higher clinical stage, the presence of B symptoms, poor PS, and higher sIL-2R level [28]. High EBV-DNA titer at the time of diagnosis is also associated with treatment resistance and frequent adverse reaction to treatment [27, 28], shorter OS

duration. In patients with detectable EBV-DNA and those without it, 3-year OS rates were 43% and 94%, respectively. Results for EBV-DNA from whole blood seem to be more sensitive compared to plasma [27], and the results from these two different samples should be interpreted accordingly. In patients who were enrolled in phase II study for SMILE, all patients with EBV-DNA of 10^5 copies/mL or more in whole blood died within 6 months, while patients who had EBV-DNA of less than 10^5 copies/mL had 2-year survival rate of approximately 70% [27]. The clinical significance of EBV-DNA was confirmed in other studies in different settings as well [55, 59]. As EBV-DNA reflects tumor load, monitoring EBV-DNA can be potentially useful as minimal residual disease analysis and detection of early relapse [60].

8.4.4 Stem Cell Transplant

In the era of CHOP-based therapy, up-front auto-SCT was often considered a treatment choice which resulted in 50–70% long-term survival [61–63]. A matched control study using Korean Prognostic index [5] concluded that auto-SCT provides survival benefit in patients who achieved CR (either CR1 or CR2) prior to auto-SCT and in patients with high-risk (group 3–4) disease [64], though 81% of patients in this study received anthracycline-based chemotherapy. In a more recent Korean retrospective study that analyzed 62 patients with newly diagnosed ENKL who underwent up-front auto-SCT between 2004 and 2013 [65], more than 80% of patients were initially treated with non-anthracycline-based chemotherapy, such as concurrent chemoradiotherapy (VIDL, VIPD) or SMILE. Median number of cycles of chemotherapy prior to auto-SCT was four (range: 3–8), and median time to auto-SCT from diagnosis was 6.6 months (range: 3.0–10.3 months). Pre-transplant and post-transplant CR rates were 61% and 78%, respectively. The number of patients achieving post-transplant CR was significantly higher in limited disease group compared to advanced disease group (90% vs. 66%, P = 0.020). With a median follow-up of 43.3 months, 3-year PFS and OS rates were 64.5% and 67.6%, respectively, in limited stage group (N = 31), and 40.1% and 52.3%, respectively, in the advanced disease group (N = 31). Although direct comparison is impossible, these survival outcomes by up-front auto-SCT seem not to be superior to concurrent chemoradiotherapy regimens such as RT+2/3DeVIC for limited stage disease and SMILE regimen for advanced stage disease raising question for value of up-front auto-SCT in current non-anthracycline chemotherapy era, and further studies are needed.

Allo-SCT has been also evaluated, mainly in more high-risk patients. Long-term survivals were reported even in stage 4 patients with 2-year PFS and OS ranging from 30 to 40% [66]. Tse and colleagues summarized outcome in 18 patients with ENKL who received allo-SCT [67]. Thirteen patients (72%) were in advanced stage, 78% of patients received SMILE prior to allo-SCT, and 89% of patients received allo-SCT in CR (CR1 50%, CR2 39%). With a median follow-up of 20.5 months, the 2-year PFS and OS were 51% and 57%, respectively. Patients

who received SMILE showed significantly higher OS rate compared to who received non-SMILE regimen prior to allo-SCT, and there was no significant difference in OS between patients who received allo-SCT in CR1 and CR2. Presently, there is no good evidence that allo-SCT provides survival benefit even in patients with advanced stage disease or relapsed disease who are receiving non-anthracycline chemotherapy, particularly SMILE. Therefore, up-front allo-SCT is not recommended as a standard therapy in ENKL unless in a prospective clinical trial.

Recently, Korean group reported outcome of 21 patients with ANKL who received L-asparaginase-based regimen (SMILE or VIDL) [68]. Three out of 13 patients who received SMILE and two out of five patients who received VIDL achieved CR and all of them (N = 5) underwent allo-SCT. Including two additional patients who responded to salvage chemotherapy, seven patients underwent allo-SCT. Patients who received allo-SCT had 2-year PFS and OS of around 65% which is remarkable considering very short median OS of less than 6 months in this disease. In contrast, Center for International Blood and Marrow Transplant Research (CIBMTR) reported relatively disappointing results in 21 patients with ANKL who received allo-SCT [69]. The 2-year non-relapse mortality, relapse, PFS, and OS were 21%, 59%, 20%, and 24%, respectively. Even in patients who achieved CR prior to allo-SCT, the 2-year PFS was only 30%. However, long-term remission is not expected in patients with ANKL without allo-SCT and therefore, allo-SCT should be considered in patients with ANKL in appropriate setting.

8.4.5 Novel Agents in Development

Autologous cytotoxic T lymphocytes (CTLs) targeting EBV-specific antigens such as LMP-1 or LMP-2 have been developed and are being investigated as a treatment of ENKL [70]. Generally, whole blood is obtained from patients, and lymphocytes are stimulated with EBV antigens and enriched for specific immune activity against LMP antigens. Bollard et al. reported the outcome of 50 patients with EBV-positive tumors including 11 patients with NK/T-cell lymphoma, who received CTLs [71]. Patients were eligible for the study if they had relapsed disease or were considered at high risk for relapse. Twenty-nine patients (5 NK/T-cell lymphoma) received CTLs in remission and 21 patients (6 NK/T-cell lymphoma) received CTLs for active disease. In patients who received CTLs in remission, 28 of 29 patients remain in remission at a median of 3.1 years after infusion. In patients who received CTLs for active disease, ORR was 62% with CR rate of 52% (95%CI: 30-74%). In five patients with NK/T-cell lymphoma who received CTLs for active disease, three patients achieved long-term remission over 4 years (2 no response, 1 relapse in 9 months). Currently, a phase II study is ongoing evaluating the efficacy of EBV targeted CTL specifically in ENKL (NCT01948180).

Programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors such as nivolumab and pembrolizumab have shown promising results in patients with Hodgkin lymphoma [72, 73]. Also in ENKL, though in a very small study,

promising results were reported in seven patients who received pembrolizumab after failing L-asparaginase-based chemotherapy [74]. Pembrolizumab was given every 3 weeks except for one patient who received every 2 weeks. All patients responded (5 CR, 2 PR) and two patients who achieved CR also achieved undetectable EBV-DNA. After median of seven (range: 2–13) cycles of pembrolizumab and a median follow-up of six (range: 2–10) months, all five CR patients still remained in remission. Adverse events were very minimal. This study was performed in a pilot fashion and reported based on retrospective analysis. PD-1/PD-L1 inhibition in ENKL should be evaluated in prospective trials. The results of ongoing studies of anti-PD1 antibody for PTCL, which can enroll patients with ENKL (NCT02535247 and NCT03021057), are of great interest.

CD38 is a transmembrane glycoprotein that is strongly expressed in plasma cells as well as NK-cells. Daratumumab, a human IgGκ CD38 antibody, was developed for a treatment of multiple myeloma, which generally has high CD38 expression [75]. While the expression of CD38 is not as impressive in lymphomas, the clinical activity of this antibody against lymphoma is interesting. Hari and colleagues used daratumumab for a patient with ENKL who experienced relapse after allo-SCT [76]. During the first 4 weeks of treatment, plasma EBV titers rapidly increased. However, it eventually decreased after 6 weeks of treatment, and the patient achieved CR with undetectable plasma EBV-DNA. Patient was still in remission at 21 weeks following daratumumab. The drug is expected to be evaluated in a prospective study in patients with ENKL (NCT02927925).

Since 2009, the US Food and Drug Administration (FDA) approved four drugs with novel mechanisms of action for the treatment of patients with recurrent PTCL, including pralatrexate in 2009, brentuximab vedotin (BV) for anaplastic large cell lymphoma in 2011, romidepsin in 2011, and belinostat in 2014. Unfortunately, these drugs have not shown specific activities against NK-cell tumors. In fact, romidepsin, a histone deacetylase inhibitor, was found to induce EBV reactivation and thus, the use of romidepsin in ENKL requires caution [77].

8.5 Future Directions

Thanks to the introduction of concurrent chemoradiation therapy and newer generation non-anthracycline-based combination chemotherapy regimens, the outcome of patients with ENKL seems to have improved over the last decade. The overall outcome, however, is still generally poor, and this is clearly a field of unmet need. Along with the clinical trials developing better induction regimens, future studies need to address the role of stem cell transplant (timing of transplant, conditioning regimens, and source of stem cells) based on risk stratification. Also for recurrent diseases, development of novel therapeutic approaches including, but not limited to, CTLs, PD-1/PD-L1 inhibitors, and CD38 antibody are critically important. Among such novel approaches, active targeted agents eventually should be incorporated in the frontline treatment.

8.6 Conclusion

NK-cell neoplasm is rare and is generally related to poor outcomes, despite the improvement in treatment approaches over the last decade such as chemoradiation therapy or non-anthracycline-based combination therapy. Enrollment of patients to clinical trials is critically important to develop better treatment strategies.

References

1. Swerdlow S, Campo E, Harris N, Jaffe E, Pileri S, Stein H et al (2008) In: Lyon F (ed) WHO classification of tumours of haematopoietic and lymphoid tissues, 4th edn. International Agency for Research on Cancer
2. Chihara D, Ito H, Matsuda T, Shibata A, Katsumi A, Nakamura S et al (2014) Differences in incidence and trends of haematological malignancies in Japan and the United States. Br J Haematol 164(4):536–545
3. Adams SV, Newcomb PA, Shustov AR (2016) Racial patterns of peripheral T-cell lymphoma incidence and survival in the United States. J Clin Oncol 34(9):963–971
4. Suzuki R, Suzumiya J, Yamaguchi M, Nakamura S, Kameoka J, Kojima H et al (2010) Prognostic factors for mature natural killer (NK) cell neoplasms: aggressive NK cell leukemia and extranodal NK cell lymphoma, nasal type. Ann Oncol 21(5):1032–1040
5. Lee J, Suh C, Park YH, Ko YH, Bang SM, Lee JH et al (2006) Extranodal natural killer T-cell lymphoma, nasal-type: a prognostic model from a retrospective multicenter study. J Clin Oncol 24(4):612–618
6. A predictive model for aggressive non-Hodgkin's lymphoma. The international non-Hodgkin's lymphoma prognostic factors project. N Engl J Med 329(14):987–994 (1993)
7. Au WY, Weisenburger DD, Intragumtornchai T, Nakamura S, Kim WS, Sng I et al (2009) Clinical differences between nasal and extranasal natural killer/T-cell lymphoma: a study of 136 cases from the International Peripheral T-Cell Lymphoma Project. Blood 113(17):3931–3937
8. Kim WS, Song SY, Ahn YC, Ko YH, Baek CH, Kim DY et al (2001) CHOP followed by involved field radiation: is it optimal for localized nasal natural killer/T-cell lymphoma? Ann Oncol 12(3):349–352
9. Song SY, Kim WS, Ko YH, Kim K, Lee MH, Park K (2002) Aggressive natural killer cell leukemia: clinical features and treatment outcome. Haematologica 87(12):1343–1345
10. Nakashima Y, Tagawa H, Suzuki R, Karnan S, Karube K, Ohshima K et al (2005) Genome-wide array-based comparative genomic hybridization of natural killer cell lymphoma/leukemia: different genomic alteration patterns of aggressive NK-cell leukemia and extranodal Nk/T-cell lymphoma, nasal type. Genes Chromosom Cancer 44(3):247–255
11. Lima M, Almeida J, Montero AG, Teixeira Mdos A, Queiros ML, Santos AH et al (2004) Clinicobiological, immunophenotypic, and molecular characteristics of monoclonal CD56∓ dim chronic natural killer cell large granular lymphocytosis. Am J Pathol 165(4):1117–1127
12. Rabbani GR, Phyliky RL, Tefferi A (1999) A long-term study of patients with chronic natural killer cell lymphocytosis. Br J Haematol 106(4):960–966
13. Oshimi K, Yamada O, Kaneko T, Nishinarita S, Iizuka Y, Urabe A et al (1993) Laboratory findings and clinical courses of 33 patients with granular lymphocyte-proliferative disorders. Leukemia 7(6):782–788
14. Huang Q, Chang KL, Gaal KK, Weiss LM (2005) An aggressive extranodal NK-cell lymphoma arising from indolent NK-cell lymphoproliferative disorder. Am J Surg Pathol 29 (11):1540–1543

15. Ohno Y, Amakawa R, Fukuhara S, Huang CR, Kamesaki H, Amano H et al (1989) Acute transformation of chronic large granular lymphocyte leukemia associated with additional chromosome abnormality. Cancer 64(1):63–67
16. Takeuchi K, Yokoyama M, Ishizawa S, Terui Y, Nomura K, Marutsuka K et al (2010) Lymphomatoid gastropathy: a distinct clinicopathologic entity of self-limited pseudomalignant NK-cell proliferation. Blood 116(25):5631–5637
17. Mansoor A, Pittaluga S, Beck PL, Wilson WH, Ferry JA, Jaffe ES (2011) NK-cell enteropathy: a benign NK-cell lymphoproliferative disease mimicking intestinal lymphoma: clinicopathologic features and follow-up in a unique case series. Blood 117(5):1447–1452
18. Emile JF, Boulland ML, Haioun C, Kanavaros P, Petrella T, Delfau-Larue MH et al (1996) CD5-CD56+ T-cell receptor silent peripheral T-cell lymphomas are natural killer cell lymphomas. Blood 87(4):1466–1473
19. Suzumiya J, Takeshita M, Kimura N, Kikuchi M, Uchida T, Hisano S et al (1994) Expression of adult and fetal natural killer cell markers in sinonasal lymphomas. Blood 83(8):2255–2260
20. Ohshima K, Suzumiya J, Shimazaki K, Kato A, Tanaka T, Kanda M et al (1997) Nasal T/NK cell lymphomas commonly express perforin and Fas ligand: important mediators of tissue damage. Histopathology 31(5):444–450
21. Mori N, Yatabe Y, Oka K, Kinoshita T, Kobayashi T, Ono T et al (1996) Expression of perforin in nasal lymphoma. Additional evidence of its natural killer cell derivation. Am J Pathol 149(2):699–705
22. Wong KF, Chan JK, Kwong YL (1997) Identification of del(6)(q21q25) as a recurring chromosomal abnormality in putative NK cell lymphoma/leukaemia. Br J Haematol 98 (4):922–926
23. Tien HF, Su IJ, Tang JL, Liu MC, Lee FY, Chen YC et al (1997) Clonal chromosomal abnormalities as direct evidence for clonality in nasal T/natural killer cell lymphomas. Br J Haematol 97(3):621–625
24. Karube K, Nakagawa M, Tsuzuki S, Takeuchi I, Honma K, Nakashima Y et al (2011) Identification of FOXO3 and PRDM1 as tumor-suppressor gene candidates in NK-cell neoplasms by genomic and functional analyses. Blood 118(12):3195–3204
25. Iqbal J, Kucuk C, Deleeuw RJ, Srivastava G, Tam W, Geng H et al (2009) Genomic analyses reveal global functional alterations that promote tumor growth and novel tumor suppressor genes in natural killer-cell malignancies. Leukemia 23(6):1139–1151
26. Suzuki R, Suzumiya J, Nakamura S, Aoki S, Notoya A, Ozaki S et al (2004) Aggressive natural killer-cell leukemia revisited: large granular lymphocyte leukemia of cytotoxic NK cells. Leukemia 18(4):763–770
27. Ito Y, Kimura H, Maeda Y, Hashimoto C, Ishida F, Izutsu K et al (2012) Pretreatment EBV-DNA copy number is predictive of response and toxicities to SMILE chemotherapy for extranodal NK/T-cell lymphoma, nasal type. Clin Cancer Res 18(15):4183–4190 An Official Journal of the American Association for Cancer Research
28. Suzuki R, Yamaguchi M, Izutsu K, Yamamoto G, Takada K, Harabuchi Y et al (2011) Prospective measurement of Epstein-Barr virus-DNA in plasma and peripheral blood mononuclear cells of extranodal NK/T-cell lymphoma, nasal type. Blood 118(23):6018–6022
29. Cai Q, Chen K, Young KH (2015) Epstein-Barr virus-positive T/NK-cell lymphoproliferative disorders. Exp Mol Med 47:e133
30. Trambas C, Wang Z, Cianfriglia M, Woods G (2001) Evidence that natural killer cells express mini P-glycoproteins but not classic 170 kDa P-glycoprotein. Br J Haematol 114(1):177–184
31. Egashira M, Kawamata N, Sugimoto K, Kaneko T, Oshimi K (1999) P-glycoprotein expression on normal and abnormally expanded natural killer cells and inhibition of P-glycoprotein function by cyclosporin A and its analogue, PSC833. Blood 93(2):599–606
32. Yamaguchi M, Kita K, Miwa H, Nishii K, Oka K, Ohno T et al (1995) Frequent expression of P-glycoprotein/MDR1 by nasal T-cell lymphoma cells. Cancer 76(11):2351–2356

33. Li YX, Yao B, Jin J, Wang WH, Liu YP, Song YW et al (2006) Radiotherapy as primary treatment for stage IE and IIE nasal natural killer/T-cell lymphoma. J Clin Oncol 24(1):181–189
34. You JY, Chi KH, Yang MH, Chen CC, Ho CH, Chau WK et al (2004) Radiation therapy versus chemotherapy as initial treatment for localized nasal natural killer (NK)/T-cell lymphoma: a single institute survey in Taiwan. Ann Oncol 15(4):618–625
35. Yang Y, Cao JZ, Lan SM, Wu JX, Wu T, Zhu SY et al (2017) Association of improved locoregional control with prolonged survival in early-stage extranodal nasal-type natural killer/T-cell lymphoma. JAMA Oncol 3(1):83–91
36. Kim GE, Cho JH, Yang WI, Chung EJ, Suh CO, Park KR et al (2000) Angiocentric lymphoma of the head and neck: patterns of systemic failure after radiation treatment. J Clin Oncol 18(1):54–63
37. Cheung MM, Chan JK, Lau WH, Foo W, Chan PT, Ng CS et al (1998) Primary non-Hodgkin's lymphoma of the nose and nasopharynx: clinical features, tumor immunophenotype, and treatment outcome in 113 patients. J Clin Oncol 16(1):70–77
38. Yamaguchi M, Tobinai K, Oguchi M, Ishizuka N, Kobayashi Y, Isobe Y et al (2009) Phase I/II study of concurrent chemoradiotherapy for localized nasal natural killer/T-cell lymphoma: Japan clinical oncology group study JCOG0211. J Clin Oncol 27(33):5594–5600
39. Yamaguchi M, Tobinai K, Oguchi M, Ishizuka N, Kobayashi Y, Isobe Y et al (2012) Concurrent chemoradiotherapy for localized nasal natural killer/T-cell lymphoma: an updated analysis of the Japan clinical oncology group study JCOG0211. J Clin Oncol 30(32):4044–4046
40. Kim SJ, Kim K, Kim BS, Kim CY, Suh C, Huh J et al (2009) Phase II trial of concurrent radiation and weekly cisplatin followed by VIPD chemotherapy in newly diagnosed, stage IE to IIE, nasal, extranodal NK/T-cell lymphoma: consortium for improving survival of lymphoma study. J Clin Oncol 27(35):6027–6032
41. Kim SJ, Yang DH, Kim JS, Kwak JY, Eom HS, Hong DS et al (2014) Concurrent chemoradiotherapy followed by L-asparaginase-containing chemotherapy, VIDL, for localized nasal extranodal NK/T cell lymphoma: CISL08-01 phase II study. Ann Hematol 93 (11):1895–1901
42. Yoon DH, Kim SJ, Jeong SH, Shin DY, Bae SH, Hong J et al (2016) Phase II trial of concurrent chemoradiotherapy with L-asparaginase and MIDLE chemotherapy for newly diagnosed stage I/II extranodal NK/T-cell lymphoma, nasal type (CISL-1008). Oncotarget 7 (51):85584–85591
43. Wang L, Wang ZH, Chen XQ, Li YJ, Wang KF, Xia YF et al (2013) First-line combination of gemcitabine, oxaliplatin, and L-asparaginase (GELOX) followed by involved-field radiation therapy for patients with stage IE/IIE extranodal natural killer/T-cell lymphoma. Cancer 119 (2):348–355
44. Jiang M, Zhang H, Jiang Y, Yang Q, Xie L, Liu W et al (2012) Phase 2 trial of "sandwich" L-asparaginase, vincristine, and prednisone chemotherapy with radiotherapy in newly diagnosed, stage IE to IIE, nasal type, extranodal natural killer/T-cell lymphoma. Cancer 118 (13):3294–3301
45. Yamaguchi M, Kwong YL, Kim WS, Maeda Y, Hashimoto C, Suh C et al (2011) Phase II study of SMILE chemotherapy for newly diagnosed stage IV, relapsed, or refractory extranodal natural killer (NK)/T-cell lymphoma, nasal type: the NK-Cell Tumor Study Group study. J Clin Oncol 29(33):4410–4416
46. Kwong YL, Kim WS, Lim ST, Kim SJ, Tang T, Tse E et al (2012) SMILE for natural killer/T-cell lymphoma: analysis of safety and efficacy from the Asia Lymphoma Study Group. Blood 120(15):2973–2980
47. Kim SM, Park S, Oh DR, Ahn YC, Ko YH, Kim SJ et al (2016) Extra-nodal natural killer/T cell lymphoma in elderly patients: the impact of aging on clinical outcomes and treatment tolerability. Ann Hematol 95(4):581–591

48. Chan A, Tang T, Ng T, Shih V, Tay K, Tao M et al (2012) To SMILE or not: supportive care matters. J Clin Oncol 30(9):1015–1016. Author reply 6–7
49. Jaccard A, Gachard N, Marin B, Rogez S, Audrain M, Suarez F et al (2011) Efficacy of L-asparaginase with methotrexate and dexamethasone (AspaMetDex regimen) in patients with refractory or relapsing extranodal NK/T-cell lymphoma, a phase 2 study. Blood 117 (6):1834–1839
50. Zhou Z, Li X, Chen C, Li X, Zhang L, Li L et al (2014) Effectiveness of gemcitabine, pegaspargase, cisplatin, and dexamethasone (DDGP) combination chemotherapy in the treatment of relapsed/refractory extranodal NK/T cell lymphoma: a retrospective study of 17 patients. Ann Hematol 93(11):1889–1894
51. Li X, Cui Y, Sun Z, Zhang L, Li L, Wang X et al (2016) DDGP versus SMILE in newly diagnosed advanced natural killer/T-cell lymphoma: a randomized controlled, multicenter, open-label study in China. Clin Cancer Res 22(21):5223–5228 An Official Journal of the American Association for Cancer Research
52. Gupta VG, Gogia A (2016) DDGP versus SMILE in NK/T-cell lymphoma-letter. Clin Cancer Res 22(16):4271 An Official Journal of the American Association for Cancer Research
53. Takahashi H, Sakai R, Hattori Y, Ohshima R, Kuwabara H, Hagihara M et al (2013) Successful disease control with L-asparaginase monotherapy for aggressive natural killer cell leukemia with severe hepatic failure. Leuk Lymphoma 54(3):662–664
54. Suzuki R (2010) Treatment of advanced extranodal NK/T cell lymphoma, nasal-type and aggressive NK-cell leukemia. Int J Hematol 92(5):697–701
55. Kim SJ, Yoon DH, Jaccard A, Chng WJ, Lim ST, Hong H et al (2016) A prognostic index for natural killer cell lymphoma after non-anthracycline-based treatment: a multicentre, retrospective analysis. Lancet Oncol 17(3):389–400
56. Yamaguchi M, Suzuki R, Oguchi M, Asano N, Amaki J, Akiba T et al (2017) Treatments and outcomes of patients with extranodal natural killer/T-cell lymphoma diagnosed between 2000 and 2013: a cooperative study in Japan. J Clin Oncol 35(1):32–39
57. Au WY, Pang A, Choy C, Chim CS, Kwong YL (2004) Quantification of circulating Epstein-Barr virus (EBV) DNA in the diagnosis and monitoring of natural killer cell and EBV-positive lymphomas in immunocompetent patients. Blood 104(1):243–249
58. Lei KI, Chan LY, Chan WY, Johnson PJ, Lo YM (2002) Diagnostic and prognostic implications of circulating cell-free Epstein-Barr virus DNA in natural killer/T-cell lymphoma. Clin Cancer Res 8(1):29–34 An Official Journal of the American Association for Cancer Research
59. Wang ZY, Liu QF, Wang H, Jin J, Wang WH, Wang SL et al (2012) Clinical implications of plasma Epstein-Barr virus DNA in early-stage extranodal nasal-type NK/T-cell lymphoma patients receiving primary radiotherapy. Blood 120(10):2003–2010
60. Wang L, Wang H, Wang JH, Xia ZJ, Lu Y, Huang HQ et al (2015) Post-treatment plasma EBV-DNA positivity predicts early relapse and poor prognosis for patients with extranodal NK/T cell lymphoma in the era of asparaginase. Oncotarget 6(30):30317–30326
61. Suzuki R, Suzumiya J, Nakamura S, Kagami Y, Kameoka JI, Sakai C et al (2006) Hematopoietic stem cell transplantation for natural killer-cell lineage neoplasms. Bone Marrow Transpl 37(4):425–431
62. Kim HJ, Bang SM, Lee J, Kwon HC, Suh C, Kim HJ et al (2006) High-dose chemotherapy with autologous stem cell transplantation in extranodal NK/T-cell lymphoma: a retrospective comparison with non-transplantation cases. Bone Marrow Transpl 37(9):819–824
63. Au WY, Lie AK, Liang R, Kwong YL, Yau CC, Cheung MM et al (2003) Autologous stem cell transplantation for nasal NK/T-cell lymphoma: a progress report on its value. Ann Oncol 14(11):1673–1676
64. Lee J, Au WY, Park MJ, Suzumiya J, Nakamura S, Kameoka J et al (2008) Autologous hematopoietic stem cell transplantation in extranodal natural killer/T cell lymphoma: a multinational, multicenter, matched controlled study. Biol Blood Marrow Transpl 14 (12):1356–1364

65. Yhim HY, Kim JS, Mun YC, Moon JH, Chae YS, Park Y et al (2015) Clinical outcomes and prognostic factors of up-front autologous stem cell transplantation in patients with extranodal natural killer/T cell lymphoma. Biol Blood Marrow Transpl 21(9):1597–1604
66. Murashige N, Kami M, Kishi Y, Kim SW, Takeuchi M, Matsue K et al (2005) Allogeneic haematopoietic stem cell transplantation as a promising treatment for natural killer-cell neoplasms. Br J Haematol 130(4):561–567
67. Tse E, Chan TS, Koh LP, Chng WJ, Kim WS, Tang T et al (2014) Allogeneic haematopoietic SCT for natural killer/T-cell lymphoma: a multicentre analysis from the Asia Lymphoma Study Group. Bone Marrow Transpl 49(7):902–906
68. Jung KS, Cho SH, Kim SJ, Ko YH, Kang ES, Kim WS (2016) L-asparaginase-based regimens followed by allogeneic hematopoietic stem cell transplantation improve outcomes in aggressive natural killer cell leukemia. J Hematol Oncol 9:41
69. Hamadani M, Kanate AS, DiGilio A, Ahn KW, Smith SM, Lee JW et al (2017) Allogeneic hematopoietic cell transplantation for aggressive NK cell leukemia. Biol Blood Marrow Transpl. A Center for International Blood and Marrow Transplant Research Analysis
70. Gottschalk S, Edwards OL, Sili U, Huls MH, Goltsova T, Davis AR et al (2003) Generating CTLs against the subdominant Epstein-Barr virus LMP1 antigen for the adoptive immunotherapy of EBV-associated malignancies. Blood 101(5):1905–1912
71. Bollard CM, Gottschalk S, Torrano V, Diouf O, Ku S, Hazrat Y et al (2014) Sustained complete responses in patients with lymphoma receiving autologous cytotoxic T lymphocytes targeting Epstein-Barr virus latent membrane proteins. J Clin Oncol 32(8):798–808
72. Armand P, Shipp MA, Ribrag V, Michot JM, Zinzani PL, Kuruvilla J et al (2016) Programmed death-1 blockade with pembrolizumab in patients with classical Hodgkin lymphoma after brentuximab vedotin failure. J Clin Oncol
73. Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M et al (2015) PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med 372 (4):311–319
74. Kwong YL, Chan TS, Tan D, Kim SJ, Poon LM, Mow B et al (2017) PD1 blockade with pembrolizumab is highly effective in relapsed or refractory NK/T-cell lymphoma failing L-asparaginase. Blood
75. Lonial S, Weiss BM, Usmani SZ, Singhal S, Chari A, Bahlis NJ et al (2016) Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. Lancet 387(10027):1551–1560
76. Hari P, Raj RV, Olteanu H (2016) Targeting CD38 in refractory extranodal natural killer cell-T-cell lymphoma. N Engl J Med 375(15):1501–1502
77. Kim SJ, Kim JH, Ki CS, Ko YH, Kim JS, Kim WS (2016) Epstein-Barr virus reactivation in extranodal natural killer/T-cell lymphoma patients: a previously unrecognized serious adverse event in a pilot study with romidepsin. Ann Oncol 27(3):508–513

Hepatosplenic T-Cell Lymphomas

9

Lohith Gowda and Francine Foss

Abstract

Hepatosplenic T-cell lymphoma (HSTL) is a rare variant of extranodal peripheral T-cell lymphomas (PTCL), associated with aggressive disease course and a relentless track record for lethal outcomes. HSTL presents commonly in young men in their third or fourth decade. Of the known causes, immune dysregulation and immunosuppression are the key players in the pathogenesis of HSTL. Clinical manifestation includes hepatosplenomegaly, fevers, and weakness. Bone marrow involvement or organomegaly can cause cytopenias. Anthracycline-based regimens provide modest responses with most individuals dying within a year of diagnosis. Hematopoietic stem cell transplant (HSCT) can be offered to fit and eligible patients to prolong remissions. Disease relapse post chemotherapy has an aggressive phenotype, with limited salvage options available in the setting of declining performance status. Understanding the disease biology further to identify mechanistic-driven drug discovery could overcome the current limitations of existing therapeutic armamentarium.

Keywords

Hepatosplenic T-cell lymphoma · Immunosuppression · Stem cell transplantation · Genomic landscape

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9.1 Introduction

The origins of HSTL reported in the medical literature can be traced back to a publication in 1981 [1]. Based on the geographic distribution of clonal T-cells, the term HSTL was first coined in 1990 [2]. Subsequently, many small case series emerged supporting the existence of HSTL as a very distinct but rare entity. However, up until 2008 lack of standardized reporting for T-cell lymphomas hindered the recognition of many different subgroups of mature PTCL, including the HSTL variant. Subsequently, two pivotal publications, World Health Organization (WHO) classification of tumors of lymphoid tissue and International peripheral T-cell and Natural Killer (NK) T-cell study, demonstrated the necessity of an improved diagnostic system for PTCL that could be applied to clinical trials [3]. As a measure of real-world problem, collective reporting from International T-cell consortium led to better understanding of the prevalence of different subtypes (nodal and extranodal) of PTCL (Fig. 9.1). From this study, HSTL was recognized as a rare (<2% of T/natural killer-NK-cell) entity that originated from cytotoxic T-cells, usually of γ/δ T-cell receptor (TCR) subtype. Despite its rarity, HSTL attracts significant medical attention owing to poor clinical outcomes with existing drugs.

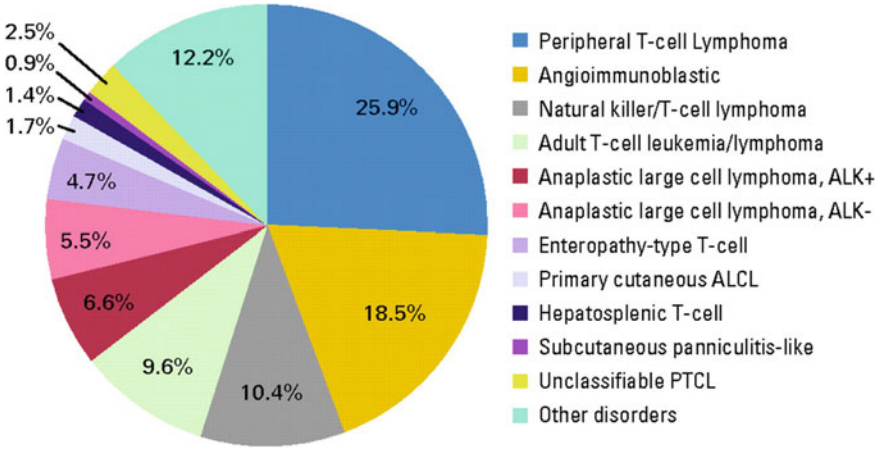

Fig. 9.1 Incidence of T-cell lymphoma subtypes based on international T-cell lymphoma project (J. Clin Oncol. 26: 4124–30, 2008)

9.2 Pathology and Pathogenesis

Mature T-lymphocytes based on the TCR expression on its surface can be broadly classified into two distinct subtypes: alpha/beta (αβ) and gamma/delta (γ/δ) T-cell variants. In a normal adult, αβ subtype is the commonest variant in the peripheral blood (PB) T-cells. The predominance of αβ T-cells is not restricted to PB and is also seen in the visceral organs with significant lymphoid reserves (skin, liver, thymus, gastrointestinal tract, lymph nodes, and spleen). In contrast, the population of γ/δ T-cells in PB and most lymphoid organs is smaller. With the exception of spleen wherein, up to 15% of mature T-cells could be comprised of the γ/δ variant, in most other lymphoid structures the prevalence of (γ/δ) T-cell is in the range of 1–4% [4]. Geographically within the spleen, γ/δ T-cells have an affinity for the sinusoids in the red pulp and αβ T-cells favor the periarteriolar zone [5, 6]. A similar anatomic preference is also seen in intestines, with γ/δ T-cells homing into epithelial layers and αβ T-cells preferring the lamina propria zone [5, 7]. Based on the variable gene rearrangements two broad subgroups of γ/δ T-cells—Vδ1 and Vδ2 exists. In an healthy individual, there is a higher representation of Vδ2 γ/δ T-cells in PB, while Vδ1 numerically supersede Vδ2 subtype at other sites [8].

Understanding the exact role of γ/δ T-cells in innate immunity is a work in progress [9]. They can develop from the CD4-/CD8-(double negative) precursors outside the thymus. On antigenic stimulus, γ/δ T-cells can act as the first line of defense prior to αβ T-cell recruitment and exert cytotoxicity with the release of lymphokines (perforins, granzyme B, and TIA-1) or lead to apoptosis with the activation of Fas/Fas ligand pathway [10]. Apart from the above cytolytic functions, the recent demonstration of a cross talk with dendritic cells has also conferred an immunosurveillance (antibody independent and non-MHC restricted) functionality akin to NK-cells for γ/δ T-cells [11]. Interestingly, TCR on γ/δ T-cells has less discriminate antigen specificity despite its ability to recognize multiple pathogens. This phenomenon contributes to the clonal evolution of HSTL, where an initial polyclonal expansion of the T-cells could be diverted to a monoclonal process by transforming events (cytogenetic evolution or mutational changes) that then heralds disease onset [12].

Morphologic review of peripheral blood or affected tissue from patients with HSTL shows clusters of monomorphic medium-sized T-cells with a loose rim of condensed chromatin, inconspicuous nucleoli and a pale cytoplasm with the indistinct cell membrane (Fig. 9.2). Hepatosplenic sinusoids are packed with clonal cells, but usually, there is sparing of hepatocytes and portal triad. On immunohistochemistry CD2+, CD3+, CD4−, CD5−, CD7+, CD8−, and either γ/δ or α/β expressing T-cell phenotype is seen. Occasional CD8+ has been observed. Majority of HSTL cases are γ/δ variant (50–85%), with rare reports suggesting origination from α/β TCR subtype [5]. TCR sequencing of clonal HSTL cells usually demonstrate restriction to Vδ1, and Vδ1 associates with different Vγ regions [13]. On flow cytometry, γ/δ phenotype can be elucidated with a characteristic absence

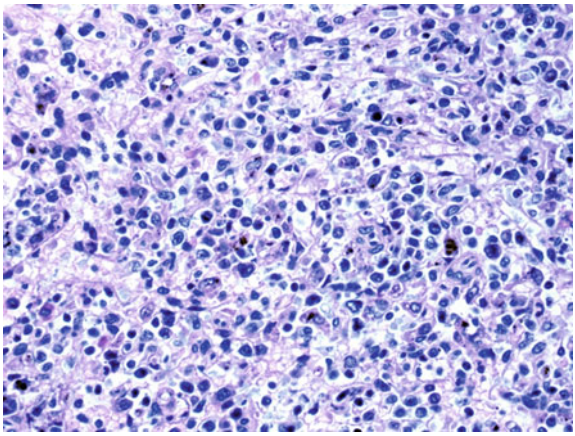

Fig. 9.2 Splenic red pulp infiltration by atypical lymphocytes in hepatosplenic T-cell lymphoma (H&E Stain)

of β F-1 staining, directed against the β-chain of αβ T-cells [14]. Trisomy 8 and isochromosome 7q are the common cytogenetic abnormalities identified with this disease entity [13]. Gene expression profiling of PTCL cases has shown overexpression of NK markers like killer immunoglobulin receptors (KIR) and killer lectin-like receptors, CD 16, CD 56, and NKG2F in γ/δ PTCL compared to α/β PTCL [15]. Oncogenes (FOS, VA3), cell trafficking-sphingosine phosphatase receptor-5 and growth and survival gene syk are overexpressed, while tumor suppressor gene AIM1 is downregulated in comparison with PTCL NOS [16]. On whole exome sequencing mutations of chromatin modifier genes like SETD2, INO80 and ARID 1B (62%) as well as STAT3–9%, STAT5B–31% and PIK3CD (9%) are documented [17, 18].

9.3 Risk Factors

Majority (around 70%) of the cases of HSTL are thought be de novo in origin with no well-defined risk factors. Individuals with autoimmune disorders (Sjogren's, lupus), infections (malaria) and those on prolonged immunosuppression (10–20% of cases) for solid organ transplantation have reported a higher incidence of HSTCL [19]. Epstein Barr virus (EBV)-associated oncoprotein expression on NK-cell lymphomas is characteristic, while the evidence for EBER-driven oncogenesis in HSTCL is limited [20, 21]. Prior therapy with biologic agents (monoclonal antibodies-infliximab for>2 years) and thiopurines for treatment of inflammatory bowel disease has a strong association with the development of HSTL. Combination of thiopurines with infliximab poses a higher risk, compared to monotherapy with either of these agents [13]. Collectively, this lends credence to the hypothesis of chronic antigenic stimulation or immune dysregulation predisposes individuals to develop HSTCL.

9.4 Clinical Features

In early 1990, Farcet al first described two cases of HSTL as a separate entity from other PTCL in young adults (23 years and 36 years) [2]. Hepatosplenomegaly and thrombocytopenia were the salient clinical manifestation with splenectomy resulting in improved blood counts. Eventually, disease recurred in liver and bone marrow. Anthracycline-based chemotherapy ± autologous HSCT was used to treat these cases. Unfortunately, one died at 24 months and the other at 42 months from the time of diagnosis. Examination of their spleen showed infiltration of red pulp by lymphocytes and atrophy of the white pulp. Monoclonal antibody studies led to the recognition of TCR-γ/δ expression on the tumor sample and paved way for identification of γ/δ-HSTL as a clonal process. After this initial recognition of a distinct γ/δ cytotoxic T-cell variant, multiple other case series subsequently were reported by utilizing novel diagnostics to study TCR region [22]. The median age appears to be in the mid-30s (range 8 months–68 years) with a slightly higher predilection for men [23]. Most series describe extranodal involvement with liver and spleen being the commonest target. Bone marrow involvement can be seen in up to two-thirds of the cases. Skin involvement although rare has been reported [24, 25]. Up to one-third of the cases can have lymphadenopathy. Cytokine mediate fever, fatigue, falling blood counts, and frailty are frequently seen and are a common cause of morbidity. Abnormalities in liver enzymes and increase in lactate dehydrogenase can coexist. Very rarely anemia due to autoimmune hemolysis or erythrophagocytosis may develop. Disease progression has been detected with extra copies of the long arm of chromosome 7q [26]. Of the many variables, elevated bilirubin, αβ TCR expression, and Trisomy 8 have prognostic significance [27].

9.5 Treatment

Lack of prospective trials in HSTL has led to a clinical practice that is driven by case series and no accepted single standard of care. In the management of thrombocytopenia, splenectomy is often an inadequate strategy [28]. In addition, complications of splenectomy (infections, thrombosis, etc.:) can be ill-afforded for many patients in the natural course of their disease [29]. Like B-cell lymphomas, anthracycline-based CHOP (Cyclophosphamide, doxorubicin, vincristine, prednisone) has been the backbone of multiagent chemotherapy over the past few decades [22, 30–32]. Considering only 30–50% reach CR, alternative to CHOP has been explored with purine analogs (fludarabine, cladribine, pentostatin), anti-CD 52 antibody (alemtuzumab) either alone or in combination [33–35]. Treatment intensification with DSHAP/AMDBIDCOS/MINE/HCVAD, either upfront or as sequential therapy has also been an alternative strategy [32, 36]. Unfortunately, with these strategies, the overall outcomes have not increased significantly. Hence, induction followed by early consolidation with HSCT has been a common practice.

