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Lymphoma classification update: T-cell lymphomas, Hodgkin lymphomas, and histiocytic/dendritic cell neoplasms

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Abstract

Introduction—Lymphomas are classified based on the normal counterpart, or cell of origin, from which they arise. Because lymphocytes have physiologic immune functions that vary both by lineage and by stage of differentiation, the classification of lymphomas arising from these normal lymphoid populations is complex. Recent genomic data have contributed additional depth to this complexity.

Areas covered—Lymphoma classification follows the World Health Organization (WHO) system, which reflects international consensus and is based on pathological, genetic, and clinical factors. The present review focuses on the classification of T-cell lymphomas, Hodgkin lymphomas, and histiocytic and dendritic cell neoplasms, summarizing changes reflected in the 2016 revision to the WHO classification. These changes are critical to hematologists and other clinicians who care for patients with these disorders.

Expert commentary—Lymphoma classification is a continually evolving field that needs to be responsive to new clinical, pathological, and molecular understanding of lymphoid neoplasia. Among the entities covered in this review, the 2016 revisions in the WHO classification particularly impact T-cell lymphomas, including a new umbrella category of T-follicular helper cell-derived lymphomas and evolving recognition of indolent T-cell lymphomas and lymphoproliferative disorders.

Keywords

Non-Hodgkin lymphoma; peripheral T-cell lymphoma; anaplastic large cell lymphoma; angioimmunoblastic T-cell lymphoma; T-cell lymphoproliferative disorder; Hodgkin lymphoma; histiocytic sarcoma; dendritic cell tumors; lymphoma classification; World Health Organization (WHO)

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Declaration of interest

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1. Introduction

Lymphomas represent a heterogeneous group of lymphoid malignancies with varied patterns of clinical behavior and responses to treatment. The prognosis depends on the histologic type, clinical factors, and, more recently, molecular characteristics. Lymphomas are classified according to a system established by the World Health Organization (WHO), with the most recent fourth edition published in 2008 [1]. The WHO classification distinguishes lymphoid neoplasms derived from precursor lymphoid cells from those derived from mature lymphoid cells and further separates each group into neoplasms of B-cell or T-cell origin. For the most part, mature lymphoid neoplasms comprise the non-Hodgkin lymphomas (NHLs); Hodgkin lymphomas are considered separately. Tumors of mature histiocytic and dendritic cell (HDC) origin are not derived from lymphoid cells but often involve lymphoid tissue and historically have been discussed along with mature lymphoid neoplasms.

While the fourth edition of the WHO tumor monograph series is not yet completed for all tumor types, it was recognized that a revision of the lymphoid and other hematologic neoplasms was necessary, in part to reflect the rapidly accumulating wealth of genetic data that impact lymphoma biology, pathology, and clinical behavior. Although this ‘2016 revision’ has not been released in book form as of this writing, an overview was recently published [2]. The current review aims to summarize those facets of the revised classification that are anticipated to be most relevant to clinicians caring for lymphoma patients, here focusing on mature T-cell neoplasms, Hodgkin lymphoma, and HDC neoplasms.

2. Mature T-cell neoplasms

Approximately 10–15% of NHLs are of T-cell or natural killer (NK)-cell origin [3]. Tumors of mature (post-thymic or peripheral) T-cell origin are often referred to collectively as peripheral T-cell lymphomas (PTCLs) and are broadly separated into those with predominantly leukemic, extranodal, or nodal presentation. Studies in recent years have confirmed that most PTCL subtypes have a poorer prognosis than most B-cell NHL subtypes [4]. To date, cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like combination chemotherapy still represents the standard approach to the treatment of most PTCLs [5]. However, except for anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL), outcomes for most patients remain poor, with low response rates and short durations of response. Recent molecular advances have allowed further distinction of new subgroups that have both diagnostic and prognostic value. The WHO classification lists over 25 definite or provisional entities under the heading of mature T- and NK-cell neoplasms; however, as outlined above, this review summarizes those for which changes in the 2016 revision of the WHO classification are most important to clinicians (Tables 1 and 2).

