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Christiane Querfeld · Jasmine Zain
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T-Cell and NK-Cell Lymphomas

From Biology to Novel Therapies

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About the Editors

Christiane Querfeld, M.D., Ph.D. is a board-certified dermatologist and dermatopathologist who specializes in the diagnosis and treatment of cutaneous lymphoma. She is the Chief of the Division of Dermatology, Director of the Cutaneous Lymphoma Program, and Assistant Professor at City of Hope National Medical Center. Her clinical practice is dedicated to patients with cutaneous lymphoma. Her research focus has been on investigations of the biology of cutaneous lymphomas and novel therapies for these diseases and she serves as co-principal investigator on several clinical Phase I and II trials of cutaneous T-cell lymphomas (CTCL). She is a member of an international collaboration of cutaneous lymphoma experts aimed towards the improved prognostication and characterization of the disease. Her laboratory-based projects are aimed to identify the contributing elements of the tumor microenvironment in CTCL and help elucidate the underlying mechanisms that lead to disease progression through maintenance and proliferation of malignant cells in the skin.

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].

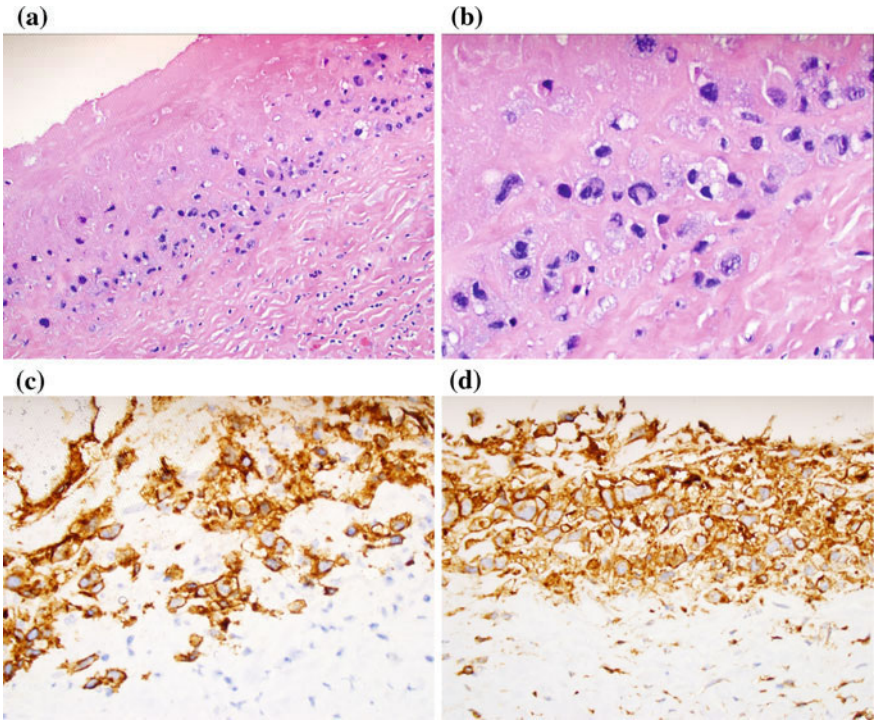

Fig. 1.1 Breast implant-associated anaplastic large-cell lymphoma. **a** Neoplastic cells are infiltrating the fibrous capsule. **b** These tumor cells are pleomorphic with some having hallmark cell morphology. **c** The tumor cells are positive for CD30 and **d** CD4