To date three large centers have reported outcomes with HSCT at their institutes. Belhadj et al. in a 21-patient series reported CHOP (90%) or platinum/cytarabine (10%)-based induction led to complete remission (CR) in 43%, partial response (PR) in 24% and induction failure in 33%. 9 (3-allo and 6-auto) of 21 patients went ahead with HSCT, with 3 allo-HSCT (2-due to toxicity, 1 due to progression) and 4 auto-HSCT recipients' dead at the time of reporting. With the 2 (9.5%) survivors, the median survival in this series was 16 months [22]. In another report investigators from MD Anderson Cancer Center (MDACC) (n-14) suggest induction followed by high dose chemotherapy (auto or allograft) can offer prolonged remission [32]. In this study, 50% of patients achieved CR (median duration of 8 months) after receiving various induction regimens. People who achieved CR had a better prognosis compared to those who did not (median OS 13 vs. 7.5 months). The median survival was 11 months (2–36 months) with transplant recipients being the long-term survivors. A similar observation was reported from Memorial Sloan Kettering Cancer Center (MSKCC) (n-15). In the MSKCC study, non-CHOP induction (Ifosfamide Carboplatin and Etoposide-ICE or Ifosfamide, Cytarabine, Methotrexate, Etoposide-IVAC) induction appeared to confer better disease control compared to CHOP. The median OS was 65.6 months with a transplant-based consolidation (auto and allo) approach [31]. Apart from single-institution studies, transplant registry data from Europe also favors allografting as the preferred consolidation strategy with 3 year PFS of 48% [37]. Finally, in a recent systematic review allo-HSCT demonstrated potent graft versus leukemia impact even in the absence of CR, with an estimated 3-year relapse-free survival (RFS) and OS of 42 and 56% for the whole cohort [38]. However, transplant-related morbidity and mortality could be substantial and hence appropriate patient selection is critical. In addition, post-transplant relapses are generally associated with poor prognosis (median survival 4 months) despite immunosuppression withdrawal and cytotoxic therapy [18]. Hence, mechanistic-based targeted agents are highly desired to further improve outcomes.

9.6 Potential Future Therapeutic Interventions

Genomic analysis of HSTL samples has shown methylation changes in tumor suppressor genes, associated with poor disease outcomes [39]. With many FDA approved hypomethylating agents currently available in clinical practice for other indications, their utility in HSTL needs further investigation. Recent recognition of *syk* expression in HSTL provides a rationale to test *syk* inhibitors in clinical trials [16]. In whole, exome sequencing data has also identified members of the JAK-STAT pathway (STAT3 and STAT 5b) to be relevant in T-cell signaling and survival in HSTL patients. This has led to a search for a suitable STAT inhibitor (pimozide) which can be tested in future clinical trials [40].

9.7 Conclusions

HSTCL is an aggressive subtype of PTCL with a high fatality rate. Immune dysregulation has been identified to be a key driver of oncogenesis. Cytotoxic therapy can help control disease with approximately half of the affected patients attaining a CR that needs further consolidation with HSCT. Without transplantation, existing therapeutic options have demonstrated a limited long-term survival advantage. Hence, a better understanding of disease biology is essential to make progress in the treatment of this disease. Application of genomics has offered an excellent platform to target mutations for which drugs are commercially available or is currently screened for. Broader multi-institutional collaboration is needed to intensify efforts in dealing with this rare but unfavorable disease.

References

1. Kadin ME, Kamoun M, Lamberg J (1981) Erythrophagocytic T gamma lymphoma: a clinicopathologic entity resembling malignant histiocytosis. N Engl J Med 304:648–653
2. Farcet JP, Gaulard P, Marolleau JP et al (1990) Hepatosplenic T-cell lymphoma: sinusal/sinusoidal localization of malignant cells expressing the T-cell receptor gamma delta. Blood 75:2213–2219
3. Vose J, Armitage J, Weisenburger D (2008) International TCLP. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol 26:4124–4130
4. Cooke CB, Krenacs L, Stetler-Stevenson M et al (1996) Hepatosplenic T-cell lymphoma: a distinct clinicopathologic entity of cytotoxic gamma delta T-cell origin. Blood 88:4265–4274
5. Bucy RP, Chen CL, Cooper MD (1989) Tissue localization and CD8 accessory molecule expression of T gamma delta cells in humans. J Immunol 142:3045–3049
6. Gaulard P, Bourquelot P, Kanavaros P et al (1990) Expression of the alpha/beta and gamma/delta T-cell receptors in 57 cases of peripheral T-cell lymphomas. Identification of a subset of gamma/delta T-cell lymphomas. Am J Pathol 137:617–628
7. Picker LJ, Brenner MB, Michie S, Warnke RA (1988) Expression of T cell receptor delta chains in benign and malignant T lineage lymphoproliferations. Am J Pathol 132:401–405
8. Moser B, Eberl M (2007) Gammadelta T cells: novel initiators of adaptive immunity. Immunol Rev 215:89–102
9. Adams EJ, Gu S, Luoma AM (2015) Human gamma delta T cells: evolution and ligand recognition. Cell Immunol 296:31–40
10. Koizumi H, Liu CC, Zheng LM et al (1991) Expression of perforin and serine esterases by human gamma/delta T cells. J Exp Med 173:499–502
11. He Y, Wu K, Hu Y et al (2014) Gammadelta T cell and other immune cells crosstalk in cellular immunity. J Immunol Res 2014:960252
12. Tripodo C, Iannitto E, Florena AM et al (2009) Gamma-delta T-cell lymphomas. Nat Rev Clin Oncol 6:707–717
13. Kotlyar DS, Osterman MT, Diamond RH et al (2011) A systematic review of factors that contribute to hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 9(36–41):e31
14. Gaulard P, Belhadj K, Reyes F (2003) Gammadelta T-cell lymphomas. Semin Hematol 40:233–243
15. Miyazaki K, Yamaguchi M, Imai H et al (2009) Gene expression profiling of peripheral T-cell lymphoma including gammadelta T-cell lymphoma. Blood 113:1071–1074

16. Travert M, Huang Y, de Leval L et al (2012) Molecular features of hepatosplenic T-cell lymphoma unravels potential novel therapeutic targets. Blood 119:5795–5806
17. Nicolae A, Xi L, Pittaluga S et al (2014) Frequent STAT5B mutations in gammadelta hepatosplenic T-cell lymphomas. Leukemia 28:2244–2248
18. McKinney M, Moffitt AB, Gaulard P et al (2017) The genetic basis of hepatosplenic T-cell lymphoma. Cancer Discov 7:369–379
19. Ross CW, Schnitzer B, Sheldon S, Braun DK, Hanson CA (1994) Gamma/delta T-cell posttransplantation lymphoproliferative disorder primarily in the spleen. Am J Clin Pathol 102:310–315
20. Kanavaros P, Lescs MC, Briere J et al (1993) Nasal T-cell lymphoma: a clinicopathologic entity associated with peculiar phenotype and with Epstein-Barr virus. Blood 81:2688–2695
21. Ohshima K, Haraoka S, Harada N et al (2000) Hepatosplenic gammadelta T-cell lymphoma: relation to Epstein-Barr virus and activated cytotoxic molecules. Histopathology 36:127–135
22. Belhadj K, Reyes F, Farcet JP et al (2003) Hepatosplenic gammadelta T-cell lymphoma is a rare clinicopathologic entity with poor outcome: report on a series of 21 patients. Blood 102:4261–4269
23. Weidmann E (2000) Hepatosplenic T cell lymphoma. A review on 45 cases since the first report describing the disease as a distinct lymphoma entity in 1990. Leukemia 14:991–997
24. Berti E, Cerri A, Cavicchini S et al (1991) Primary cutaneous gamma/delta T-cell lymphoma presenting as disseminated pagetoid reticulosis. J Invest Dermatol 96:718–723
25. Ralfkiaer E, Wollf-Sneedorff A, Thomsen K, Geisler C, Vejlsgaard GL (1992) T-cell receptor gamma delta-positive peripheral T-cell lymphomas presenting in the skin: a clinical, histological and immunophenotypic study. Exp Dermatol 1:31–36
26. Wlodarska I, Martin-Garcia N, Achten R et al (2002) Fluorescence in situ hybridization study of chromosome 7 aberrations in hepatosplenic T-cell lymphoma: isochromosome 7q as a common abnormality accumulating in forms with features of cytologic progression. Genes Chromosom Cancer 33:243–251
27. Yabe M, Medeiros LJ, Tang G et al (2016) Prognostic factors of hepatosplenic T-cell lymphoma: clinicopathologic study of 28 cases. Am J Surg Pathol 40:676–688
28. Gumbs AA, Zain J, Neylon E, MacGregor-Cortelli B, Patterson M, O'Connor OA (2009) Importance of early splenectomy in patients with hepatosplenic T-cell lymphoma and severe thrombocytopenia. Ann Surg Oncol 16:2014–2017
29. Weledji EP (2014) Benefits and risks of splenectomy. Int J Surg 12:113–119
30. Takamatsu Y, Suzumiya J, Utsunomiya A et al (2010) THP-COP regimen for the treatment of peripheral T-cell lymphoma and adult T-cell leukemia/lymphoma: a multicenter phase II study. Eur J Haematol 84:391–397
31. Voss MH, Lunning MA, Maragulia JC et al (2013) Intensive induction chemotherapy followed by early high-dose therapy and hematopoietic stem cell transplantation results in improved outcome for patients with hepatosplenic T-cell lymphoma: a single institution experience. Clin Lymphoma Myeloma Leuk 13:8–14
32. Falchook GS, Vega F, Dang NH et al (2009) Hepatosplenic gamma-delta T-cell lymphoma: clinicopathological features and treatment. Ann Oncol 20:1080–1085
33. Jaeger G, Bauer F, Brezinschek R, Beham-Schmid C, Mannhalter C, Neumeister P (2008) Hepatosplenic gammadelta T-cell lymphoma successfully treated with a combination of alemtuzumab and cladribine. Ann Oncol 19:1025–1026
34. Mittal S, Milner BJ, Johnston PW, Culligan DJ (2006) A case of hepatosplenic gamma-delta T-cell lymphoma with a transient response to fludarabine and alemtuzumab. Eur J Haematol 76:531–534
35. Moleti ML, Testi AM, Giona F et al (2006) Gamma-delta hepatosplenic T-cell lymphoma. Description of a case with immunophenotypic and molecular follow-up successfully treated with chemotherapy alone. Leuk Lymphoma 47:333–336
36. Tey SK, Marlton PV, Hawley CM, Norris D, Gill DS (2008) Post-transplant hepatosplenic T-cell lymphoma successfully treated with HyperCVAD regimen. Am J Hematol 83:330–333

37. Tanase A, Schmitz N, Stein H et al (2015) Allogeneic and autologous stem cell transplantation for hepatosplenic T-cell lymphoma: a retrospective study of the EBMT lymphoma working party. Leukemia 29:686–688
38. Rashidi A, Cashen AF (2015) Outcomes of allogeneic stem cell transplantation in hepatosplenic T-cell lymphoma. Blood Cancer J 5:e318
39. Opavsky R, Wang SH, Trikha P et al (2007) CpG island methylation in a mouse model of lymphoma is driven by the genetic configuration of tumor cells. PLoS Genet 3:1757–1769
40. Kucuk C, Jiang B, Hu X et al (2015) Activating mutations of STAT5B and STAT3 in lymphomas derived from gammadelta-T or NK cells. Nat Commun 6:6025

Rare T-Cell Subtypes

10

C. van der Weyden, C. McCormack, S. Lade, R. W. Johnstone and H. M. Prince

Abstract

There are a number of rare T-cell lymphoma subtypes that may be encountered in clinical practice. In recent years, improved immunohistochemical techniques and molecular tumor profiling have permitted refinement of some of the diagnostic categories in this group, as well as the recognition of distinct

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conditions not previously well elucidated. In this chapter, we cover the diagnostic and clinical features of some of the more common of these conditions, including subcutaneous panniculitis-like T-cell lymphoma, cutaneous gamma-delta T-cell lymphoma, enteropathy-associated T-cell lymphoma, monomorphic epitheliotropic intestinal T-cell lymphoma, primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma, CD4-positive small/medium T-cell lymphoproliferative disorder, and acral CD8-positive T-cell lymphoma. Given the rarity of these conditions, optimal treatments approaches are not always well established, not least as data from large-scale clinical trials are lacking. In this chapter, we aim to provide a summation of current thinking around best treatment, as well as highlighting some controversies in the management of these diagnoses.

Keywords

Subcutaneous panniculitis-like T-cell lymphoma · Cutaneous gamma-delta T-cell lymphoma · Enteropathy-associated T-cell lymphoma · Monomorphic epitheliotropic intestinal T-cell lymphoma · Primary cutaneous T-cell lymphoma Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma · CD4-positive small/medium T-cell lymphoproliferative disorder Acral CD8-positive T-cell lymphoma

10.1 Introduction

This chapter will focus on selected rare subtypes of T-cell and NK-lymphomas, including subcutaneous panniculitis-like T-cell lymphoma (SPTCL), cutaneous gamma-delta T-cell lymphoma (CGD-TCL), and the primary intestinal T-cell lymphomas, enteropathy-associated T-cell lymphoma (EATL), and monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL). It also includes an overview of some other uncommon, primarily cutaneous T-cell lymphoma variants, with specific reference to CD8-positive aggressive epidermotropic T-cell lymphoma, CD4-positive small–medium T-cell lymphoproliferative disorder, and acral CD8-positive T-cell lymphoma. The rarity of these conditions means there is a paucity of high-grade evidence to guide our understanding of etiology, pathogenesis, and best treatment. Nonetheless, we will attempt to provide a perspective of how these disorders are currently conceptualized and managed.

10.2 Subcutaneous Panniculitis-like T-Cell Lymphoma

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) was first described by Gonzalez et al. in a 1991 case series, in which all patients had characteristic pathologic features of a clonal T-cell subcutaneous infiltrate mimicking panniculitis. That initial

report, also described co-existent hemophagocytosis [1]. The entity was thereafter formally recognized by the European Organization for Research and Treatment of Cancer (EORTC) and included in the 2001 World Health Organization (WHO) classification of hematopoietic and lymphoid tumors [2, 3]. Subsequent case reports and case series, however, suggested that there were two distinct subgroups of this condition: an alpha-beta subtype, characterized by an overall more indolent course and better prognosis, and a gamma-delta subtype with a much poorer prognosis [4–8].

It is important to recognize that the term SPTCL is now exclusively used to denote the alpha-beta subtype, with the gamma-delta subtype instead referred to as primary cutaneous gamma-delta T-cell lymphoma in both the 2005 WHO-EORTC classification and the 2016 revision of the WHO Classification of Tumors of Haematopoietic and Lymphoid Tissue [9, 10].

Based on the rarity of SPTCL, as well as the difficulty in diagnosis, exact incidence and prevalence rates are not known. Early incidence estimates suggested SPTCL comprised <1% of all lymphomas; however, this estimate included both alpha-beta and gamma-delta subtypes, and as such, the true incidence figure is likely to be much less [2]. Willemze et al. reported a male: female ratio of 1:2, with a median age at diagnosis of 36 years (range 9–79) in their case series [4].

10.3 Diagnosis—Clinical Features, Histology, and Molecular Profile

The condition classically presents with indurated, poorly circumscribed, cutaneous nodules and plaques, which are often multifocal, and most commonly affect the limbs and trunk. Residual lipoatrophy may also be seen, although ulceration is rare. Nodal or systemic involvement is uncommon [4, 5]. In our experience, patients can present with a spectrum of skin changes, varying from tender erythematous nodules similar to the nodules seen in erythema nodosum, to areas of lipoatrophy similar to that seen in lupus profundus, which is an important differential diagnosis. As there are multiple causes of panniculitic histology, careful clinicopathological correlation is required.

All patients should be fully staged including bone marrow biopsy for the presence of hemophagocytic syndrome (HPS). In our experience, FDG-PET can be useful for determining if multifocal disease is apparent, as demonstrated in Fig. 10.1.

In their series of 62 patients with alpha-beta subtype SPTCL, Willemze et al. reported B symptoms in 37 patients, and HPS in 11 (fatal in seven patients). This series also reported concomitant autoimmune conditions in 12 of 63 patients, including connective tissue disorders such as lupus or rheumatoid arthritis, type 1 diabetes, multiple sclerosis, and Kikuchi disease, a finding which has been replicated in later case series [4, 11]. The close association between SPTCL and autoimmune disease underscores the difficulties inherent in the diagnosis of SPTCL

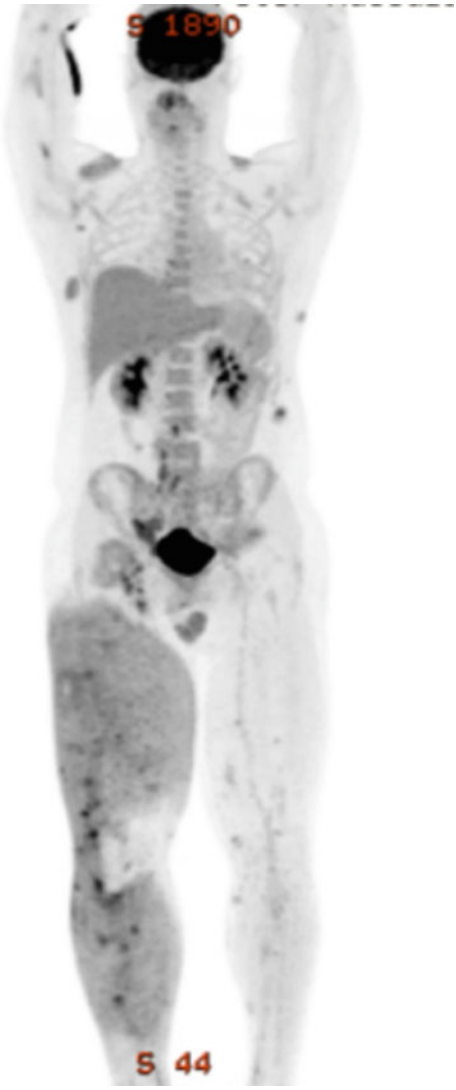

Fig. 10.1 PET scan for a 31-year-old male, diagnosed with subcutaneous panniculitis-like T-cell lymphoma after presenting with unexplained fevers, right thigh swelling, and pain, with multifocal subcutaneous mass lesions. Some of the lesions demonstrated on this PET scan were not well appreciated on examination. The patient was treated initially with cyclosporine and prednisolone, with subsequent prednisolone weaning and cessation. At twelve months of treatment with single-agent cyclosporine, he remains well and in clinical remission

and highlights the importance of careful histologic assessment to distinguish between clonal and reactive panniculitides.

The pathological features of SPTCL include a predominantly subcutaneous infiltrate of atypical T-cells of variable size. Adipotropism is present and resembles lobular panniculitis; individual adipocyte rimming is common, as demonstrated in Fig. 10.2a, b, with variable degrees of fat necrosis and karyorrhexis. Superficial dermal and epidermal involvement is uncommon, as are angioinvasion and angiodestruction. The T-cell infiltrate is positive for CD3 and CD8, as well as cytotoxic proteins such as granzyme B, TIA-1, and perforin. CD4 is negative;

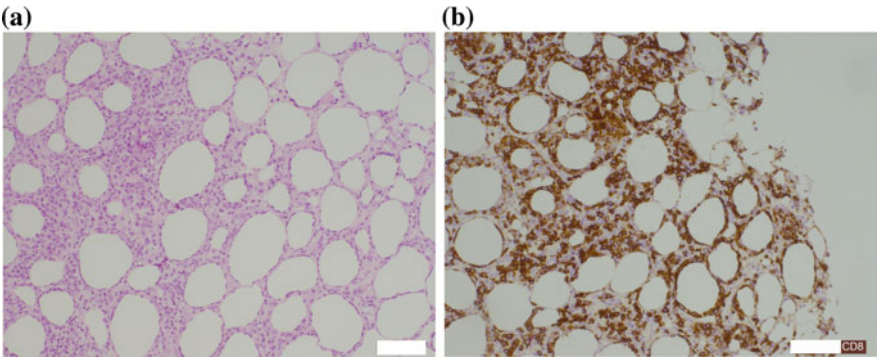

Fig. 10.2 Cutaneous punch biopsy, high power. **a** Demonstrates a lymphocytic infiltrate of variable size, with prominent rimming of the adipocytes. Immunoperoxidase staining **b** demonstrates this is a CD8-positive infiltrate, and illustrates the adipocentrism characteristic of SPTCL

there is a variable loss of CD2, CD5, and CD7. ßF1 staining is positive, and CD56 is positive in only a minority of cases. In contrast to nasal-type NK/T-cell lymphoma, in situ hybridization for EBV is negative [4, 12].

Careful clinicopathological evaluation is required to exclude non-clonal causes of panniculitis. Indeed, a number of case reports have highlighted the difficulties facing the anatomical pathologist when distinguishing between clonal and non-clonal causes of panniculitis, especially in overlap syndromes that demonstrate features of both lupus profundus and SPTCL [13–16]. This is compounded by the fact that T-cell clonal selection can occur in autoimmune conditions, resulting in oligoclonal or monoclonal T-cell receptor gene rearrangement studies [17, 18]. Wang et al. proposed that myxovirus resistance protein 1 (M×A) staining can help distinguish between lupus panniculitis and SPTCL, with this protein much more commonly upregulated in connective tissue disorders, resulting in a more diffuse and intense staining pattern than that seen in SPTCL [19]. Additionally, Liau et al. proposed that clusters of plasmacytoid dendritic cells and the presence of epidermal interface change were specific findings of lupus panniculitis [20]. These features, while not pathognomonic, can be helpful in some difficult cases.

The mutational landscape of SPTCL has not been well studied, however, Maliniemi et al. have reported gene expression microarray results for a cohort of 20 patients with SPTCL. In this study, the most commonly upregulated genes included *IFGN*, *CXCR3*, and *CCL5* (the protein counterparts of which are involved in promotion of a pro-inflammatory state via enhancement of a Th1-type response), as well as IFGN-inducible protein IDO-1 (Indoleamine 2, 3-dioxygenase). Interestingly, IDO-1 has been implicated in the development of autoimmunity, as well in promoting an immunosuppressive environment that may permit evasion of immune surveillance by tumor cells [21]. These findings raise interesting questions about the link between autoimmunity and the development of SPTCL.

10.4 Treatment Options

Early case reports for the treatment of SPTCL focused predominantly on the use of anthracycline-based multi-agent chemotherapy, with a reported long-term complete response (CR) rate of around 30% in one large systematic analysis including 156 patients [22]. Radiotherapy has also been used with good effect for isolated lesions [4, 22].

Over time, however, refinement of the diagnostic criteria for SPTCL, as well as the recognition that the diagnosis carries an excellent long-term prognosis has led to a reassessment of the role of chemotherapy in treating this disease. In their analysis, Willemze et al. suggested that the duration of complete remission after chemotherapy did not seem to differ from the outcomes with immunosuppression alone. Ohtsuka et al. also reported similar CR rates between the chemotherapy and non-chemotherapy cohorts in their case series [23]. Case reports and small series have built on these foundations, reporting durable CRs to cyclosporine alone or in combination with prednisolone, as well as reports of success with cyclosporine as salvage for relapsed or chemotherapy refractory disease, even in patients with confirmed HPS [24–29].

In their retrospective, multicenter cohort study of 27 patients, Michonneau et al. reported an overall CR rate of 74%. Among the 16 patients who received immunosuppression (prednisolone, oral methotrexate, cyclosporine or hydroxychloroquine), the overall CR rate was 81.2%, compared to a CR rate of 30.5% in the seven patients who received multi-agent chemotherapy ($p = 0.025$). Progression rates for the two groups were 6.2% and 42.8%, respectively ($p = 0.067$). The two groups were otherwise well matched with respect to co-morbid autoimmune disorders, B symptoms, ß2 microglobulin levels, and HPS [11]. While these results in concert suggest that immunosuppression is a reasonable first-line treatment, if and when to prioritize the use of chemotherapy is an unanswered question.

The role and timing of stem cell transplant is similarly ill-defined, with data drawn from case reports and small case series. Transplant outcomes have been reported by Gibson et al. in a small case series: this included four patients with SPTCL, one of whom received an autologous transplant (auSCT) and one of whom received an allogeneic transplant. All patients with SPTCL were alive at a median follow-up time of 4.7 years, the authors, however, did not report the patients' remission status. Notably, all of these patients were treated with chemotherapy or histone deacetylase inhibitors rather than immunosuppressive therapies prior to transplant [30]. Other case series report median remission durations of between 5 months and 3 years after auSCT, similarly in patients previously treated with chemotherapy [29, 31–34]. Data for the utility of allogeneic transplant for SPTCL is limited to case reports only [30, 35, 36]. Taken together, we recommend the use of immunosuppressive agents, particularly cyclosporine, as first-line treatment for multifocal SPLTCL. As the outcome is not influenced by the presence or absence of HPS, this is not an indication for the use of chemotherapy. Radiotherapy alone can be considered for unifocal or limited disease. Ongoing monitoring is required.

10.5 Prognosis

Prognosis for SPTCL is very good. The 2004 systematic analysis by Go and Wester reported an overall median survival of 27 months; however, when the cohort was segregated based on T-cell clonality, median survival was not reached in the alpha-beta cohort, at a median follow-up of 24 months [22]. Willemze et al. reported a 5-year OS rate of 82% and disease-specific survival of 85%. In patients without HPS, 5-year survival was 91% [4].

10.6 Cutaneous Gamma-Delta T-Cell Lymphoma

As already outlined, cutaneous gamma-delta T-cell lymphoma (CGD-TCL) encompasses the older diagnostic term of gamma-delta SPTCL. This uncommon condition is characterized by an aggressive clinical course, often associated with hemophagocytosis, and commonly either relapses soon after treatment, or is treatment refractory. Given its rarity, data are predominantly drawn from case reports and small series. Median age at diagnosis is reported as 59 and 61 years, respectively, in the two largest case series [4, 37].

10.7 Diagnosis—Clinical Features, Histology, and Molecular Profile

The clinical features of CGD-TCL are protean, with symptoms and signs reflective of a variety of cutaneous manifestations, end-organ dysfunction, and/or HPS [4, 5, 37, 38]. Cutaneous lesions are frequently disseminated and can be nodular, panniculitis-like, or epidermotropic with patches or plaques, as well as erosive and ulcerated. The most commonly involved locations are the extremities and the trunk. Dissemination to other extra-nodal sites can be seen, although lymph node or hepatosplenic involvement is uncommon. B symptoms or symptoms of HPS are frequently seen. Involvement of the central nervous system has been reported, particularly with progressive disease [37, 39–41].

The histology of CGD-TCL is likewise variable, and a variety of patterns can be seen in the same patient. The T-cell infiltrate is usually comprised of medium to large cells and can involve subcutaneous tissue, dermis, and/or epidermis. Angiodestruction or angioinvasion is not uncommon. Adipotropism can be seen, although the infiltrate is usually not confined to the subcutaneous layer, unlike in cases of SPTCL. These features are demonstrated in Fig. 10.3a, b. The immunophenotype is classically CD2 and CD3 positive, with strong expression of cytotoxic markers. Cases are usually negative for both CD4 and CD8, although

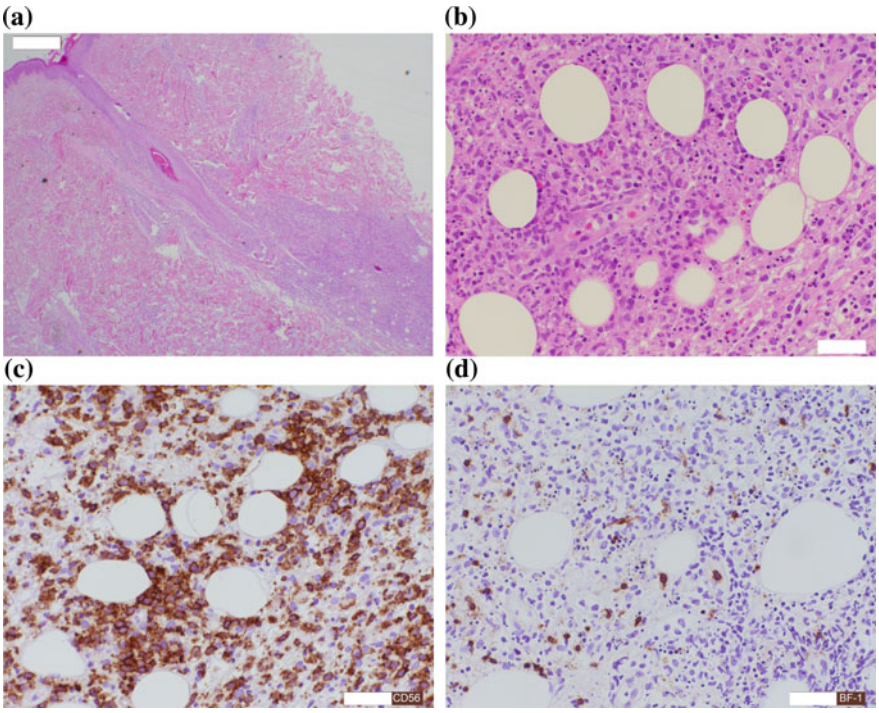

Fig. 10.3 Cutaneous punch biopsy. At low power (**a**), the lymphocytic infiltrate is appreciable in both dermal layers and in subcutaneous tissue, with invasion of the adjacent hair follicle. Examination at higher power (**b**) shows a pleomorphic lymphocytic infiltrate and absence of the characteristic adipotropism seen in SPTCL. Immunoperoxidase staining confirms the infiltrate is CD56 positive (**c**), and BF-1 staining is negative (**d**)

some cases have been reported with CD8 expression. CD5 is usually negative, CD7 expression is variable, and CD56 is usually positive, as demonstrated in Fig. 10.3c. This immunophenotype alone is not pathognomonic, and the demonstration of a gamma/delta positive phenotype and/or negative alpha/beta phenotype is required (as seen in Fig. 10.3d), although performing the latter test alone is less preferred. In situ hybridization for EBV is negative [4, 12, 42].

Molecular profiling of CGD-TCL has been performed by one group, who reported an increased frequency of STAT-5B mutations in their 15 cases, predominantly in the SH2 domain. Interestingly, exposure of the gamma-delta T-cell lines to JAK1/2 inhibitors resulted in dose-dependent T-cell growth inhibition. This may suggest a role for JAK inhibition as part of the therapeutic armamentarium of CGD-TCL [43].

10.8 Treatment Options

Multi-agent chemotherapy is the most commonly reported treatment modality, however, without promising long-term results. CHOP and CHOP-like regimens in one series resulted in complete remissions in only three out of 14 patients, of whom one patient also received auSCT in first remission [4]. The use of an etoposide-containing regimen would seem attractive given its utility in treating HPS, however, there is minimal data that specifically addresses this.

Indeed, apart from selected case reports suggesting benefit from different high-dose chemotherapy regimens, the question of the optimal treatment selection for CGD-TCL has not been examined in any depth [38, 44–46].

With respect to other therapeutic strategies, there are a handful of case reports and a single small case series that suggest there is a role for allogeneic stem cell transplant in achieving and maintaining long-term remission in patients with CGD-TCL, however, more data are needed [30, 47, 48]. Taken together, we recommend aggressive multi-agent chemotherapy as induction therapy, followed by allogeneic transplantation if suitable. High-dose chemotherapy with auSCT should be considered. We note that, while three patients with CGD-TCL were treated in the pivotal phase II trials for romidepsin in PTCL, no patients had a documented response [49, 50]. The role of novel agents such as histone deacetylase inhibitors or JAK2 inhibitors requires further investigation.

10.9 Prognosis

Even with intensive therapy, the prognosis for CGD-TCL is dismal, with a reported median survival of 15 months [6]. In one series of 20 patients, 15 patients had died at a median follow-up time of 12 months (range 1–108 months), with most patients succumbing to either HPS or lymphoma progression including CNS involvement. OS rates were 31% and 11% at two and 5 years, respectively [4]. Toro et al. reported a similar 5-year survival rate of around 10% [6].

10.10 Primary Intestinal T-Cell Lymphomas: Enteropathy-Associated T-Cell Lymphoma and Monomorphic Epitheliotropic T-Cell Lymphoma

Primary intestinal T-cell lymphomas (ITCL) incorporate the older diagnostic group of enteropathy-associated T-cell lymphoma, which was subcategorized into type 1 (EATL-I) and type 2 (EATL-II) depending on whether the condition was associated with celiac disease or sporadic, respectively. These intra-epithelial lymphomas can affect the intestinal tract at any site, although they are most commonly located in the jejunum or ileum.

The 2016 update to the WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues has renamed these conditions with the recognition that they are in fact distinct subtypes. EATL-I, which occurs predominantly in patients of Northern European origin and is closely associated with celiac disease, is now referred to as enteropathy-associated T-cell lymphoma (EATL). EATL-II is now referred to as monomorphic epitheliotrophic T-cell lymphoma (MEITL), occurring more commonly in patients of Asian or Hispanic origin, and is not associated with celiac disease [10]. In one large international case series, ITCL comprised 5.4% of all peripheral T-cell lymphoma (PTCL) cases in the North American cohort, and 9.1% of the European cohort [51]. Incidence in Western countries is 0.5–1 per million people [52]. Median age at diagnosis is been reported as 60–70 years, with no gender predominance [53, 54].

The association between celiac disease and ITCL was first described by Gough et al. in 1962 [55], with multiple case series in subsequent decades affirming this link. Thereafter, interest in identifying which patients with celiac disease are most at risk of lymphomatous transformation, has identified refractory celiac disease (RCD) as a key risk factor. RCD is the development of persistent and/or refractory symptoms despite strict adherence to a gluten-free diet; formally, this definition includes the presence of persisting villous atrophy with crypt hyperplasia and increased intra-epithelial lymphocytes (IELs) in spite of a strict gluten-free diet for more than 12 months, or the presence of severe symptoms necessitating intervention, independent of the diet duration [56, 57].

The presence of IELs is the hallmark of RCDII, which carries the highest risk of transformation to EATL, whereas the development of EATL in the setting of RCDI is rare [57]. Several groups have identified aberrant clonal T-cell populations among the IELs seen in RCDII; the aberrant populations commonly show absent surface lineage markers, but usually retain expression of intracellular CD3, as well as showing incomplete or out-of-frame TCR gene rearrangements. Additionally, some IELs demonstrate the characteristic immunophenotype of EATL, suggesting a pathogenic link between RCD and EATL [58–62]. Kooy-Winkelaar et al. demonstrated that the presence of gluten-specific CD4-positive T-cells perpetuated the proliferation and activation of lineage-negative IELs via the production of cytokines TNF, Il-2, and IL-21 [63]. By way of contrast, a similar precursor lesion and the likely pathogenic factors contributing to the development of MEITL have not been clearly elucidated.

10.11 Diagnosis—Clinical Features, Histology, and Molecular Profile

The hallmark clinical features of ITCL may reflect the mechanical effects of the tumor mass, or symptoms of increasingly refractory or progressive celiac disease, such as malnutrition or altered bowel habits. The majority of patients have

advanced disease at diagnosis, as early-stage disease may be clinically silent or present with a prolonged period of ill-defined symptoms. It is relatively common for the first presentation of the condition to be with intestinal obstruction or perforation necessitating emergent surgical intervention. Indeed, the diagnosis was made at laparotomy in 80–91% of patients in two large series [51, 64].

EATL commonly presents as multifocal mucosal lesions with variable ulceration in the jejunum and ileum, although single large exophytic lesions or multiple flat mucosal ulcers can also be seen. Involvement of the stomach, duodenum, or colon is much less common. Invasion of the mesentery and/or involvement of mesenteric nodes is not infrequent [65]. Despite frequent presentations with advanced disease, involvement of systems outside of the gastrointestinal tract is uncommon [51, 64, 66, 67].

Given the connection between RCD and the evolution of EATL, several groups have examined the utility of noninvasive modalities in diagnosis. Mallant et al. suggested that there are relatively specific CT changes for advanced RCD and EATL, such as more prominent bowel thickening, lymphadenopathy, especially if the nodes show central necrosis, intussusception, and splenic volume of < 120 mL [68]. Other groups have suggested that PET is more sensitive and specific than CT for detecting EATL [69, 70]. MRI may assist in identifying multifocal lesions or tumors confined to the epithelial layer of the bowel mucosa [71]. While these modalities are helpful in identifying those patients with RCD who merit closer evaluation, endoscopic and/or surgical evaluation with biopsy remains the gold standard for the diagnosis of ITCL.

There is a difference between the characteristic histopathologic and immunophenotypic findings of EATL and MEITL. In EATL, the tumor is most commonly comprised of variably pleomorphic infiltrates of medium to large cells with prominent nucleoli and moderate amounts of cytoplasm. A concomitant inflammatory infiltrate of lymphocytes, eosinophils, and histiocytes is frequently seen and may be so heavy as to obscure the clonal lymphocytic population. Enteropathic changes are usually seen in the adjacent mucosa, although to varying degrees. These changes are demonstrated in Fig. 10.4a.

By way of contrast, the changes in MEITL include a relatively monomorphic infiltrate of medium-sized cells with a high nuclear:cytoplasm ratio with condensed nuclei, as well as a prominent lymphocytic infiltration of the intestinal crypts. An inflammatory infiltrate is less prominent or absent when compared to EATL biopsies. Necrosis is uncommon. These changes are demonstrated in Fig. 10.5a.

The immunophenotype of each diagnosis is also distinct: EATL is usually CD3 positive, CD5 negative, CD7 positive, CD4 negative, CD8 mostly negative, CD103 positive, CD56 negative and variably CD30 positive, with positive cytotoxic markers. MEITL has the phenotype CD3 positive, CD4 negative, CD8 positive, and CD56 positive. TCR genes are clonally rearranged in both variants; some groups have reported that gamma-delta rearrangements are more common in MEITL [12, 67, 72]. These contrasting findings can be seen in Figs. 10.4b–d and 10.5a.

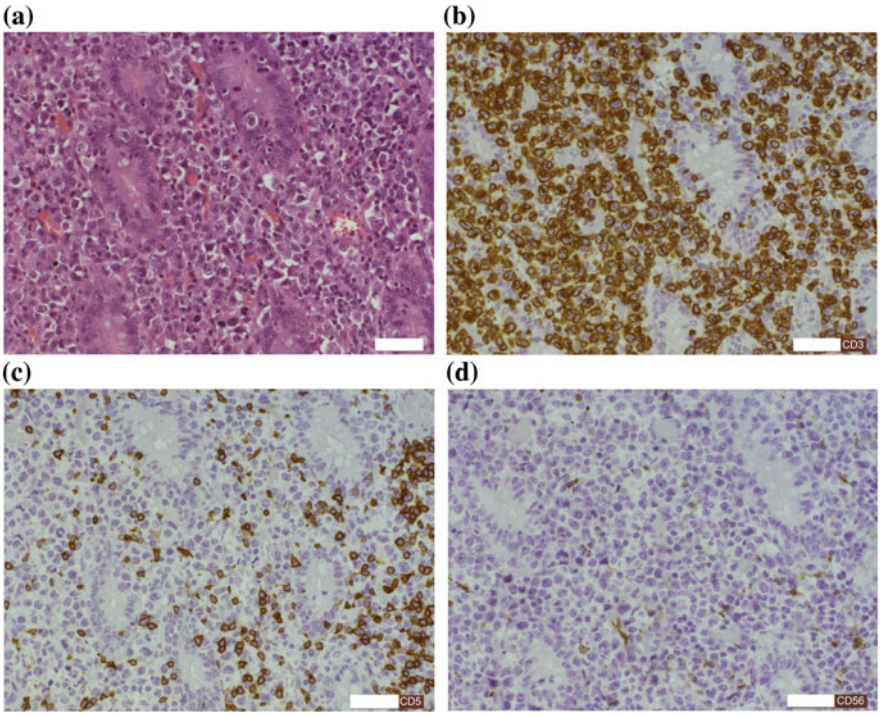

Fig. 10.4 Intestinal biopsy. This specimen from a patient diagnosed with EATL shows a pleomorphic lymphocytic infiltrate in the intestinal mucosa, with a predominance of larger nucleolated lymphocytes. A concomitant inflammatory infiltrate of small lymphocytes and eosinophils is seen. Immunoperoxidase demonstrates the abnormal infiltrate is CD3 positive, CD5 negative, and CD56 negative

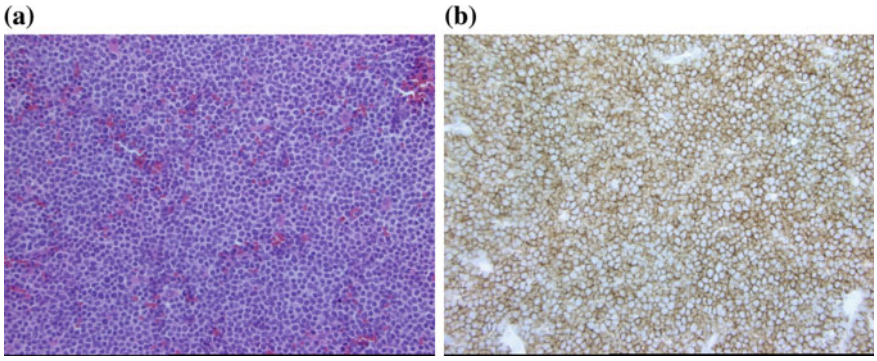

Fig. 10.5 Intestinal biopsy. This specimen from a patient diagnosed with MEITL demonstrates the relatively monomorphic lymphocytic infiltrate of this condition, especially when contrasted with the characteristic appearance of EATL (see Fig. 10.4). In contrast to EATL, this specimen is strongly CD56 positive

Recent studies have begun to assess the genomic and mutational profile of ITCL. CGH microarray studies found frequent 9q gains/16q losses in both diagnoses, as well as gains on chromosome 1q and 5q in EATL, and gains of 8q24 (MYC amplifications) in MEITL [72–74]. Subsequent targeted NGS sequencing in EATL and MEITL cases revealed frequent mutations in JAK/STAT and RAS signaling pathways [75]. Building on these results, whole exome sequencing in MEITL suggests that its genomic profile is different from EATL, with frequent loss-of-function mutations in the tumor-suppressor gene *SETD2*, as well as a distinct pattern of perturbations in the JAK/STAT signaling pathway unlike those seen in EATL, with activating mutations predominantly in *STAT5B, JAK3*, and *SH2B3* [76, 77]. These findings suggest a possible role for targeted therapies against the JAK/STAT pathway in ITCL. While agents specifically targeting the RAS pathway are not yet available in the clinic, MEK inhibitors are being used for solid organ malignancies, and given that other RAS-mutated hematologic malignancies have shown in vitro sensitivity to MEK inhibition, these agents may be worthy of further investigation [78].