2.1. Anaplastic large-cell lymphoma

ALCLs represent a group of neoplasms of mature T-cell origin that express the lymphocyte activation marker, CD30 [6]. Broadly, ALCLs can be grouped based on the expression of the ALK (positive or negative) and by clinical presentation (systemic or localized). Localized

forms of ALCL include primary cutaneous (pc) ALCL and breast implant-associated ALCL (BIA-ALCL).

ALK-positive ALCL is a systemic lymphoma characterized by recurrent chromosomal rearrangements involving the *ALK* gene on 2p23. These can be identified by genetic studies or, more commonly, by detecting the resultant ALK fusion protein by immunohistochemistry [7]. Most carry t(2;5)(p23;q25) translocations and express nucleophosmin (NPM)–ALK fusion proteins, leading to constitutive activation of ALK and downstream signaling pathways that regulate cell growth and survival [6–9]. Other *ALK* rearrangement partners have been identified in ALK-positive ALCL, including *ATIC* associated with the inv(2)(p23q35) inversion [10] and *TRAF1* [11]. ALK-positive ALCL occurs mainly in children and young adults, has a male predominance (male to female ratio of 3), and typically presents with stage III to IV disease and systemic symptoms [4,12]. ALK-positive ALCL is associated with a better prognosis and overall survival (OS) rate than ALK-negative ALCL. The diagnostic criteria for ALK-positive ALCL remain unchanged from the 2008 WHO classification.

ALK-negative ALCL was recognized as a provisional entity distinct from ALK-positive ALCL in the 2008 WHO classification and has been upgraded to a definite entity in the 2016 classification [2]. As with ALK-positive ALCL, the term ‘ALK-negative ALCL’ refers to patients with systemic disease. ALK-negative ALCL mainly occurs in an older population with a median age of 43 years and presents with stage III to IV disease or extranodal involvement less frequently than ALK-positive ALCL [12]. Overall, ALK-negative ALCL has a prognosis inferior to that of ALK-positive ALCL, but recent data have shown that it is a genetically heterogeneous disease and that different genetic subgroups have distinct prognoses. Chromosomal rearrangements of the *DUSP22-IRF4* locus on 6p25.3, most commonly associated with the t(6;7)(p25.3;q32.3) translocation, occur in 30% of cases and have a 5-year OS rate of 90%, similar to ALK-positive ALCL (Figure 1(a–c)) [13]. These cases have markedly downregulated the expression of *DUSP22*, which encodes a dual-specificity phosphatase with tumor suppressor functions [14–16]. In contrast, 8% of ALK-negative ALCLs have rearrangements of *TP63*, a *TP53* homolog on 3q28, and demonstrate an aggressive clinical course and poor prognosis, with a 5-year OS rate of only 17% [13,17]. *TP63* rearrangements most commonly involve the *TBL1XR1* gene and form fusion proteins homologous to ΔNp63, a dominant-negative p63 isoform with oncogenic potential [18]. ALCLs that are negative for all three rearrangements (*ALK, DUSP22*, and *TP63*, or ‘triple-negative’ ALCLs) have a 42% 5-year OS rate [13]. Clinical trials are needed to answer the question of whether ALK-negative ALCLs with *DUSP22* rearrangements ought to be treated less aggressively than the remaining ALK-negative ALCLs. Clinically available fluorescence *in situ* hybridization testing can identify *DUSP22* or *TP63* rearrangements in ALCL [13]; the 2016 WHO classification recognizes the prognostic significance of these rearrangements, but currently does not require this testing in the diagnosis of ALK-negative ALCL [2].

Interestingly, activation of the Janus kinase (JAK)/Signal Transducer and Activator of Transcription (STAT) signaling pathway has been identified in both ALK-positive ALCL and ALK-negative ALCL [19]. This finding may suggest a common signaling pathway

underlying the pathogenesis of most or all ALCLs, provide a molecular basis for the morphological similarities among these entities, and represent a candidate therapeutic target [2,19].