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

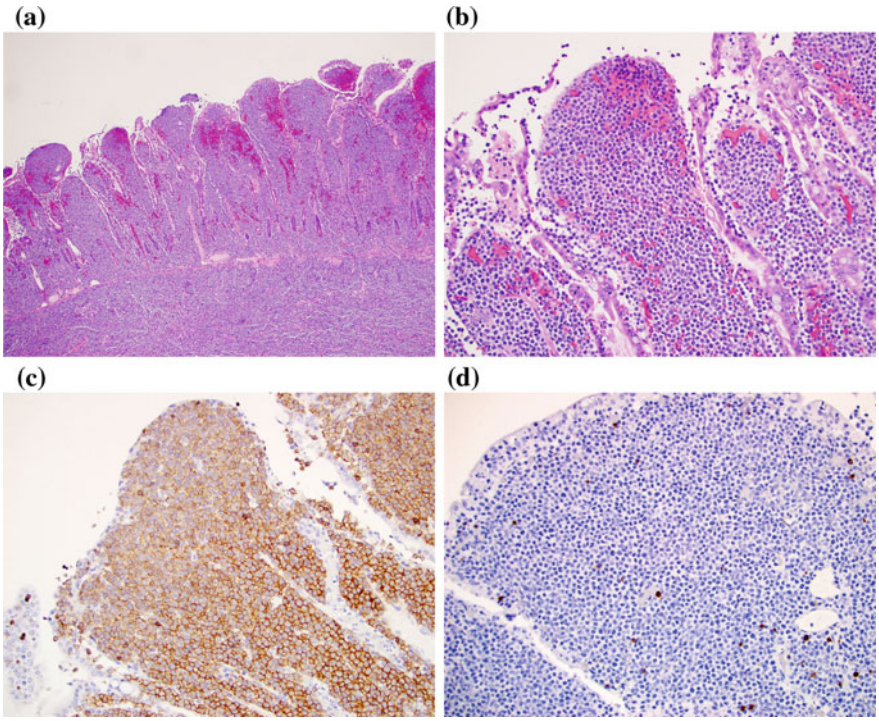

Fig. 1.2 Monomorphic epitheliotropic intestinal T-cell lymphoma. **a** and **b** Diffuse monomorphic infiltrate is expanding the small intestinal villi and invading the submucosa. The tumor cells are positive for **c** CD3 and **d** negative for CD5

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.

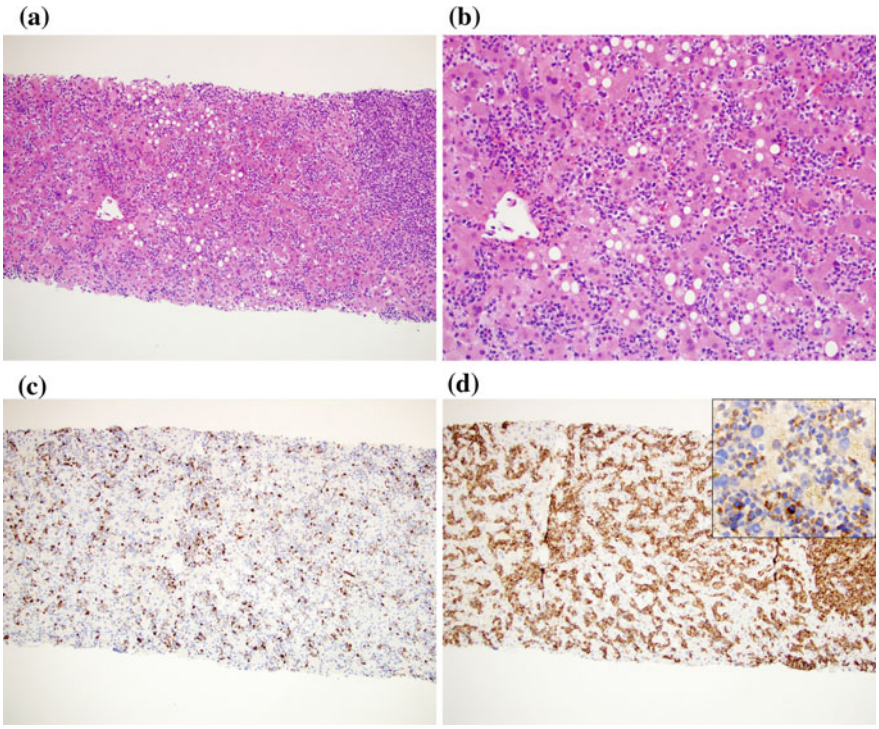

Fig. 1.3 Hepatosplenic T-cell lymphoma involving the liver. **a** and **b** Sinusoidal infiltration of atypical lymphoid cells. **c** A subset express CD3 and **d** many express CD8 with a minor subset positive for TCR gamma immunostaining (inset)

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.