Prognostication in ITCL has traditionally relied on the Prognostic Index for Peripheral T-cell lymphoma (PIT), which assesses four parameters including LDH, age, bone marrow involvement, and performance status. This has been found to more accurately predict outcomes in ITCL patients compared to the standard International Performance Index (IPI) for lymphoma [79]. Delabie et al. found that a large tumor mass ($\geq$ 5 cm), non-ambulatory performance status, and elevated serum LDH and CRP levels, were more closely associated with worse overall and failure-free survival (FFS) in their ITCL cohort, while a clinical history of celiac sprue was also an independent predictor of poorer FFS [53]. More recently, de Baaij et al. have suggested an updated clinical prognostic model specifically for EATL, the EPI score, which incorporates the presence of B symptoms with the IPI [80]. Notably, this excludes patients with MEITL.

10.12 Treatment Options

The most commonly used treatment modality in the literature is multi-agent chemotherapy, with or without debulking surgery. The use of auSCT to consolidate first remission has also been explored in an attempt to ameliorate historically poor treatment outcomes.

As outlined earlier, patients with ITCL commonly undergo laparotomy for diagnosis. One important question is whether there is a role for surgery in treatment of ITCL outside of diagnostic or emergency surgical procedures. Surgery alone is not recommended for definitive management [51, 64]. However, this leaves unanswered the question of whether debulking surgery or, indeed, complete resection of all tumor should be considered in all patients. Certainly, the risks inherent in surgical intervention may be heightened in those patients with preceding celiac disease or RCD, who may present with long-term malnutrition and immune

system dysfunction. However, there are some case reports that suggest that complete surgical resection of the tumor improves the deliverability of chemotherapy by reducing the risk of intestinal perforation with cytotoxic therapy [81–87]. Nijeboer et al. reported that the best outcomes in their cohort were in the group of patients who underwent surgery followed by chemotherapy, with or without auSCT, although they acknowledge that the strength of these conclusions is hampered by a small number of patients in each group [66].

Given the rarity of this condition, there are no phase III clinical trials to guide the selection of the preferred chemotherapy regimen/s. Data are drawn from case series or cohort studies, or from studies including a mix of PTCL diagnoses, of which ITCL may comprise only a minority.

As with other PTCL subtypes, CHOP chemotherapy delivers underwhelming results, with reported 5-year survival rates varying between 9 and 22% [64, 84, 88]. Moving beyond CHOP, Ellin et al. reported that the addition of etoposide to CHOP chemotherapy (CHOEP) resulted in an improved progression-free survival (HR 0.49, 95% CI 0.29-0.83, P = 0.008) in PTCL patients younger than 60 years [54]. Of note, however, only 34 of the 252 patients treated in this study had a diagnosis of ITCL. Wohrer et al. subsequently reported discouraging outcomes in their CHOEP-treated cohort of 10 patients with ITCL. While two complete responses and three partial responses were seen (ORR 50%), only two patients were still alive at a median follow-up of seven months (range 2–16), one of whom was in ongoing CR [82].

Multi-agent systemic regimens used include: CHOP with alemtuzumab; CHOP with methotrexate; CAVmP (cyclophosphamide, doxorubicin, teniposide, and prednisolone, alternating with bleomycin and vincristine) [66]; ProMACE-MOPP (prednisone, doxorubicin, cyclophosphamide, etoposide, mechlorethamine, vincristine, and procarbazine); BACOP (bleomycin, doxorubicin, cyclophosphamide, vincristine, and prednisone) [88]; VAMP (vincristine, doxorubicin, high-dose methotrexate, and prednisolone); PEACE-BOM (prednisolone, etoposide, doxorubicin, cyclophosphamide, bleomycin, vincristine, and methotrexate) [64]; hyperC-VAD [83]; and SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide) [89]. As these regimens have been reported in small numbers of patients—and not always consistently reported alongside treatment outcomes—the data is insufficient to decide whether any one particular regimen delivers clear benefit, a decision made even more difficult when weighed against the increased risk of toxicity conferred by the more intensive combinations.

Looking at these results, the question arises whether these poor outcomes are reflective of relative insensitivity of the tumor to standard multi-agent chemotherapy, or whether there are disease-specific factors that impact on the deliverability of chemotherapy in this cohort. The risk of intestinal perforation after the initiation of chemotherapy is well documented, resulting in failure to complete the planned course of chemotherapy in a proportion of patients [64, 81, 85]. Additionally, those patients with preceding celiac disease, especially those with RCD, appear to fare especially poorly, due—at least in part—to moderate to severe long-term

malnutrition as well as poor performance status [66, 81, 90]. Relative immunodeficiency due to splenic hypofunction may also contribute to the risks of severe infection in this patient group [91].

Early anecdotal case reports in ITCL and selected case series in PTCL cohorts suggested that the use of auSCT merited closer consideration in the ITCL treatment algorithm - for example, the retrospective, single-center case series in PTCL patients authored by Gritti et al, in which it was noted that the five patients with ITCL who received an auSCT all remained free of relapse at a median follow-up of 5.61 years [92–98]. Two larger retrospective case series specifically focused on auSCT in ITCL patients, reported encouraging outcomes.

Sieniawski et al. from the Scotland and Newcastle Lymphoma Group reported on the use of a novel chemotherapy regimen IVE-MTX (one cycle of CHOP, followed by three cycles of ifosfamide, epirubicin, and etoposide, alternating with intermediate-dose methotrexate), paired with auSCT using either high-dose melphalan/total body irradiation or BEAM (carmustine, etoposide, cytarabine, melphalan) conditioning. This regimen achieved an overall remission rate of 69% in comparison to a remission rate of 42% in a historical cohort treated with anthracycline-based chemotherapy ($p = 0.06$) [51]. Twenty-one patients completed the full number of planned chemotherapy cycles, with 14 proceeding thereafter to transplant. Remission rates were 93% versus 41% ($P = 0.004$) in those who completed the full course of treatment versus those who did not. Five-year progression-free survival (PFS) and OS were both 68% in the transplanted cohort, in comparison with 33% and 50% in the cohort not completing the full protocol, albeit with only the difference in PFS reaching statistical significance ($p = 0.028$) [51].

Jantunen et al. reported results for 44 patients who had consolidation treatment with auSCT. Four-year PFS was 54% and OS was 59%, with an apparent plateau to both these curves over time; there was a trend toward better OS in those patients in CR versus PR when treated with auSCT, however, these results did not reach statistical significance [99]. Later, smaller case reports have also reported favorable outcomes in those patients consolidated with a first-line auSCT [66, 67, 89].

There are some caveats to bear in mind when interpreting this data. Not all patients in these reported series were transplanted in first remission, and the question remains whether outcomes may be better if auSCT is prioritized as part of first-line therapy. The other issue which has been unsatisfactorily addressed is whether the auSCT outcome data reflects a self-selecting patient population who generally perform better, whether this is due to more chemotherapy sensitive disease, better treatment tolerance, or better performance status. Despite this, there is a suggestion that the best treatment outcomes occur in the subgroup of patients treated with surgery and chemotherapy followed by auSCT [66].

Allogeneic transplant (alloSCT) has been reported in selected cases, with variable outcomes: two cases reporting ongoing complete remission after reduced-intensity conditioning (RIC) alloSCT at 70 days and 11 months, respectively, and a later report of two patients treated with sibling RIC alloSCT, both of

whom relapsed within eight weeks of transplant and died of progressive disease soon thereafter. Tse et al. reported on a MEITL patient who underwent fludarabine-busulfan alloSCT in partial remission. The patient achieved CR after allogeneic transplant with ongoing survival of at least 26 months at the time of the report [89, 100–102].

Given the variable outcomes with chemotherapy, other non-cytotoxic therapies have been investigated, albeit in very small numbers of patients. The phase II trial of romidepsin in PTCL reported by Coiffier et al. included six patients with ITCL, however, none of this group responded [49]. In contrast, one patient with ITCL was treated in the phase II romidepsin trial reported by Piekarz et al. and achieved a CR, which was maintained at 8 months of follow-up [50]. The two patients with ITCL in the phase II trial of lenalidomide monotherapy reported by Toumishey et al. did not have a documented response [103]; no patients with ITCL were included in the EXPECT phase II trial of lenalidomide [104]. The addition of the anti-CD52 monoclonal antibody alemtuzumab to CHOP or gemcitabine chemotherapy has been reported in a handful of ITCL cases, albeit with mixed results [105–107].

The standard of care for patients with relapsed or refractory disease has not been established. Small case series have reported the use of salvage chemotherapy, either with or without auSCT, in relapsed patients who did not receive a transplant in first line. The results, however, are not encouraging. Whole abdominal radiotherapy has also been suggested as a palliative measure. In lieu of good standard alternatives, participation in clinical trials would seem a reasonable option where feasible, although the poor performance status of many ITCL patients in relapse may preclude this [86, 108, 109].

In summary, for fit patients, we recommend the "Newcastle regimen" with auSCT. If surgical resection is feasible, it should be considered in suitable patients prior to commencement of chemotherapy.

10.13 Prognosis

Outcomes are poor, even with aggressive treatment. Nijeboer et al. reported an overall mortality rate of 82% in their cohort, with a median survival of 7.4 months. One year and 5-year survival rates were 40% and 11%, respectively [66.]. These results parallel those from earlier case studies, which reported median survivals of 7 to 10 months, 1- or 2-year survival rates of 38.7% and 34.5%, respectively, and 5-year survival rates between 19.7% and 25.8% [53, 64, 87]. With respect to subgroup analyses, Nijeboer et al. suggested a statistically significant survival disadvantage in patients with a preceding diagnosis of RCD (median survival of 4 months versus 14 in patients without preceding RCD, $p = 0.016$). Progressive disease, infection, and complications of therapy are the major contributors to mortality [17, 64, 66, 81, 87].

10.14 Other Rare T-cell Lymphoma Subtypes

Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma and CD4-positive small/medium T-cell lymphoproliferative disorder were first included as provisional entities in the 2008 WHO Classification of Tumors of Haematopoietic and Lymphoid Tissue, while CD8-positive acral T-cell lymphoma was included as a provisional entity in the 2016 update [10, 12]. In addition, there has been some recent literature addressing the putative entity of primary cutaneous follicular helper T-cell lymphoma, although this diagnosis was not included in the 2016 update.

10.14.1 Primary Cutaneous CD8-positive Aggressive Epidermotropic Cytotoxic T-cell Lymphoma

Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma is distinguished from other CD8-positive cutaneous lymphomas by its aggressive clinical behavior, often having widely disseminated lesions at diagnosis, and the presence of marked epidermotropism on biopsy.

10.14.1.1 Diagnosis, Clinical Features, and Histopathology

Patients commonly present with multifocal cutaneous lesions at diagnosis. There can be a spectrum of cutaneous lesions, varying from patch and plaque disease to nodules and tumors, any of which may be ulcerated or necrotic. Extra-cutaneous involvement is not uncommon, with mucosal and systemic involvement reported, including sites such as the central nervous system and testis. Lymph node involvement is less commonly seen [110].

The histologic features of this condition are variable and may overlap with other, more indolent cutaneous lymphomas. Epidermotropism by definition is always seen and can be associated with epidermal necrosis and ulceration. Deeper nodular infiltrates may also be present, while dermal involvement of varying extents is almost always seen. The T-cell infiltrate may be comprised of small–medium cells or larger cells with a more blastoid appearance. Angiodestruction and invasion of surrounding skin structures may be present to a variable degree. Immunophenotype is CD3 and CD8 positive, with an expression of cytotoxic markers, and variable expression of CD2, CD7, and CD45RA. TCR is clonal, and EBV is negative [12, 111].

The differential diagnosis includes pagetoid reticulosis, CD8-positive mycosis fungoides, and CD8-positive peripheral T-cell lymphoma, all of which have quite different prognostic implications. Given this overlap, several groups have emphasized the importance of clinical correlation in establishing the diagnosis [111, 112]. A recent retrospective clinicopathologic review of 35 cases of CD8-positive cutaneous lymphomas underscored the importance of clinical correlation in establishing a diagnosis in this patient group, finding that there were no pathognomonic

histopathological features in their cohort that would permit easy distinction between these lymphoma subtypes based on biopsy alone [113].

10.14.1.2 Treatment Options

Skin-directed or low-intensity therapies as used in mycosis fungoides are usually ineffective, and treatment with PUVA or interferon may actually worsen disease [110, 114]. Total skin electron beam therapy may be considered, however, the durability of this response is usually short.

The aggressive behavior of this condition and the presence of disseminated lesions with frequent systemic involvement would seem to suggest that multi-agent chemotherapy is an appropriate treatment. However, given the rarity of the condition, there is minimal data to guide selection between different regimens. The other unanswered question is the utility of augmenting therapy through autologous or allogeneic transplantation, with recommendations for these mostly being extrapolated from the use of transplant in other forms of advanced cutaneous T-cell lymphoma, with the exception of a few case reports [114–116]. We generally recommend aggressive multi-agent chemotherapy such as hyperCVAD and/or high-dose chemotherapy with auSCT. Allogeneic transplantation can be considered.

10.14.1.3 Prognosis

Median survival in the case series from Berti et al. was 32 months, with a later small series reporting median survival of 22.5 months [110, 117]. The reported 5-year survival rate is 18% [9].

10.14.2 CD8-positive Acral T-cell Lymphoma

CD8-positive acral T-cell lymphoma is a provisional inclusion in the 2016 update of the WHO classification of Tumors of Haematopoietic and Lymphoid Tissues. Previously, these lymphomas were subclassified as cutaneous variants of PTCL, however, an accumulation of case reports and case series strongly suggest that the clinical behavior of this entity is at odds with the diagnosis of PTCL, and that the clinicopathologic features are specific enough to justify its provisional inclusion as a distinct entity. It is important to recognize that while this lesion histologically is a differential diagnosis for CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma, the clinical behavior and prognosis of the two conditions are vastly different.

10.14.2.1 Diagnosis—Clinical Features and Histopathology

In 2007, Petrella et al. reported four cases of CD8-positive solitary cutaneous nodular lesions, all of which were located on the ear, and which had an indolent clinical course [118]. This report was followed by several case reports and series, all of which reported similar clinical presentations and histopathologic appearances

[119–123]. Additional reports acknowledged the possibility of involvement of the extremities or the face rather than the ear alone, as well as reporting cases with bilateral, symmetrical lesions [113, 124–133]. Kluk et al. reported one case with disseminated, recurrent nodular lesions [134].

The lesions in this condition are characteristically small, papular or nodular, usually isolated, and only very rarely associated with patch or plaque disease. Ulceration is not seen. Patients are often asymptomatic, and systemic involvement is not usually a feature.

Classical histopathology findings are of a monotonous population of medium-sized cells in the dermis, classically with a well-demarcated Grenz zone. Focal epidermotropism may be present. Immunophenotype is CD3/CD8 positive, with TIA-1 positivity. EBV and CD56 are negative, and the proliferative fraction is low. In contradistinction to CD4-positive small–medium T-cell lymphoproliferative disorder, there is minimal pleomorphism, and PD1/ICOS/CXCL13 have been negative when tested in selected case series. This would argue against the condition being merely a CD8-positive variant of small–medium T-cell lymphoproliferative disorder [126, 131, 134].

Wobser et al. reported that CD68 expression was a discriminatory factor that permitted distinction between this condition and other more aggressive CD8-positive aggressive lymphomas [133].

10.14.2.2 Treatment Options

Reported treatment modalities include surgical excision, and radiotherapy, both with good disease control; observation has also been adopted in some cases [126, 134]. Apart from one case in which interferon-alfa was used for recurrent multifocal lesions, albeit without any significant disease control, the use of systemic therapies has not been explored in any detail [134].

10.14.2.3 Prognosis

This condition appears to have an indolent course with a good prognosis. No deaths attributable to progressive disease are reported in the existing case series.

10.14.3 CD4-positive Small/Medium T-cell Lymphoproliferative Disorder

CD4-positive small/medium T-cell lymphoproliferative disorder is characterized by the presence of cutaneous nodules, which are usually solitary, and which have very indolent clinical behavior and a good prognosis. Men and women are equally affected, and the median age at diagnosis in one large retrospective series was 51 years (range 3–90) [135].

10.14.3.1 Diagnosis—Clinical Features and Histopathology

The condition usually presents with an isolated nodule, most commonly on the head and neck. Presentation with multifocal nodules is uncommon. Systemic

involvement is extremely rare, although can be seen at relapse or in advanced cases [135, 136].

The characteristic histologic finding is of a dense T-cell infiltrate, predominantly located in the dermis, but which may also involve subdermal tissues. The infiltrate may be diffuse or nodular. As distinct from mycosis fungoides, epidermotropism is not usually a prominent feature. Cells are predominantly small to medium in size with pleomorphic nuclei, and a reactive infiltrate lymphocytes and histiocytes may be present [137]. Clonal rearrangement of TCR genes should be present, which assists in distinguishing this condition from pseudo-lymphomatous inflammatory conditions—this is important given the common finding of a concomitant reactive or inflammatory infiltrate [12].

In their series of 12 patients, Rodriguez Pinilla et al. demonstrate the expression of PD1 and CXCL13 in occasional large CD4 positive cells within the neoplastic infiltrates—a phenotype which is seen in other cutaneous B- and T-cell neoplasms, but rarely in reactive conditions [138]. The immunophenotype is CD3 and CD4 positive, and CD8/CD30 negative. Subsequent to this, this condition has been characterized by Ally et al. as a clonal proliferation of follicular T-helper cells, given the distinct immunophenotype and the expression of PD1 in a rosette pattern and the over-expression of PD1 [139]. However, this needs to be carefully distinguished from primary cutaneous follicular helper T-cell lymphoma, which can present with multifocal nodules and which can have a clinically more aggressive course [140].

10.14.3.2 Treatment Options

The most commonly used treatment approaches include excision and/or radiotherapy, with excellent long-term disease control. Interventional approaches may not be required in some patients, with one case report describing three patients in whom lesions remained stable for a median of 50 months [141]. Local recurrence or persistent cutaneous disease is uncommon [135, 142, 143].

Chemotherapy is used in a minority of cases and seems to be reserved for a minority who present with systemic or multifocal involvement, although cases with this presentation may actually represent a different entity, that is, primary cutaneous follicular helper T-cell lymphoma.

10.14.3.3 Prognosis

This condition generally behaves in a very indolent fashion. The case series from Beltraminelli et al. reported 41 of 45 patients alive and lymphoma-free at a median follow-up time of 63 months (range 1–357 months); the other four patients were alive with lymphoma that remained limited to the skin [135]. A recent literature review by James et al. found that of the 289 reported cases, only nine deaths were recorded, of which five were from a series published by Garcia-Herrera et al. and occurred in patients with tumors of > 5 cm and systemic involvement at diagnosis [142, 144]. Again, the question arises whether these cases represent a different entity.

10.14.4 Primary Cutaneous Follicular Helper T-cell Lymphoma

Primary cutaneous follicular helper T-cell lymphoma has been the focus of recent discussion as a potential distinct entity, although this has not been formally recognized in the 2016 update to the WHO classification of lymphoid neoplasms. Battistella et al. initially described a case series of five patients with disseminated cutaneous patches, plaques, and nodules, with an immunophenotype expressing characteristic T follicular helper markers including CD10, Bcl-6, PD1, CXCL13, and ICOS [140]. Later case reports have supported the finding of this being a distinct entity, although have also highlighted the diagnostic pitfalls, such as misdiagnosis as primary cutaneous follicular center cell lymphoma, or the difficulty in distinguishing this from angioimmunoblastic T-cell lymphoma [145–147].

The condition appears to be characterized by skin-limited disease, albeit with disseminated lesions with a variable clinical appearance. Treatment recommendations are based on small series; the condition appears to have a relapsing or refractory course to both novel agents and multi-agent chemotherapy, with durable responses reported in two patients who received alloSCT [145, 146].

10.15 Summary

In this chapter, we have covered several rare subtypes of T-cell lymphomas and summarized some of the challenges in diagnosis and treatment. Given that these conditions are rare, and also, in some cases, have been only recently recognized as distinct entities, we anticipate that there will be further refinement of the diagnostic criteria over time. The use of molecular profiling may help in delineating diagnostic subcategories, and we believe that more entities are likely to be identified in coming years. Hopefully, these more stringent diagnostic criteria may assist in better understanding the conditions' pathogenesis and natural history, with a view to refining optimum approaches to management.

References

1. Gonzalez CL, Medeiros LJ, Braziel RM, Jaffe ES (1991) T-cell lymphoma involving subcutaneous tissue. A clinicopathologic entity commonly associated with hemophagocytic syndrome. Am J Surg Pathol 15(1):17–27
2. Jaffe ES, Harris NL, Stein H, Vardiman JW (2001) Pathology and genetics of tumours of haematopoietic and lymphoid tissues. IARC Press, Lyon, France
3. Willemze R, Kerl H, Sterry W, Berti E, Cerroni L, Chimenti S et al (1997) EORTC classification for primary cutaneous lymphomas: a proposal from the Cutaneous Lymphoma Study Group of the European Organization for Research and Treatment of Cancer. Blood 90(1):354–71

4. Willemze R, Jansen PM, Cerroni L, Berti E, Santucci M, Assaf C et al (2008) Subcutaneous panniculitis-like T-cell lymphoma: definition, classification, and prognostic factors: an EORTC Cutaneous Lymphoma Group Study of 83 cases. Blood 111(2):838–45
5. Salhany KE, Macon WR, Choi JK, Elenitsas R, Lessin SR, Felgar RE et al (1998) Subcutaneous panniculitis-like T-cell lymphoma: clinicopathologic, immunophenotypic, and genotypic analysis of alpha/beta and gamma/delta subtypes. Am J Surg Pathol 22(7):881–93
6. Toro JR, Liewehr DJ, Pabby N, Sorbara L, Raffeld M, Steinberg SM et al (2003) Gamma-delta T-cell phenotype is associated with significantly decreased survival in cutaneous T-cell lymphoma. Blood 101(9):3407–12
7. Hoque SR, Child FJ, Whittaker SJ, Ferreira S, Orchard G, Jenner K et al (2003) Subcutaneous panniculitis-like T-cell lymphoma: a clinicopathological, immunophenotypic and molecular analysis of six patients. Br J Dermatol 148(3):516–25
8. Kong YY, Dai B, Kong JC, Zhou XY, Lu HF, Shen L et al (2008) Subcutaneous panniculitis-like T-cell lymphoma: a clinicopathologic, immunophenotypic, and molecular study of 22 Asian cases according to WHO-EORTC classification. Am J Surg Pathol 32(10):1495–502
9. Willemze R, Jaffe ES, Burg G, Cerroni L, Berti E, Swerdlow SH et al (2005) WHO-EORTC classification for cutaneous lymphomas. Blood 105(10):3768–85
10. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R et al (2016) The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 127(20):2375–90
11. Michonneau D, Petrella T, Ortonne N, Ingen-Housz-Oro S, Franck N, Barete S et al (2017) Subcutaneous Panniculitis-like T-cell Lymphoma: Immunosuppressive Drugs Induce Better Response than Polychemotherapy. Acta Derm Venereol 97(3):358–64
12. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H (2008) WHO classification of tumours of haematopoietic and lymphoid tumours. IARC Press, Lyon, France
13. He A, Kwatra SG, Kazi N, Sweren RJ (2016) Atypical lymphocytic lobular panniculitis: an overlap condition with features of subcutaneous panniculitis-like T-cell lymphoma and lupus profundus. BMJ Case Rep 2016
14. Bosisio F, Boi S, Caputo V, Chiarelli C, Oliver F, Ricci R et al (2015) Lobular panniculitic infiltrates with overlapping histopathologic features of lupus panniculitis (lupus profundus) and subcutaneous T-cell lymphoma: a conceptual and practical dilemma. Am J Surg Pathol 39(2):206–11
15. Pincus LB, LeBoit PE, McCalmont TH, Ricci R, Buzio C, Fox LP et al (2009) Subcutaneous panniculitis-like T-cell lymphoma with overlapping clinicopathologic features of lupus erythematosus: coexistence of 2 entities? Am J Dermatopathol 31(6):520–6
16. Arps DP, Patel RM (2013) Lupus profundus (panniculitis): a potential mimic of subcutaneous panniculitis-like T-cell lymphoma. Arch Pathol Lab Med 137(9):1211–5
17. Magro CM, Crowson AN, Kovatich AJ, Burns F (2001) Lupus profundus, indeterminate lymphocytic lobular panniculitis and subcutaneous T-cell lymphoma: a spectrum of subcuticular T-cell lymphoid dyscrasia. J Cutan Pathol 28(5):235–47
18. Dornmair K, Goebels N, Weltzien HU, Wekerle H, Hohlfeld R (2003) T-cell-mediated autoimmunity: novel techniques to characterize autoreactive T-cell receptors. Am J Pathol 163(4):1215–26
19. Wang X, Magro CM (2012) Human myxovirus resistance protein 1 (MxA) as a useful marker in the differential diagnosis of subcutaneous lymphoma versus lupus erythematosus profundus. Eur J Dermatol. 22(5):629–33
20. Liau JY, Chuang SS, Chu CY, Ku WH, Tsai JH, Shih TF (2013) The presence of clusters of plasmacytoid dendritic cells is a helpful feature for differentiating lupus panniculitis from subcutaneous panniculitis-like T-cell lymphoma. Histopathology 62(7):1057–66
21. Maliniemi P, Hahtola S, Ovaska K, Jeskanen L, Vakeva L, Jantti K et al (2014) Molecular characterization of subcutaneous panniculitis-like T-cell lymphoma reveals upregulation of immunosuppression- and autoimmunity-associated genes. Orphanet J Rare Dis. 9:160

22. Go RS, Wester SM (2004) Immunophenotypic and molecular features, clinical outcomes, treatments, and prognostic factors associated with subcutaneous panniculitis-like T-cell lymphoma: a systematic analysis of 156 patients reported in the literature. Cancer 101(6):1404–13
23. Ohtsuka M, Miura T, Yamamoto T (2017) Clinical characteristics, differential diagnosis, and treatment outcome of subcutaneous panniculitis-like T-cell lymphoma: a literature review of published Japanese cases. Eur J Dermatol. 27(1):34–41
24. Lee WS, Hwang JH, Kim MJ, Go SI, Lee A, Song HN et al (2014) Cyclosporine A as a Primary Treatment for Panniculitis-like T-cell Lymphoma: A Case with a Long-Term Remission. Cancer Res Treat. 46(3):312–6
25. Iqbal N, Raina V (2014) Successful treatment of disseminated subcutaneous panniculitis-like T-cell lymphoma with single agent oral cyclosporine as a first line therapy. Case Rep Dermatol Med. 2014:201836
26. Chen R, Liu L, Liang YM (2010) Treatment relapsed subcutaneous panniculitis-like T-cell lymphoma together HPS by Cyclosporin A. Hematol Rep. 2(1):e9
27. Mizutani S, Kuroda J, Shimura Y, Kobayashi T, Tsutsumi Y, Yamashita M et al (2011) Cyclosporine A for chemotherapy-resistant subcutaneous panniculitis-like T-cell lymphoma with hemophagocytic syndrome. Acta Haematol 126(1):8–12
28. Rojnuckarin P, Nakorn TN, Assanasen T, Wannakrairot P, Intragumtornchai T (2007) Cyclosporin in subcutaneous panniculitis-like T-cell lymphoma. Leuk Lymphoma 48(3):560–3
29. Jung HR, Yun SY, Choi JH, Bae SH, Ryoo HM, Kum YS (2011) Cyclosporine in Relapsed Subcutaneous Panniculitis-like T-cell Lymphoma after Autologous Hematopoietic Stem Cell Transplantation. Cancer Res Treat. 43(4):255–9
30. Gibson JF, Alpdogan O, Subtil A, Girardi M, Wilson LD, Roberts K et al (2015) Hematopoietic stem cell transplantation for primary cutaneous gammadelta T-cell lymphoma and refractory subcutaneous panniculitis-like T-cell lymphoma. J Am Acad Dermatol. 72(6):1010–5e5
31. Mukai HY, Okoshi Y, Shimizu S, Katsura Y, Takei N, Hasegawa Y et al (2003) Successful treatment of a patient with subcutaneous panniculitis-like T-cell lymphoma with high-dose chemotherapy and total body irradiation. Eur J Haematol 70(6):413–6
32. Reimer P, Rudiger T, Muller J, Rose C, Wilhelm M, Weissinger F (2003) Subcutaneous panniculitis-like T-cell lymphoma during pregnancy with successful autologous stem cell transplantation. Ann Hematol 82(5):305–9
33. Nakahashi H, Tsukamoto N, Yamane A, Saitoh T, Uchiumi H, Handa H et al (2009) Autologous peripheral blood stem cell transplantation to treat CHOP-refractory aggressive subcutaneous panniculitis-like T-cell lymphoma. Acta Haematol 121(4):239–42
34. Sakurai E, Satoh T, Akiko YA, Maesawa C, Tsunoda K, Endo M et al (2013) Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) with hemophagocytosis (HPS): successful treatment using high-dose chemotherapy (BFM-NHL & ALL-90) and autologous peripheral blood stem cell transplantation. J Clin Exp Hematop. 53(2):135–40
35. Yuan L, Sun L, Bo J, Zhou Y, Li HH, Yu L et al (2011) Durable remission in a patient with refractory subcutaneous panniculitis-like T-cell lymphoma relapse after allogeneic hematopoietic stem cell transplantation through withdrawal of cyclosporine. Ann Transplant. 16(3):135–8
36. Ichii M, Hatanaka K, Imakita M, Ueda Y, Kishino B, Tamaki T (2006) Successful treatment of refractory subcutaneous panniculitis-like T-cell lymphoma with allogeneic peripheral blood stem cell transplantation from HLA-mismatched sibling donor. Leuk Lymphoma 47(10):2250–2
37. Guitart J, Weisenburger DD, Subtil A, Kim E, Wood G, Duvic M et al (2012) Cutaneous gammadelta T-cell lymphomas: a spectrum of presentations with overlap with other cytotoxic lymphomas. Am J Surg Pathol 36(11):1656–65

38. Vin H, Talpur R, Tetzlaff MT, Duvic M (2014) T-cell receptor-gamma in gamma-delta phenotype cutaneous T-cell lymphoma can be accompanied by atypical expression of CD30, CD4, or TCRbetaF1 and an indolent clinical course. Clin Lymphoma Myeloma Leuk 14(6): e195–200
39. Youn SH, Lee YW, Min SK, Park HR, Kim KH, Kim KJ (2011) Fatal Cutaneous gamma/delta T-cell Lymphoma with Central Nerve System Metastasis. Ann Dermatol 23 (Suppl 1):S100–4
40. Chakrapani A, Avery A, Warnke R (2013) Primary cutaneous gamma delta T-cell lymphoma with brain involvement and hemophagocytic syndrome. Am J Dermatopathol 35(2):270–2
41. Harrington L, Sokol L, Holdener S, Shao H, Zhang L (2014) Cutaneous gamma-delta T-cell lymphoma with central nervous system involvement: report of a rarity with review of literature. J Cutan Pathol 41(12):936–43
42. Toro JR, Beaty M, Sorbara L, Turner ML, White J, Kingma DW et al (2000) gamma delta T-cell lymphoma of the skin: a clinical, microscopic, and molecular study. Arch Dermatol 136(8):1024–32
43. Kucuk C, Jiang B, Hu X, Zhang W, Chan JK, Xiao W et al (2015) Activating mutations of STAT5B and STAT3 in lymphomas derived from gammadelta-T or NK cells. Nat Commun. 6:6025
44. Trottestam H, Horne A, Arico M, Egeler RM, Filipovich AH, Gadner H et al (2011) Chemoimmunotherapy for hemophagocytic lymphohistiocytosis: long-term results of the HLH-94 treatment protocol. Blood 118(17):4577–84
45. Kao GF, Resh B, McMahon C, Gojo I, Sun CC, Phillips D et al (2008) Fatal subcutaneous panniculitis-like T-cell lymphoma gamma/delta subtype (cutaneous gamma/delta T-cell lymphoma): report of a case and review of the literature. Am J Dermatopathol 30(6):593–9
46. Guan YK, Gan CC (2016) Primary Cutaneous T-cell Lymphoma (Gamma Delta subtype). Med J Malaysia 71(5):296–7
47. Koch R, Jaffe ES, Mensing C, Zeis M, Schmitz N, Sander CA (2009) Cutaneous gamma/delta T-cell lymphoma. J Dtsch Dermatol Ges. 7(12):1065–7
48. Paralkar VR, Nasta SD, Morrissey K, Smith J, Vassilev P, Martin ME et al (2012) Allogeneic hematopoietic SCT for primary cutaneous T-cell lymphomas. Bone Marrow Transplant 47(7):940–5
49. Coiffier B, Pro B, Prince HM, Foss F, Sokol L, Greenwood M et al (2012) Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. J Clin Oncol 30(6):631–6
50. Piekarz RL, Frye R, Prince HM, Kirschbaum MH, Zain J, Allen SL et al (2011) Phase 2 trial of romidepsin in patients with peripheral T-cell lymphoma. Blood 117(22):5827–34
51. Sieniawski M, Angamuthu N, Boyd K, Chasty R, Davies J, Forsyth P et al (2010) Evaluation of enteropathy-associated T-cell lymphoma comparing standard therapies with a novel regimen including autologous stem cell transplantation. Blood 115(18):3664–70
52. Verbeek WH, Van De Water JM, Al-Toma A, Oudejans JJ, Mulder CJ, Coupe VM (2008) Incidence of enteropathy–associated T-cell lymphoma: a nation-wide study of a population-based registry in The Netherlands. Scand J Gastroenterol 43(11):1322–8
53. Delabie J, Holte H, Vose JM, Ullrich F, Jaffe ES, Savage KJ et al (2011) Enteropathy-associated T-cell lymphoma: clinical and histological findings from the international peripheral T-cell lymphoma project. Blood 118(1):148–55
54. Ellin F, Landstrom J, Jerkeman M, Relander T (2014) Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the Swedish Lymphoma Registry. Blood 124(10):1570–7
55. Gough KR, Read AE, Naish JM (1962) Intestinal reticulosis as a complication of idiopathic steatorrhoea. Gut 3:232–9
56. Ludvigsson JF, Leffler DA, Bai JC, Biagi F, Fasano A, Green PH et al (2013) The Oslo definitions for coeliac disease and related terms. Gut 62(1):43–52

57. Al-Toma A, Verbeek WH, Hadithi M, von Blomberg BM, Mulder CJ (2007) Survival in refractory coeliac disease and enteropathy-associated T-cell lymphoma: retrospective evaluation of single-centre experience. Gut 56(10):1373–8
58. Cellier C, Delabesse E, Helmer C, Patey N, Matuchansky C, Jabri B et al (2000) Refractory sprue, coeliac disease, and enteropathy-associated T-cell lymphoma. French Coeliac Disease Study Group. Lancet. 356(9225):203–8
59. Daum S, Weiss D, Hummel M, Ullrich R, Heise W, Stein H et al (2001) Frequency of clonal intraepithelial T lymphocyte proliferations in enteropathy-type intestinal T-cell lymphoma, coeliac disease, and refractory sprue. Gut 49(6):804–12
60. Farstad IN, Johansen FE, Vlatkovic L, Jahnsen J, Scott H, Fausa O et al (2002) Heterogeneity of intraepithelial lymphocytes in refractory sprue: potential implications of CD30 expression. Gut 51(3):372–8
61. Tack GJ, van Wanrooij RL, Langerak AW, Tjon JM, von Blomberg BM, Heideman DA et al (2012) Origin and immunophenotype of aberrant IEL in RCDII patients. Mol Immunol 50(4):262–70
62. Verbeek WH, Goerres MS, von Blomberg BM, Oudejans JJ, Scholten PE, Hadithi M et al (2008) Flow cytometric determination of aberrant intra-epithelial lymphocytes predicts T-cell lymphoma development more accurately than T-cell clonality analysis in Refractory Celiac Disease. Clin Immunol. 126(1):48–56
63. Kooy-Winkelaar YM, Bouwer D, Janssen GM, Thompson A, Brugman MH, Schmitz F et al (2017) CD4 T-cell cytokines synergize to induce proliferation of malignant and nonmalignant innate intraepithelial lymphocytes. Proc Natl Acad Sci U S A. 114(6):E980–E9
64. Gale J, Simmonds PD, Mead GM, Sweetenham JW, Wright DH (2000) Enteropathy-type intestinal T-cell lymphoma: clinical features and treatment of 31 patients in a single center. J Clin Oncol 18(4):795–803
65. Isaacson PG, Du MQ (2005) Gastrointestinal lymphoma: where morphology meets molecular biology. J Pathol. 205(2):255–74
66. Nijeboer P, de Baaij LR, Visser O, Witte BI, Cillessen SA, Mulder CJ et al (2015) Treatment response in enteropathy associated T-cell lymphoma; survival in a large multicenter cohort. Am J Hematol 90(6):493–8
67. Chan JK, Chan AC, Cheuk W, Wan SK, Lee WK, Lui YH et al (2011) Type II enteropathy-associated T-cell lymphoma: a distinct aggressive lymphoma with frequent gammadelta T-cell receptor expression. Am J Surg Pathol 35(10):1557–69
68. Mallant M, Hadithi M, Al-Toma AB, Kater M, Jacobs M, Manoliu R et al (2007) Abdominal computed tomography in refractory coeliac disease and enteropathy associated T-cell lymphoma. World J Gastroenterol 13(11):1696–700
69. Hoffmann M, Vogelsang H, Kletter K, Zettinig G, Chott A, Raderer M (2003) 18F-fluoro-deoxy-glucose positron emission tomography (18F-FDG-PET) for assessment of enteropathy-type T-cell lymphoma. Gut 52(3):347–51
70. Hadithi M, Mallant M, Oudejans J, van Waesberghe JH, Mulder CJ, Comans EF (2006) 18F-FDG PET versus CT for the detection of enteropathy-associated T-cell lymphoma in refractory celiac disease. J Nucl Med 47(10):1622–7
71. Laird J, Leach M, Ballantyne S (2008) The value of small bowel magnetic resonance imaging in the management of enteropathy associated T-cell lymphoma. Br J Haematol 142(1):136–7
72. Tomita S, Kikuti YY, Carreras J, Kojima M, Ando K, Takasaki H et al (2015) Genomic and immunohistochemical profiles of enteropathy-associated T-cell lymphoma in Japan. Mod Pathol 28(10):1286–96
73. Zettl A, Ott G, Makulik A, Katzenberger T, Starostik P, Eichler T et al (2002) Chromosomal gains at 9q characterize enteropathy-type T-cell lymphoma. Am J Pathol 161(5):1635–45
74. Deleeuw RJ, Zettl A, Klinker E, Haralambieva E, Trottier M, Chari R et al (2007) Whole-genome analysis and HLA genotyping of enteropathy-type T-cell lymphoma reveals 2 distinct lymphoma subtypes. Gastroenterology 132(5):1902–11