BIA-ALCL has been emerged as a clinically distinct form of ALCL in recent years and now is included as a provisional entity. The disease was first described in 1997. A retrospective study of 19 BIA-ALCLs showed a median age of 61 years and a median interval of 9 years between the placement of the breast implants and the development of ALCL [20]. The neoplastic cells are CD30 positive and ALK negative [21]. Most cases have demonstrated T-cell antigen loss and nuclear expression of phosphorylated STAT3 [20,21]. BIA-ALCL may be confined to the fibrous capsule (the so-called 'in situ' form; Figure 1(d)) or may infiltrate adjacent tissues [20]. The *in situ* form of BIA-ALCL has an indolent clinical course and is associated with excellent event-free survival. The infiltrative form tends to have a more aggressive clinical course [20]. Complete surgical excision is critical to achieve optimal outcomes in patients with BIA-ALCL [22]. To date, it remains unclear whether additional treatment modalities beyond capsulectomy are of benefit; in one of the largest retrospective studies [23], the addition of chemotherapy was not associated with a statistically significant improvement in progression-free survival (PFS) or OS. However, patients with masses had PFS and OS rates inferior to patients without masses (e.g. 5-year OS rates of 75% versus 100%).

pcALCL is a distinct entity classified under the primary cutaneous CD30-positive T-cell lymphoproliferative disorders (TLPDs), which also include lymphomatoid papulosis (LyP) and cases borderline between LyP and pcALCL. pcALCL initially presents in the skin and must be distinguished from systemic ALK-negative ALCL that involves the skin secondarily by history, physical examination, and staging procedures. Diagnostic criteria for pcALCL remain unchanged from the 2008 WHO classification. Clinically, pcALCL behaves indolently, with a 5-year cumulative risk of progression to systemic ALCL of 14% based on the British Columbia Cancer Agency experience [24]. In this retrospective study, the 5-year disease-specific survival and OS were 86% and 75%, respectively. Patients with limited stage disease had excellent outcomes following treatment with radiation therapy alone.

LyP is an indolent TLPD with a spectrum of pathologic variants. While these variants are recognized by the WHO and should be specified when possible, they have similar clinical behavior, and their major significance relates to the differential diagnosis with other, more aggressive entities. In one of the largest reported retrospective studies of LyP, histologic variant did not affect prognosis, though patients with LyP type D were less likely to be associated with other type of lymphoma [25]. Interestingly, subsets of both LyP and pcALCL carry the same *DUSP22* rearrangements seen in systemic ALK-negative ALCL [26,27].

2.2. T-cell lymphomas of T-follicular helper origin

Angioimmunoblastic T-cell lymphoma (AITL) is the classic form of T-cell lymphoma of T-follicular helper (TFH) origin, with diagnostic criteria that remain essentially unchanged from the 2008 WHO classification. AITL is one of the most common mature T-cell neoplasms and is an aggressive disease characterized by lymphadenopathy, systemic

symptoms, and often immune manifestations such as hypergammaglobulinemia [4]. Pathologically, there is a polymorphic immune infiltrate in lymph node specimens, composed not only of tumor cells but also of a rich microenvironment containing small reactive lymphocytes, histiocytes, eosinophils, expanded follicular den-dritic cell meshworks, prominent endothelial venules, and Epstein–Barr virus (EBV)-positive large B immunoblasts [28]. The tumor cells express TFH cell markers, which may include CD10 and CD279 (PD-1, PDCD1), CXCL13, BCL6, CD40L, and NFATC1 [28–30].

The 2016 WHO classification includes two additional provisional entities representing neoplasms of TFH origin [2]. Nodal T-cell lymphomas with a TFH phenotype represent T-cell lymphomas that have a TFH phenotype but do not meet other criteria for AITL, while follicular T-cell lymphoma represents a T-cell lymphoma primarily involving the follicles, which morphologically may resemble follicular lymphoma of B-cell origin. Cases in both of these provisional categories previously would have been classified as PTCL, not otherwise specified (PTCL, NOS; see below). While they are kept distinct from AITL, they are included in the umbrella category of T-cell lymphomas of TFH origin not only because of their phenotype but also because of common genetic findings among these entities, including recurrent somatic mutations of *TET2, RHOA, IDH2, CD28*, and *DNMT3A*, as well as fusions of *ITK-SYK* and *CD28-CTLA4* [31,32]. In the era of individualized medicine, these findings will likely lead to trials of epigenetic modifiers and/or immunotherapy. Of note, *TET2* mutations are associated with advanced-stage disease, high international prognostic index scores, and a shorter PFS [33]. Typically, AITLis managed aggressively, similar to most other PTCLs. A trial of less-aggressive therapy (e.g. corticosteroids or cyclosporine) can be attempted in older patients with comorbidities but is not standard of care.