75. Nicolae A, Xi L, Pham TH, Pham TA, Navarro W, Meeker HG et al (2016) Mutations in the JAK/STAT and RAS signaling pathways are common in intestinal T-cell lymphomas. Leukemia 30(11):2245–7
76. Roberti A, Dobay MP, Bisig B, Vallois D, Boechat C, Lanitis E et al (2016) Type II enteropathy-associated T-cell lymphoma features a unique genomic profile with highly recurrent SETD2 alterations. Nat Commun. 7:12602
77. Nairismagi ML, Tan J, Lim JQ, Nagarajan S, Ng CC, Rajasegaran V et al (2016) JAK-STAT and G-protein-coupled receptor signaling pathways are frequently altered in epitheliotropic intestinal T-cell lymphoma. Leukemia 30(6):1311–9
78. Irving J, Matheson E, Minto L, Blair H, Case M, Halsey C et al (2014) Ras pathway mutations are prevalent in relapsed childhood acute lymphoblastic leukemia and confer sensitivity to MEK inhibition. Blood 124(23):3420–30
79. Gallamini A, Stelitano C, Calvi R, Bellei M, Mattei D, Vitolo U et al (2004) Peripheral T-cell lymphoma unspecified (PTCL-U): a new prognostic model from a retrospective multicentric clinical study. Blood 103(7):2474–9
80. de Baaij LR, Berkhof J, van de Water JM, Sieniawski MK, Radersma M, Verbeek WH et al (2015) A New and Validated Clinical Prognostic Model (EPI) for Enteropathy-Associated T-cell Lymphoma. Clin Cancer Res 21(13):3013–9
81. Daum S, Ullrich R, Heise W, Dederke B, Foss HD, Stein H et al (2003) Intestinal non-Hodgkin's lymphoma: a multicenter prospective clinical study from the German Study Group on Intestinal non-Hodgkin's Lymphoma. J Clin Oncol 21(14):2740–6
82. Wohrer S, Chott A, Drach J, Puspok A, Hejna M, Hoffmann M et al (2004) Chemotherapy with cyclophosphamide, doxorubicin, etoposide, vincristine and prednisone (CHOEP) is not effective in patients with enteropathy-type intestinal T-cell lymphoma. Ann Oncol 15(11):1680–3
83. Honemann D, Prince HM, Hicks RJ, Seymour JF (2005) Enteropathy-associated T-cell lymphoma without a prior diagnosis of coeliac disease: diagnostic dilemmas and management options. Ann Hematol 84(2):118–21
84. Novakovic BJ, Novakovic S, Frkovic-Grazio S (2006) A single-center report on clinical features and treatment response in patients with intestinal T-cell non-Hodgkin's lymphomas. Oncol Rep 16(1):191–5
85. Babel N, Paragi P, Chamberlain RS (2009) Management of Enteropathy-Associated T-cell Lymphoma: An Algorithmic Approach. Case Rep Oncol. 2(1):36–43
86. Di Sabatino A, Biagi F, Gobbi PG, Corazza GR (2012) How I treat enteropathy-associated T-cell lymphoma. Blood 119(11):2458–68
87. Malamut G, Chandesris O, Verkarre V, Meresse B, Callens C, Macintyre E et al (2013) Enteropathy associated T-cell lymphoma in celiac disease: a large retrospective study. Dig Liver Dis. 45(5):377–84
88. Egan LJ, Walsh SV, Stevens FM, Connolly CE, Egan EL, McCarthy CF (1995) Celiac-associated lymphoma. A single institution experience of 30 cases in the combination chemotherapy era. J Clin Gastroenterol 21(2):123–9
89. Tse E, Gill H, Loong F, Kim SJ, Ng SB, Tang T et al (2012) Type II enteropathy-associated T-cell lymphoma: a multicenter analysis from the Asia Lymphoma Study Group. Am J Hematol 87(7):663–8
90. Wierdsma NJ (2016) Nijeboer P, de van der Schueren MA, Berkenpas M, van Bodegraven AA, Mulder CJ. Refractory celiac disease and EATL patients show severe malnutrition and malabsorption at diagnosis. Clin Nutr 35(3):685–91
91. Di Sabatino A, Brunetti L, Carnevale Maffe G, Giuffrida P, Corazza GR (2013) Is it worth investigating splenic function in patients with celiac disease? World J Gastroenterol 19(15):2313–8
92. Gritti G, Boschini C, Rossi A, Delaini F, Grassi A, Algarotti A et al (2015) Primary treatment response rather than front line stem cell transplantation is crucial for long term outcome of peripheral T-cell lymphomas. PLoS ONE 10(3):e0121822

93. Bishton MJ, Haynes AP (2007) Combination chemotherapy followed by autologous stem cell transplant for enteropathy-associated T-cell lymphoma. Br J Haematol 136(1):111–3
94. d'Amore F, Relander T, Lauritzsen GF, Jantunen E, Hagberg H, Anderson H et al (2012) Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01. J Clin Oncol 30(25):3093–9
95. Jantunen E, Juvonen E, Wiklund T, Putkonen M, Nousiainen T (2003) High-dose therapy supported by autologous stem cell transplantation in patients with enteropathy-associated T-cell lymphoma. Leuk Lymphoma 44(12):2163–4
96. Al-Toma A, Verbeek WH, Visser OJ, Kuijpers KC, Oudejans JJ, Kluin-Nelemans HC et al (2007) Disappointing outcome of autologous stem cell transplantation for enteropathy-associated T-cell lymphoma. Dig Liver Dis. 39(7):634–41
97. Rongey C, Micallef I, Smyrk T, Murray J (2006) Successful treatment of enteropathy-associated T-cell lymphoma with autologous stem cell transplant. Dig Dis Sci 51(6):1082–6
98. Okuda M, Nomura J, Tateno H, Kameoka J, Sasaki T (2002) CD56 positive intestinal T-cell lymphoma: treatment with high dose chemotherapy and autologous peripheral blood stem cell transplantation. Intern Med 41(9):734–7
99. Jantunen E, Boumendil A, Finel H, Luan JJ, Johnson P, Rambaldi A et al (2013) Autologous stem cell transplantation for enteropathy-associated T-cell lymphoma: a retrospective study by the EBMT. Blood 121(13):2529–32
100. Chonabayashi K, Kondo T, Tanaka Y, Ichinohe T, Ishikawa T, Uchiyama T (2007) Sustained complete remission of refractory enteropathy-type T-cell lymphoma following reduced-intensity unrelated cord blood transplantation. Bone Marrow Transplant 40(9): 905–6
101. Nava VE, Cohen P, Bishop M, Fowler D, Jaffe ES, Ozdemirli M (2007) Enteropathy-type T-cell lymphoma after intestinal diffuse large B-cell lymphoma. Am J Surg Pathol 31(3):476–80
102. Regelink JC, Tack GJ, Huijgens PC, Mulder CJ, Janssen JJ, Visser O (2010) Disappointing outcome of allogeneic hematopoietic SCT in two EATL patients. Bone Marrow Transplant 45(5):959–60
103. Toumishey E, Prasad A, Dueck G, Chua N, Finch D, Johnston J et al (2015) Final report of a phase 2 clinical trial of lenalidomide monotherapy for patients with T-cell lymphoma. Cancer 121(5):716–23
104. Morschhauser F, Fitoussi O, Haioun C, Thieblemont C, Quach H, Delarue R et al (2013) A phase 2, multicentre, single-arm, open-label study to evaluate the safety and efficacy of single-agent lenalidomide (Revlimid) in subjects with relapsed or refractory peripheral T-cell non-Hodgkin lymphoma: the EXPECT trial. Eur J Cancer 49(13):2869–76
105. Gallamini A, Zaja F, Patti C, Billio A, Specchia MR, Tucci A et al (2007) Alemtuzumab (Campath-1H) and CHOP chemotherapy as first-line treatment of peripheral T-cell lymphoma: results of a GITIL (Gruppo Italiano Terapie Innovative nei Linfomi) prospective multicenter trial. Blood 110(7):2316–23
106. Kircher SM, Gurbuxani S, Smith SM (2007) CHOP plus alemtuzumab can induce metabolic response by FDG-PET but has minimal long-term benefits: a case report and literature review. J Gastrointest Cancer. 38(1):59–62
107. Soldini D, Mora O, Cavalli F, Zucca E, Mazzucchelli L (2008) Efficacy of alemtuzumab and gemcitabine in a patient with enteropathy-type T-cell lymphoma. Br J Haematol 142(3): 484–6
108. Ferreri AJ, Zinzani PL, Govi S, Pileri SA (2011) Enteropathy-associated T-cell lymphoma. Crit Rev Oncol Hematol 79(1):84–90
109. Raderer M, Troch M, Kiesewetter B, Puspok A, Jaeger U, Hoffmann M et al (2012) Second line chemotherapy in patients with enteropathy-associated T-cell lymphoma: a retrospective single center analysis. Ann Hematol 91(1):57–61

110. Berti E, Tomasini D, Vermeer MH, Meijer CJ, Alessi E, Willemze R (1999) Primary cutaneous CD8-positive epidermotropic cytotoxic T-cell lymphomas. A distinct clinicopathological entity with an aggressive clinical behavior. Am J Pathol 155(2):483–92
111. Nofal A, Abdel-Mawla MY, Assaf M, Salah E (2012) Primary cutaneous aggressive epidermotropic CD8 + T-cell lymphoma: proposed diagnostic criteria and therapeutic evaluation. J Am Acad Dermatol 67(4):748–59
112. Diwan H, Ivan D (2009) CD8-positive mycosis fungoides and primary cutaneous aggressive epidermotropic CD8-positive cytotoxic T-cell lymphoma. J Cutan Pathol 36(3):390–2
113. Wobser M, Reinartz T, Roth S, Goebeler M, Rosenwald A, Geissinger E (2016) Cutaneous CD8 + Cytotoxic T-cell Lymphoma Infiltrates: Clinicopathological Correlation and Outcome of 35 Cases. Oncol Ther. 4(2):199–210
114. Gormley RH, Hess SD, Anand D, Junkins-Hopkins J, Rook AH, Kim EJ (2010) Primary cutaneous aggressive epidermotropic CD8 + T-cell lymphoma. J Am Acad Dermatol 62(2):300–7
115. Liu V, Cutler CS, Young AZ (2007) Case records of the Massachusetts General Hospital. Case 38-2007. A 44-year-old woman with generalized, painful, ulcerated skin lesions. N Engl J Med 357(24):2496–505
116. Introcaso CE, Leber B, Greene K, Ubriani R, Rook AH, Kim EJ (2008) Stem cell transplantation in advanced cutaneous T-cell lymphoma. J Am Acad Dermatol 58(4):645–9
117. Santucci M, Pimpinelli N, Massi D, Kadin ME, Meijer CJ, Muller-Hermelink HK et al (2003) Cytotoxic/natural killer cell cutaneous lymphomas. Report of EORTC Cutaneous Lymphoma Task Force Workshop. Cancer 97(3):610–27
118. Petrella T, Maubec E, Cornillet-Lefebvre P, Willemze R, Pluot M, Durlach A et al (2007) Indolent CD8-positive lymphoid proliferation of the ear: a distinct primary cutaneous T-cell lymphoma? Am J Surg Pathol 31(12):1887–92
119. Li XQ, Zhou XY, Sheng WQ, Xu YX, Zhu XZ (2009) Indolent CD8 + lymphoid proliferation of the ear: a new entity and possible occurrence of signet ring cells. Histopathology 55(4):468–70
120. Swick BL, Baum CL, Venkat AP, Liu V (2011) Indolent CD8 + lymphoid proliferation of the ear: report of two cases and review of the literature. J Cutan Pathol 38(2):209–15
121. Geraud C, Goerdt S, Klemke CD (2011) Primary cutaneous CD8 + small/medium-sized pleomorphic T-cell lymphoma, ear-type: a unique cutaneous T-cell lymphoma with a favourable prognosis. Br J Dermatol 164(2):456–8
122. Zeng W, Nava VE, Cohen P, Ozdemirli M (2012) Indolent CD8-positive T-cell lymphoid proliferation of the ear: a report of two cases. J Cutan Pathol 39(7):696–700
123. Valois A, Bastien C, Granel-Broca F, Cuny JF, Barbaud A, Schmutz JL (2012) Indolent lymphoma of the ear. Ann Dermatol Venereol 139(12):818–23
124. Suchak R, O'Connor S, McNamara C, Robson A (2010) Indolent CD8-positive lymphoid proliferation on the face: part of the spectrum of primary cutaneous small-/medium-sized pleomorphic T-cell lymphoma or a distinct entity? J Cutan Pathol 37(9):977–81
125. Ryan AJ, Robson A, Hayes BD, Sheahan K, Collins P (2010) Primary cutaneous peripheral T-cell lymphoma, unspecified with an indolent clinical course: a distinct peripheral T-cell lymphoma? Clin Exp Dermatol 35(8):892–6
126. Greenblatt D, Ally M, Child F, Scarisbrick J, Whittaker S, Morris S et al (2013) Indolent CD8(+) lymphoid proliferation of acral sites: a clinicopathologic study of six patients with some atypical features. J Cutan Pathol 40(2):248–58
127. Butsch F, Kind P, Brauninger W (2012) Bilateral indolent epidermotropic CD8-positive lymphoid proliferations of the ear. J Dtsch Dermatol Ges. 10(3):195–6
128. Beltraminelli H, Mullegger R, Cerroni L (2010) Indolent CD8 + lymphoid proliferation of the ear: a phenotypic variant of the small-medium pleomorphic cutaneous T-cell lymphoma? J Cutan Pathol 37(1):81–4

129. Milley S, Bories N, Balme B, Thomas L, Dalle S (2012) Indolent CD8 + lymphoid proliferation on the nose. Ann Dermatol Venereol 139(12):812–7
130. Wobser M, Petrella T, Kneitz H, Kerstan A, Goebeler M, Rosenwald A et al (2013) Extrafacial indolent CD8-positive cutaneous lymphoid proliferation with unusual symmetrical presentation involving both feet. J Cutan Pathol 40(11):955–61
131. Kempf W, Kazakov DV, Cozzio A, Kamarashev J, Kerl K, Plaza T et al (2013) Primary cutaneous CD8(+) small- to medium-sized lymphoproliferative disorder in extrafacial sites: clinicopathologic features and concept on their classification. Am J Dermatopathol 35(2):159–66
132. Hagen JW, Magro CM (2014) Indolent CD8 + lymphoid proliferation of the face with eyelid involvement. Am J Dermatopathol 36(2):137–41
133. Wobser M, Roth S, Reinartz T, Rosenwald A, Goebeler M, Geissinger E (2015) CD68 expression is a discriminative feature of indolent cutaneous CD8-positive lymphoid proliferation and distinguishes this lymphoma subtype from other CD8-positive cutaneous lymphomas. Br J Dermatol 172(6):1573–80
134. Kluk J, Kai A, Koch D, Taibjee SM, O'Connor S, Persic M et al (2016) Indolent CD8-positive lymphoid proliferation of acral sites: three further cases of a rare entity and an update on a unique patient. J Cutan Pathol 43(2):125–36
135. Beltraminelli H, Leinweber B, Kerl H, Cerroni L (2009) Primary cutaneous CD4 + small-/medium-sized pleomorphic T-cell lymphoma: a cutaneous nodular proliferation of pleomorphic T lymphocytes of undetermined significance? A study of 136 cases. Am J Dermatopathol 31(4):317–22
136. Choi M, Park SY, Park HS, Byun HJ, Cho KH (2011) A Case of Primary Cutaneous CD4 Positive Small/medium T-cell Lymphoma. Ann Dermatol 23(1):76–80
137. Beljaards RC, Meijer CJ, Van der Putte SC, Hollema H, Geerts ML, Bezemer PD et al (1994) Primary cutaneous T-cell lymphoma: clinicopathological features and prognostic parameters of 35 cases other than mycosis fungoides and CD30-positive large cell lymphoma. J Pathol. 172(1):53–60
138. Rodriguez Pinilla SM, Roncador G, Rodriguez-Peralto JL, Mollejo M, Garcia JF, Montes-Moreno S et al (2009) Primary cutaneous CD4 + small/medium-sized pleomorphic T-cell lymphoma expresses follicular T-cell markers. Am J Surg Pathol 33(1):81–90
139. Ally MS, Prasad Hunasehally RY, Rodriguez-Justo M, Martin B, Verdolini R, Attard N et al (2013) Evaluation of follicular T-helper cells in primary cutaneous CD4 + small/medium pleomorphic T-cell lymphoma and dermatitis. J Cutan Pathol 40(12):1006–13
140. Battistella M, Beylot-Barry M, Bachelez H, Rivet J, Vergier B, Bagot M (2012) Primary cutaneous follicular helper T-cell lymphoma: a new subtype of cutaneous T-cell lymphoma reported in a series of 5 cases. Arch Dermatol 148(7):832–9
141. von den Driesch P, Coors EA (2002) Localized cutaneous small to medium-sized pleomorphic T-cell lymphoma: a report of 3 cases stable for years. J Am Acad Dermatol 46(4):531–5
142. James E, Sokhn JG, Gibson JF, Carlson K, Subtil A, Girardi M et al (2015) CD4 + primary cutaneous small/medium-sized pleomorphic T-cell lymphoma: a retrospective case series and review of literature. Leuk Lymphoma 56(4):951–7
143. Grogg KL, Jung S, Erickson LA, McClure RF, Dogan A (2008) Primary cutaneous CD4-positive small/medium-sized pleomorphic T-cell lymphoma: a clonal T-cell lymphoproliferative disorder with indolent behavior. Mod Pathol 21(6):708–15
144. Garcia-Herrera A, Colomo L, Camos M, Carreras J, Balague O, Martinez A et al (2008) Primary cutaneous small/medium CD4 + T-cell lymphomas: a heterogeneous group of tumors with different clinicopathologic features and outcome. J Clin Oncol 26(20):3364–71
145. Buder K, Poppe LM, Brocker EB, Goebeler M, Rosenwald A, Geissinger E et al (2013) Primary cutaneous follicular helper T-cell lymphoma: diagnostic pitfalls of this new lymphoma subtype. J Cutan Pathol 40(10):903–8

146. Ohmatsu H, Sugaya M, Fujita H, Kadono T, Sato S (2014) Primary cutaneous follicular helper T-cell lymphoma treated with allogeneic bone marrow transplantation: immunohistochemical comparison with angioimmunoblastic T-cell lymphoma. Acta Derm Venereol 94(1):54–7
147. Shamsuyarova A, Kamil Z, Delabie J, Al-Faraidy N, Ghazarian D (2017) Primary Cutaneous Follicular Helper T-cell Lymphoma in a Patient With Neurofibromatosis Type 1: Case Report and Review of the Literature. Am J Dermatopathol 39(2):134–9

Primary Cutaneous T-Cell Lymphomas: Mycosis Fungoides and Sezary Syndrome

11

Christiane Querfeld, Jasmine Zain and Steven T. Rosen

Abstract

Mycosis fungoides and Sézary syndrome are the most common subtypes of all primary cutaneous lymphomas and represent complex diseases that require a multidisciplinary assessment by dermatologists, oncologists, and pathologists. Staging and work-up are critical to guarantee an optimal treatment plan that includes skin-directed and/or systemic regimens depending on the clinical stage, tumor burden, drug-related side effect profile, and patient comorbidities. However, there is no cure and patients frequently relapse, requiring repeated treatment courses for disease control. The study of the tumor microenvironment and molecular mechanisms of these rare neoplasms may assist in the development of new immune therapies providing promising treatment approaches tailored for patients with relapse/refractory disease.

Keywords

Cutaneous T-cell lymphoma · Mycosis fungoides · Sézary syndrome · Clinical and pathologic features · Molecular hallmarks · Tumor microenvironment · Treatment strategies · Immunotherapies

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11.1 Introduction

Primary cutaneous T-cell lymphomas (CTCL) account for approximately 70% of all primary cutaneous lymphomas with an annual age-adjusted incidence of 6.4–9.6 cases per million people in the United States [1]. CTCL are skin homing non-Hodgkin lymphomas that include marked heterogeneous subtypes with differences in histopathologic and clinical presentation (Table 1) [2]. Based on the revised World Health Organization and European Organization for Research and Treatment of Cancer (WHO-EORTC) classification, mycosis fungoides (MF) and the leukemic form Sézary syndrome (SS) are the most common subtypes representing 53% of all

Table 1 The revised World Health Organization/European Organization for Research and Treatment of Cancer consensus classification for primary cutaneous lymphomas with relative frequency and survival [2]

Cutaneous T-cell and NK-cell lymphomas	Frequency (%)	5 year survival (%)
Indolent		
Mycosis Fungoides	44	88
MF variants and subtypes		
• Folliculotropic MF • Pagetoid reticulosis • Granulomatous slack skin	4 <1 <1	80 100 100
Primary cutaneous CD30+ lymphoproliferative disorders		
• Lymphomatoid papulosis • Primary cutaneous anaplastic large cell lymphoma	12 8	100 95
Subcutaneous panniculitis-like T-cell lymphoma	1	82
Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoproliferative disorder (provisional)	2	72
Aggressive		
Sézary syndrome	3	24
Extranodal NK/T-cell lymphoma, nasal type	<1	–
Primary cutaneous peripheral T-cell lymphoma, unspecified		
• Primary cutaneous epidermotropic CD8+ T-cell lymphoma (provisional) • Cutaneous γ/δ T-cell lymphoma (provisional)	<1 <1	18 –
Cutaneous B-cell lymphomas		
Indolent clinical behavior		
Primary cutaneous marginal zone lymphoma	7	99
Primary cutaneous follicular lymphoma	11	95
Primary cutaneous diffuse large B-cell lymphoma, leg type	4	55
Primary cutaneous diffuse large B-cell lymphoma, other	<1	50
• Intravascular large B-cell lymphoma	<1	65
Precursor hematologic neoplasm		
• CD4+/CD56+ blastic plasmacytoid dendritic cell neoplasm	–	–

EORTC, European Organization for Research and Treatment of Cancer; NK, natural killer; *WHO*, World Health Organization

cutaneous lymphomas [2]. MF and SS share overlapping features but are generally considered to be distinct entities. The prognosis of the disease depends on the skin disease burden and extracutaneous involvement [3]. While classic MF is characterized by an indolent course with slow progression and a five-year overall survival of 78%, SS progresses rapidly with a five-year overall survival of 26% [4]. Appropriate diagnostic procedures in MF/SS include complete physical examination with the evaluation of type and extension of skin lesions captured by the modified Severity Weighted Assessment Tool (mSWAT), lymphadenopathy and/or hepatosplenomegaly, peripheral blood cell count (CBC); comprehensive chemistry panel with lactate dehydrogenase levels (LDH), positron emission tomography/computed tomography (PET/CT) scans, skin biopsy with immunophenotyping, peripheral flow cytometry for circulating Sézary cells and T-cell receptor (TCR) gene rearrangement (Table 2) [3]. The following chapter will focus on MF/SS, providing a concise review

Table 2 Recommended staging and work-up for patients with mycosis fungoides and Sézary syndrome [3]

Complete physical examination
Identification of skin burden
• Percentage of BSA involved in each type of skin lesions (patches, plaques, tumors, erythroderma, and/or any ulcerated, crusted/oozing lesion) • mSWAT
Identification of any palpable lymph node or organomegaly
Skin biopsy
• Immunophenotyping to include at least the following markers CD3, CD4, CD5, CD7, CD8, and one B-cell marker such as CD20 • CD30 in large cell transformed MF, or if lymphomatoid papulosis, pcALCL is considered • T-cell receptor rearrangement analysis
Laboratory work-up
• CBC with differential • Comprehensive metabolic panel • LDH • T-cell receptor rearrangement analysis (compare to skin if positive) • Flow cytometry for circulating Sézary cells (CD4+ CD7- or CD4+ CD26-) (erythrodermic patients) • HTLV-I/II titers in selected patients
Imaging studies
• No imaging studies are required for stage IA/IB (T1N0M0B0; T2N0M0B0) • CT scans of chest, abdomen, and pelvis (disseminated stage IB and higher) • Combined PET/CT scans are recommended
Lymph node biopsy
• Excisional biopsy for lymph nodes ≥ 1.5 cm and/or firm, irregular, clustered, or fixed nodes • Biopsy of the largest lymph node draining an involved area or the node with highest standardized uptake value on PET/CT scans
Multidisciplinary assessment by dermatologists, oncologists, pathologists/dermatopathologists and social worker is highly recommended

BSA body surface area; *CBC* complete blood cell count; *CMP* comprehensive metabolic panel; *CT* computed tomography; *HTLV-I/II* human lymphotropic virus I/II; *LDH* lactate dehydrogenase; *mSWAT* modified severity weighted assessment tool; *pcALCL* primary cutaneous anaplastic large cell lymphoma; *PET* positron emission tomography

of clinical and histological patterns, pathogenesis, immunologic and molecular hallmarks and recent discoveries in the tumor microenvironment that has assisted in the development of current and new immune therapies.

11.2 Clinicopathological Features

Classic MF initially presents with erythematous patches and/or plaques with a propensity for sun-protected areas including the breasts, buttocks, lower trunk, and inguinal areas (Fig. 1a, b). MF patients may progress to cutaneous tumors (Fig. 1c, d), erythroderma, or systemic disease with nodal, blood or visceral involvement. Three major subtypes of MF are recognized in the WHO-EORTC classification: folliculotropic MF (FMF), pagetoid reticulosis (PR), and granulomatous slack skin (GSS). However, MF has numerous manifestations that often require clinicopathological correlation for accurate diagnosis [5]. FMF often presents with papules and plaques with associated alopecia involving the face with characteristic eyebrow involvement, scalp, neck, and upper torso (Fig. 2a–c). Patients may also present with comedones, pustules, cysts, milia, and prurigo nodularis-like lesions and have significant pruritus. FMF has a worse prognosis compared to classic MF [6]. Pagetoid reticulosis

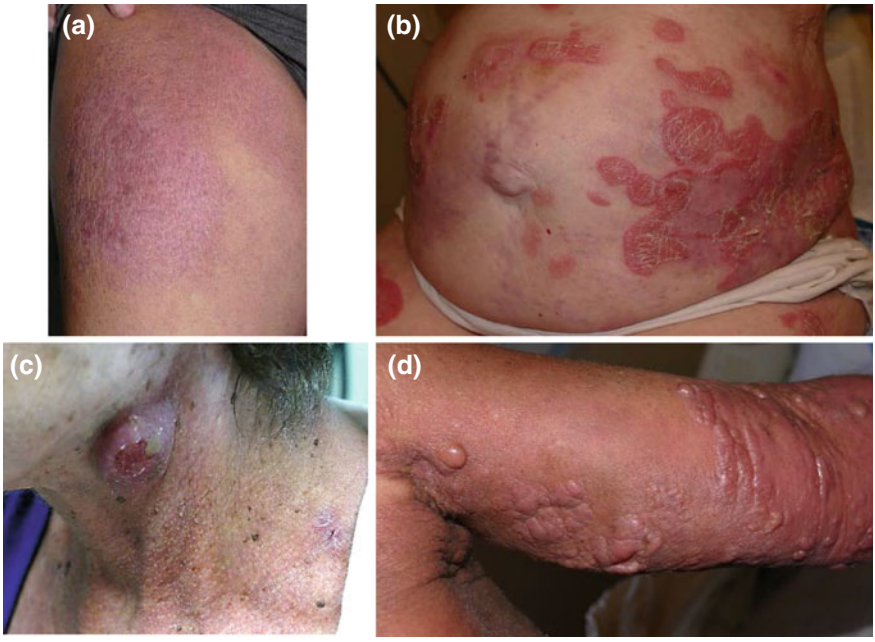


Fig. 1 Clinical features of patients with mycosis fungoides. Patients presenting with large poikilodermatous patches/plaques (**a**), erythematosquamous plaques (**b**), solitary and partially ulcerated tumor on the neck (**c**) and presenting with numerous plaques and tumor nodules (**d**)

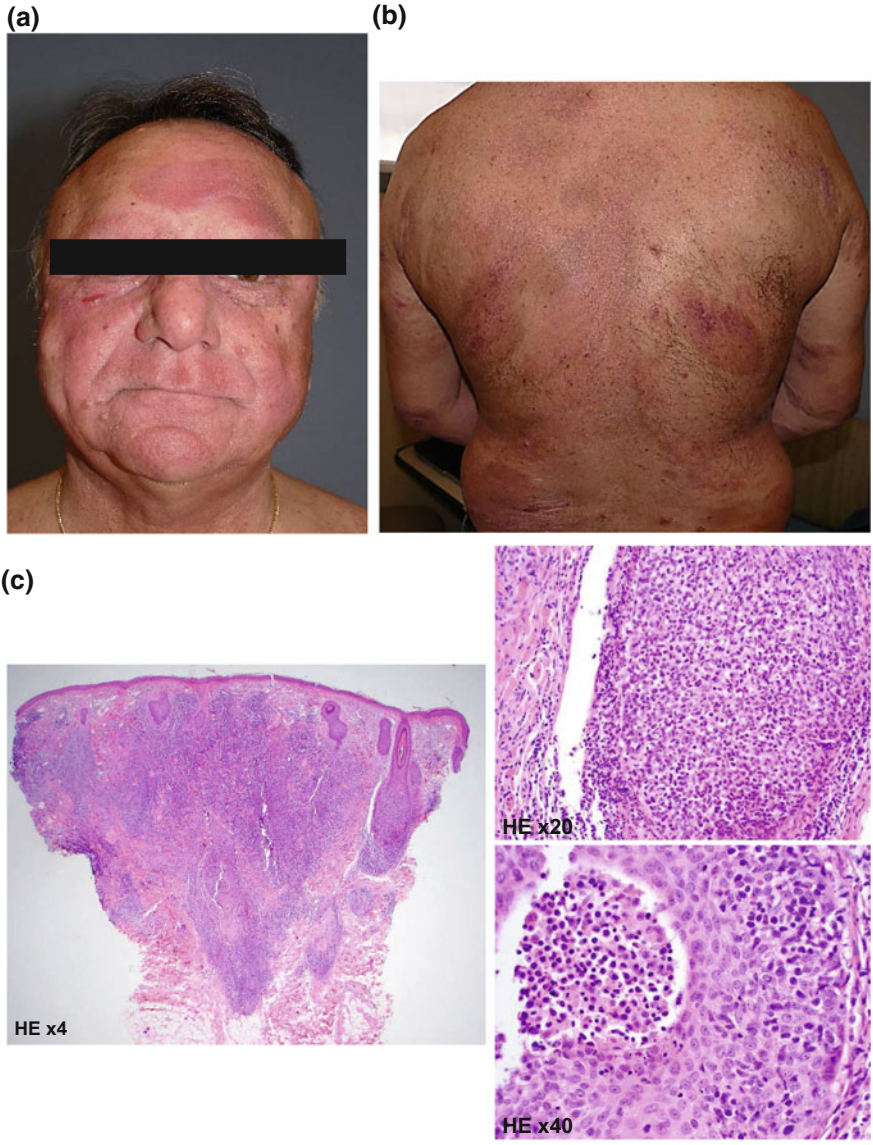


Fig. 2 Patient with folliculotropic mycosis fungoides presenting with erythematous plaques on face, with characteristic alopecia of the eyebrows and periocular milia (**a**) and back with erythematous plaques with associated alopecia (**b**). Histopathologic features of the skin biopsy performed shows a dense deep dermal lymphoid infiltrate of atypical lymphocytes with prominent folliculotropism of single and clusters (Pautrier microabscesses) of atypical lymphocytes (**b**) (Hematoxylin eosin [HE] x40 magnification; HE x200 and HE x400 magnification)

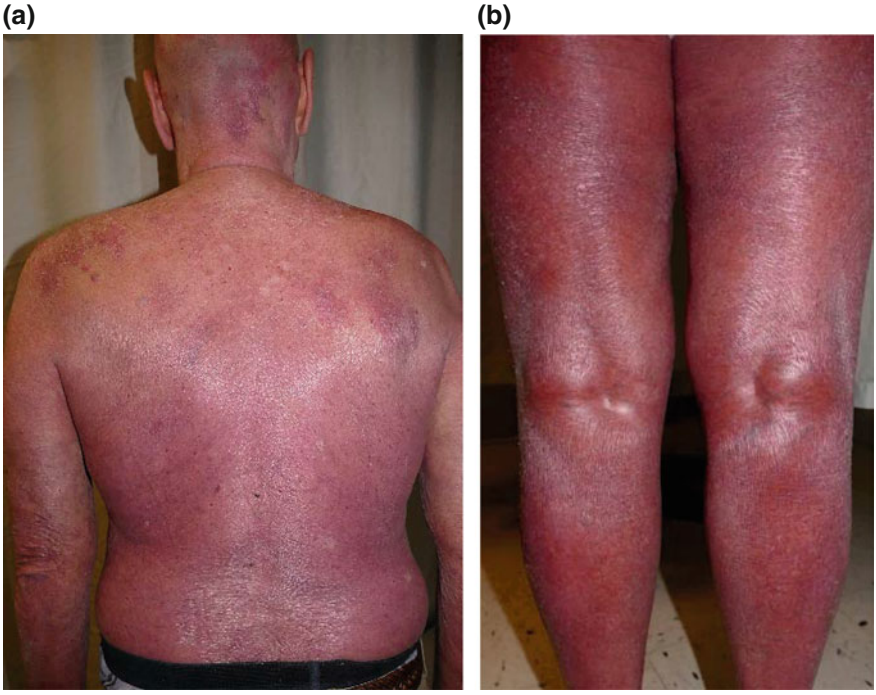


Fig. 3 Patient with Sézary syndrome presenting with erythroderma covering the entire body surface area (**a**) with areas of lichenification noted on bilateral lower extremities (**b**)

(Woringer-Kolopp disease) is an indolent MF variant that presents with a solitary, slowly progressing, hyperkeratotic plaque on acral areas. The development of circumscribed erythematous pendulous or redundant skin with poikilodermatous surface on axillary and inguinal folds is characteristic of GSS. This uncommon MF variant requires close monitoring since GSS has been associated with secondary malignancy, especially Hodgkin lymphoma [2, 7]. Other variants include hypopigmented MF, predominantly seen in children/young adults and/or dark-skinned individuals and is frequently misdiagnosed as vitiligo. Whereas MF is generally considered to have an indolent and protracted clinical course, SS is characterized by an aggressive course; patients present with erythroderma and circulating malignant T lymphocytes with cerebriform nuclei (Sézary cells), with or without peripheral lymphadenopathy (Fig. 3a, b). SS patients have severe disabling pruritus and dry flaky skin and are distinguished from patients with erythrodermic MF by the initial presentation of a high number of circulating malignant T-cells (≥ 1000 cells/mm^3).

Patch/plaque lesions of MF show various degrees of epidermotropism consisting of single or clusters (Pautrier microabscess) of atypical lymphocytes and a superficial band-like lymphoid infiltrate composed of small to medium-sized atypical T-cells with irregular, hyperconvoluted nuclei interspersed with small tumor-infiltrating T-cells and histiocytes (Fig. 4a). With progression to tumor

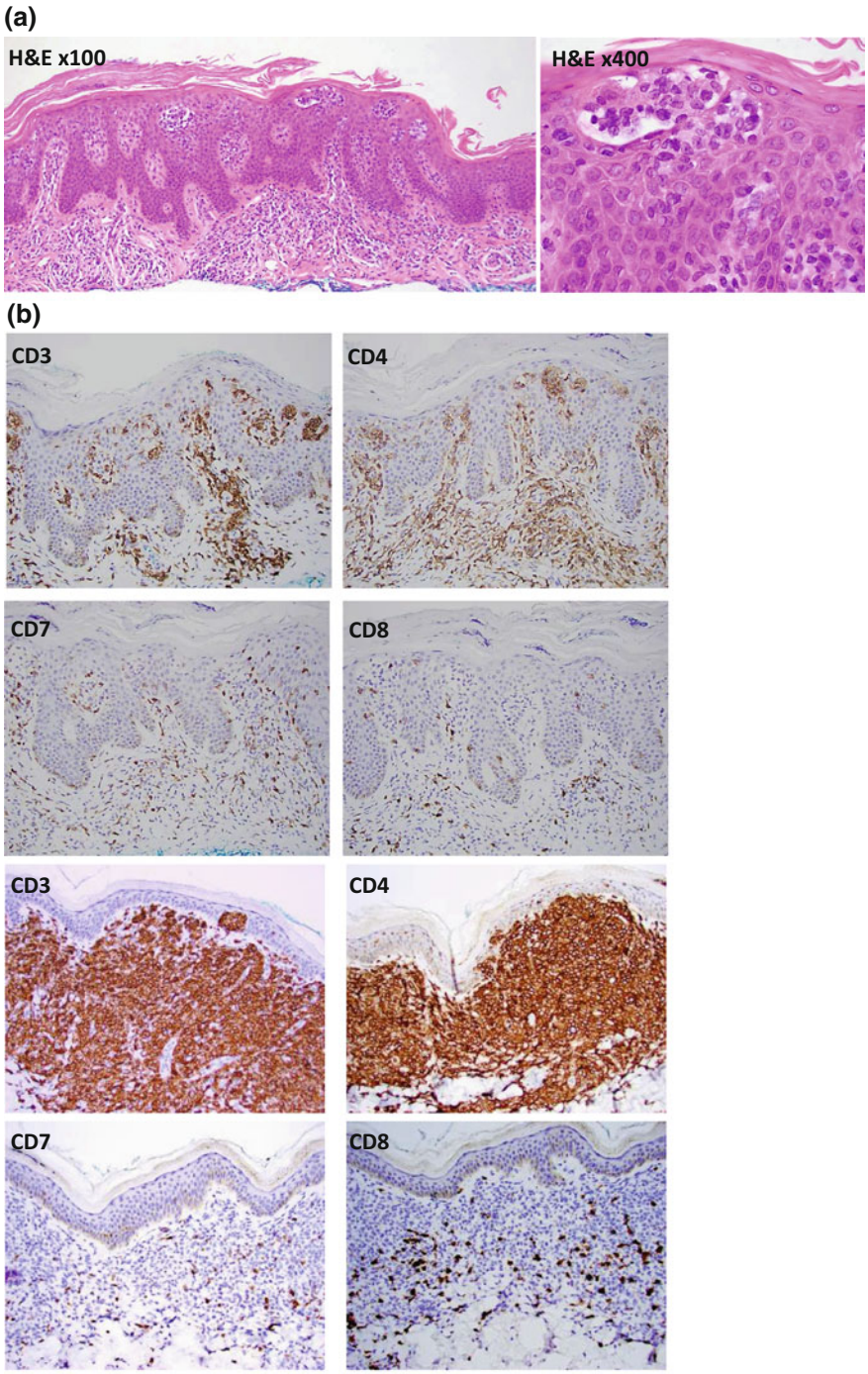


Fig. 4 Histopathologic findings of classic mycosis fungoides. The superficial dermis shows a band-like infiltrate with atypical lymphocytes. There is epidermotropism of atypical lymphocytes with Pautrier microabscesses seen (**a**) (HE x100 & 400 magnification). The atypical lymphocytes are positive for CD3, CD4, and negative for CD8 with loss of CD7. **b** (x200 magnification)

lesions the infiltrate becomes more diffuse extending into deep dermis with absence of epidermotropism. The malignant T-cells have a CD4+ CD8-phenotype (Fig. 4b) with frequent loss of CD7 and to a lesser extent CD5. PR shows striking pagetoid epidermotropism of atypical T-cells having either a CD4+ or CD8+ phenotype. A CD8+ phenotype is characteristic of hypopigmented MF. Of note, cases of CD8+ phenotype show the same clinical behavior and prognosis as cases with a CD4+ phenotype [8].

Large cell transformation (LCT) is a worse prognostic factor that is defined by the presence of large lymphoid cells comprising $\geq$ 25% of the total infiltrate (Fig. 5a, b) and is mostly seen in newly developed tumors (Fig. 5c) and associated with disease progression. The large cells may express CD30 and cytotoxic markers (TIA1, granzyme B, and perforin). Histopathologic features of erythrodermic MF and SS can be challenging due to subtle or nondiagnostic findings. A combination of immunophenotypic markers including PD1 may be helpful to differentiate from benign inflammatory skin disorders [9]. Peripheral blood flow cytometry analysis determines circulating Sézary cells by showing an abnormal CD4+ CD26- or CD4+ CD7- T-cell population [3].

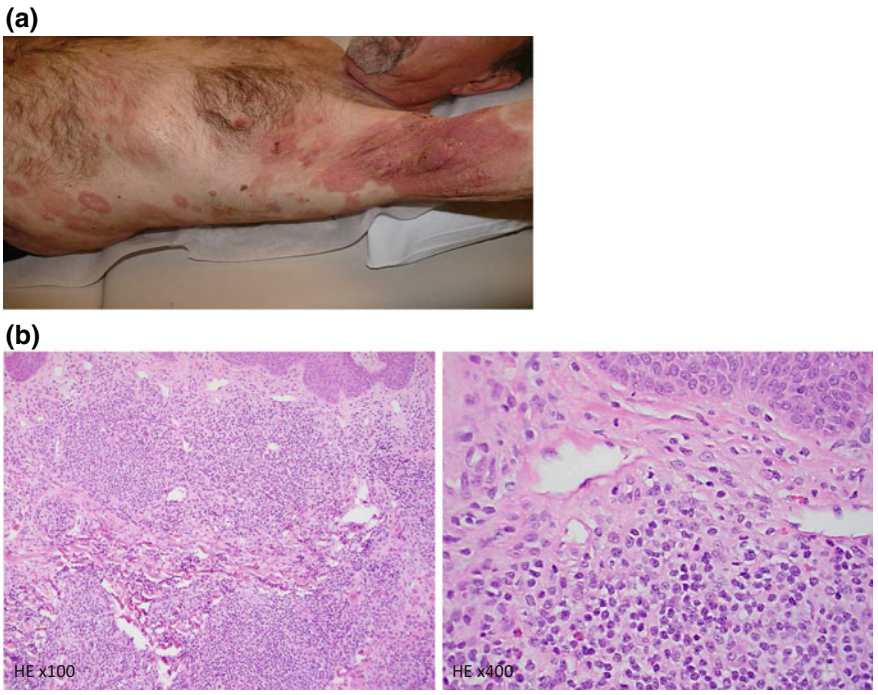


Fig. 5 Patient with transformed mycosis fungoides presenting with plaques and tumors in right axilla and trunk (**a**). Histopathologic features of corresponding skin biopsy show a dense nodular and deep dermal lymphoid infiltrate composed of sheets large atypical lymphocytes (**b**) (HE x100; HE x400 magnification)

11.3 Etiology

The malignant T-cell phenotype in CTCL is thought to arise from a background of chronic antigenic stimulation with underlying cytogenetic abnormalities that leads to clonal proliferation of malignant lymphocytes manifesting as MF and SS [10]. In vitro investigations have shown an upregulation of antigen presenting cell (APC) ligands such as B7 and CD40, as well as their costimulatory molecules CD28 and CD40L in MF lesions, supporting the hypothesis of an inflammatory milieu that contributes to the tumor growth [11]. Other studies have shown increased expression of Toll-like receptors (TLRs) 2, 4, and 9 by keratinocytes in MF patients [12]. Specifically, TLR2 recognizes pathogen-associated molecular patterns (PAMPs) from *Staphylococcus aureus*, and a number of studies provided evidence that cutaneous colonization with *Staphylococcus aureus* influences the disease activity of MF/SS and may be the cause of the upregulation of the mentioned TLRs in MF. A significant improvement of erythroderma and skin disease burden after the eradication of *Staphylococcus aureus* with antibiotics in patients with erythrodermic MF and SS [13]. In vitro treatment of Sézary cells with staphylococcal exfoliating toxin and toxic shock syndrome toxin-1, both known to activate the TCR-Vb2 region has led to selective proliferation of Vb2.11 bearing Sézary cells that were enhanced in the presence of proinflammatory interleukin-1 (IL-1) [14]. Viral agents, such as human T-cell lymphotropic virus type 1 (HTLV-1), Ebstein–Barr virus (EBV), and Cytomegalovirus (CMV) have been investigated but the serologic results and the detection of viral genomic sequences in MF skin lesions were controversial [15–17].

11.4 Pathogenesis and Immune Dysregulation

The skin homing malignant lymphocytes in MF and SS derive from mature CD4+ memory T-cells and can display differentiation markers of CD25+FOXP3+ regulatory T-cells (Tregs), T helper type 2 cells (Th2) or Th17 cells [18–20]. Tregs produce IL-10 and transforming growth factor beta (TGF-β) to promote an immunosuppressive microenvironment in MF [21]. Patch/plaque lesions (early stage MF) have a Th1 cytokine profile with high expression of IL-2, IL-12, and interferon-gamma (INF-γ), whereas in advanced tumor stage MF the immune milieu changes from a Th1 to Th2 cytokine profile. The Th2 cytokines (IL-4, IL-5, IL-10, and IL-13) may lead to peripheral eosinophilia and high serum levels of IgE, erythroderma, immunosuppression and increased susceptibility to bacterial infections that are major causes of death in advanced MF/SS. Treatments that inhibit Th2 cytokine activity, such as interferon-alpha-2b (IFNα2b) and extracorporeal photopheresis have shown a therapeutic benefit in CTCL, enhancing the antitumor response and thereby clearing the malignant T-cells [22]. In contrast to Th1 and Th2 phenotypes, the Th17 phenotype has been observed in all stages of MF. The Th17 cells produce proinflammatory IL-17, which is promoted by the JAK3/STAT3 pathway and hereby facilitating the growth of CTCL growth [20].

Malignant T-cells of SS are of the central memory T-cell subset and are capable of circulating between skin, lymph nodes and blood; while those in MF are considered as non-recirculating skin resident effector memory T-cells [23, 24]. The migration of malignant T-cells to the skin is driven by the expression of various chemokine receptors (CCR) and adhesion molecules involved in normal skin immunosurveillance. While all MF stages show an increased expression of the skin homing CCR4 that facilitates migration of the neoplastic T-cells into the skin an increased expression of the lymph node homing CCR7 is seen in advanced/tumor stage of MF and SS [25, 26]. CCR7 expression correlates with loss of epidermotropism and promotes extracutaneous spread with the migration of T-cells to blood, lymph nodes and internal organs [27, 28]. Chemokines produced by epidermal and dermal dendritic cells (DCs) in the CTCL microenvironment, may also play important roles in attracting malignant T-cells to the skin and may be involved in the subsequent T-cell activation.

Dysfunctional apoptosis due to decreased and/or defective FAS death receptor expression in neoplastic T-cells has been associated with advanced disease and was recognized as an immune escape mechanism in CTCL. Multiple abnormalities including FAS gene mutations, promoter hypermethylation and the production of nonfunctioning splice variants have been observed, leading to apoptosis resistance and enabling continued proliferation of CTCL cells [29, 30]. Malignant T-cells in MF and SS overexpress IL-2 receptor subunit alpha (IL2RA; CD25) that results from a cascade of phosphorylation of several proteins including JAK3, STAT3 and STAT5 [31, 32]. High expression of IL-2RA (CD25) statistically correlated with advanced TNM stage and with better responses to IL-2RA-directed fusion protein, such as denileukin diftitox [33]. Genomic analysis studies have detected recurrent gain-of-function mutations targeting JAK1, JAK3, STAT3, and STAT5B in SS genomes, which suggest a role for JAK/STAT inhibitors for the treatment of CTCL. An incomplete understanding of molecular regulators involved in CTCL has limited the development of effective targeted therapies. One candidate regulator is p38γ. Zhang et al. demonstrated that p38γ gene expression is selectively increased in CTCL patient samples and cell lines, but not in healthy T-cells [34]. The authors found that p38γ is a molecular regulator for mitogen-activated protein kinase (MAPK) and crucial for malignant T-cell activation and growth through the nuclear factor of activated T-cells (NFAT) pathway hereby targeting DLGH1 an important scaffolding protein for T-cell receptor signaling. Querfeld et al. have provided evidence for T-cell exhaustion as an immunosuppressive mechanism in CTCL [35]. Compared with healthy skin, CD4+ CTCL populations contained more T-cells expressing PD-1, CTLA-4, and LAG-3. CD8+ CTCL populations contained more T-cells expressing CTLA-4 and LAG-3. CTCL populations also contained more T-cells expressing the inducible T-cell costimulator (ICOS), a marker of T-cell activation. DC émigrés from healthy and lesional CTCL skin biopsies expressed PD-L1, indicating that maturation during migration resulted in PD-L1 expression irrespective of disease. CTCL cells might be functionally exhausted due to continuous antigen overload lead by the immature DCs and similar to what is seen in chronic viral infections [36].

11.5 Molecular Hallmarks

The accumulation of cytogenetic abnormalities during disease progression has been observed in CTCL. Some of these include genomic mutations that upregulate the activity of several transcription factors such as JUNB and STAT3 that are involved in T-cell proliferation, differentiation and/or apoptosis. The constitutive activation of STAT3 that has been proposed as a novel therapeutic target in CTCL. Other mutations that are involved in cell cycle control include the decreased expression of regulating cell cycle proteins p15 and p16, the hemi or homozygous deletion of CDKN2A and CKN2B, as well as the aberrant cytosine-guanine (CpG) island methylation leading to epigenetic silencing of multiple suppressor genes [32, 37, 38]. Studies also identified loss-of-function aberrations targeting members of the chromatin remodeling, such as ARID1A, as well as potential oncogenic driver genes in SS including POT1, TP53 and DNMT3A [39, 40].

Using whole-genomic sequencing in MF/SS samples, one study found genetic mutations affecting NF-kβ signaling pathway and recurrent point mutations and gains of TNFRSF1B gene encoding the tumor necrosis factor receptor TNFR2 [41]. The same study also observed a recurrent CTLA-CD28 fusion mutation with large deletion of chromosome 2 and thought to be an oncogenic driver in a subset of patients with SS [41]. Other chromosomal abnormalities, such as allelic losses on chromosomes 10p and 17p have been described in CTCL, but their clinical and prognostic significance is still unclear [38, 42].

Recent discoveries indicate that the oncogenic microRNA (miR)-155 is over-expressed in lesional skin from CTCL patients, and its expression is regulated by the JAK/STAT5 pathway [43]. In mouse models, knockdown of STAT5 resulted in a 40% inhibition of miR-155 expression, supporting the use of miR-155 and JAK/STAT inhibitors as future therapeutic targets for relapsed/refractory CTCL [44, 45]. Other studies have shown that approximately 30% of CTCL skin biopsies demonstrated microsatellite instability (MSI) by PCR amplification, while it was only seen in 5% of PCR products from control tissue of patients with lichen planus. These results suggest that MSI might be used to assess genetic heterogeneity and instability, and for detecting tumor subclones in early stage MF [46].

11.6 CTCL Microenvironment

The tumor microenvironment in CTCL is composed of malignant T-cells and of nonmalignant immune cells including CD8+ tumor-infiltrating T-cells, Tregs, DCs, macrophages and mast cells. In early stage MF, the infiltrate mainly consists of nonmalignant tumor-infiltrating T-cells and histiocytes [47, 48]. A higher proportion of CD8+ tumor-infiltrating T-cells were found in skin biopsies from patients with early stage of MF compared with those with advanced T-stage disease and correlated with improved survival [49]. Tregs have also been associated with improved outcomes in MF and other CTCL variants but has not been substantiated

by others [50, 51]. The malignant T-cells are known to adopt a Treg phenotype expressing FOXP3 and producing the immunosuppressive cytokines IL-10 and TGF-β [52]. Of note, the FOXP3+ phenotype is dependent on the IL-2Rβ-signaling cytokines IL-2 and/or IL-15 by activating JAK3 and STAT5 [53]. Noteworthy, mogamulizumab is a new treatment option that is being used for MF with the potential to modulate/deplete Tregs.

The close interaction between DCs and MF cells is evident in the classic morphology of an epidermal Pautrier microabscess. Berger et al. showed that the neoplastic T-cells grew in long-term cultures when they were cocultured with immature DCs [52]. The malignant T-cell proliferation was inhibited by the addition of anti-TCR and anti-CD40 antibodies, supporting the hypothesis that the growth of CTCL is driven by the interaction between the MHC class II peptides on DCs and the TCR on neoplastic T-cells. Additionally, the atypical lymphocytes would aid in the maintenance of DC survival through the interaction of the CD40 ligand on malignant T-cells with the CD40 receptor expressed on the DC [52]. Based on this data, the DCs may be presumably activated by tumor-specific antigens and promote uncontrolled T-cell proliferation and progression to a full-blown skin lymphoma [54].

Recent studies have shown the protumorigenic role of mast cells and macrophages in CTCL [55, 56]. One investigational study demonstrated that the numbers of CD163+ and CD68+ cells increased as more neoplastic T-cells were found in the infiltrate of CTCL lesions, and their number decreased after treatment with topical steroids and ultraviolet light [57]. Wu X et al. observed a delay in the development of the cutaneous lymphoma in mouse xenografts after the depletion of M2-like tumor-associated macrophages [56]. These data support a role of these phagocytic cells in the MF pathogenesis, which may be through immune inhibitory receptors, such as PD-L1. PD-1 and other inhibitory immune checkpoints are overexpressed in exhausted T-cells [35]. Their binding to corresponding ligands such as PD-L1 on DCs and macrophages in the microenvironment directly reduces the functional and proliferative capabilities of T-cells by repressing T-cell receptor signaling and inducing genes that impair T-cell function. Consequently, malignant CTCL cells escape immune surveillance and are not eliminated.

11.7 Cytokine Milieu

Advanced MF and SS show a Th2 cytokine profile characterized by secretion of the immunosuppressive cytokines IL-10 and TGF-β. IL-10 compromises antigen-loaded DC-functions inhibiting the maturation of DCs, and promote a T-cell exhausted/dysregulated phenotype [52, 58]. TGF-β is often secreted by Tregs and inhibits the proliferation of both tumor-infiltrating CD4+ and CD8+ T-cells, arresting the cell cycle at G1 phase. Whether the TGF-β-producing Tregs in MF are malignant Tregs (putative origin of MF) or are part of the antitumor immune response remains elusive and further studies are needed before definitive conclusions can be drawn [59]. Malignant T-cells in skin and blood of Sézary patients

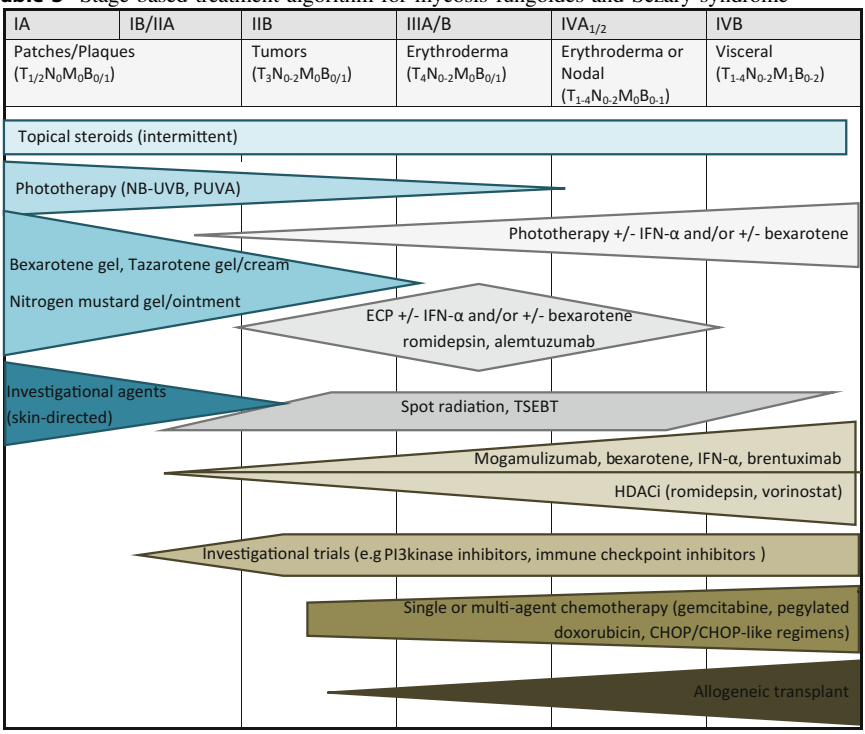
produce IL-13 and IL-13Rα1 and IL-13Rα2. IL-13 induces CTCL growth in vitro mediated by IL-13Rα1 interaction [60]. These data suggest the role of IL-13 signaling inhibitors as a future therapeutic target for CTCL. IL-2 and IL-15 stimulate the adoption of a Treg phenotype by effector T-cells and promote the expression of FoxP3 in CTCL cells. Marzec et al. observed that both cytokines were upregulated in isolated skin cells from CD4+ cutaneous T-cell lymphomas and promoted their proliferation through the JAK1 and JAK3 kinase pathway [61]. Therefore, the treatment with JAK inhibitors may be useful in the future to suppress tumor growth in patients with MF and other T-cell lymphomas.

11.8 Treatment Regimens

Recommended staging and work-up for patients with MF/SS is highlighted in Table 2 and is critical to assess treatment plan and disease prognosis [3]. The National Comprehensive Cancer Network (NCCN) guidelines outline classic treatments for MF/SS as determined by stage of the diseases, estimated skin tumor burden by mSWAT, presence of unfavorable prognostic factors (folliculotropism large cell transformation, and elevated lactate dehydrogenase and/or β2 microglobulin levels), age and other comorbidities (cardiovascular disease, dyslipidemia, low thyroid function, etc.) that can impact quality of life (Table 3) [62]. Early stage MF (stages IA-IIA) has a favorable prognosis and skin-directed therapies are the first-line regimens with complete response rates (CRR) ranging between 60 and 100%. High-potency topical steroids, topical retinoids and rexinoids, topical nitrogen mustard (NM), and phototherapy are used in early stage MF patients with a low-risk profile. The most common side effects include redness and local irritation for topical NM, skin atrophy and telangiectasias for topical steroids, and photodamage and increase risk of skin cancer for nbUVB or PUVA phototherapy [63]. A combined regimen with biologic agents such as IFN-α, retinoids (all-trans retinoic acid, isotretinoin), rexinoids (bexarotene) and methotrexate is preferred for early stage MF patients, who failed to skin-directed regimens alone. Local radiation therapy is considered in patients with unifocal transformation, isolated/localized cutaneous tumors, or chronic, painful/ulcerated lesions, with CRR of >90% and a mean time to relapse of 9.25 months (range 5–14 months). A single fraction radiation of 700 cGy–800 cGy provides excellent palliation for CTCL lesions and is cost effective and convenient for the patient [64]. Extensive radiation therapies, such as total electron beam radiation (TSEBT) should be reserved for elderly patients or patients with rapidly progressing or refractory widespread plaques and tumors. Long-term side effects of this approach include cosmetic disfigurement (permanent hair loss, pigmentation) as well as the development of skin cancers and subsequent radiation is limited or not possible.

Current approaches for treating advanced MF include biologic and targeted therapies that can provide long-term treatment with minimal side effects while maintaining quality of life. None of these approaches are curative and hence

Table 3 Stage-based treatment algorithm for mycosis fungoides and Sézary syndrome



Abbreviations: *ECP* extracorporeal photopheresis, *HDACi* histone deacetylase inhibitor; *IFN-α* interferon-alpha, *NB-UVB* narrowband-ultraviolet light B; *PUVA* psoralen ultraviolet light A; *TSEBT* total electron beam therapy; *CHOP* cyclophosphamide, doxorubicin, vincristine, prednisone

patients frequently have relapses necessitating ongoing treatments. Here we discuss the various systemic agents in more detail.

1. IFN-α monotherapy has shown efficacy in all stages of MF, with an overall response rate (ORR) of 38% for the low-dose regimen of 3 M IU per day, versus 79% for the high dose regimen of 36 M IU per day, and responses lasting 4–27.5 months [65, 66]. Moreover, the clinical trials highlighted that some patients, who were not able to achieve a complete response on low-dose IFN were able to achieve a remission with dose escalation [66]. Common side effects are dose-related and include headaches, flu-like symptoms, fatigue, anorexia, weight loss, and depression [66]. Combined regimens with INF-α and oral retinoids have been used but the combination did not show higher responses compared with INF-α monotherapy [66]. Combined regimens with low-dose INF-α at 3–9 M IU a week and phototherapy (nbUVB or PUVA) have shown higher benefit with CRR of 70% [67].
2. Oral bexarotene was approved in the US by the FDA for relapsed/refractory CTCL in all stages. In the early stage MF phase 2 and 3 trial, 58 patients

randomized to doses of 6.5, 300, or 650 mg/m^2 daily achieved response rates (defined as >50% improvement in skin lesions) of 20%, 54%, and 67%, respectively [68]. Combination with PUVA or narrowband-UVB has led to ORR of 50–80% in patients with refractory disease and early stage MF [68]. In phase II and III trials of 94 patients with advanced stage MF (IIB-IVB) bexarotene showed ORR of 45% and 55% with daily doses of 300 and 650 mg/m^2 respectively. The median response duration was 7–9 months [68–70]. A daily dosing regimen of 300 mg/m^2 is recommended based on the safety profile. The most common side effects included hypertriglyceridemia, hypercholesterolemia, and central hypothyroidism, requiring dose adjustments and additional treatment with lipid-lowering agents and thyroid hormone replacement.

3. Methotrexate is an antifolate and can be given orally or intravenously in a wide range of doses depending on the clinical indication. Low-dose weekly methotrexate (15–40 mg) administered orally once a week has ORR of 33 and 58% for plaque (T2) MF and erythrodermic (T4) MF, respectively, with median time to treatment failure of 15 months for patients with stage IB (T2) disease and 31 months for erythrodermic MF [71, 72]. Methotrexate interferes with the synthesis of purines and pyrimidines as well as blocking the conversion of homocysteine to methionine. Studies have shown that methotrexate enhances FAS (CD95)-dependent apoptosis in CTCL cells, which is particularly effective in patients with LCT and advanced stage MF [30]. Common side effects include oral mucositis/stomatitis, gastrointestinal symptoms, bone marrow suppression, and hepatotoxicity. Folic acid supplementation is recommended during methotrexate therapy in order to prevent these side effects [73].
4. Pralatrexate is an antifolate that has been shown to have a higher affinity for the transporter RFC-1 (reduced folate carrier-1) and increased polyglutamylation which results in enhanced intracellular drug concentration as compared to MTX resulting in distinct cytotoxicity profile [74]. While it is approved for the treatment of relapsed or refractory peripheral T-cell lymphomas (PTCL), there is also activity in CTCL with an ORR of 45% with the optimized schedule of 15 mg/m2/wk IV for 3 of 4 weeks after a median of 4 cycles [75]. Mucositis is the most common toxicity encountered in different studies. To lower this risk, vitamin B12 and folate supplementation and folinic acid (leucovorin rescue) are used during pralatrexate treatment. The median response duration was not reached in the study that evaluated the efficacy of pralatrexate in patients with relapsed/refractory CTCL; the Kaplan–Meier estimates showed that the 73% of responses were continuing at 6 months.
5. Histone deacetylase inhibitors (HDACi) are active in T-cell lymphomas and 2 agents (vorinostat, romidepsin) are approved for the treatment of CTCL [76, 77]. Vorinostat is an oral HDAC class I and II inhibitor with reported ORR of 24–30%, with a median response duration of 6 months [76, 77]. While no CRs were seen, improvement in itching was demonstrated in the 58% of cases. Main side effects are fatigue, nausea, dysgeusia, and hematologic abnormalities. Based on two large phase 2 studies, the FDA approved the intravenously administered HDAC inhibitor romidepsin for relapsed/refractory advanced

CTCL [76, 78]. The reported ORR was 36% with a median duration of response of 15 months. Romidepsin showed prolonged clinical responses in a subset of patients, particularly in SS patients with blood involvement with manageable side-effect profile. Most common side effects included fatigue, nausea, vomiting, diarrhea, and poor appetite and occurred in >30% of patients; but were predictable in terms of t onset, duration, and severity, and usually resolved following completion of therapy. Significant pruritus reduction was reported in treated patients; however, this did not correlate with clinical response. Romidepsin may act at least in part by reducing IL-31 via an apoptotic- and/or an epigenetic-modifying pathway, which may be also involved in providing a pruritus relief in patients with CTCL [79, 80].

6. Brentuximab vedotin (BV) is an antibody–drug conjugate that selectively delivers a toxic microtubule-disrupting agent into CD30-expressing T-cells, inducing cell cycle arrest and apoptosis. This drug has been approved by the FDA for patients with refractory/advanced MF/SS expressing CD30. A phase 2 trial in patients with refractory/advanced MF/ SS showed an ORR of 70% (90% CI, 53–83%) [81]. A wide range of CD30 expression levels (nondetectable–100%) was observed. Patients with $\leq$5% of CD30 expression within cutaneous lesions showed lower responses ($p < 0.005$). The ALCANZA study (NCT01578499), a randomized phase 3 trial assessed the efficacy of BV to standard treatment with oral methotrexate or bexarotene as determined by physicians choice (PC) in patients with CD30+ CTCL. Results have demonstrated a superior benefit of BV with ORR of 67% and CRR of 16%, compared to ORR of 20% and CRR 2% for PC (methotrexate or brentuximab). Progression-free survival (PFS) strongly favored BV over PC with a median PFS of 16.7 versus 3.5 months, respectively [82]. With BV, the most common adverse effects include reversible peripheral neuropathy that occurs in the 67% of patients, fatigue, nausea, alopecia, and neutropenia.
7. Alemtuzumab is an humanized antibody targeting the CD52 cell surface antigen on T and B-cells, that was initially approved by the FDA for the treatment of chronic lymphocytic leukemia and has shown high efficacy in patients with erythrodermic MF and SS [63, 83]. Original studies recommended subcutaneous/intravenous doses of 30 mg 3 times weekly, but lower doses of 10 mg 3 times per week have shown similar responses in terms of efficacy [84]. A phase 2 open-label clinical trial performed in 19 patients with refractory and erythrodermic CTCL (erythrodermic MF and SS) showed ORR of 84%, with CRR of 47% and PRR of 37%. The median follow-up was 24 months (range 6–62 months). Median overall survival (OS) was 41 months, whereas median PFS was 6 months. The treatment was well tolerated with the majority of toxicities being grade 1 or 2 in severity and transient [83]. The most frequent toxicities included hematologic abnormalities (anemia, leukopenia, thrombocytopenia, neutropenia and pancytopenia), pruritus, pain, constitutional symptoms, opportunistic infections related with prolonged immunosuppression, infusion reactions and dry skin [63, 83].

8. Mogamulizumab is a humanized anti-CC-chemokine receptor 4 (CCR4) monoclonal antibody with a defucosylated Fc region leading to increased antibody- dependent cellular cytotoxicity [85]. CCR4 is expressed on Tregs and T helper memory cells and plays an important role in skin homing. Mogamulizumab is approved for ATLL in Japan and for relapsed/refractory CTCL by the FDA. The effectiveness of mogamulizumab in CTCL has been demonstrated in separate phase 1 and 2 randomized controlled trials [85]. In a phase 1/2 study, mogamulizumab induced an overall response rate of 47.1% in SS patients and 28.6% in MF patients [86]. In a multicenter Japanese phase 2 study involving 37 patients with relapsed CCR4-positive tumors, mogamulizumab treatment induced 35% of objective response, including 5 patients (14%) achieving CR [87]. The most common adverse effect of this treatment is lymphocytopenia (81%), and cases of severe Stevens–Johnson syndrome due to induced immune deficiency of regulatory T-cells have been reported [88]. Results for MAVORIC, a randomized, multicenter, open-label phase 3 trial comparing mogamulizumab with vorinostat in patients with MF and SS showed a significant difference between the treatment arms in ORR for both MF (21% vs. 7.1%; $p = 0.0042$) and SS (37% vs. 2.3%; $p < 0.0001$) [89]. Median PFS was 7.7 months for the mogamulizumab cohort, compared with 3.1 months for vorinostat. Treatment was generally well tolerated, with the most common adverse event consisted of skin rashes.
9. Pembrolizumab is a PD1 antibody that has shown high antitumor activity in patients with relapsed/refractory Hodgkin Lymphoma, chronic lymphocytic leukemia, multiple myeloma, and mediastinal B-cell lymphoma. A recent phase 2 study of pembrolizumab in 24 patients with relapsed/refractory MF/ SS has demonstrated an ORR of 38%, with 6 patients showing an improvement greater than 90% of skin disease measured by mSWAT. Twenty-three (96%) patients had advanced stage MF/SS (stage IIB or higher) and pembrolizumab was administered at 2 mg/kg every 3 weeks for up to 2 years [90]. The most common adverse events included pyrexia, hypothyroidism, diarrhea, fatigue, headache, rash/ immune-mediated skin flare reaction such as bullous pemphigoid that occurred exclusively in Sézary patients, nausea, neutropenia, and thrombocytopenia [90]. Immune-mediated adverse reactions occurred in 13% of patients and included pneumonitis, colitis, hypophysitis, and thyroid disorders [91].
10. Single-agent chemotherapy regimens, including liposomal doxorubicin and gemcitabine are reserved for patients with rapidly progressing tumors or refractory advanced stage disease given its short response duration and associated toxicities including infectious complications.
11. Allogenic stem cell transplant (SCT) is the only potential curative treatment option in MF but treatment-related mortality rates are about 25–30% with both myeloablative and reduced-intensity conditioning regimens [92]. Therefore, allogeneic SCT is usually reserved for young patients with refractory and advanced stage MF. Patients are given bridging treatment with combination chemotherapies that are reserved for more aggressive systemic lymphomas.

These regimens have a high response rate but a short duration of response that can be utilized to prepare the transplant. While there is little consensus on the conditioning regimen, there is limited data from a single center that the use of TSEBT before an allogenic transplant provides improved skin outcomes [93] A proposed graft-versus-lymphoma (GVL) effect is thought to be responsible for higher effectiveness of allogeneic transplants. Autologous transplant has yielded disappointing results with rapid disease relapses [94].

12. Laboratory investigations focusing on the tumor microenvironment has assisted in the development of novel and more effective immunotherapeutic strategies for relapsed/refractory CTCL, including IL-2R-directed protein toxins such as denileukin diftitox (reengineered E7777 with improved prurity), anti-CD47, anti-PD1/anti-PDL1 agents, Toll-like receptor agonists, protein kinase C inhibitors, phosphoinositide 3-kinase delta and gamma inhibitor duvelisib, and IL-2 inhibitor [63, 87, 95, 96]. Unlike benign inflammatory skin diseases, lesional skin biopsies from CTCL patients have shown upregulation of miR-155, whereas miR-203 and 205 are repressed [43]. Currently, the efficacy of intralesional and subcutaneous and intravenously administered antagomir of miR-155 (cobomarsen) for patients with MF is being evaluated in a dose-escalating phase 1 national clinical trial. Preliminary results showed that 23/24 patients (95%) had improvement in either the individually treated lesion (intralesional cohort) or total skin disease (SC/IV cohorts) as measured by maximal change in CAILS or mSWAT [97]. A PD-L1 inhibitor (durvalumab) is currently being evaluated in a clinical phase 1/2 trial in patients with advanced CTCL with promising responses seen. The study is ongoing [98]. CD47 is an innate immune checkpoint that binds to signal regulatory protein alpha (SIRPα) and delivers a "do not eat" signal to suppress macrophage phagocytosis. TTI-621 (SIRPαFc) is an immune checkpoint inhibitor consisting of the CD47 binding domain of human SIRPα linked to the Fc region of human IgG1 designed to both: (1) block the CD47 "do not eat" signal, and (2) engage macrophage Fcγ receptors with IgG1 Fc to enhance phagocytosis and antitumor activity. Preliminary results of a dose-escalating phase 1 of intralesional application showed promising and rapid onset of responses [99].

11.9 Supportive Measures

The use of supportive measures and skin care is of utmost importance in the care of patients with CTCL and MF and to improve quality of life for these patients. Patients are disabled by severe pruritus and antihistamines, gabapentin or aprepitant are used for symptom control. Low-dose prednisone can be given for short-term symptom relief in severe cases, but the course should be limited to avoid side effects of long-term steroid use. Mild skin care using unscented mild soaps and emollients is mandatory to improve the pruritus, dryness/scaling and keep barrier function

intact. Regular bleach baths are recommended to minimize bacterial colonization with *Staphylococcus aureus* and risk of secondary infections.

11.10 Conclusions

MF and SS are complex diseases that require a multidisciplinary team of dermatologists, oncologists and (dermato) pathologists to optimize a treatment plan that includes skin-directed and/or systemic regimens depending on the skin tumor burden, systemic involvement, drug-related toxicity profile, and patient comorbidities. The study of the tumor microenvironment and molecular mechanisms of these rare neoplasms may assist in the development of new immune therapies providing promising treatment approaches tailored for patients with relapsed/refractory disease.

References

1. Bradford PT, Devesa SS, Anderson WF, Toro JR (2009) Cutaneous lymphoma incidence patterns in the United States: a population-based study of 3884 cases. Blood 113(21):5064–5073
2. Willemze R, Jaffe ES, Burg G et al (2005) WHO-EORTC classification for cutaneous lymphomas. Blood 105(10):3768–3785
3. Olsen E, Vonderheid E, Pimpinelli N et al (2007) Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 110(6):1713–1722
4. Agar NS, Wedgeworth E, Crichton S et al (2010) Survival outcomes and prognostic factors in mycosis fungoides/Sezary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. J Clin Oncol Off J Am Soc Clin Oncol 28(31):4730–4739
5. Cho-Vega JH, Tschen JA, Duvic M, Vega F (2010) Early-stage mycosis fungoides variants: case-based review. Ann Diagn Pathol 14(5):369–385
6. Olsen EA, Whittaker S, Kim YH et al (2011) Clinical end points and response criteria in mycosis fungoides and Sezary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. J Clin Oncol Off J Am Soc Clin Oncol 29(18):2598–2607
7. Kempf W, Ostheeren-Michaelis S, Paulli M et al (2008) Granulomatous mycosis fungoides and granulomatous slack skin: a multicenter study of the Cutaneous Lymphoma Histopathology Task Force Group of the European Organization For Research and Treatment of Cancer (EORTC). Arch Dermatol 144(12):1609–1617
8. Massone C, Crisman G, Kerl H, Cerroni L (2008) The prognosis of early mycosis fungoides is not influenced by phenotype and T-cell clonality. Br J Dermatol 159(4):881–886
9. Klemke CD, Booken N, Weiss C et al (2015) Histopathological and immunophenotypical criteria for the diagnosis of Sezary syndrome in differentiation from other erythrodermic skin diseases: a European Organisation for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Task Force Study of 97 cases. Br J Dermatol 173(1):93–105

10. Jawed SI, Myskowski PL, Horwitz S, Moskowitz A, Querfeld C (2014) Primary cutaneous T-cell lymphoma (mycosis fungoides and Sezary syndrome): part I. Diagnosis: clinical and histopathologic features and new molecular and biologic markers. J Am Acad Dermatol 70 (2):205 e201–216. Quiz 221–202
11. Nickoloff BJ, Nestle FO, Zheng XG, Turka LA (1994) T lymphocytes in skin lesions of psoriasis and mycosis fungoides express B7-1: a ligand for CD28. Blood 83(9):2580–2586
12. Jarrousse V, Quereux G, Marques-Briand S, Knol AC, Khammari A, Dreno B (2006) Toll-like receptors 2, 4 and 9 expression in cutaneous T-cell lymphoma (mycosis fungoides and Sezary syndrome). Eur J Dermatol EJD 16(6):636–641
13. Talpur R, Bassett R, Duvic M (2008) Prevalence and treatment of Staphylococcus aureus colonization in patients with mycosis fungoides and Sezary syndrome. Br J Dermatol 159 (1):105–112
14. Tokura Y, Heald PW, Yan SL, Edelson RL (1992) Stimulation of cutaneous T-cell lymphoma cells with superantigenic staphylococcal toxins. J Invest Dermatol 98(1):33–37
15. Wood GS, Schaffer JM, Boni R et al (1997) No evidence of HTLV-I proviral integration in lymphoproliferative disorders associated with cutaneous T-cell lymphoma. Am J Pathol 150 (2):667–673
16. Pancake BA, Zucker-Franklin D, Coutavas EE (1995) The cutaneous T cell lymphoma, mycosis fungoides, is a human T cell lymphotropic virus-associated disease. A study of 50 patients. J Clin Invest 95(2):547–554
17. Herne KL, Talpur R, Breuer-McHam J, Champlin R, Duvic M (2003) Cytomegalovirus seropositivity is significantly associated with mycosis fungoides and Sezary syndrome. Blood 101(6):2132–2136
18. Berger CL, Tigelaar R, Cohen J et al (2005) Cutaneous T-cell lymphoma: malignant proliferation of T-regulatory cells. Blood 105(4):1640–1647
19. Dummer R, Heald PW, Nestle FO et al (1996) Sezary syndrome T-cell clones display T-helper 2 cytokines and express the accessory factor-1 (interferon-gamma receptor beta-chain). Blood 88(4):1383–1389
20. Krejsgaard T, Ralfkiaer U, Clasen-Linde E et al (2011) Malignant cutaneous T-cell lymphoma cells express IL-17 utilizing the Jak3/Stat3 signaling pathway. J Invest Dermatol 131 (6):1331–1338
21. Pandiyan P, Zhu J (2015) Origin and functions of pro-inflammatory cytokine producing Foxp3+ regulatory T cells. Cytokine 76(1):13–24
22. Guenova E, Watanabe R, Teague JE et al (2013) TH2 cytokines from malignant cells suppress TH1 responses and enforce a global TH2 bias in leukemic cutaneous T-cell lymphoma. Clin Cancer Res Off J Am Assoc Cancer Res 19(14):3755–3763
23. Campbell JJ, O'Connell DJ, Wurbel MA (2007) Cutting Edge: Chemokine receptor CCR4 is necessary for antigen-driven cutaneous accumulation of CD4 T cells under physiological conditions. J Immunol 178(6):3358–3362
24. Clark RA, Watanabe R, Teague JE et al (2012) Skin effector memory T cells do not recirculate and provide immune protection in alemtuzumab-treated CTCL patients. Sci Trans Med 4(117):117ra117
25. Reiss Y, Proudfoot AE, Power CA, Campbell JJ, Butcher EC (2001) CC chemokine receptor (CCR)4 and the CCR10 ligand cutaneous T cell-attracting chemokine (CTACK) in lymphocyte trafficking to inflamed skin. J Exp Med 194(10):1541–1547
26. Ferenczi K, Fuhlbrigge RC, Pinkus J, Pinkus GS, Kupper TS (2002) Increased CCR4 expression in cutaneous T cell lymphoma. J Invest Dermatol 119(6):1405–1410
27. Kallinich T, Muche JM, Qin S, Sterry W, Audring H, Kroczek RA (2003) Chemokine receptor expression on neoplastic and reactive T cells in the skin at different stages of mycosis fungoides. J Invest Dermatol 121(5):1045–1052

28. Sokolowska-Wojdylo M, Wenzel J, Gaffal E et al (2005) Circulating clonal CLA(+) and CD4 (+) T cells in Sezary syndrome express the skin-homing chemokine receptors CCR4 and CCR10 as well as the lymph node-homing chemokine receptor CCR7. Br J Dermatol 152 (2):258–264
29. Dereure O, Levi E, Vonderheid EC, Kadin ME (2002) Infrequent Fas mutations but no Bax or p53 mutations in early mycosis fungoides: a possible mechanism for the accumulation of malignant T lymphocytes in the skin. J Invest Dermatol 118(6):949–956
30. Wu J, Nihal M, Siddiqui J, Vonderheid EC, Wood GS (2009) Low FAS/CD95 expression by CTCL correlates with reduced sensitivity to apoptosis that can be restored by FAS upregulation. J Invest Dermatol 129(5):1165–1173
31. Nielsen M, Kaestel CG, Eriksen KW et al (1999) Inhibition of constitutively activated Stat3 correlates with altered Bcl-2/Bax expression and induction of apoptosis in mycosis fungoides tumor cells. Leukemia 13(5):735–738
32. Sommer VH, Clemmensen OJ, Nielsen O et al (2004) In vivo activation of STAT3 in cutaneous T-cell lymphoma. Evidence for an antiapoptotic function of STAT3. Leukemia 18 (7):1288–1295
33. Querfeld C, Rosen ST, Guitart J et al (2007) Phase II trial of subcutaneous injections of human recombinant interleukin-2 for the treatment of mycosis fungoides and Sezary syndrome. J Am Acad Dermatol 56(4):580–583
34. Zhang XH, Nam S, Wu J et al (2018) Multi-Kinase Inhibitor with Anti-p 38gamma Activity in Cutaneous T-Cell Lymphoma. J Investig Dermatol
35. Querfeld C, Leung S, Myskowski PL et al (2018) Primary T cells from cutaneous T-cell lymphoma skin explants display an exhausted immune checkpoint profile. Cancer Immunol Res 6(8):900–909
36. Zajac AJ, Blattman JN, Murali-Krishna K et al (1998) Viral immune evasion due to persistence of activated T cells without effector function. J Exp Med 188(12):2205–2213
37. Mao X, Orchard G, Lillington DM, Russell-Jones R, Young BD, Whittaker SJ (2003) Amplification and overexpression of JUNB is associated with primary cutaneous T-cell lymphomas. Blood 101(4):1513–1519
38. Mao X, Lillington D, Scarisbrick JJ et al (2002) Molecular cytogenetic analysis of cutaneous T-cell lymphomas: identification of common genetic alterations in Sezary syndrome and mycosis fungoides. Br J Dermatol 147(3):464–475
39. Kiel MJ, Sahasrabuddhe AA, Rolland DC et al (2015) Genomic analyses reveal recurrent mutations in epigenetic modifiers and the JAK-STAT pathway in Sezary syndrome. Nat Commun 6:8470
40. Woollard WJ, Pullabhatla V, Lorenc A et al (2016) Candidate driver genes involved in genome maintenance and DNA repair in Sezary syndrome. Blood 127(26):3387–3397
41. Ungewickell A, Bhaduri A, Rios E et al (2015) Genomic analysis of mycosis fungoides and Sezary syndrome identifies recurrent alterations in TNFR2. Nat Genet 47(9):1056–1060
42. Scarisbrick JJ, Woolford AJ, Calonje E et al (2002) Frequent abnormalities of the p15 and p16 genes in mycosis fungoides and sezary syndrome. J Invest Dermatol 118(3):493–499
43. Ralfkiaer U, Hagedorn PH, Bangsgaard N et al (2011) Diagnostic microRNA profiling in cutaneous T-cell lymphoma (CTCL). Blood 118(22):5891–5900
44. Kopp KL, Ralfkiaer U, Gjerdrum LM et al (2013) STAT5-mediated expression of oncogenic miR-155 in cutaneous T-cell lymphoma. Cell Cycle 12(12):1939–1947
45. Rubio Gonzalez B, Zain J, Rosen ST, Querfeld C (2016) Tumor microenvironment in mycosis fungoides and Sezary syndrome. Curr Opin Oncol 28(1):88–96
46. Rubben A, Kempf W, Kadin ME, Zimmermann DR, Burg G (2004) Multilineage progression of genetically unstable tumor subclones in cutaneous T-cell lymphoma. Exp Dermatol 13 (8):472–483
47. Vermeer MH, van Doorn R, Dukers D, Bekkenk MW, Meijer CJ, Willemze R (2001) CD8+ T cells in cutaneous T-cell lymphoma: expression of cytotoxic proteins, Fas Ligand, and killing inhibitory receptors and their relationship with clinical behavior. J Clin Oncol Off J Am Soc Clin Oncol 19(23):4322–4329