The B cells in the microenvironment of AITL and related neoplasms may give rise to concurrent, abnormal B-cell pro-liferations in about one-third of cases, which may progress into overt EBV-positive or EBV-negative B-cell lymphomas [34,35]. In some cases, the B cells in the background mimic Reed–Sternberg cells and may lead to a misdiagnosis of Hodgkin lymphoma if the neoplastic T-cell population is not recognized [36,37].

2.3. PTCL, not otherwise specified

PTCL, NOS comprises a heterogeneous group of mature T-cell lymphomas that do not meet diagnostic criteria for one of the more specific mature T-cell neoplasms; as such, it is a diagnosis of exclusion or a so-called ‘wastebasket’ diagnosis [1]. However, PTCL, NOS remains the most commonly diagnosed subtype of T-cell lymphoma, underscoring the need for increased understanding of this group of diseases. Despite the heterogeneous nature of PTCL, NOS, molecular subgroups with distinct features have been identified. Gene expression profiling studies have stratified PTCL, NOS based on expression of GATA3, TBX21, and cytotoxic markers [38]. One subgroup is characterized by high expression of GATA3 and its target genes, including *CCR4, IL18RA, CXCR7*, and *IK*. GATA3 is a T-cell transcription factor that binds to the DNA sequence, GATA, to regulate T helper cell differentiation via transcription of interleukin 4 (IL4) and IL13 and epigenetic modulation of IL10 [38–42]. A second subgroup is characterized by high expression of the T-box

transcription factors TBX21 (Tbet) and eomesodermin (EOMES or Tbr2) and their target genes *CXCR3, IL2RB, CCL3*, and *IFNG* [38]. Both subgroups have generally poor clinical outcomes, but the GATA3 subgroup has an inferior prognosis, with a 5-year OS rate of 19% versus 38% for the TBX21 subgroup. However, within the TBX21 subgroup, expression of cytotoxic markers is associated with adverse outcomes. Whole-exome sequencing studies of PTCL, NOS have revealed marked heterogeneity but have identified recurrent mutations in genes involved in epigenetic regulation, DNA damage response, and Src signaling, including *FYN, ATM, B2M, CD58*, and *RHOA* [43].

2.4. T-cell lymphomas of the gastrointestinal tract

The nomenclature of enteropathy-associated T-cell lymphomas (EATLs) has changed in the 2016 WHO classification. In the past, these were classified as EATL type I and EATL type II, but only EATL type I was truly associated with enteropathy (celiac disease). In the 2016 classification, EATL refers only to the type I cases, whereas type II cases are renamed monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL). In addition to the association with celiac disease, distinct genetic alterations have been identified in these two entities that further support this reclassification [44].

EATL is an extranodal T-cell NHL primarily affecting the gastrointestinal (GI) tract with an intraepithelial T-cell phenotype [1]. EATL typically has a highly aggressive clinical course and is associated with celiac disease, typically in northern European populations [45]. EATL is characterized by pleomorphic, anaplastic, or immunoblastic tumor cells, most commonly with an αβ T-cell receptor (TCR) phenotype, though γδ TCR cases exist [45]. EATL patients usually carry human leukocyte antigen (HLA)-DQ2 or DQ8, and the tumors often show copy number gains of 1q and 5q [1].