48. Goteri G, Filosa A, Mannello B et al (2003) Density of neoplastic lymphoid infiltrate, CD8+ T cells, and CD1a+ dendritic cells in mycosis fungoides. J Clin Pathol 56(6):453–458
49. Hoppe RT, Medeiros LJ, Warnke RA, Wood GS (1995) CD8-positive tumor-infiltrating lymphocytes influence the long-term survival of patients with mycosis fungoides. J Am Acad Dermatol 32(3):448–453
50. Gjerdrum LM, Woetmann A, Odum N et al (2007) FOXP3+ regulatory T cells in cutaneous T-cell lymphomas: association with disease stage and survival. Leukemia 21(12):2512–2518
51. Krejsgaard T, Odum N, Geisler C, Wasik MA, Woetmann A (2012) Regulatory T cells and immunodeficiency in mycosis fungoides and Sezary syndrome. Leukemia 26(3):424–432
52. Berger CL, Hanlon D, Kanada D et al (2002) The growth of cutaneous T-cell lymphoma is stimulated by immature dendritic cells. Blood 99(8):2929–2939
53. Kasprzycka M, Zhang Q, Witkiewicz A et al (2008) Gamma c-signaling cytokines induce a regulatory T cell phenotype in malignant CD4+ T lymphocytes. J Immunol 181(4):2506–2512
54. Querfeld C. CS, Leung S, Myskowski P, Horwitz S, Halpern A, Young J (2014) 1695 T cells in CTCL have an exhausted phenotype while cutenaous dentritic cells display a normally activated mature phenotype. Blood
55. Rabenhorst A, Schlaak M, Heukamp LC et al (2012) Mast cells play a protumorigenic role in primary cutaneous lymphoma. Blood 120(10):2042–2054
56. Wu X, Schulte BC, Zhou Y et al (2014) Depletion of M2-like tumor-associated macrophages delays cutaneous T-cell lymphoma development in vivo. J Invest Dermatol 134(11):2814–2822
57. Sugaya M, Miyagaki T, Ohmatsu H et al (2012) Association of the numbers of CD163(+) cells in lesional skin and serum levels of soluble CD163 with disease progression of cutaneous T cell lymphoma. J Dermatol Sci 68(1):45–51
58. Mocellin S, Marincola FM, Young HA (2005) Interleukin-10 and the immune response against cancer: a counterpoint. J Leukoc Biol 78(5):1043–1051
59. Zayed AA, Abdel-Halim MR, Sayed KS, Mohammed FN, Hany DM, Amr KS (2014) Transforming growth factor-beta1 gene polymorphism in mycosis fungoides. Clin Exp Dermatol 39(7):806–809
60. Geskin LJ, Viragova S, Stolz DB, Fuschiotti P (2015) Interleukin-13 is over-expressed in cutaneous T-cell lymphoma cells and regulates their proliferation. Blood
61. Marzec M, Halasa K, Kasprzycka M et al (2008) Differential effects of interleukin-2 and interleukin-15 versus interleukin-21 on CD4+ cutaneous T-cell lymphoma cells. Cancer Res 68(4):1083–1091
62. Zelenetz AD GL, Wierde WG et al (2015) NCCN clinical practive guidelines in oncology: Non-Hodking's lymphomas, v 2.2015. Accessed 28 July 2015
63. Jawed SI, Myskowski PL, Horwitz S, Moskowitz A, Querfeld C (2014) Primary cutaneous T-cell lymphoma (mycosis fungoides and Sezary syndrome): part II. Prognosis, management, and future directions. J Am Acad Dermatol 70(2):223 e221–217; quiz 240-222
64. Thomas TO, Agrawal P, Guitart J et al (2013) Outcome of patients treated with a single-fraction dose of palliative radiation for cutaneous T-cell lymphoma. Int J Radiat Oncol Biol Phys 85(3):747–753
65. Olsen EA, Rosen ST, Vollmer RT et al (1989) Interferon alfa-2a in the treatment of cutaneous T cell lymphoma. J Am Acad Dermatol 20(3):395–407
66. Olsen EA (2003) Interferon in the treatment of cutaneous T-cell lymphoma. Dermatol Ther 16 (4):311–321
67. Stadler R, Otte HG (1995) Combination therapy of cutaneous T cell lymphoma with interferon alpha-2a and photochemotherapy. Recent results in cancer research. Fortschritte der Krebsforschung. Progres dans les recherches sur le cancer 139:391–401
68. Duvic M, Martin AG, Kim Y et al (2001) Phase 2 and 3 clinical trial of oral bexarotene (Targretin capsules) for the treatment of refractory or persistent early-stage cutaneous T-cell lymphoma. Arch Dermatol 137(5):581–593

69. Duvic M, Hymes K, Heald P et al (2001) Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II-III trial results. J Clin Oncol Off J Am Soc Clin Oncol 19(9):2456–2471
70. Querfeld C, Rosen ST, Guitart J et al (2004) Comparison of selective retinoic acid receptor- and retinoic X receptor-mediated efficacy, tolerance, and survival in cutaneous t-cell lymphoma. J Am Acad Dermatol 51(1):25–32
71. Zackheim HS, Kashani-Sabet M, Hwang ST (1996) Low-dose methotrexate to treat erythrodermic cutaneous T-cell lymphoma: results in twenty-nine patients. J Am Acad Dermatol 34(4):626–631
72. Zackheim HS, Kashani-Sabet M, McMillan A (2003) Low-dose methotrexate to treat mycosis fungoides: a retrospective study in 69 patients. J Am Acad Dermatol 49(5):873–878
73. Menting SP, Dekker PM, Limpens J, Hooft L, Spuls PI (2016) Methotrexate dosing regimen for Plaque-type Psoriasis: a Systematic review of the use of test-dose, start-dose, dosing scheme, dose adjustments, maximum dose and folic acid supplementation. Acta Dermato-Venereologica 96(1):23–28
74. Izbicka E, Diaz A, Streeper R et al (2009) Distinct mechanistic activity profile of pralatrexate in comparison to other antifolates in in vitro and in vivo models of human cancers. Cancer Chemother Pharmacol 64(5):993–999
75. Wood GS, Wu J (2015) Methotrexate and Pralatrexate. Dermatol Clin 33(4):747–755
76. Whittaker SJ, Demierre MF, Kim EJ et al (2010) Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma. J Clin Oncol Off J Am Soc Clin Oncol 28(29):4485–4491
77. Olsen EA, Kim YH, Kuzel TM et al (2007) Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. J Clin oncol Off J Am Soc Clin Oncol 25(21):3109–3115
78. Piekarz RL, Frye R, Turner M et al (2009) Phase II multi-institutional trial of the histone deacetylase inhibitor romidepsin as monotherapy for patients with cutaneous T-cell lymphoma. J Clin oncol Off J Am Soc Clin Oncol 27(32):5410–5417
79. Cedeno-Laurent F, Singer EM, Wysocka M et al (2015) Improved pruritus correlates with lower levels of IL-31 in CTCL patients under different therapeutic modalities. Clin Immunol (Orlando, FLA) 158(1):1–7
80. Singer EM, Shin DB, Nattkemper LA et al (2013) IL-31 is produced by the malignant T-cell population in cutaneous T-Cell lymphoma and correlates with CTCL pruritus. J Invest Dermatol 133(12):2783–2785
81. Kim YH, Tavallaee M, Sundram U et al (2015) Phase II investigator-initiated study of Brentuximab Vedotin in Mycosis Fungoides and Sezary Syndrome with variable CD30 expression level: a multi-institution collaborative project. J Clin oncol Off J Am Soc Clin Oncol 33(32):3750–3758
82. Kim YWS, Horwitz S, Duvic M, Dummer R, Scarisbrick J, Quaglino P, Zinzani PL, Wolter P, Wang Y, Palanca-Wessels MC, Zagadailov E, Trepicchio W, Liu Y, Little M, Prince M (2016) Brentuximab Vedotin Demonstrates Significantly Superior Clinical Outcomes in Patients with CD30-Expressing Cutaneous T Cell Lymphoma Versus Physician's Choice (Methotrexate or Bexarotene): the Phase 3 Alcanza Study. ASH 182
83. Querfeld C, Mehta N, Rosen ST et al (2009) Alemtuzumab for relapsed and refractory erythrodermic cutaneous T-cell lymphoma: a single institution experience from the Robert H. Lurie Comprehensive Cancer Center. Leukemia & lymphoma 50(12):1969–1976
84. Bernengo MG, Quaglino P, Comessatti A et al (2007) Low-dose intermittent alemtuzumab in the treatment of Sezary syndrome: clinical and immunologic findings in 14 patients. Haematologica 92(6):784–794
85. Duvic M, Evans M, Wang C (2016) Mogamulizumab for the treatment of cutaneous T-cell lymphoma: recent advances and clinical potential. Therapeutic Adv Hematol 7(3):171–174

86. Duvic M, Pinter-Brown LC, Foss FM et al (2015) Phase 1/2 study of mogamulizumab, a defucosylated anti-CCR4 antibody, in previously treated patients with cutaneous T-cell lymphoma. Blood 125(12):1883–1889
87. Ogura M, Ishida T, Hatake K et al (2014) Multicenter phase II study of mogamulizumab (KW-0761), a defucosylated anti-cc chemokine receptor 4 antibody, in patients with relapsed peripheral T-cell lymphoma and cutaneous T-cell lymphoma. J clin Oncol Off J Am Soc Clin Oncol 32(11):1157–1163
88. Ishida T, Ito A, Sato F et al (2013) Stevens-Johnson Syndrome associated with mogamulizumab treatment of adult T-cell leukemia/ lymphoma. Cancer Sci 104(5):647–650
89. Kim YH, Bagot M, Pinter-Brown L et al (2017) Anti-CCR4 monoclonal antibody, mogamulizumab, demonstrates significant improvement in PFS compared to vorinostat in patients with previously treated cutaneous T-cell lymphoma (CTCL): results from the phase III MAVORIC study. Blood 130(Supplement 1):817. Blood 130(supplement 1):817a
90. Khodadoust M, Rook A, Porcu P, Foss F, Moskowitz A,Shustov A, Shanbhag S, Sokol L, Shine R, Fling S, Li S, Rabhar Z, Kim J,Yang Y, Yearley j, Chartash E, Townson S, Subrahmanyam P, Maecker H, Alizadeh A, Dai J, Horwitz S, Sharon E, Kohrt H, MD24, Cheever M, Kim Y (2016) Pembrolizumab for treatment of relapsed/Refractory Mycosis Fungoides and Sezary Syndrome: clinical Efficacy in a Citn Multicenter Phase 2 Study ASH 181
91. Sul J, Blumenthal GM, Jiang X, He K, Keegan P, Pazdur R (2016) FDA approval summary: Pembrolizumab for the treatment of patients with metastatic non-small cell lung cancer whose tumors express programmed death-ligand 1. Oncologist 21(5):643–650
92. Duarte RF, Canals C, Onida F et al (2010) Allogeneic hematopoietic cell transplantation for patients with mycosis fungoides and Sezary syndrome: a retrospective analysis of the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol Off J Am Soc Clin Oncol 28(29):4492–4499
93. Duvic M, Donato M, Dabaja B et al (2010) Total skin electron beam and non-myeloablative allogeneic hematopoietic stem-cell transplantation in advanced mycosis fungoides and Sezary syndrome. J Clin Oncol Off J Am Soc Clin Oncol 28(14):2365–2372
94. Wu PA, Kim YH, Lavori PW, Hoppe RT, Stockerl-Goldstein KE (2009) A meta-analysis of patients receiving allogeneic or autologous hematopoietic stem cell transplant in mycosis fungoides and Sezary syndrome. Biol Blood Marrow Trans J Am Soc Blood Marrow Transpl 15(8):982–990
95. Balakrishnan K, Peluso M, Fu M et al (2015) The phosphoinositide-3-kinase (PI3 K)-delta and gamma inhibitor, IPI-145 (Duvelisib), overcomes signals from the PI3 K/AKT/S6 pathway and promotes apoptosis in CLL. Leukemia
96. Horwitz S, Porcu P, Flinn I, Kahl B, Sweeney J, Stern H, Douglas M, Allen M, Kelly P, Foss F (2014) 803 Duvelisib (IPI-145), a Phosphoinositide-3-Kinase-δ,γ Inhibitor, Shows Activity in Patients with Relapsed/Refractory T-Cell Lymphoma. Blood Suppl 803
97. Querfeld C, Foss FM, Pinter-Brown L et al (2017) Phase 1 study of the safety and efficacy of MRG-106, a synthetic Inhibitor of microRNA-155, in CTCL patients. Blood 130:820
98. Trialsgov C (2017) A phase 1/2 trial of durvalumab (medi4736) when given as a single agent or in combiantion with lenalidomide in patients with relapsed/refractory peripheral t cell lymphoma inclduing cutaneous T cell lymphoma. NCT03011814
99. Querfeld C, Thompson JA, Taylor M et al (2017) A single direct intratumoral injection of TTI-621 (SIRPαFc) induces antitumor activity in patients with relapsed/refractory mycosis fungoides and Sézary syndrome: preliminary findings employing an immune checkpoint inhibitor blocking the CD47 “do not eat” signal. Blood 103. Abstract 4076

CD30-Positive Lymphoproliferative Disorders

12

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Abstract

Primary cutaneous CD30-positive lymphoproliferative disorders (CD30+ LPD) encompass lymphomatoid papulosis (LyP), primary cutaneous anaplastic large cell lymphoma (pcALCL), and borderline lesions [1]. CD30+ LPD are the second most common cutaneous T-cell lymphomas (CTCL) after mycosis fungoides (MF) and represent approximately 25% of all CTCL cases [2]. Their common phenotypic hallmark is an expression of the CD30 antigen, a cytokine receptor belonging to the tumor necrosis factor (TNF) receptor superfamily. Both LyP and pcALCL show numerous clinical, histological and immunophenotypic variants, and generally have an indolent course with a favorable prognosis. Overlapping features of LyP and pcALCL with other CD30+ T-cell

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lymphomas, inflammatory, and/or infectious conditions emphasize the importance of careful clinicopathologic correlation and staging.

Keywords
CD30+ lymphoproliferative disorder · Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma · Borderline lesions
Cutaneous T-cell lymphoma · Extensive limb disease · Therapeutic targets

12.1 Introduction

The World Health Organization (WHO) and European Organization for Research and Treatment of Cancer (EORTC) consensus classification of cutaneous lymphomas recognize a distinct group of primary cutaneous CD30-positive lymphoproliferative diseases (CD30+ LPD), which represent the second most common types of cutaneous T-cell lymphomas (CTCL) accounting for approximately 25% of all CTCL [3]. The spectrum of CD30+ LPD includes lymphomatoid papulosis (LyP), cutaneous anaplastic large cell lymphoma (pcALCL), and borderline lesions that refer to cases in which a difference between the clinical and histologic appearance exists. The use of the term CD30+ LPD in the initial clinical assessment and especially in the pathological diagnosis is preferable over LyP or pcALCL because often the histological criteria are not sufficient to distinguish these two entities (Table 12.1). A short observation period of 6–8 weeks may allow detection of spontaneous regression and is critical in establishing a diagnosis before initiation of therapy. The phenotypic hallmark of CD30+ LPD is the CD30 antigen, a cell surface cytokine receptor and transmembrane glycoprotein of the tumor necrosis factor receptor superfamily member 8 (TNFRSF8) gene and previously known as Ki-1 antigen [4–6]. Other T-cell lymphoproliferative diseases/lymphomas that may express the CD30 antigen include mycosis fungoides (MF) with large cell transformation, other NK/T-cell lymphomas including systemic ALCL, gamma/delta T-cell lymphoma, peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) and Hodgkin disease (HD).

12.2 Clinical Features

LyP was first described by Dupont in 1965 and in 1968 coined by Macaulay as benign, recurrent, and self-regressing erythematous papules affecting trunk and extremities that often occur in clusters or as disseminated lesions with malignant histology [7, 8]. Lesions vary from papules and nodules to less commonly larger plaques, follicular, vesicular and pustular presentations that may become hemorrhagic, necrotic, and/or ulcerative [9] (Fig. 12.1a–c). Oral or genital involvement is rarely observed [10] (Fig. 12.1d). Another clinical variation is a regional LyP,

where the lesions are localized to one anatomical area, usually involving an extremity [11]. The tendency to regress spontaneously is characteristic for the disease and crucial to establish a clinical diagnosis. In general, the lesions last 3–12 weeks, although in some severe cases the lesions may be more persistent. The condition can permanently resolve or recur over decades. In about 20% of cases LyP may precede, follow or be concurrent with other malignancies; most commonly associated with MF, pcALCL, and HD [12]. LyP generally occurs in adults between the third and fourth decade with a median age of 45 years at onset, although the disorder may affect any age. It has also been described in children, including regional LyP [13]. Patients may have mild associated pruritus but lack systemic symptoms of weight loss, fevers, or night sweats. The prognosis for patients with LyP is excellent, showing a near 100% 5-year survival [14–16].

In contrast to LyP, larger non-regressing lesions are seen in patients with pcALCL. PcALCL accounts for approximately 9% of all CTCL and affects older patients in the sixth decade with a median age of 61 years. It has rarely been described in the pediatric population [2, 17]. The prevalence of pcALCL in the USA is unknown. Most patients with pcALCL present with a cutaneous solitary nodule or localized multiple nodules that often show ulceration (Fig. 12.2a).

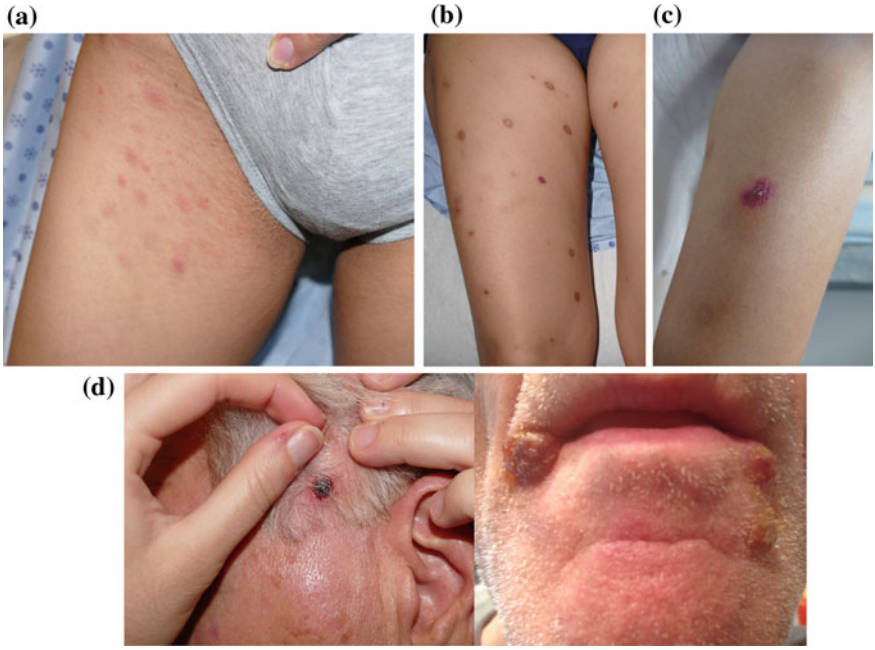

Fig. 12.1 Clinical presentations of lymphomatoid papulosis (LyP). **a** Patient presenting with locoregional multiple erythematous papules on the upper thigh. **b** Patient with disseminated papules that are at various stages of evolution. Resolving papules heal with central scar. **c** Patient presenting with a single erythematous plaque on lower leg. **d** Patient with LyP, type F presenting with recurrent juicy folliculotropic papules on face clinically mimicking HSV infection

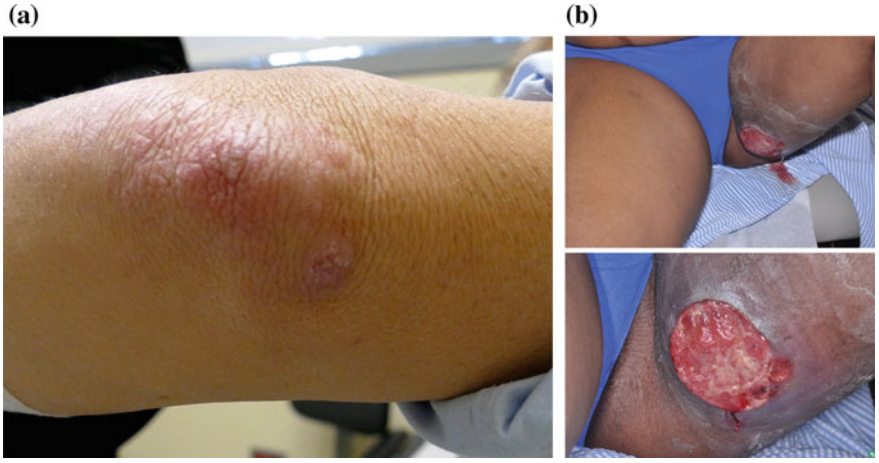

Fig. 12.2 Patients with primary cutaneous anaplastic large cell lymphoma (pcALCL). **a** Patient presenting with single erythematous nodule on elbow. **b** Patient with coalescing ulcerated plaques on inner/posterior thigh

Generalized or multifocal lesions are seen in about 20% of the patients [3]. Extracutaneous involvement is rare and is seen in 5–10% of patients at presentation involving most commonly regional lymph nodes [2, 18]. The cutaneous nodules may undergo spontaneous regression but mostly persist without treatment [2, 19]. Another variant of pcALCL is extensive limb disease (ELD), a more aggressive form of pcALCL, presenting with multiple skin tumors in one limb (Fig. 12.2b). ELD is associated with inferior outcomes and progression to extracutaneous disease [20]. The prognosis of patients with pcALCL is otherwise excellent and with reported 5-year survival of 90% [21].

The distinction between LyP and pcALCL is not always possible based on histologic criteria. Borderline lesions refer to cases in which a difference between the clinical and histologic appearance exists. These include cases with the clinical presentation of pcALCL but histologic features are suggestive of LyP, and, conversely, cases with a recurrent, self-healing skin eruption that shows histologic features characteristic of pcALCL. LyP type C has been described as a borderline lesion of pcALCL. Thus, the clinical appearance and the clinical course over time are used as decisive criteria for the definite diagnosis and the choice of treatment.

12.3 Pathologic Features

Histologically, LyP is divided into the following six subtypes, which represent a spectrum of histopathologic variants with overlapping features but do not carry prognostic significance [13, 16, 22]. Type A lesions are the most common type

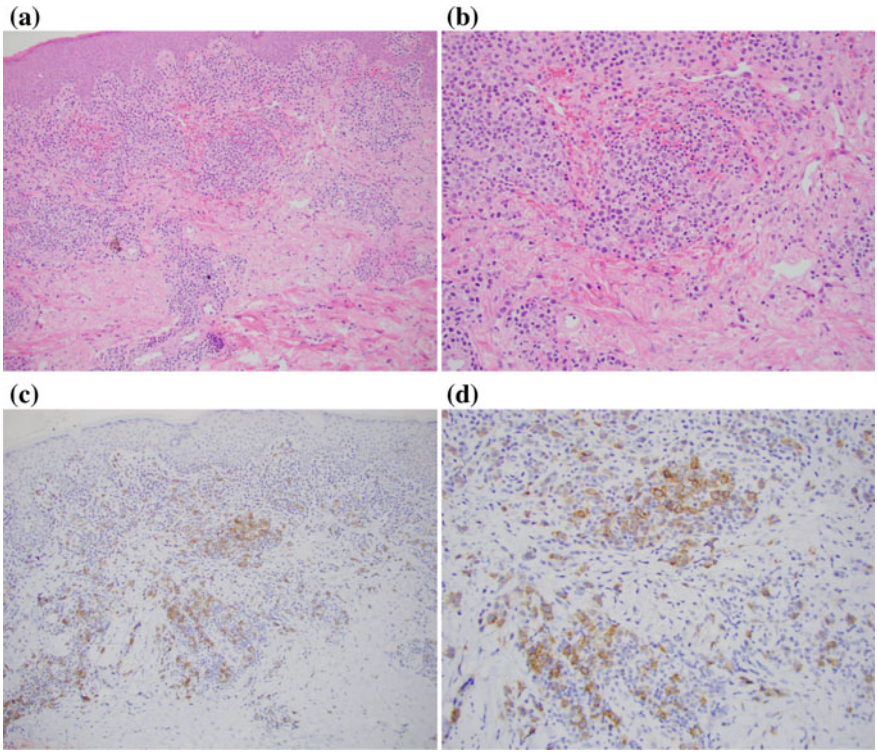

Fig. 12.3 Lymphomatoid papulosis, type A show a wedge-shaped dermal lymphoid infiltrate (hematoxylin and eosin [H&E]; original magnification ×100). Higher magnification with large atypical cells intermingled with histiocytes, rare neutrophils, eosinophils and small lymphocytes (H&E; ×200) (**b**). Immunostaining with CD30 highlights numerous large cells decorated with CD30 (anti-CD30; ×100 (**c**) and ×200 (**d**))

characterized by a wedge-shaped infiltrate with large pleomorphic CD30+ lymphoid cells within a prominent inflammatory background composed of neutrophils, eosinophils, histiocytes, and/or small lymphocytes (Fig. 12.3a–d) resembling Reed Sternberg–like cells in HD. Type B lesions are characterized by epidermotropic lymphocytes with cerebriform nuclei resembling MF [13, 16, 22]. Type C lesions have sheets of large atypical lymphoid cells with only a few admixed inflammatory cells. The large atypical lymphoid cells are of T-cell origin [23]. In types A and C, the large atypical cells express CD30, CD3, CD4, and cytotoxic granules (TIA1, granzyme B) and other T-cell lineage-specific markers such as CD2 and CD5 [24]. They are usually negative for CD8, CD7, CD15, and CD56. In LyP type B, the atypical cells are usually CD30 negative. Other rare and more recently defined LyP types include type D characterized by infiltrates similar to those in CD8+ aggressive epidermotropic T-cell lymphoma. LyP type E is defined by angiodestructive infiltrates of small- to medium-sized lymphocytes expressing CD30 and CD8.

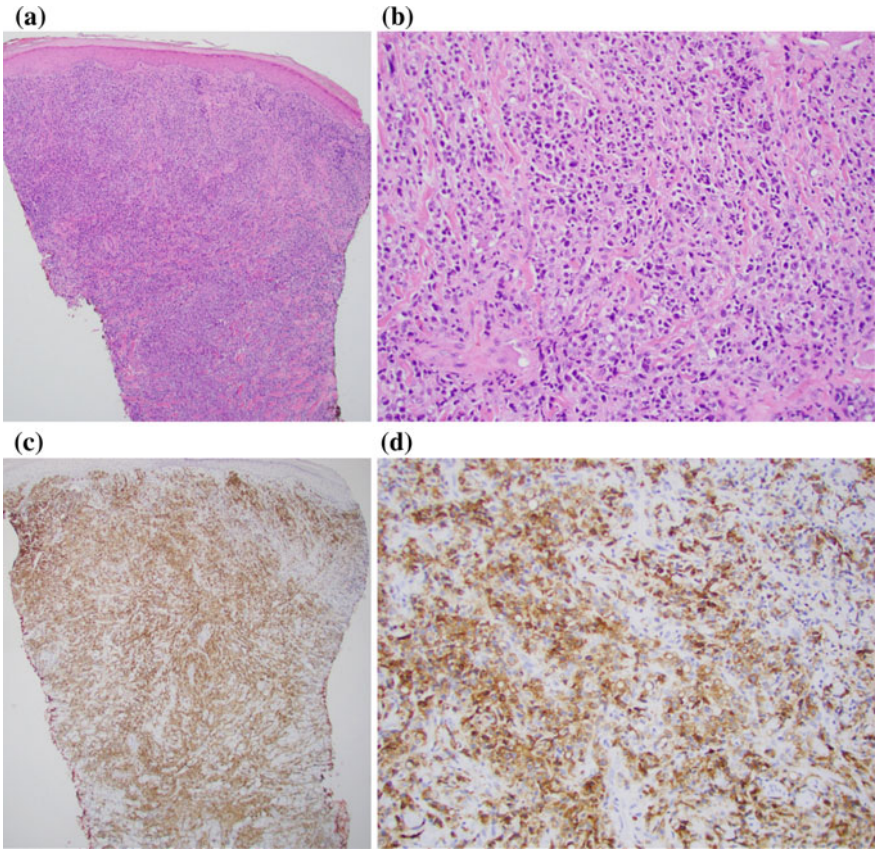

Fig. 12.4 Histologic features of pcALCL with a dense dermal lymphoid infiltrate **a** [hematoxylin and eosin [HE]; original magnification ×40]; higher magnification shows sheets of large anaplastic lymphocytes with prominent nucleoli (H&E; original magnification ×200) (**a**). Immunostaining for CD30 antigen produced a strong cytoplasmic membrane staining of the tumor cells [original magnification ×100 (**c**); ×200 (**d**)]

Type E lesions appear as vasculitis, affecting small- to medium-sized dermal vessels and may clinically behave more aggressively with the development of large ulcerative lesions [25]. Type F presents with a perifollicular infiltrate with folliculotropism [26].

PcALCL is composed of cohesive sheets of large cells with an anaplastic, pleomorphic, or immunoblastic morphology (Fig. 12.4a–d). There is no difference in the prognosis and survival rate based on cytomorphology. According to the WHO/EORTC consensus classification, pcALCL is defined by CD30 expression of at least 75% of the large lymphoid cells [3, 27]. Unlike in LyP, only a few neutrophils or eosinophils are present in the pcALCL environment; however, neutrophil-rich (pyogenic) tumors have been seen [28]. Other variants such as

sarcomatoid variant with prominent spindle-cell morphology, myxoid, and keratoacanthoma-like variants have also been described [29, 30]. The atypical cells generally show an activated CD4+ T-helper cell phenotype with variable loss of T-cell markers and expression of cytotoxic proteins such as TIA1, granzyme B, and perforin in about 50% of the cases [31]. A CD8+ T-cell phenotype as well as a CD4-CD8-phenotype and/or co-expression of CD56 and CD30 have also been reported.

In contrast to primary nodal ALCL, pcALCL rarely carry the t(2; 5) translocation and are usually ALK negative [32]. Unlike nodal ALCL, most pcALCL express cutaneous lymphocyte antigen (CLA) but lack epithelial membrane antigen (EMA) expression [21, 22]. The diagnostic and prognostic significance of tumor necrosis factor receptor-associated factor 1 (TRAF-1), multiple myeloma oncogene-1 (MUM-1), Bcl-2 and CD15 expression have not been found to reliably differentiate pcALCL from other CD30+ LPD, secondary ALCL, or large cell transformed MF [33].

12.4 Molecular Findings

CD30 signaling is known to have an effect on growth and survival of CD30+ LPD. Apoptosis rates and expression of apoptosis-related proteins such Bax, Bcl-x, c-kit, and Mcl-1 were analyzed in evolutional stages of LyP and pcALCL, and CD30 + lymphoma cell lines. While a higher apoptotic index was found in LyP than pcALCL, the proapoptotic protein Bax was expressed at high levels in all evolutional stages of LyP and pcALCL and may contribute to the regression of cutaneous lesions. Expression of Bcl-2 appears to protect tumor cells from apoptosis in CD30 + LPD [34]. Stimulation of cell growth and apoptosis have been noted with activation of CD30 and therefore, CD30 ligand-mediated cytotoxicity may participate in the pathophysiology of clinical regression. The interaction between Fas/APO-1 (CD95) and its ligand FasL has also been studied. CD95 expression appears to be expressed at high levels in all cutaneous CD30+ LPD and suggest that CD95 activation may induce regression of CD30+ skin lesions [31]. Unraveling further, recent experiments in molecular mechanisms involved in apoptosis of pcALCL have shown that CD30-mediated FLICE-inhibitory protein (c-FLIP)-upregulation leads to enhanced resistance to apoptosis by death ligands such as CD95 and TRAIL [35, 36].

Molecular studies have found that nearly all pcALCL are of clonal origin. Array-based comparative genomic hybridization studies disclosed chromosomal imbalances in approximately 40% of the cases [37]. More recently, pcALCL is characterized by gains on chromosome 7q and 17q and losses on 6q and 13q. In addition, pcALCL showed higher expression of the skin-homing chemokine receptor genes CCR10 and CCR8, and aberrant expression of genes implicated in apoptosis (TNFRSF8/CD30, TRAF-1), and proliferation (IRF4/MUM-1, PRKCQ) [38].

LyP with chromosomal rearrangements of the DUSP22-IRF4 locus on 6p25.3 was reported by Karai et al. and likely represent a novel variant of LyP with improved prognosis [39]. LyP with 6p25 rearrangement tends to have small- to medium-sized atypical CD30-positive cells in the epidermal layer resembling pagetoid reticulosis [22, 27, 40]. Patients have benign clinical course despite pathologic features mimicking an aggressive lymphoma with spontaneous regression of the lesions [39]. DUSP22-IRF4 locus on 6p25.3 has been reported in 28% of patient with pcALCL predicting favorable clinical behavior [39, 41].

Histopathologic dermal lymphovascular involvement was found in pcALCL with a trend towards higher prevalence in patients with ELD [42]. Genes that were found to be upregulated in ELD were STAT5A and IL2RA, both play a role in regulating T-cell activation. Retinoid X receptor alpha (RXRA) gene was downregulated in ELD [20].

12.5 Staging and Workup

Routine evaluation includes complete physical examination with assessment of skin burden. Laboratory studies include a complete blood count with differential, flow cytometry if lymphocytosis is present, comprehensive metabolic panel, LDH, HIV, HTLV-1, and EBV serologies as some aggressive T-cell lymphoma/leukemia may have cutaneous manifestations and can be associated with viral etiologies [43]. Skin biopsy for histopathologic evaluation, immunophenotyping, and gene rearrangement studies, and lymph node biopsies in cases with enlarged nodes at presentation are necessary to establish the diagnosis and staging. Immunostaining with antibodies against ALK and/or fluorescence in situ hybridization (FISH) and reverse transcriptase-polymerase chain reaction (RT-PCR) can be performed to detect the t (2; 5) translocation for diagnostic purposes. Imaging studies such as whole body PET/CT scans are reserved for patients with clinical and laboratory findings suggestive of systemic disease or prominent lymphadenopathy. Histopathologic and molecular results should be correlated with clinical findings and patients classified according to the WHO-EORTC consensus classification. Bone marrow biopsy are recommended if patients have cytopenias, constitutional symptoms, or multifocal disease, suggestive of pcALCL.

12.6 Prognosis

The overall prognosis for LyP and pcALCL is favorable with 5-year survival near 100% [14–16, 21]. Most patients have recurrence of localized lesions, which can be managed by resection or topical agents with no to minimal systemic side effects. Molecular studies identified a group of patients with LyP and DUSP22-IRF4

rearrangement on 6p25.3 that had localized disease, spontaneously regressing with benign clinical course, emphasizing the importance of incorporating molecular and genetic factors in identifying patients likely with favorable prognosis of CD30+ LPD [39]. On the other hand, some patients with LyP have a higher risk of developing associated lymphoma. Several factors appear to have prognostic value in the progression of the disease and association with the development of the second lymphoma, such as older age, the location of the lesion in the limb or head with higher rates of recurrence, as well as expression of fascin by CD30+ large cells and T-cell receptor rearrangement in LyP. Most patients with pcALCL are ALK-negative and have an indolent course, but ALK+ pcALCL cases exist and often present in younger individuals and may represent large, rapidly growing tumors with a more aggressive course [44, 45]. Patients with ELD have inferior outcomes with 5-year survival rate of 76% [21]. Tumor growth and progression has been shown to depend largely on microenvironment. De Souza et al. showed that the predominant immune cells in the vicinity of CD30+ lymphoid cells in LyP and pcALCL were CD163+ M2 macrophages, suggesting a direct influence on tumorigenesis in LyP and ALCL [46].

12.7 Treatment

Lymphomatoid Papulosis

There is no curative treatment available for LyP. Historically, the most commonly used treatments include low-dose methotrexate, topical and intralesional steroids, bexarotene, doxycycline, psoralens, and ultraviolet light A (PUVA), UVB, narrowband (NB)-UVB, interferon-alpha (INF-α), and radiation therapy [47–49]. However, none of these treatments alter the natural course of the disease; therefore, the short-term benefits should be weighed against the potential side effects (Table 12.2).

LyP lesions usually resolve spontaneously without intervention but may take weeks to months for complete resolution. Observation is recommended for patients with a few, asymptomatic lesions.

12.7.1 Phototherapy

Other treatment options for disseminated LyP lesions include psoralen combined with ultraviolet A light (PUVA) therapy twice weekly for 6–8 weeks with or without maintenance for patients that do not respond to oral methotrexate or other treatment modalities [50]. An alternative to oral psoralen PUVA therapy is a PUVA-bath phototherapy using diluted methoxsalen solution prior to UVA irradiation, which was well tolerated and resulted in low serum levels of methoxsalen,

Table 12.1 Summary of clinicopathologic and molecular features of lymphomatoid papulosis, primary cutaneous anaplastic large cell lymphoma, and its variant with extensive limb disease

Criteria	Lymphomatoid papulosis	Anaplastic large cell lymphoma	Anaplastic large cell lymphoma—extensive limb disease
Demographics	• 4th decade • Slight male preponderance	• 6th decade • Male predominance	• 7th decade • Male predominance
Clinical features	• Single, localized or disseminated papulonodular eruption • Chronic, self-remitting course • Associated with other malignancies (MF, pcALCL, or HD)	• Solitary, localized, multifocal cutaneous nodules often with ulceration • Rarely self-regression • Extracutaneous disease in 10%, mostly involving draining lymph node region	• Aggressive variant • Regional involvement (one limb) of multiple to extensive skin nodules • Inferior outcomes and progression to extracutaneous disease
Pathology	• **Type A**: wedge-shaped infiltration of large pleomorphic cells (Reed Sternberg-like) background of neutrophils, eosinophils, histiocytes • **Type B**: infiltrate of medium-sized lymphocytes with cerebriform nuclei, varies CD30 positivity and epidermotropism, resembling MF • **Type C**: Sheets of large pleomorphic cells, resembling ALCL • **Type D**: CD8 + epidermotropic infiltrate resembling aggressive CD8 + cytotoxic T-cell lymphoma • **Type E**: perivascular and transmural CD30 + infiltrate • **Type F**: lesions with perifollicular infiltrate with folliculotropism	• Diffuse, deep, dermal sheets of large anaplastic and pleomorphic cells • CD30 expression in $\geq$75% of infiltrate • Neutrophil-rich, sarcomatoid, small cell (ALK+), keratoacanthoma-like, pyoderma gangrenosum-like variants	• Diffuse, deep, dermal sheets of large anaplastic and pleomorphic cells • CD30 expression in $\geq$75% of infiltrate
Immunophenotype	• CD4+, CD30+, BF1 + (alpha/beta TCR), TIA1+, granzyme B+, CD56$\mp$ • CD8+, gamma/delta TCR (type D)	• CD4+, CD30+, BF1+, CD56$\pm$ TIA1+, granzyme B+, ALK-, EMA$\mp$ • Variable loss of CD2, CD3 and CD5	• Similar to classic pcALCL

(continued)

Table 12.1 (continued)

Criteria	Lymphomatoid papulosis	Anaplastic large cell lymphoma	Anaplastic large cell lymphoma—extensive limb disease
Genetic signature	• Rearrangement of the DUSP22-IRF4 locus on 6p25.3 in small subset (LyP variant with pagetoid reticulosis-like features)	• Rearrangement of the DUSP22-IRF4 locus on 6p25.3 • No t(2; 5) (p23; q35; ALK/NPM genes) translocation	• Upregulation of STAT5 • Overexpression of high-affinity ILR2A • Downregulation of RXR alpha gene
Prognosis	• 5-year OS is 100%	• 5-year OS is 95%	• 5-year OS is 76%

Abbreviation ALK anaplastic lymphoma kinase; *EMA* epithelial membrane antigen; *HD* Hodgkin disease; *LyP* lymphomatoid papulosis; *MF* mycosis fungoides; *NPM* nucleophosmin; *pcALCL* primary cutaneous anaplastic large cell lymphoma; *RXR* retinoic acid X receptor; *TCR* T-cell receptor

minimizing systemic side effects of nausea and vomiting that can be associated with oral psoralen [51–54].

12.7.2 Methotrexate

Patients with the more extensive cutaneous disease, involving multiple sites not amenable to localized management, are potential candidates for systemic therapy. Oral methotrexate can produce good response rates in patients with LyP with complete resolution of the lesions and maintenance of such response was reported while on methotrexate therapy [55]. Starting dose of methotrexate is 15 mg once per week, while monitoring for toxicity and responses [48, 56]. Response rates are usually seen within the first few weeks of therapy and median duration of response is approximately three years. Once patients achieve remissions, they can be transitioned to maintenance dosing once or twice per month to maintain the best response. Common side effects of methotrexate include gastrointestinal symptoms and fatigue with more serious adverse effects being liver toxicity, renal impairment, and myelosuppression. Liver fibrosis was reported with long-term methotrexate use; therefore, treatment-free interval after maximum of three years of maintenance therapy is reasonable. Methotrexate is contraindicated in pregnancy or with active hepatitis; patients should be evaluated for these conditions prior to starting therapy. Lesions tend to recur after discontinuation of methotrexate and can be rechallenged with methotrexate.

12.7.3 Brentuximab Vedotin

Brentuximab vedotin (BV) is a humanized CD30 antibody conjugated to monomethyl auristatin E (MMAE), an anti tubulin agent, and highly effective for systemic ALCL. BV was evaluated in phase II clinical trial for CD30+ CTCL and LyP. Overall response rate (ORR) was 73% with complete response (CR) rate of 35%. Patients with MF had ORR of 54% compared with ORR of 100% in patients with LyP and pcALCL on the study. Patients with LyP/pcALCL had a shorter time to response as compared to patients with MF, 3 weeks (range, 3–9 weeks) versus 12 weeks (range, 3–39 weeks), respectively. The most common side effect was peripheral neuropathy, followed by fatigue and rash [57].

12.8 Primary Cutaneous Anaplastic Large Cell Lymphoma

Treatment modalities for pcALCL include topical and intralesional formulations, surgical resection, radiation therapy for local lesions, oral methotrexate, bexarotene, or CD30-targeted therapy with brentuximab vedotin. Systemic chemotherapy is reserved for more aggressive or refractory disease, as well as stem cell transplantation is offered to selected patients (Table 12.2).

Table 12.2 Treatment algorithms for CD30+ lymphoproliferative disorders (excluding systemic ALCL)

Treatment	Lymphomatoid papulosis	Anaplastic large cell lymphoma	Anaplastic large cell lymphoma—extensive limb disease w/regional nodal involvement	References
Solitary/limited	• Observation • Topical steroids • Phototherapy (NB-UVB, PUVA)	• Observation • Intralesional steroids • Surgical excision • Radiation therapy (30–40 Gy)	• N/A	• Kempf et al. *Blood* 2011 • Querfeld et al. *Oncology* 2007 • Paul et al. *Pediatr Dermatol* 1996 • Vonderheid et al. *J Am Acad Dermatol* 1989 • Horwitz et al. *Blood* 2012 • Wu et al. *Int J Dermatol* 2003 • Duvic et al. *J Clin Oncol* 2015 • Woo et al. *Arch Dermatol* 2009 • Prince HM et al. *Lancet* 2017
Multifocal/extensive ± Symptoms	• Observation • Phototherapy • Methotrexate (5–40 mg PO weekly) • Systemic retinoids • Topical steroids • Intralesional steroids • Topical nitrogen mustard	• Radiation therapy • Methotrexate (weekly) • Systemic retinoids • Interferon-alpha • Pralatrexate • Brentuximab vedotin • Liposomal doxorubicin (Doxil) • Multiagent chemotherapy	• Radiation therapy (selected cases) • Methotrexate (weekly) ± RT • Systemic retinoids ± RT • Pralatrexate • Brentuximab vedotin ± RT • CHOP, CHOEP ± RT	
Treatment refractory (multifocal/extensive)	• Brentuximab vedotin • Clinical trial	• Clinical trial • Stem cell transplant	• Clinical trial • Stem cell transplant	

Abbreviations CHOEP Cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone; *RT* radiation therapy

Skin-Directed Therapies:

Skin-directed therapies to localized lesions that have been shown to produce responses include imiquimod, topical bexarotene gel, topical nitrogen mustard, and intralesional interferon-alfa or methotrexate [58–64]. Side effects of skin-directed treatment can include irritation, burning sensation or irritative/contact dermatitis. Consultation with a dermatologist, who is familiar with the use of these agents and management of symptoms associated with these regimens, is recommended.

12.8.1 Surgery and Radiation Therapy

PcALCL with a single lesion or localized nodules without nodal involvement can be removed with complete surgical excision or local radiation with 30–40 Gy [65, 66]. Single-fraction radiotherapy of 750–800 cGy has been shown to be well tolerated and as effective as a multifractionated course in CD30+ LyP, producing complete responses including patients previously failing first-line therapy [67]. Addition of radiation therapy to complete surgical resection does not appear to benefit patients with localized disease. Surgery or radiation to local tumors can achieve remission; however, most patients will relapse and require additional therapy. For patients with regional nodal involvement, radiation to the primary tumors and nodal structures is recommended [48].

Recurrent disease is common and most patients will relapse within 5 years of achieving complete remission with initial localized therapy [21]. Management of relapsed disease depends on the location of the recurrence, the extent of the disease, and prior treatment that was received. Surgical excision of the localized lesions can be attempted or use of local radiotherapy to the sites that have not been radiated previously to limit cumulative toxicity.

12.8.2 Antifolates

For more extensive disease, oral methotrexate has been used for patients with pcALCL with good responses. Similar to LyP, the patient should be started on a lower dose and tapered up while monitoring for toxicities. Pralatrexate, a novel antifolate with high affinity for reduced folate carrier-1, was evaluated in patients with relapsed/refractory T-cell lymphoma including pcALCL and demonstrated activity with a response rate of 45%. Most common grade 3–4 adverse events were mucositis and leukopenia [68].

12.8.3 Vitamin A Derivative

Bexarotene is an oral agent, a vitamin A derivative that binds to retinoid X receptor, used systemically in patients with cutaneous T-cell lymphomas but is reserved as a

second line for patients with CD30+ LPD, who progressed on or with toxicity to methotrexate [69]. Patients should be started at a 25–50% lower dose with subsequent dose escalation as tolerated, but not to exceed 300 mg/m^2 per day [70]. Bexarotene is contraindicated in pregnancy or in patients who are trying to get pregnant due to teratogenic effects. Serious side effects include hypertriglyceridemia and hypothyroidism often requiring lipid-lowering agent and thyroid replacement therapy, as well as liver toxicity and pancreatitis have been reported. Patients should be monitored with complete blood cell counts, comprehensive metabolic panel, fasting lipid panel, and thyroid function tests to assess for hematologic and liver toxicity, central hypothyroidism, and lipid abnormalities [71]. A combination therapy of bexarotene and interferon-alpha 2a has been reported, showing rapid and marked regression of cutaneous lesions in a patient with CD30+ pcALCL [72].

12.8.4 Brentuximab Vedotin

Activity of brentuximab vedotin (BV) in pcALCL was also demonstrated in phase III randomized clinical trial comparing BV 1.8 mg/kg every 21 days to physician's choice of methotrexate or bexarotene in patients with CD30+ CTCL after progression on local or systemic therapy. Objective global response rate lasting at least 4 months (ORR4) for the whole study was 56.3% with BV and 12.5% in the control arm (physician's choice) and for the subgroup of patients with pcALCL reported ORR4 was 75% with BV compared with 20% in the control arm. Median PFS was 16.7 months versus 3.5 months in the control arm [73]. The trial has met its primary endpoint when reached a statistically significant objective response. BV received a breakthrough designation for the treatment of CD30+ CTCL, including pcALCL in 2016. The most common side effect of BV was peripheral sensory neuropathy seen in over 60% of the patients in both studies, which improved after discontinuation of therapy or dose reduction. Rare severe toxicities included neutropenia, deep vein thrombosis, and transaminitis.

12.8.5 Chemotherapy

Single-agent chemotherapy such as gemcitabine or etoposide also has been used in CTCL, including CD30+ ALCL [74–76]. Pegylated doxorubicin has been shown to be very effective as a single agent in ALCL presumably due to increased efficacy of liposomal doxorubicin in the skin [77]. Multidrug chemotherapy is generally not indicated in patients with pcALCL without extensive disseminated skin lesions or extracutaneous disease. Doxorubicin-based combination chemotherapy has been used with high response rates and complete remission and would be recommended in patients with extensive and extracutaneous disease; however, relapses are common and seen in over 60% of patients [18, 78, 79].

12.9 Extensive Limb Disease

Optimal treatment for patients with ELD remains to be defined, but given that ELD is a highly aggressive and rapidly progressing disease, multidrug regimen should be considered. Woo et al. reported clinical complete response rate of 25% to multidrug chemotherapy in patients with ELD compared with 79% in patients without ELD. Regional progression was noted to occur within 3 months in these patients. Patients with ELD do not typically respond to bexarotene, perhaps because of *RXR* alpha downregulation [20].

12.10 Role of Stem Cell Transplantation

Patients with progressive disease, uncontrolled by systemic therapy could be considered for high-dose chemotherapy followed by autologous or allogeneic stem cell transplantation. Patients presenting with upfront aggressive disease may benefit from autologous stem cell transplantation after achieving remission to consolidate the response. Clinical data on allogeneic stem cell transplantation is limited for this patient population and enrollment on a clinical trial is encouraged [12, 76, 80, 81].

12.11 Conclusions

Primary cutaneous $CD30^+$ lymphoproliferative diseases demonstrate a wide spectrum of clinical and histopathologic features. Clinicians and pathologists should be aware of the pathologic findings and the clinical presentation and behavior for correct diagnosis. $CD30^+$ lymphoproliferative diseases have an excellent prognosis with a 5-year survival exceeding 90%. Management includes close monitoring for LyP cases and skin-directed regimens for solitary or localized pcALCL. Systemic regimens including single-agent methotrexate or brentuximab vedotin are reserved for patients with refractory or progressive disease. Patients with extensive or extracutaneous involvements may respond to liposomal doxorubicin or doxorubicin-based chemotherapy. The increased understanding of the biology and molecular alterations of $CD30^+$ atypical lymphoid cells and their relationship to the microenvironment will be critical to develop new therapeutic targets. Nonetheless, all patients with CD30+ LPD should be followed closely for signs of relapses and risk of development of a second malignancy.

References

1. Willemze R, Meijer CJ (2003) Primary cutaneous CD30-positive lymphoproliferative disorders. Hematol Oncol Clin North Am 17(1319–1332):vii–viii

2. Bekkenk MW, Geelen FA, van Voorst Vader PC et al (2000) Primary and secondary cutaneous CD30(+) lymphoproliferative disorders: a report from the Dutch cutaneous lymphoma group on the long-term follow-up data of 219 patients and guidelines for diagnosis and treatment. Blood 95:3653–3661
3. Willemze R, Jaffe ES, Burg G et al (2005) WHO-EORTC classification for cutaneous lymphomas. Blood 105:3768–3785
4. Stein H, Mason DY, Gerdes J et al (1985) The expression of the Hodgkin's disease associated antigen Ki-1 in reactive and neoplastic lymphoid tissue: evidence that Reed-Sternberg cells and histiocytic malignancies are derived from activated lymphoid cells. Blood 66:848–858
5. Falini B, Pileri S, Pizzolo G et al (1995) CD30 (Ki-1) molecule: a new cytokine receptor of the tumor necrosis factor receptor superfamily as a tool for diagnosis and immunotherapy. Blood 85:1–14
6. Assaf C, Hirsch B, Wagner F et al (2007) Differential expression of TRAF1 aids in the distinction of cutaneous CD30-positive lymphoproliferations. J Invest Dermatol 127:1898–1904
7. Dupont A, Thulliez A (1956) Histio-monocytic reticulosis and mycosis fungoides; four case reports. Arch Belg Dermatol Syphiligr 12:263–272
8. Macaulay WL (1968) Lymphomatoid papulosis. A continuing self-healing eruption, clinically benign–histologically malignant. Arch Dermatol 97:23–30
9. Kempf W (2006) CD30+ lymphoproliferative disorders: histopathology, differential diagnosis, new variants, and simulators. J Cutan Pathol 33(Suppl 1):58–70
10. Pujol RM, Muret MP, Bergua P, Bordes R, Alomar A (2005) Oral involvement in lymphomatoid papulosis. Report of two cases and review of the literature. Dermatology 210:53–57
11. Scarisbrick JJ, Evans AV, Woolford AJ, Black MM, Russell-Jones R (1999) Regional lymphomatoid papulosis: a report of four cases. Br J Dermatol 141:1125–1128
12. Querfeld C, Khan I, Mahon B, Nelson BP, Rosen ST, Evens AM (2010) Primary cutaneous and systemic anaplastic large cell lymphoma: clinicopathologic aspects and therapeutic options. Oncology (Williston Park). 24:574–587
13. Wieser I, Wohlmuth C, Nunez CA, Duvic M (2016) Lymphomatoid papulosis in children and adolescents: a systematic review. Am J Clin Dermatol 17:319–327
14. Sauder MB, O'Malley JT, LeBoeuf NR (2017) CD30+ lymphoproliferative disorders of the skin. Hematol Oncol Clin North Am 31:317–334
15. Cordel N, Tressieres B, D'Incan M et al (2016) Frequency and risk factors for associated lymphomas in patients with lymphomatoid papulosis. Oncologist 21:76–83
16. Wieser I, Tetzlaff MT, Torres Cabala CA, Duvic M (2016) Primary cutaneous CD30(+) lymphoproliferative disorders. J der Dtsch Dermatol Ges = J Ger Soc Dermatol JDDG 14:767–782
17. Kumar S, Pittaluga S, Raffeld M, Guerrera M, Seibel NL, Jaffe ES (2005) Primary cutaneous CD30-positive anaplastic large cell lymphoma in childhood: report of 4 cases and review of the literature. Pediatr Dev Pathol 8:52–60
18. Liu HL, Hoppe RT, Kohler S, Harvell JD, Reddy S, Kim YH (2003) CD30+ cutaneous lymphoproliferative disorders: the stanford experience in lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma. J Am Acad Dermatol 49:1049–1058
19. Booken N, Goerdt S, Klemke CD (2012) Clinical spectrum of primary cutaneous CD30-positive anaplastic large cell lymphoma: an analysis of the mannheim cutaneous lymphoma registry. J der Dtschn Dermatol Ges = J Ger Soc Dermatol JDDG 10:331–339
20. Woo DK, Jones CR, Vanoli-Storz MN et al (2009) Prognostic factors in primary cutaneous anaplastic large cell lymphoma: characterization of clinical subset with worse outcome. Arch Dermatol 145:667–674
21. Benner MF, Willemze R (2009) Applicability and prognostic value of the new TNM classification system in 135 patients with primary cutaneous anaplastic large cell lymphoma. Arch Dermatol 145:1399–1404

22. Kempf W (2017) A new era for cutaneous CD30-positive T-cell lymphoproliferative disorders. Semin Diagn Pathol 34:22–35
23. El Shabrawi-Caelen L, Kerl H, Cerroni L (2004) Lymphomatoid papulosis: reappraisal of clinicopathologic presentation and classification into subtypes A, B, and C. Arch Dermatol 140:441–447
24. Saggini A, Gulia A, Argenyi Z et al (2010) A variant of lymphomatoid papulosis simulating primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma. Description of 9 cases. Am J Surg Pathol 34:1168–1175
25. Kempf W, Kazakov DV, Paredes BE, Laeng HR, Palmedo G, Kutzner H (2013) Primary cutaneous anaplastic large cell lymphoma with angioinvasive features and cytotoxic phenotype: a rare lymphoma variant within the spectrum of CD30+ lymphoproliferative disorders. Dermatology 227:346–352
26. Kempf W, Kazakov DV, Baumgartner HP, Kutzner H (2013) Follicular lymphomatoid papulosis revisited: a study of 11 cases, with new histopathological findings. J Am Acad Dermatol 68:809–816
27. Swerdlow SH, Campo E, Pileri SA et al (2016) The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 127:2375–2390
28. Mann KP, Hall B, Kamino H, Borowitz MJ, Ratech H (1995) Neutrophil-rich, Ki-1-positive anaplastic large-cell malignant lymphoma. Am J Surg Pathol 19:407–416
29. Lin JH, Lee JY (2004) Primary cutaneous CD30 anaplastic large cell lymphoma with keratoacanthoma-like pseudocarcinomatous hyperplasia and marked eosinophilia and neutrophilia. J Cutan Pathol 31:458–461
30. Wang J, Sun NC, Nozawa Y et al (2001) Histological and immunohistochemical characterization of extranodal diffuse large-cell lymphomas with prominent spindle cell features. Histopathology 39:476–481
31. Felgar RE, Macon WR, Kinney MC, Roberts S, Pasha T, Salhany KE (1997) TIA-1 expression in lymphoid neoplasms. Identification of subsets with cytotoxic T lymphocyte or natural killer cell differentiation. Am J Pathol 150:1893–1900
32. Stein H, Foss HD, Durkop H et al (2000) CD30(+) anaplastic large cell lymphoma: a review of its histopathologic, genetic, and clinical features. Blood 96:3681–3695
33. Benner MF, Jansen PM, Meijer CJ, Willemze R (2009) Diagnostic and prognostic evaluation of phenotypic markers TRAF1, MUM1, BCL2 and CD15 in cutaneous CD30-positive lymphoproliferative disorders. Br J Dermatol 161:121–127
34. Greisser J, Doebbeling U, Roos M et al (2005) Apoptosis in CD30-positive lymphoproliferative disorders of the skin. Exp Dermatol 14:380–385
35. Braun FK, Hirsch B, Al-Yacoub N et al (2010) Resistance of cutaneous anaplastic large-cell lymphoma cells to apoptosis by death ligands is enhanced by CD30-mediated overexpression of c-FLIP. J Invest Dermatol 130:826–840
36. Stutz N, Johnson RD, Wood GS (2012) The Fas apoptotic pathway in cutaneous T-cell lymphomas: frequent expression of phenotypes associated with resistance to apoptosis. J Am Acad Dermatol 67(1327):e1–e10
37. Mao X, Orchard G, Lillington DM, Russell-Jones R, Young BD, Whittaker S (2003) Genetic alterations in primary cutaneous CD30+ anaplastic large cell lymphoma. Genes Chromosomes Cancer 37:176–185
38. van Kester MS, Tensen CP, Vermeer MH et al (2010) Cutaneous anaplastic large cell lymphoma and peripheral T-cell lymphoma NOS show distinct chromosomal alterations and differential expression of chemokine receptors and apoptosis regulators. J Invest Dermatol 130:563–575
39. Karai LJ, Kadin ME, Hsi ED et al (2013) Chromosomal rearrangements of 6p25.3 define a new subtype of lymphomatoid papulosis. Am J Surg Pathol 37:1173–1181
40. Swerdlow S, Campo E, Harris N et al (2008) WHO classification of tumors of hematopoietic and lymphoid tissues 4th edn.

41. Xing X, Feldman AL (2015) Anaplastic large cell lymphomas: ALK positive, ALK negative, and primary cutaneous. Adv Anat Pathol 22:29–49
42. Gratzinger D, Million L, Kim YH (2015) Occult dermal lymphatic involvement is frequent in primary cutaneous anaplastic large cell lymphoma. Am J Dermatopathol 37:767–770
43. Kerschmann RL, Berger TG, Weiss LM et al (1995) Cutaneous presentations of lymphoma in human immunodeficiency virus disease. Predominance of T cell lineage. Arch Dermatol 131:1281–1288
44. Xue D, Li X, Ren Y, Liu Q, Yen Y, Xue L (2015) Primary cutaneous anaplastic large cell lymphoma with positive ALK expression and a rapidly progressive cutaneous nodule. Int J Surg Pathol 23:333–335
45. Uzuncakmak TK, Akdeniz N, Karadag AS, Taskin S, Zemheri EI, Argenziano G (2017) Primary cutaneous CD30(+) ALK(-) anaplastic large cell lymphoma with dermoscopic findings: a case report. Dermatol Prac Concept 7:59–61
46. De Souza A, Tinguely M, Burghart DR, Berisha A, Mertz KD, Kempf W (2016) Characterization of the tumor microenvironment in primary cutaneous CD30-positive lymphoproliferative disorders: a predominance of CD163-positive M2 macrophages. J Cutan Pathol 43:579–588
47. Paul MA, Krowchuk DP, Hitchcock MG, Jorizzo JL (1996) Lymphomatoid papulosis: successful weekly pulse superpotent topical corticosteroid therapy in three pediatric patients. Pediatr Dermatol 13:501–506
48. Kempf W, Pfaltz K, Vermeer MH et al (2011) EORTC, ISCL, and USCLC consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. Blood 118:4024–4035
49. Bilgic Temel A, Unal B, Erdi Sanli H, Duygulu S, Uzun S (2017) A severe case of lymphomatoid papulosis type E successfully treated with interferon-alfa 2a. Case Rep Dermatol Med 2017:3194738
50. Thomsen K, Wantzin GL (1987) Lymphomatoid papulosis. A follow-up study of 30 patients. J Am Acad Dermatol 17:632–636
51. Wantzin GL, Thomsen K (1982) PUVA-treatment in lymphomatoid papulosis. Br J Dermatol 107:687–690
52. Lange-Wantzin G, Thomsen K, Hou-Jensen K (1984) Lymphomatoid papulosis: a follow-up study. Acta Derm Venereol 64:46–51
53. Volkenandt M, Kerscher M, Sander C, Meurer M, Rocken M (1995) PUVA-bath photochemotherapy resulting in rapid clearance of lymphomatoid papulosis in a child. Arch Dermatol 131:1094
54. Errichetti E, Piccirillo A, Ricciuti F, Ricciuti F (2013) Steroid-resistant localized lymphomatoid papulosis treated with local bath-PUVA therapy. Indian J Dermatol 58:163
55. Bruijn MS, Horvath B, van Voorst Vader PC, Willemze R, Vermeer MH (2015) Recommendations for treatment of lymphomatoid papulosis with methotrexate: a report from the Dutch cutaneous lymphoma group. Br J Dermatol 173:1319–1322
56. Vonderheid EC, Sajjadian A, Kadin ME (1996) Methotrexate is effective therapy for lymphomatoid papulosis and other primary cutaneous CD30-positive lymphoproliferative disorders. J Am Acad Dermatol 34:470–481
57. Duvic M, Tetzlaff MT, Gangar P, Clos AL, Sui D, Talpur R (2015) Results of a phase II trial of brentuximab vedotin for CD30+ Cutaneous T-Cell lymphoma and lymphomatoid papulosis. J Clin Oncol 33:3759–3765
58. Didona B, Benucci R, Amerio P, Canzona F, Rienzo O, Cavalieri R (2004) Primary cutaneous CD30+ T-cell lymphoma responsive to topical imiquimod (Aldara). Br J Dermatol 150:1198–1201
59. Oliveira A, Fernandes I, Alves R, Lima M, Selores M (2011) Primary cutaneous CD30 positive anaplastic large cell lymphoma–report of a case treated with bexarotene. Leuk Res 35:e190–e192

60. Ardigo M, Marulli GC, Cota C, Mastroianni A, Berardesca E (2007) Bexarotene and interferon-alpha combination therapy in a patient affected by relapsing anaplastic large cell lymphoma with cutaneous involvement. J Drugs Dermatol JDD 6:216–219
61. Qiu B, Chen M (1996) Treatment of cutaneous T cell lymphoma with low doses of interferon alpha-2b. Chin Med J (Engl) 109:404–406
62. Yokoi I, Ishikawa E, Koura A et al (2014) Successful treatment of primary cutaneous anaplastic large cell lymphoma with intralesional methotrexate therapy. Acta Derm Venereol 94:319–320
63. Querfeld C, Kuzel TM, Guitart J, Rosen ST (2007) Primary cutaneous CD30+ lymphoproliferative disorders: new insights into biology and therapy. Oncol 21:689–696; discussion 99–700 (Williston Park)
64. Vonderheid EC, Tan ET, Kantor AF, Shrager L, Micaily B, Van Scott EJ (1989) Long-term efficacy, curative potential, and carcinogenicity of topical mechlorethamine chemotherapy in cutaneous T cell lymphoma. J Am Acad Dermatol 20:416–428
65. Beljaards RC, Kaudewitz P, Berti E et al (1993) Primary cutaneous CD30-positive large cell lymphoma: definition of a new type of cutaneous lymphoma with a favorable prognosis. A European multicenter study of 47 patients. Cancer 71:2097–2104
66. Yu JB, McNiff JM, Lund MW, Wilson LD (2008) Treatment of primary cutaneous CD30+ anaplastic large-cell lymphoma with radiation therapy. Int J Radiat Oncol Biol Phys 70:1542–1545
67. Gentile MS, Martinez-Escala ME, Thomas TO et al (2015) Single-fraction radiotherapy for CD30(+) lymphoproliferative disorders. Biomed Res Int 2015:629587
68. Horwitz SM, Kim YH, Foss F et al (2012) Identification of an active, well-tolerated dose of pralatrexate in patients with relapsed or refractory cutaneous T-cell lymphoma. Blood 119:4115–4122
69. Krathen RA, Ward S, Duvic M (2003) Bexarotene is a new treatment option for lymphomatoid papulosis. Dermatology 206:142–147
70. Cervigon-Gonzalez I, Torres-Iglesias LM, Palomo-Arellano A, Gil-Pascual B (2011) Advanced-stage primary cutaneous T-cell lymphoma treated with bexarotene and denileukin diftitox. Case Rep Dermatol 3:13–17
71. Scarisbrick JJ, Morris S, Azurdia R et al (2013) U.K. consensus statement on safe clinical prescribing of bexarotene for patients with cutaneous T-cell lymphoma. Br J Dermatol 168:192–200
72. French LE, Shapiro M, Junkins-Hopkins JM, Vittorio CC, Rook AH (2001) Regression of multifocal, skin-restricted, CD30-positive large T-cell lymphoma with interferon alfa and bexarotene therapy. J Am Acad Dermatol 45:914–918
73. Kim YH, Whittaker S, Horwitz SM et al (2016) Brentuximab vedotin demonstrates significantly superior clinical outcomes in patients with CD30-expressing cutaneous T cell lymphoma versus physician's choice (Methotrexate or Bexarotene): the phase 3 alcanza study. Am Soc Hematology, 2016
74. Duvic M, Talpur R, Wen S, Kurzrock R, David CL, Apisarnthanarax N (2006) Phase II evaluation of gemcitabine monotherapy for cutaneous T-cell lymphoma. Clin Lymphoma Myeloma 7:51–58
75. Rijlaarsdam JU, Huijgens PC, Beljaards RC, Bakels V, Willemze R (1992) Oral etoposide in the treatment of cutaneous large-cell lymphomas. A preliminary report of four cases. Br J Dermatol 127:524–528
76. Boudova L, Kazakov DV, Jindra P et al (2006) Primary cutaneous histiocyte and neutrophil-rich CD30+ and CD56 + anaplastic large-cell lymphoma with prominent angioinvasion and nerve involvement in the forehead and scalp of an immunocompetent woman. J Cutan Pathol 33:584–589
77. Wu JJ, Guitart J, Tucker RM, Kuzel TM, Rosen ST (2003) Secondary cutaneous anaplastic large cell lymphoma treated with liposomal doxorubicin (Doxil) leading to complete remission. Int J Dermatol 42:464–465

78. Akpek G, Koh HK, Bogen S, O'Hara C, Foss FM (1999) Chemotherapy with etoposide, vincristine, doxorubicin, bolus cyclophosphamide, and oral prednisone in patients with refractory cutaneous T-cell lymphoma. Cancer 86:1368–1376
79. Chao-Lo MP, King-Ismael D, Lopez RA (2008) Primary cutaneous CD30+ anaplastic large cell lymphoma: report of a rare case. J Dermatol Case Rep 2:31–34
80. Wehkamp U, Oschlies I, Nagel I et al (2015) ALK-positive primary cutaneous T-cell-lymphoma (CTCL) with unusual clinical presentation and aggressive course. J Cutan Pathol 42:870–877
81. Meier F, Schaumburg-Lever G, Kaiserling E, Scheel-Walter HG, Scherwitz C (1992) Primary cutaneous large-cell anaplastic (Ki-1) lymphoma in a child. J Am Acad Dermatol 26:813–817

Transplantation

13

Jasmine Zain

Abstract

Mature T-cell non-Hodgkin lymphomas (T-cell NHL) are a heterogeneous group of lymphoid malignancies including NK/T-cell lymphomas. Hematopoietic cell transplantation (HCT) is an important component of the management of T-cell NHL; however, the optimal timing and type of transplant for each different subtype is an ongoing debate. For the purpose of this chapter, PTCL will be classified as (1) systemic PTCL that includes nodal as well as non-nodal histologies in PTCL (2) CTCL—or cutaneous T-cell lymphomas that arise primarily in the skin and (3) NK/T-cell lymphomas both nasal and extranasal types. It is difficult to do any large trials in PTCL as they are rare diseases with variable clinical and biological characteristics and most patients are not transplant eligible due to various reasons including poor disease control. There are no randomized trials in transplant for PTCL but there is an experience based on retrospective as well as some well-designed prospective trials that have helped outline the role of HSCT in the treatment paradigm of PTCL. High-dose therapy and autologous HCT is recommended in first complete remission for most systemic (non-cutaneous) nodal subtypes, or peripheral T-cell lymphomas (PTCL). Autologous HCT can provide long-term remission for relapsed PTCL but is ineffective for refractory/chemoresistant disease. Allogeneic stem cell transplantation harnesses the graft-versus-lymphoma effect, providing long-term remission for relapsed PTCL. AlloHCT is also being used successfully to provide long-term disease control for advanced cutaneous T-cell lymphoma (CTCL). The use of transplant in NK/T-cell lymphoma is increasingly being

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recommended in the relapsed setting only as there are more effective treatments available for the upfront setting in limited stage disease.

Keywords
Peripheral T-cell lymphoma · Cutaneous T-cell lymphoma
NK/T-cell lymphoma · Autologous hematopoietic cell transplantation
Allogeneic hematopoietic cell transplantation · Graft-versus-lymphoma

13.1 Introduction

Mature T-cell and natural killer cell non-Hodgkin lymphomas (T-cell NHL) comprise about 12% of all non-Hodgkin lymphomas and 15–20% of aggressive lymphomas worldwide. T-cell NHL exhibits great morphological diversity and histological variation even within individual disease entities as outlined in the current *2016 World Health Organization* (*WHO*) *Classification of Tumors of Haematopoietic and Lymphoid Tissues* [1]. Systemic PTCL includes nodal and non-nodal presentations of PTCL, whereas NK/T-cell lymphoma both nasal and nonnasal types represent unique biological features and their treatment paradigm is shifting away from other subtypes of PTCL. Cutaneous T-cell lymphomas (CTCL) represent a clinically distinct subgroup of T-cell NHL [2] that arise primarily in the skin, have a more indolent behavior with the exception of a few subtypes including Sézary syndrome (SS) and transformed mycosis fungoides (tMF).

For aggressive lymphomas, the T-cell phenotype tends to confer poorer clinical outcomes with long-term survival of 10–30% at 5 years [3] Comprehensive Oncology Measures for Peripheral T-cell Lymphoma (COMPLETE) project prospectively reported on 440 patients with PTCL in North American. The median survival of the whole cohort was 43 months [4, 5]. Advanced disease stage, high prognostic index at presentation [6], and inherent chemoresistance [7] contribute to the unsatisfactory outcomes for this disease group. Increasing understanding of these diseases will allow a more individualized approach to each subtype and molecular markers will eventually define the biomarkers that can predict outcomes [5]. However for now, most systemic PTCLs are treated with a similar paradigm: with stem cell transplantation considered as the "curative options" as it is the only modality that results in long-term disease-free outcome. Immune checkpoint inhibitors and other immune modifiers are starting to alter the landscape of treatment of most cancers including mature T-cell lymphomas. The use of bispecific antibodies as well as chimeric antigen receptor (CAR) therapy to harness immunologically active T-cells to treat these cancers will eventually result in redefining the timing and utility of stem cell transplants as is already becoming evident in the treatment of NK/T-cell lymphomas [8]. Generally, CTCL have an indolent course but a small percentage of patients with aggressive CTCL histologies, Sézary syndrome, and

advanced mycosis fungoides, will have a disease course with multiple failed treatment regimens, ultimately resulting in chemoresistance [9]. In these cases, an allogeneic stem cell transplant can provide long-term remission and disease control.

13.2 Introduction to Transplant

Hematopoietic stem cell transplantation (HSCT) previously called bone marrow transplant is a unique form of therapy first introduced in 1957 by E Donnell Thomas [10]. Multipotent hematopoietic stem cells (HSC) are capable of self-renewal and are able to differentiate and into all types of blood cells including erythroid, myeloid, lymphoid and platelets. They are responsible for maintaining the hematopoetic and immune system and reside in the specialized niches in the marrow spaces [11]. HSC have the ability to repopulate bone marrow that has been ablated either with radiation or myeloablative chemotherapy. Bone marrow, mobilized peripheral blood, and cord blood are sources of HSC. They are characterized by the presence of CD34+ on their surface. Initially, HSCT was designed to replace diseased marrow that had been treated with intensive chemoradiation therapy, but we now understand its immunological effects harnessed by the donor T-cells that mount a response against host tumor cells. Depending on the source of HSCT, the patient can undergo either an autologous stem cell (ASCT) or an allogeneic stem cell (alloHCT) transplant. In ASCT, patients are given high dose myeloablative treatment called conditioning regimen either with chemotherapy alone, a combination of total body radiation with chemotherapy or more recently radioimmunotherapy with the intent of eradicating the malignancy followed by an infusion of autologous stem cells that have previously been collected and cryopreserved. This process depends upon the high dose therapy to provide the therapeutic effectiveness of the procedure and requires chemosensitive disease while the stem cell infusion allows recovery of adequate marrow function. This can only be accomplished if the patient has a bone marrow that is free of disease and has healthy HSC cells. The most common indications are lymphoma and myeloma. There is data to suggest that ASCT can also eradicate adaptive immunity including autoimmunity and has been used in the treatment of autoimmune diseases [12].

On the other hand, an allogeneic transplant from an HLA matched sibling or unrelated donor allows a graft-versus-disease effect to take place in addition to the antitumor effects of the conditioning regimen. The donor derived T-cells are sensitized to the patient's tumor antigens and can result in a significant graft-versus tumor effect [13]. Increasingly, this is becoming more prominent and the role of the conditioning regimen is being reduced to immunosuppression as seen in less toxic non-myeloablative and reduced intensity transplants that have also allowed older and more frail patients to undergo these procedures [14]. Besides lymphoma and acute leukemia, these transplants are also performed in hematologic disorders like sickle cell disease and thalassemia. Proof of a graft-versus-tumor effect can be deduced from the following; effective use of a reduced intensity conditioning

regimen, posttransplant relapses treated with withdrawal of immunosuppression and infusion of donor lymphocyte infusion (DLI), and association of graft-versus host disease (GVHD) with decreased incidence of posttransplant relapse [15]. Allogeneic transplants can result in a 20–80% chance of either acute, chronic or both graft-versus host disease, a need for almost lifelong immunosuppression and its associated risk for infections and second malignancies. Most studies quote the risk of transplant-related mortality at about 20% [16]. Sources of stem cells now also include haploidentical donors and cord blood. Improvements in supportive care, including improved treatment for GVHD are changing these outcomes making transplants safer and more available to all patients.

13.3 HSCT for Systemic Peripheral T-Cell Lymphoma (PTCL)

13.3.1 Autologous Hematopoietic Cell Transplantation for PTCL

Upfront treatments for most histologies of PTCL are considered to be noncurative with the exception of alk+ALCL and now possibly DUSP22+alk-ve ALCL [17]. High dose therapy and ASCT is used as consolidation for eligible patients if they achieve a chemosensitive remission after initial therapy with the intent to improve progression-free (PFS) and overall survival (OS). There are no randomized studies to show the superiority of this approach compared to no further therapy. Hence, the experts remain divided on this questions.

There are several review articles and meta-analysis that have looked at published data to support or negate this approach [18, 19]. Retrospective studies have reported on the experience of ASCT in PTCL [20–25]. These studies are descriptive and have an inherent selection bias in terms of favoring younger healthier patients who are able to undergo transplant. In addition, most studies are heterogeneous in terms of patient populations, upfront treatment regimens, and conditioning regimens. Almost all studies exclude patients with leukemic variants of PTCL and are limited to otherwise healthy patients with median ages under 60. There is no real consensus on prognostic factors that affect outcomes after ASCT in PTCL. 5-year median OS varies from 34 to 70% and PFS from 30 to 61%. Outcomes are better if transplants are performed in the first remission. Chemosensitive disease and ALCL histology seem to confer better outcomes in several studies. In most studies, the outcome for refractory or chemoresistant disease remains dismal with fewer than 15% long-term survivors.

Can upfront transplant impact the outcome of the disease ?. Some of the earlier data suggested that outcomes were better when ASCT is performed in the first remission. There is no randomized trial to support this statement. In lieu of randomized data, several centers have used prospective studies on transplant-eligible patients with intent to perform ASCT on patients who achieve a CR but these have

the inherent bias of selecting young healthy patients. These studies are listed in Table 13.1. This is the best data that we have to support this approach at least in the more common nodal subtypes. To date, the largest study is a [26] prospective multicenter trial from the Nordic Lymphoma group that takes a dose-dense approach to the treatment of PTCL followed by ASCT. This study has the advantages of long follow-up (median 5 years) and a large enough population to look at some histologic subtypes of PTCL (n = 160). Patients age 60 or younger received primary induction therapy with CHOEP 14 (doxorubicin/vincristine/etoposide/prednisone), and those over age 60 received CHOP-14 (no etoposide). Of the 131 responders to initial therapy, 114 patients underwent BEAM/BEAC conditioning and ASCT after which 90 patients were in CR, and 9 in PR, at 3 months posttransplant. In the posttransplant setting, there were 39 relapses, with 28 in the first 2 years and the remaining relapses as late as 71 months posttransplantation. In an analysis of the entire cohort, with a median follow-up of 60 months, TRM was 4%, OS was 51%, and DFS was 44%. In subset analysis, best outcomes were seen in patients with ALK-ALCL with 5-year OS of 70% and PFS of 61%; AILT, OS 52%, PFS 49%; PTCL-nos, OS 47%, PFS 38%; EATL, OS 48%, DFS 38% Female sex, and ALCL histology had positive prognostic value, and IPI had predictive value for OS in AILT, and for PFS in AILT and PTCL-nos. Bone marrow involvement and increasing age were negative prognostic factors.

Others have taken different approaches to address this with differing results. The latest US study reported in 2013 was a retrospective analysis of 65 patients that confirmed that upfront consolidation in first CR with stem cell transplantation resulted in a 4 year PFS and OS of 66 and 67% compared to only 27% in the non-transplanted patients [27] Similar data is emerging from non-US centers esp far east Asia. Han et al. reported on 46 patients with PTCL who underwent ASCT in CR1. The 5-year OS and PFS was 77% and 61%, respectively. Multivariate analysis showed that pretransplant CR was associated with improved outcomes [28]. Rohlfing et al. tried to address this question retrospectively and evaluated data on 117 PTCL patients. Some of them had been referred to the center with the intention of transplant in first remission and others were considered ineligible for transplant. The authors compared these two groups and concluded that there was no advantage to an upfront transplant. The latest multicenter retrospective study to address this is from the French LYSA group. 527 patients from 14 centers were screened out of which a cohort of 269 patients was identified who were transplant eligible who achieved a CR or PR after initial therapy. 134 patients were in the ITT plan for ASCT and it was performed in 112 patients. There were 135 patients for whom ASCT was not planned but 2 of whom did undergo this procedure. The two groups were compared using sophisticated statistical methods of propensity score matching and multivariate analysis and in the end, the authors did not find a benefit for ASCT in the first remission. However, this study is heavily criticized for being retrospective and for non-uniformity of treatment and conditioning regimens. Most importantly, there may have been apriori allocation of transplant (ITT) in more aggressive patients hence creating potential bias [29].