MEITL is not associated with celiac disease and is characterized by monomorphic small- to medium-sized tumor cells that express CD8, CD56, and megakaryocyte-associated tyrosine kinase [46]. MEITL is associated with frequent gains of the 8q24 locus involving the *MYC* oncogene [47,48]. The majority of MEITLs express γδ TCR, though there are αβ TCR variants [49]. Recurrent mutations in STAT5B have been identified in 37% of γδ MEITLs [44,50]. In a recent whole-exome sequencing study of 15 MEITLs, 93% of cases displayed loss-of-function *SETD2* alterations with defective H3K36 trimethylation [51]. These findings were not observed in (type I) EATL, further highlighting the genomic differences between the two entities. Of note, preclinical data suggest that H3K36 trimethylation-deficient tumors may be particularly sensitive to WEE1 kinase inhibitors (e.g. AZD1775) [52].

Indolent TLPD of the GI tract is added as a new provisional entity in the 2016 WHO classification [2]. The whole GI tract is frequently involved and shows nondestructive infiltration by small, mature lymphoid cells [53]. The cells are commonly CD8 +/CD4−/CD56− and express the cytotoxic marker TIA1. Some cases may express CD4 (Figure 2). An NK-cell variant has been described but is not addressed specifically in the WHO classification. Most patients have an indolent course and do not need aggressive treatment, though occasional cases may progress [53].

2.5. Cutaneous T-cell lymphomas

The most common CTCLs are mycosis fungoides (MF) and Sézary syndrome, for which diagnostic criteria have not changed significantly in the 2016 WHO classification, and the CD30-positive TLPDs discussed above in the section on ALCL.

The 2016 WHO classification has changed the nomenclature of primary cutaneous CD4-positive small/medium T-cell lymphoma to primary cutaneous CD4-positive small/medium TLPD to reflect the indolent clinical behavior of this entity. Clinically, patients typically present with a solitary cutaneous papule or nodule, especially on the upper part of the body, without a history of skin patches or plaques to suggest MF. The classic histopathologic changes include dermal infiltration by small lymphocytes with hyperchromatic nuclei, without significant epidermal, follicular, or adnexal involvement. Most cases have an indolent course and favorable outcome following excision, radiation, and/or other local therapies [2,54–56].

Primary cutaneous acral CD8-positive T-cell lymphoma is added as a new provisional entity in the 2016 WHO classification [2]. This entity is characterized by an indolent, slow-growing nodule localized to a single site, usually the ear, and can be managed conservatively with excision only, topical or intralesional steroids, or local radiotherapy [57]. No differences in outcomes were observed among these treatment modalities. Although primary cutaneous acral CD8-positive T-cell lymphoma has an indolent course, the histologic features of a dense, diffuse monomorphic infiltrate of medium-sized T cells throughout the dermis and subdermis can mimic higher-grade lymphomas. The indolent nature of these entities must be recognized to avoid overly aggressive management.

Primary cutaneous γδ T-cell lymphoma shows an EBV-negative, cytotoxic γδ T-cell phenotype and clonal rearrangements of the TCR receptor genes [58]. When the disease involves subcutaneous tissue, the process can resemble subcutaneous panniculitis-like T-cell lymphoma (SCPTCL) but is classified as a distinct entity because it tends to be clinically more aggressive than SCPTCL, which typically presents as cutaneous nodules in the trunk or extremities and has an αβ cytotoxic T-cell phenotype [2,59–61]. It should be noted that a γδ T-cell phenotype may be seen in cases meeting criteria for other WHO entities, including MF and LyP.

2.6. EBV-associated neoplasms of T and NK cells

The most common of these disorders is extranodal NK-/T-cell lymphoma, nasal type, though still relatively infrequent in western countries. Diagnostic criteria remain unchanged from the 2008 WHO classification.

Systemic EBV-positive T-cell lymphoma of childhood is characterized by a monoclonal proliferation of EBV-infected T cells with an activated cytotoxic phenotype (TIA1 positive) and a fulminant and aggressive clinical course, with survival measured in weeks due to multiple organ failure and sepsis [62]. The disease most often arises in the context of chronic active EBV infection in children, though it may follow acute EBV infection. The nomenclature of the entity was changed in the 2016 WHO classification from ‘lymphoproliferation’ to ‘lymphoma’ due to the aggressive clinical course [2].