Table 13.1 Prospective trials for ASCT in PTCL

References	N	Histologies	Induction therapy	Conditioning regimen	% Patients transplanted (%)	OS	PFS	Comments
d'Amore et al. [26]	166	Excludes ALK + ALCL, 1° leukemic	age $\leq$60 CHOEP 14 age >60 CHOP 14	BEAM/BEAC	72	51% (5 yr)	44% (5 yr)	Best outocmes with alk-ve ALCL-
Reimer et al. [30]	83	No ALK+ ALCL	CHOP × 4–6 cycles	TBI/Cy	66	48% (3 yr)	36% (3 yr)	
Corradini et al. [31]	62	Includes ALK + ALCL (30%)	APO alternating with DHAP, or MACOP-B followed by Mitoxantrone/Ara-C	BEAM	71	34% (12 yr)	30% (12 yr)	
Ahn et al. [33]	46	25% had NK/T No ALK+ ALCL	CHOP, CHOP-like or non anthracycline	Bu/Cy/VP-16	66	57% (5 yr)	55% (5 yr)	
Mercadal et al. [32]	41	No ALK+ ALCL	High dose CHOP alternating with ESHAP	BEAM/BEAC	41	39% (4 yr)	30% (4 yr)	
Rodriguez et al. [34]	26	No ALK+ ALCL	Mega-CHOP, if PR or SD after 3 cycles, got IFE	BEAM	73	73% (3 yr)	53% (3 yr)	

N number of patients; *ALK* anaplastic lymphoma kinase; *ALCL* anaplastic large-cell lymphoma; *NK/T* NK/T-cell lymphoma; *CHOEP* cyclophosphamide/doxorubicin/vincristine/etoposide/prednisone; *CHOP* cyclophosphamide/doxorubicin/vincristine/prednisone; *APO* doxorubicin/vincristine/prednisone, *DHAP* cisplatin/ara-C/prednisone; *MACOP-B* methotrexate with leucovorin rescue/doxorubicin/cyclophosphamide/vincristine/prednisone/bleomycin; *PR* partial response; *SD* stable disease; *CR* complete response; *BEAM* BCNU/etoposide/ara-C/melphalan; *BEAC* BCNU/etoposide/ara–C/cyclophosphamide; *TBI* total body irradiation; *Bu* busulfan, *Cy* cyclophosphamide; *VP-16* etoposide; *OS* overall survival; *yr* year; *PFS* progression-free survival

Review of these studies has brought to light several concerns. Even in patients who are otherwise healthy fit and are transplant eligible, with ITT analysis, only 41–73% of the PTCL are able to maintain eligibility for, and receive, ASCT [30–34]. The remaining patients are taken off study due to progressive or unresponsive disease, inability to mobilize sufficient stem cells, or comorbidities that prohibit ASCT. Follow-up is typically 3–5 years, with OS ranging from 34 to 73% and PFS from 30 to 53%. Best results are from studies including ALCL patients [26, 35]. Additionally, a good number of patients are ineligible to start with as they are frail or have comorbidities that make them ineligible for transplant. When compared to historical controls as outlined in the International T-cell Lymphoma Project, it appears that there is an advantage to performing high dose therapy and ASCT as consolidation in the first remission at least for the nodal histologies of PTCL-nos, AITL and ALCL alk negative. The failure of a significant number of patients to get to transplant also speaks to the ineffectiveness of initial therapy resulting in primary refractory disease that is not chemosensitive. There continues to be a need for more aggressive and targeted therapies to improve the initial response rate and reduce the number of early relapses. Review of the follow-up data and the late treatment failure patterns supports the need to better define patients at risk for late relapse through biomarker and minimal residual disease (MRD) evaluation. This could define a subset of patients that would benefit from maintenance therapy.

Very aggressive and leukemic variants of PTCL including HSTCL, HTLV-1-associated adult T-cell leukemia/lymphoma (ATLL), extranasal NK/T-cell lymphomas, T-cell prolymphocytic leukemia (T-PLL), and primary cutaneous γ/δ T-cell lymphoma, do not benefit from ASCT. These diseases have a very aggressive clinical course due to inherent chemoresistance and patients tend to experience multiple failures of primary therapy; hence ASCT approaches have generally not been successful in these patients [36, 37]. Long-term remissions and improved survival have been seen in patients with these highly aggressive variants following allogeneic transplantation in first remission.

Based on the above data, current NCCN guidelines, ESMO and the ASBMT recommend and support the use of high dose therapy and ASCT in the first remission as consolidation in nodal histologies of PTCL other than alk+ALCL [38–40]. The recommendation for performing this procedure in non-nodal histologies is weak as will be discussed in the following section.

There are several reports of ASCT being used as salvage for relapsed disease. In the relapsed setting, the use of ASCT can salvage about a third of patients with relapsed chemosensitive disease, again with best outcomes for ALCL, particularly ALK+ if the patient has not had a prior transplant [41–45]. However, as we move into more targeted therapies, there may be changes that may improve the outcomes of salvage ASCT. In a recent study, Pro et al. [46] reported on 16 patients with relapsed or refractory systemic ALCL who received salvage therapy with Brentuximab Vedotin and achieved a response rate of 87%. 16 out of the 38 patients who achieved a CR went on to receive a stem cell transplant either an ASCT or allogeneic stem cell transplant. In this group, the 5 year OS and PFS was 88% and 75%, respectively, indicating the importance of improved disease control prior to SCT.

13.3.2 Allogeneic Hematopoietic Cell Transplantation for PTCL

Allogeneic hematopoietic cell transplantation (alloHCT) relies on a graft-versus lymphoma effect and has been used in PTCL. It is generally considered to be "curative" as it provides long-term remission with eventual plateaus in overall survival (OS) and progression-free survival (PFS). AlloHCT is associated with a high risk of complications related to continued immunosuppression, graft-versus-host disease (GVHD), and the long-term toxicities of conditioning regimens. This therapy is limited by co-morbid conditions of the patient, availability of a donor source, and lingering effects of previous treatments. The chance of cure or long-term remission has to be weighed against the risk of morbidity and mortality associated with the transplant procedure. For PTCL, alloHCT has been used in the setting of relapsed or refractory disease although increasingly transplant physicians are using this modality in the upfront setting for particularly aggressive histologies like the γ/δT-cell lymphomas, hepatosplenic T-cell lymphomas, ATLL, and extranasal NK/T-cell lymphomas.

Several centers have published the results of their experience with alloHCT in PTCL as listed in Table 13.2 and there are several excellent reviews that have summarized these findings [18, 47]. A prospective phase II study of 17 PTCL patients with relapsed disease reported by Corradini et al. [48] was the first study to report on the use of reduced intensity conditioning to reduce high TRM (previously reported at ~30%. With this particular approach, after a median follow-up of 28 months, the NRM was only 6% and the 3-year OS and DFS were 81% and 62%, respectively. This study established that RIC could be used in PTCL with good long-term outcomes implicating a graft-versus-T-cell lymphoma effect. The largest PTCL alloHCT study published to date includes 77 patients from multiple centers in France and was reported by Le Gouill et al. [49]. This study reports differences in the common histological subtypes of PTCL in the context of allogeneic stem cell transplant. All patients had relapsed disease and about 25% of the patients had failed a prior transplant indicating the heavily pretreated nature of the population. Seventy percent of patients had chemosensitive disease at the time of transplant and 67% of the patients received ablative conditioning regimens. TRM was high at 33%, and 5-year OS and DFS were 57 and 53%. This is the only study demonstrating the differences in outcomes based on histology. At 5 years, OS and PFS were 80 and 80% for AITL, 63 and 58% for PTCL-nos, 55 and 48% for ALCL, and 33% for other histologies. Both OS and PFS curves reached plateau a after 20 months. Grades III and IV acute GVHD and chemoresistant disease were negative prognostic factors by multivariate analysis. The 5-year OS of 29% for chemoresistant patients is encouraging and supports a graft-versus-lymphoma effect. Most published studies have reported similar numbers at 3–5 years of follow-up, with OS between 50 and 70% and PFS up to 60, and a plateau in relapse incidence within the first 2 years. Chemosensitive disease at the time of transplant results in better OS and PFS [49–52] indicating that achievement of disease control before allogeneic transplant is crucial to outcome. In one of the larger studies of 52

PTCL patients, Dodero et al. report superior 5-year relapse for patients allografted in CR compared to PR (24% vs. 54%), and for those with chemosensitive compared to refractory disease (40% vs. 77%) [50]. From the City of Hope, the 5-year OS for patients in CR/PR compared to those with active disease was 72.9% versus 43.2% [53]. The effect of conditioning regimen is unclear but there is an increasing shift toward RIC in the last 5 years due to the high TRM reported in earlier studies. TRM after alloHCT for PTCL has been reported to be as high as 30%, likely due to advanced stage disease and poor performance status. Several centers have reported on the results of RIC [54, 55] and there may be a decrease in TRM to around 19–20% with this approach. A study from the City of Hope compared outcomes for RIC and fully ablative conditioning and found no differences in OS and DFS [53]. The use of DLI to induce remission for the relapsed disease after the allogeneic transplant is considered validation of a graft-versus-disease effect and there are reports in the literature documenting response to DLI for PTCL. The largest experience is from Dodero et al. where 8/12 patients with documented relapse responded to DLI and achieved a state of remission [50]. There were 2 patients in the Le Gouill series [49], 2 in the Corradini series [48], 2 in the Hamadani series [56], and 1 of 2 in the Goldberg series [57] who responded to DLI after disease relapse and had long remissions.

There are a few studies that have focused on specific histologies and at least one study that has looked at the use of alloHCT in the upfront setting in PTCL as consolidation. Loirat et al. [58] reported on the results of upfront allogeneic stem cell transplant in 29 PTCL patients who responded to upfront therapy, had an HLA matched donor and were otherwise healthy enough to undergo alloHCT. Most common histologies were PTCL-nos, Alk negative ALCL and AITL. There were only a handful of cases who had the more "aggressive histologies". There were 20 patients in the original cohort of 49 who did not undergo an alloHCT due to disease progression, inability to find a donor, medical contraindications to an alloHCT and refusal in one case. The outcomes were impressive. The 1 and 2 year OS of the transplanted patients were 76% and 72.5% respectively and the TRM at 1 year was only 8.2%. In comparison, the 2 year PFS of the non-transplanted patients was less than 30%. Disease status at the time of relapse was the only predictive marker for OS and PFS. In another study, alloHCT resulted in 64% survival at 4.7 years in patients with highly aggressive subpanninculitic T-cell lymphoma and primary cutaneous T-cell lymphoma, [59]. ATLL associated with HTLV1 has an very aggressive course and poor outcome with chemotherapy only with most patients dying within a year. The use of upfront alloHCT resulted in a 3-year OS at 33% in a multicenter retrospective study of 386 ATLL patients in Japan [60]. Some smaller studies have a 3 year OS of up to 73% [61]. Fuji et al. reported on the role of upfront allogeneic stem cell transplant in patients with aggressive ATLL and using the existing data constructed a model that has confirmed that chemotherapy followed by an alloHCT is the optimal strategy for best long-term outcomes for these patients [62].

In conclusion, the use of alloHCT can provide long-term disease control for patients with relapsed chemosensitive disease, with most post transplant relapses

Table 13.2 Selected studies of allogeneic stem cell transplant for PTCL

References	N	Histologies	Disease status at transplant	GVHD	Mortality/Relapse	Survival outcomes
Loirat et al. [58] Single Center	49	PTCL except Alk + ALCL and limited CTCL	CR1 n = 12 PR1 n = 17	Acute GVHD 42% cGVHD extensive 7%, limited 21%	TRM 7%	2 yr PFS 65% and OS 72% in transplanted patients
						OS 61% (2 yr) PFS 50% (2 yr)
Dodero et al. [50] Multicenter	52	PTCL mixed	CR 40%	aGVHD 22% cGVHD 27%	NRM 12% (5 yr) Relapse 49% (5 yr)	OS 50% (5 yr) PFS 40% (5 yr) 8/12 DLI responses
Zain et al. [53] Single center	38	PTCL mixed CTCL 35%	CR 18%	aGVHD 51% cGVHD 82%	NRM 29% (5 yr) RPR 24% (5 yr)	OS 54% (5 yr) PFS 46% (5 yr)
					NRM 25% (2 yr) RPR 30% (2 yr)	OS 55% (2 yr) PFS 47% (2 yr)
Kyriakou et al. [52] Multicenter	45	AILD only	CR 27%	aGVHD 20% cGVHD 54%	NRM 25% (1 yr) RPR 20% (3 yr)	OS 64% (3 yr) PFS 53% (3 yr)
Le Gouill et al. [49] Multicenter	77	PTCL mixed	CR 40%	Grades III/IV aGVHD 21%	TRM 34% (5 yr)	OS 57% (5 yr) EFS 53% (5 yr) 2/2 DLI responses
Corradini et al. [48] Phase II Multicenter	17	PTCL nodal	CR 12%	aGVHD 35% cGVHD 41%	NRM 6% (2 yr)	OS 81% DFS 62% (3 yr) 2/2 DLI responses

PTCL peripheral T-cell lymphoma; *ALCL* anaplastic large-cell lymphoma; *AILD* angioimmunoblastic lymphoma; *NK/T-cell*, natural killer/T-cell lymphoma; *CR* complete response; *autoHCT* autologous hematopoietic cell transplantation; *MAC* myeloablative conditioning; *RIC* reduced intensity conditioning; *TBI* total body irradiation; *Hap* haploidentical donor; *PBSC* peripheral blood stem cells; *SIB* sibling donor; *DLI* donor lymphocyte infusion; *aGVHD* acute graft-versus-host disease; *cGVHD* chronic graft-versus-host disease; *TRM* transplant-related mortality; *NRM* non-relapse mortality; *RPR* relapse progression rate; *OS* overall survival; *PFS* progression-free survival; *EFS* event-free survival; *yr* year; *mos* months

occurring within the first 2 years. The risk of acute and chronic GVHD remains high, but TRM can be reduced using RIC to minimize regimen-related toxicities. A graft-versus-lymphoma effect is implicated by the success of RIC regimens and use of posttransplantation DLI to induce remission. However, chemosensitivity and optimal disease control are crucial for the best outcomes with this modality. For the most aggressive histologies, alloHCT can provide disease control if performed early in remission, but the experience is quite limited. Most physicians use fully ablative conditioning if possible to provide the best option for disease control, particularly in young patients. Since most relapses occur within the first two years after transplant, consideration should be given to maintenance therapies using targeted agents to reduce residual disease and improve outcomes following allogeneic transplantation for PTCL.

13.4 HSCT for Cutaneous T-Cell Lymphoma (CTCL)

CTCL are comprised of many different subtypes out of which Mycosis Fungoides is the most common subtype. Cutaneous CD30+ lymphoproliferative disorders are also part of this classification as has been discussed elsewhere in this book. These diseases differ in their biology and clinical manifestations as compared to other systemic PTCL subtypes and tend to have a more indolent course. Several excellent studies have looked at outcomes of large cohort of patients and only a small percentage has features of aggressive disease including large-cell transformation and sezary syndrome or patients with extensive cutaneous involvement who have run out of other treatment options. Hence, the role of stem cell transplant in the management of these diseases remains limited. It is offered to a small number of patients with above features where it has become clear that control of disease is becoming more difficult. The overall data is still unclear about the optimal indication and timing for transplant but most centers will consider it in young patients who exhibit a more aggressive course early on in their disease. The decision to proceed to transplant is wrought with uncertainty and has to be balanced against available therapies, clinical trials and the risk of transplantation and its associated morbidity and mortality. As more targeted and immunotherapies become available, the role of transplant will continue to be redefined.

13.4.1 Hematopoietic Cell Transplantation

Cutaneous T-cell lymphomas are best treated in a multidisciplinary fashion with skin-directed therapies as initial management for most cases. The use of systemic chemotherapy is limited early on in the disease course and ASCT is not recommended for these patients even in advanced disease states. A few small studies have looked at the experience of ASCT in CTCL but results were disappointing with most patients relapsing within a year incidence [63–69].

Allogeneic HSCT is the stem cell therapy of choice for patients with CTCL who are transplant candidates and is considered curative since long-term disease-free survival has been demonstrated. Due to the general immunosuppressive state and the broken skin barrier, infectious complications remain a major challenge in the management of CTCL patients. Initial studies and reports established that alloHCT can be performed in CTCL patients with no apparent disease-specific complications [70–77]. Several centers have now reported their experience of alloHCT in patients with CTCL that are summarized in several reviews [78, 79]. Almost all alloHCT are performed in heavily pretreated patients but long-term disease control and survival can be demonstrated based on clearance of clinical symptoms as well as molecular evidence of disease by TCR gene rearrangements [73–75, 80–83]. Most studies focus on MF and SS and most physicians use this data to extrapolate for other types of CTCL. Patients with aggressive histologies like gamma delta, or primary cutaneous aggressive epidermotropic cytotoxic CD8 positive T-cell lymphoma subtypes are evaluated for alloHCT early in the course of their disease [84] though large studies to support this approach are still lacking and may be reported with more aggressive systemic lymphomas.

For MF/SS, the largest transplant US registry experience was reported by Lechowicz et al. [85] in 129 patients from various centers. At 5 years the OS and PFS was 32% and 17% respectively. European Group for Blood and Marrow Transplantation (EBMT) database reported the outcome of 60 patients that included 36 patients with MF and 24 with SS. This report was updated in 2014 [86] and the 7 year OS and PFS is 44% and 30% respectively with a TRM at 22%. Graft-versus-lymphoma (GVL) effects are evident from the successful use of RIC regimens, remission of relapse after withdrawal of immunosuppression and donor lymphocyte infusions [75], as well as an association of disease remission with GVHD [81]. MD Anderson has reported on 47 patients who underwent alloHCT for cutaneous lymphomas. Estimated OS and PFS at 4 years were 51 and 26%. Acute and ch GVHD was reported as 40% and 28% respectively with a non-relapse mortality (NRM) of 17.7% at 2 years [87, 88]. In Sezary syndrome (SS), the 4 year PFS was 52%. TSEB therapy prior to transplant was associated with improved disease control [72]. Other studies are summarized in Table 13.3. A meta-analysis of 39 cases of advanced MF/SS has confirmed that at 5 years, alloHCT resulted in a better outcome (80% OS, n = 20) compared to autoHCT (23% OS, n = 19) [76]. With advances in the field of allogeneic transplants, there is now data regarding the use of alternative sources of stem cells like cord blood [89] and haploidentical transplant [90, 91]. A review of these cases in detail indicates that an allogeneic transplant can achieve a CR even in the most refractory cases and RIC appears to be just as effective and less toxic. Disease recurrence in the skin can occur after alloHCT but seems to respond well to adjustment of immunosuppression, DLI infusion or mild treatments for the skin. There appear to be few blood or systemic recurrences.

Technological advances are now being incorporated into the care of patients to answer some of the fundamental questions in this field. High throughput sequencing can help analyze the B-cell receptor (BCR) and T-cell receptor (TCR) repertoire.

Table 13.3 Selected reports on allogeneic HCT for CTCL

References	N	Disease stage at transplant	GVHD	Survival	Comments
Duvic et al. [72], Hosing et al. [88]	47	Advanced stage	aGVHD 40% cGVHD 28% NRM 16.7% at 2 yr	4-yr OS 51% 4-yr PFS 26%, 52% in SS	Relapses responded to DLI
Lechowicz et al. [85]	129		5 yr NRM 22%	5-yr OS 32% 5 yr PFS 17%	Salvage in a third of patients and half remain disease free
Duarte et al. [86, 101]	60	47% chemoresistant 17% in CR	aGVHD 40% cGVHD 32% 7 yr NRM 22%	5 yr OS– 46% and 7 yr 44% PFS 32% at 5 yr and 30% at 7 yr	Myeloablative conditioning and poor performance status associated with a worse outcome
				57% alive	
Gibson et al. [59]	14	PCGD- n = 10 SPTCL n = 4			AlloHCT can provide long-term remission in very aggressive diseases where disease is chemo - refractory and outcome is dismal

SIB sibling donor; *MUD* matched unrelated donor; *BM* bone marrow; *PBSC* peripheral blood stem cells; *TSEB* total skin electron beam therapy; *TBI* total body irradiation; *mos* months; *yr* years; *aGVHD* acute graft-versus-host disease; *cGVHD* chronic graft-versus-host disease; *RIC* reduced intensity conditioning; *MAC* myeloablative conditioning; *TCD* T-cell depletion; *FU* follow-up; *DLI* donor lymphocyte infusion; *OS* overall survival; *PFS* progression-free survival. PCGD-TCL Primary cutaneous gamma delta T-cell lymphoma, SPTCL Panninculitic cutaneous T-cell lymphoma

Using a patients known tumor's repertoire, tissue samples can be followed for the presence of MRD or emergence of disease. This is particularly helpful in patients with SS where the leukemic clone is easily available for this study. Stanford has reported on the use of this technology in the setting of alloHCT to demonstrate that MRD negativity can be achieved in the blood and skin of patients with alloHCT in CTCL patients [92]. The use of TLI and ATG in the conditioning regimen has been designed to permit donor hematopoiesis while protecting against GVHD and is currently being evaluated in CTCL patients. In patients with MDS, this regimen has shown to have a cumulative 14% incidence of aGVHD grades II to IV 4% for grades III to IV. The cumulative incidence of non-relapse mortality (NRM) at 100 days, 12 months, and 36 months was 0, 7, and 11% [93]. More effective targeted therapies like Brentuximab vedotin and epigenetic agents are providing bridging treatments that can result in deeper remissions with less toxicity prior to transplant thus improving overall outcomes [94]. There continues to be a need for a

more systematic approach to stem cell transplant in cutaneous lymphomas with the integration of targeted therapies and precision medicine to optimize patient outcomes.

13.4.2 NK/T-Cell Lymphomas

Both nasal type and extranasal type have unique biological features that require differing treatment approaches as compared to other systemic T-cell lymphomas. The long-term survival of patients who received upfront autologous HSCT ranged from 50 to 70% [51, 95] However, the use of combined chemoradiation approaches in the upfront treatment of NK/T-cell lympbomas has resulted in improved long-term outcomes thus mitigating the advantage of an upfront transplant in limited stage favorable disease and this approach is no longer recommended. On the other hand, patients with more advanced disease need to be considered for upfront HSCT in first remission and this recommendation has recently been endorsed by the American Society of Blood and Bone Marrow Transplantation [40].

For relapsed/refractory disease, an allogeneic stem cell transplant can be considered and is recommended in eligible patients. Recent reports of immune checkpoint inhibitors having exceptionally high activity in relapsed/refractory NK/T-cell lymphoma is likely to impact the current practice of stem cell transplant for relapsed/refractory NK/T-cell lymphoma. Kwong et al. have reported nearly 100% response rate with Pembrolizumab and Nivolumab [8, 96] in highly refractory patients including those who had relapsed after stem cell transplant. Further trials are ongoing to confirm these results that may alter the overall management of relapsed disease. It is likely that immune checkpoint inhibitors will be incorporated into the treatment paradigm in the relapse setting and may result in changes when the transplant needs to be considered. It is also possible that some kind of a maintenance regimen of immune checkpoint inhibitor may be incorporated with stem cell therapy as is being evaluated and clinical trials at the moment.

13.5 Conclusion and Future Directions

The recent approval of targeted therapies for PTCL and CTCL is changing the landscape of these diseases. For patients with relapsed refractory NK/T-cell NHL, single-agent treatment with pralatrexate [97], vorinostat [98], romidepsin [99], or brentuximab vedotin [100] and now immune checkpoint inhibitors can serve as a bridging therapy prior to transplant. In the next few years, they will likely be chimeric antigen receptor (CAR) based treatments available for targeting T-cell lymphomas that will likely need to be incorporated into the treatment regimens for these patients. We also expect that in time, novel agents will be approved for use in conditioning regimens and be considered for maintenance therapy in patients harboring residual disease posttransplantation.

References

1. Jaffe ES, Barr PM, Smith SM (2017) Understanding the new WHO classification of lymphoid malignancies: why it's important and how it will affect practice. Am Soc Clin Oncol Educ Book 37:535–546
2. Willemze R et al (2005) WHO-EORTC classification for cutaneous lymphomas. Blood 105(10):3768–3785
3. Vose J, Armitage J, Weisenburger D (2008) International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol 26(25):4124–4130
4. Carson KR et al (2017) A prospective cohort study of patients with peripheral T-cell lymphoma in the United States. Cancer 123(7):1174–1183
5. Iqbal J et al (2016) Genomic signatures in T-cell lymphoma: how can these improve precision in diagnosis and inform prognosis? Blood Rev 30(2):89–100
6. Gallamini A et al (2004) Peripheral T-cell lymphoma unspecified (PTCL-U): a new prognostic model from a retrospective multicentric clinical study. Blood 103(7):2474–2479
7. Jillella AP et al (2000) P-glycoprotein expression and multidrug resistance in cutaneous T-cell lymphoma. Cancer Invest 18(7):609–613
8. Kwong YL et al (2017) PD1 blockade with pembrolizumab is highly effective in relapsed or refractory NK/T-cell lymphoma failing l-asparaginase. Blood 129(17):2437–2442
9. Zackheim HS et al (1999) Prognosis in cutaneous T-cell lymphoma by skin stage: long-term survival in 489 patients. J Am Acad Dermatol 40(3):418–425
10. Thomas ED et al (1957) Intravenous infusion of bone marrow in patients receiving radiation and chemotherapy. N Engl J Med 257(11):491–496
11. Busch K et al (2015) Fundamental properties of unperturbed haematopoiesis from stem cells in vivo. Nature 518(7540):542–546
12. Brinkman DM et al (2007) Resetting the adaptive immune system after autologous stem cell transplantation: lessons from responses to vaccines. J Clin Immunol 27(6):647–658
13. Thomas ED et al (1977) One hundred patients with acute leukemia treated by chemotherapy, total body irradiation, and allogeneic marrow transplantation. Blood 49(4):511–533
14. Slavin S (2004) Reduced intensity versus truly nonmyeloablative conditioning for stem-cell transplant recipients. Transplantation 78(7):964–965
15. Porter DL (2011) Allogeneic immunotherapy to optimize the graft-versus-tumor effect: concepts and controversies. Hematol Am Soc Hematol Educ Program 2011:292–298
16. Shimoni A et al (2016) Long-term survival and late events after allogeneic stem cell transplantation from HLA-matched siblings for acute myeloid leukemia with myeloablative compared to reduced-intensity conditioning: a report on behalf of the acute leukemia working party of European group for blood and marrow transplantation. J Hematol Oncol 9(1):118
17. Pedersen MB et al (2017) DUSP22 and TP63 rearrangements predict outcome of ALK-negative anaplastic large cell lymphoma: a Danish cohort study. Blood 130(4): 554–557
18. Sharma M, Pro B (2015) Bone marrow transplantation for peripheral T-cell non-Hodgkins' lymphoma in first remission. Curr Treat Options Oncol 16(7):34
19. Yared J, Kimball A (2013) The role of high dose chemotherapy and autologous stem-cell transplantation in peripheral T-cell lymphoma: a review of the literature and new perspectives. Cancer Treat Rev 39(1):51–59
20. Beitinjaneh A et al (2011) Autologous stem cell transplantation (ASCT) as upfront or salvage therapy for noncutaneous T-cell lymphoma (TCL): The University of Texas M. D. Anderson Cancer Center (MDACC) experience. In: ASCO Meeting Abstracts, vol 29, no 15 suppl, p 6565

21. Nademanee A et al (2011) High-dose therapy and autologous hematopoietic cell transplantation in peripheral T Cell lymphoma (PTCL): analysis of prognostic factors. Biol Blood Marrow Transpl 17(10):1481–1489
22. Numata A et al (2010) Long-term outcomes of autologous PBSCT for peripheral T-cell lymphoma: retrospective analysis of the experience of the Fukuoka BMT group. Bone Marrow Transpl 45(2):311–316
23. Kyriakou C et al (2008) High-dose therapy and autologous stem-cell transplantation in angioimmunoblastic lymphoma: complete remission at transplantation is the major determinant of outcome—lymphoma working party of the European group for blood and marrow transplantation. J Clin Oncol 26(2):218–224
24. Yang D-H et al (2009) Prognostic factors and clinical outcomes of high-dose chemotherapy followed by autologous stem cell transplantation in patients with peripheral T cell lymphoma, unspecified: complete remission at transplantation and the prognostic index of peripheral T cell lymphoma are the major factors predictive of outcome. Biol Blood Marrow Transpl 15(1):118–125
25. Smith SD et al (2007) Autologous hematopoietic stem cell transplantation in peripheral T-cell lymphoma using a uniform high-dose regimen. Bone Marrow Transpl 40(3):239–243
26. d'Amore F et al (2012) Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01. J Clin Oncol 30(25):3093–3099
27. Mehta N et al (2013) A retrospective analysis of peripheral T-cell lymphoma treated with the intention to transplant in the first remission. Clin Lymphoma Myeloma Leuk 13(6):664–670
28. Han X et al (2017) Autologous stem cell transplantation as frontline strategy for peripheral T-cell lymphoma: a single-centre experience. J Int Med Res 45(1):290–302
29. Fossard G et al (2017) Role of up-front autologous stem cell transplantation in peripheral T-cell lymphoma for patients in response after induction: an analysis of patients from LYSA centers. Ann Oncol
30. Reimer P et al (2009) Autologous stem-cell transplantation as first-line therapy in peripheral T-cell lymphomas: results of a prospective multicenter study. J Clin Oncol 27(1):106–113
31. Corradini P et al (2006) Long-term follow-up of patients with peripheral T-cell lymphomas treated up-front with high-dose chemotherapy followed by autologous stem cell transplantation. Leukemia 20(9):1533–1538
32. Mercadal S et al (2008) Intensive chemotherapy (high-dose CHOP/ESHAP regimen) followed by autologous stem-cell transplantation in previously untreated patients with peripheral T-cell lymphoma. Ann Oncol 19(5):958–963
33. Ahn JS et al (2011) Frontline autologous stem cell transplantation as intensive consolidation in patients with peripheral T cell lymphomas: multicenter phase II trial in Korea. In: Proceedings of ASH Annual Meeting Abstracts, vol 118, no 21, p 4477
34. Rodriguez J et al (2007) Frontline autologous stem cell transplantation in high-risk peripheral T-cell lymphoma: a prospective study from The Gel-Tamo Study Group. Eur J Haematol 79(1):32–38
35. Cohen AD et al (2007) Risk-adapted autologous stem cell transplantation with adjuvant dexamethasone ± thalidomide for systemic light-chain amyloidosis: results of a phase II trial. Br J Haematol 139(2):224–233
36. Al-Toma A et al (2007) Disappointing outcome of autologous stem cell transplantation for enteropathy-associated T-cell lymphoma. Dig Liver Dis 39(7):634–641
37. Terras S et al (2012) Allogeneic haematopoietic stem cell transplantation in a patient with cutaneous gamma/delta-T-cell lymphoma. Acta Dermato-Venereol
38. NCCN guidelines version 3.2018
39. d'Amore F et al (2015) Peripheral T-cell lymphomas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 26(Suppl 5):v108–v115
40. Kharfan-Dabaja MA et al (2017) Clinical practice recommendations on indication and timing of hematopoietic cell transplantation in mature T cell and NK/T cell lymphomas: an international collaborative effort on behalf of the guidelines Committee of the American

Society for blood and marrow transplantation. Biol Blood Marrow Transplant 23(11): 1826–1838
41. Zamkoff KW et al (2004) High-dose therapy and autologous stem cell transplant does not result in long-term disease-free survival in patients with recurrent chemotherapy-sensitive ALK-negative anaplastic large-cell lymphoma. Bone Marrow Transpl 33(6):635–638
42. Jantunen E et al (2004) Autologous stem cell transplantation in adult patients with peripheral T-cell lymphoma: a nation-wide survey. Bone Marrow Transpl 33(4):405–410
43. Jagasia M et al (2004) Histology impacts the outcome of peripheral T-cell lymphomas after high dose chemotherapy and stem cell transplant. Leuk Lymphoma 45(11):2261–2267
44. Kewalramani T et al (2006) Autologous transplantation for relapsed or primary refractory peripheral T-cell lymphoma. Br J Haematol 134(2):202–207
45. Kim MK et al (2007) High-dose chemotherapy and autologous stem cell transplantation for peripheral T-cell lymphoma: complete response at transplant predicts survival. Ann Hematol 86(6):435–442
46. Pro B et al (2017) Five-year results of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma. Blood 130(25):2709–2717
47. Moskowitz AJ, Lunning MA, Horwitz SM (2014) How I treat the peripheral T-cell lymphomas. Blood 123(17):2636–2644
48. Corradini P et al (2004) Graft-versus-lymphoma effect in relapsed peripheral T-cell non-Hodgkin's lymphomas after reduced-intensity conditioning followed by allogeneic transplantation of hematopoietic cells. J Clin Oncol 22(11):2172–2176
49. Le Gouill S et al (2008) Graft-versus-lymphoma effect for aggressive T-cell lymphomas in adults: a study by the Societe Francaise de Greffe de Moelle et de Therapie Cellulaire. J Clin Oncol 26(14):2264–2271
50. Dodero A et al (2012) Allogeneic transplantation following a reduced-intensity conditioning regimen in relapsed/refractory peripheral T-cell lymphomas: long-term remissions and response to donor lymphocyte infusions support the role of a graft-versus-lymphoma effect. Leukemia 26(3):520–526
51. Suzuki R et al (2006) Hematopoietic stem cell transplantation for natural killer-cell lineage neoplasms. Bone Marrow Transpl 37(4):425–431
52. Kyriakou C et al (2009) Allogeneic stem cell transplantation is able to induce long-term remissions in angioimmunoblastic T-cell lymphoma: a retrospective study from the lymphoma working party of the European group for blood and marrow transplantation. J Clin Oncol 27(24):3951–3958
53. Zain J et al (2011) Allogeneic hematopoietic cell transplant for peripheral T-cell non-Hodgkin lymphoma results in long-term disease control. Leuk Lymphoma 52(8): 1463–1473
54. Shustov AR et al (2010) Allogeneic haematopoietic cell transplantation after nonmyeloablative conditioning in patients with T-cell and natural killer-cell lymphomas. Br J Haematol 150(2):170–178
55. Delioukina M et al (2012) Reduced-intensity allogeneic hematopoietic cell transplantation using fludarabine-melphalan conditioning for treatment of mature T-cell lymphomas. Bone Marrow Transpl 47:65–72
56. Hamadani M et al (2008) Allogeneic hematopoietic stem cell transplantation for peripheral T cell lymphomas; evidence of graft-versus-T cell lymphoma effect. Biol Blood Marrow Transpl 14(4):480–483
57. Goldberg JD et al (2012) Long-term survival in patients with peripheral T-cell non-Hodgkin lymphomas after allogeneic hematopoietic stem cell transplant. Leuk Lymphoma 53(6): 1124–1129
58. Loirat M et al (2015) Upfront allogeneic stem-cell transplantation for patients with nonlocalized untreated peripheral T-cell lymphoma: an intention-to-treat analysis from a single center. Ann Oncol 26(2):386–392
59. Gibson JF et al (2015) Hematopoietic stem cell transplantation for primary cutaneous gammadelta T-cell lymphoma and refractory subcutaneous panniculitis-like T-cell lymphoma. J Am Acad Dermatol 72(6):1010–5 e5

60. Hishizawa M et al (2010) Transplantation of allogeneic hematopoietic stem cells for adult T-cell leukemia: a nationwide retrospective study. Blood 116(8):1369–1376
61. Shiratori S et al (2008) A retrospective analysis of allogeneic hematopoietic stem cell transplantation for adult T cell leukemia/lymphoma (ATL): clinical impact of graft-versus-leukemia/lymphoma effect. Biol Blood Marrow Transpl 14(7):817–823
62. Fuji S et al (2018) Role of up-front allogeneic hematopoietic stem cell transplantation for patients with aggressive adult T-cell leukemia-lymphoma: a decision analysis. Bone Marrow Transpl
63. Bigler RD et al (1991) Autologous bone marrow transplantation for advanced stage mycosis fungoides. Bone Marrow Transpl 7(2):133–137
64. Ingen-Housz-Oro S et al (2004) High-dose therapy and autologous stem cell transplantation in relapsing cutaneous lymphoma. Bone Marrow Transpl 33(6):629–634
65. Moreau P et al (1994) Autologous bone marrow transplantation using TBI and CBV for disseminated high/intermediate grade cutaneous non-epidermotropic non-Hodgkin's lymphoma. Bone Marrow Transpl 14(5):775–778
66. Olavarria E et al (2001) T-cell depletion and autologous stem cell transplantation in the management of tumour stage mycosis fungoides with peripheral blood involvement. Br J Haematol 114(3):624–631
67. Russell-Jones R et al (2001) Autologous peripheral blood stem cell transplantation in tumor-stage mycosis fungoides: predictors of disease-free survival. Ann N Y Acad Sci 941:147–154
68. Sterling JC et al (1995) Erythrodermic mycosis fungoides treated with total body irradiation and autologous bone marrow transplantation. Clin Exp Dermatol 20(1):73–75
69. Ferra C et al (1999) Autologous haematopoietic progenitor transplantation in advanced mycosis fungoides. Br J Dermatol 140(6):1188–1189
70. Duarte RF et al (2008) Haematopoietic stem cell transplantation for patients with primary cutaneous T-cell lymphoma. Bone Marrow Transpl 41(7):597–604
71. Oyama Y et al (2003) Combined radioguided parathyroidectomy and intravenous vitamin D therapy for the treatment of uraemic hyperparathyroidism. Nephrol Dial Transpl 18(Suppl 3):iii76–78
72. Duvic M et al (2010) Total skin electron beam and non-myeloablative allogeneic hematopoietic stem-cell transplantation in advanced mycosis fungoides and Sezary syndrome. J Clin Oncol 28(14):2365–2372
73. Molina A et al (2005) Durable clinical, cytogenetic, and molecular remissions after allogeneic hematopoietic cell transplantation for refractory Sezary syndrome and mycosis fungoides. J Clin Oncol 23(25):6163–6171
74. Molina A et al (1999) Remission of refractory Sezary syndrome after bone marrow transplantation from a matched unrelated donor. Biol Blood Marrow Transpl 5(6):400–404
75. Guitart J et al (2002) Long-term remission after allogeneic hematopoietic stem cell transplantation for refractory cutaneous T-cell lymphoma. Arch Dermatol 138(10): 1359–1365
76. Wu PA et al (2009) A meta-analysis of patients receiving allogeneic or autologous hematopoietic stem cell transplant in mycosis fungoides and Sezary syndrome. Biol Blood Marrow Transpl 15(8):982–990
77. Paralkar VR et al (2011) Allogeneic hematopoietic SCT for primary cutaneous T cell lymphomas. Bone Marrow Transpl
78. Virmani P et al (2015) Hematopoietic stem cell transplant for mycosis fungoides and Sezary syndrome. Dermatol Clin 33(4):807–818
79. Whittaker S, Hoppe R, Prince HM (2016) How I treat mycosis fungoides and Sezary syndrome. Blood 127(25):3142–3153
80. Masood N et al (2002) Induction of complete remission of advanced stage mycosis fungoides by allogeneic hematopoietic stem cell transplantation. J Am Acad Dermatol 47(1):140–145
81. Soligo D et al (2003) *Treatment of advanced* mycosis fungoides by allogeneic stem-cell transplantation with a nonmyeloablative regimen. Bone Marrow Transpl 31(8):663–666

82. Introcaso CE et al (2008) Stem cell transplantation in advanced cutaneous T-cell lymphoma. J Am Acad Dermatol 58(4):645–649
83. Kahata K et al (2008) Durable remission of Sezary syndrome after unrelated bone marrow transplantation by reduced-intensity conditioning. Acta Haematol 120(1):14–18
84. Cyrenne BM et al (2018) Transplantation in the treatment of primary cutaneous aggressive epidermotropic cytotoxic CD8-positive T-cell lymphoma. Clin Lymphoma Myeloma Leuk 18(1):e85–e93
85. Lechowicz MJ et al (2014) Allogeneic hematopoietic cell transplantation for mycosis fungoides and Sezary syndrome. Bone Marrow Transpl 49(11):1360–1365
86. Duarte RF et al (2014) Long-term outcome of allogeneic hematopoietic cell transplantation for patients with mycosis fungoides and Sezary syndrome: a European society for blood and marrow transplantation lymphoma working party extended analysis. J Clin Oncol 32(29):3347–3348
87. Belinostat is active in peripheral T-cell lymphoma. Cancer Discov 5(8):795
88. Hosing C et al (2015) Allogeneic stem-cell transplantation in patients with cutaneous lymphoma: updated results from a single institution. Ann Oncol 26(12):2490–2495
89. Nakaike T et al (2013) Reduced-intensity conditioning followed by cord blood transplantation in a patient with refractory folliculotropic mycosis fungoides. Int J Hematol 98(4): 491–495
90. Fukushima T et al (2008) Successful cord blood transplantation for mycosis fungoides. Int J Hematol 88(5):596–598
91. Tsuji H et al (2010) Two cases of mycosis fungoides treated by reduced-intensity cord blood transplantation. J Dermatol 37(12):1040–1045
92. Weng et al (2013) Minimal residual disease monitoring with high-throughput sequencing of T cell receptors in cutaneous T cell lymphoma. Sci Transl Med Dec 4; 5(214)
93. Benjamin J et al (2014) Total lymphoid irradiation-antithymocyte globulin conditioning and allogeneic transplantation for patients with myelodysplastic syndromes and myeloproliferative neoplasms. Biol Blood Marrow Transpl 20(6):837–843
94. Schneeweiss M et al (2016) Transformed mycosis fungoides: bridging to allogeneic stem cell transplantation with brentuximab vedotin. Leuk Lymphoma 57(1):206–208
95. Au WY et al (2003) Autologous stem cell transplantation for nasal NK/T-cell lymphoma: a progress report on its value. Ann Oncol 14(11):1673–1676
96. Chan TSY et al (2018) PD1 blockade with low-dose nivolumab in NK/T cell lymphoma failing L-asparaginase: efficacy and safety. Ann Hematol 97(1):193–196
97. O'Connor OA et al (2011) Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. J Clin Oncol 29(9):1182–1189
98. Duvic M et al (2007) Phase 2 trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). Blood 109(1):31–39
99. Piekarz RL et al (2009) Phase II multi-institutional trial of the histone deacetylase inhibitor romidepsin as monotherapy for patients with cutaneous T-cell lymphoma. J Clin Oncol 27(32):5410–5417
100. Younes A et al (2010) Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. N Engl J Med 363(19):1812–1821
101. Duarte RF et al (2010) Allogeneic hematopoietic cell transplantation for patients with mycosis fungoides and Sezary syndrome: a retrospective analysis of the lymphoma working party of the European group for blood and marrow transplantation. J Clin Oncol 28(29):4492–4499