In contrast, the name of hydroa vacciniforme-like lymphoproliferative disorder (HVLLD) was changed from ‘lymphoma’ to ‘lymphoproliferative disorder’ due to its wide spectrum of clinical behavior [2]. HVLLD is characterized by skin lesions, typically vesicles or vesicopapular eruptions, in sun-exposed areas and is associated with fever, lymphadenopathy, hepatosplenomegaly, and mosquito-bite hypersensitivity in some patients [63]. The abnormal cells in HVLLD may demonstrate an αβ T-cell, γδ T-cell, or NK-cell phenotype, and occasional patients progress to systemic lymphomas [63,64].

2.7. Leukemic mature T-cell neoplasms

T-cell large granular lymphocyte leukemia (T-LGL) is a rare leukemic TLPD characterized by clonal expansion of cytotoxic T cells and associated with autoimmune processes and immune-mediated cytopenias [65–67]. Most are of αβ T-cell origin, but some have a γδ T-cell phenotype. Koskela et al. have identified somatic *STAT3* mutations in 40% of T-LGLs [68]. *STAT3* mutations also are found in chronic lymphoproliferative disorders of NK cells, suggesting a possible common pathogenesis in these two clonal lymphoproliferations [69]. Less-frequent *STAT5B* mutations have also been identified in T-LGL [70]. Of note, somatic mutations in the *STAT3* and *STAT5B* genes with activation of the corresponding proteins are also seen in a variety of γδ T-cell neoplasms, including hepatosplenic T-cell lymphomas, CTCLs, and MEITLs of γδ type [44,50,71]. The clinical relevance of these findings is yet to be established. *STAT5B* mutations may be associated with a more aggressive phenotype [66]. In a phase II study of immunosuppressive therapy with methotrexate in LGL, *STAT3* Y640F mutations were associated with therapeutic response to methotrexate [72]. These findings will need to be reproduced; clinical trials with STAT3 inhibitors in LGL also should be explored.

3. Hodgkin lymphomas

While recent data indicate that most if not all Hodgkin lymphomas are of mature B-cell origin, they are classified separately from B-cell NHLs [1,2]. There are two main entities, classical Hodgkin lymphoma (CHL) and nodular lymphocyte predominant Hodgkin lymphoma (NLPHL). These diseases share several important features that distinguish them from many NHLs. Clinically, they often present in young adults, primarily as nodal disease (most often with involvement of cervical lymph nodes). Pathologically, they are characterized by large neoplastic cells that represent the minority of the total cellular composition and are scattered in a rich background of non-neoplastic cells. Significant changes in the 2016 WHO revision that relate to Hodgkin lymphomas are summarized in Table 3.

3.1. Classical Hodgkin lymphoma

CHL is the more common of the two Hodgkin lymphoma entities and can be further divided into four histological subtypes: lymphocyte-rich CHL (LRCHL), nodular sclerosis CHL, mixed cellularity CHL, and lymphocyte-depleted CHL [1]. The classification and diagnostic criteria remain unchanged for CHL in the 2016 revision [2]. LRCHL is relatively infrequent, accounting for 3–5% of CHL; it typically presents with stage I or II disease and has a better prognosis than other CHL subtypes [1,73,74]. It shares some features with NLPHL

morphologically and clinically, though it has a distinct immunophenotype and a lower frequency of relapse [73]. A comparison of markers of B-cell lineage, transcription factors, nuclear factor (NF)-κB signaling, and the T-cell microenvironment has demonstrated similarities among LRCHL, NLPHL, and CHL and has suggested that LRCHL has features intermediate between those of CHL and NLPHL [75].

3.2. Nodular lymphocyte predominant Hodgkin lymphoma

NLPHL is a rare entity that accounts for 3–5% of Hodgkin lymphomas [74,76]. The neoplastic cells of NLPHL are derived from germinal center B cells and express CD20, CD79a, CD75, BCL6, CD45, and J chain [77]. NLPHL typically occurs in young and middle-aged males and has an indolent clinical course [78]. NLPHL can be separated into nodular and diffuse histological patterns [77,79]. Most cases are nodular and show a mixed infiltrate of small reactive B cells with only occasional large, neoplastic ‘lymphocyte predominant’ cells, also referred to as ‘popcorn cells’ [1]. Fan et al. identified six distinct immunoarchitectural patterns of NLPHL, including classic nodular B-cell-rich (pattern A), serpiginous nodular (pattern B), nodular with prominent extranodular tumor cells (pattern C), T-cell-rich nodular (pattern D), diffuse T-cell-rich (pattern E), and diffuse B-cell-rich (p attern F) [80]. The variant patterns C through F are associated with advanced disease and a higher relapse rate at 5 years than the classic patterns A and B, and thus the pattern should be specified if possible in the pathology report [2,81].

Cases of NLPHL with diffuse architectural patterns must be distinguished from T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL), a subtype of diffuse large B-cell lymphoma characterized by neoplastic CD20-positive B cells that usually constitute less than 10% of the infiltrate and are scattered among the non-neoplastic T cells with or without histiocytes [1]. THRLBCL usually presents with advanced clinical stage and is associated with a worse prognosis than NLPHL [82]. Nevertheless, NLPHL and THRLBCL share a number of features, and a recent study comparing the gene expression profiles of the diffuse T-cell-rich NLPHL (pattern E, also known as THRLBCL-like NLPHL) and THRLBCL revealed no significant differences [81,83]. Furthermore, classic NLPHL, THRLBCL-like NLPHL, and THRLBCL share common genetic alterations, including gains of 2p16.1 and losses of 2p11.2 and 9p11.2 [84]. It has been suggested that the diffuse patterns of NLPHL represent progression from NLPHL to THRLBCL or that these entities represent a spectrum of a single disease [81,83,84]. Cases of NLPHL transforming into THRLBCL or occurring synchronously with THRLBCL at a different site have been reported [2]. The 2008 WHO classification recommended describing NLPHL cases that progressed to a diffuse T-cell-rich pattern as ‘THRLBCL-like NLPHL’ to distinguish them from primary THRLBCL and indicated that at least focal presence of a typical NLPHL nodule be required for the diagnosis of NLPHL [1,2,80]. In the 2016 revision of the WHO classification, these cases are designated ‘THRLBCL-like transformation of NLPHL’ and have a more aggressive clinical course than typical NLPHL [2,85,86].

Since CD20 is expressed by the neoplastic cells in NLPHL, studies have looked at rituximab use as a single agent or in combination with chemotherapy. In one study [87], rituximab was studied as a single agent or single agent with a maintenance schedule in either newly

diagnosed or relapsed cases of NLPHL. Despite an objective response rate of 100%, responses were not durable in most patients. Maintenance rituximab was associated with a trend towards longer PFS, but demonstrated no OS benefit. Choices of chemotherapy vary from CHL-like regimens with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) to CHOP-like chemotherapy with the addition of rituximab. However, no randomized trial has compared these regimens side by side, and no standard of care for advanced NLPHL has yet been established.

4. HDC neoplasms

HDC neoplasms are derived from the mononuclear phagocytic system comprising dendritic cells and mononuclear phagocytes also referred to as histiocytes. Most tumors are of myeloid lineage, but some tumors such as follicular dendritic cell sarcoma have a mesenchymal origin [2]. Though these neoplasms are not lymphomas, historically they are often discussed with the mature lymphoid neoplasms as they have a mature state of differentiation and typically present in lymph nodes and other solid tissue sites, in contrast to many other myeloid tumors that are precursor neoplasms and often have a leukemic presentation. In addition, distinction of lymphoid and histiocytic neoplasms was difficult prior to immunophenotyping. Interestingly, HDC tumors may develop in patients with underlying mature or precursor B- or T-cell neoplasms and demonstrate clonal identity to the lymphoid component, including the same clonal immunoglobulin and/or TCR gene rearrangement, a phenomenon known as transdifferentiation [2,88–95]. Significant changes in the 2016 WHO revision that relate to HDC neoplasms are summarized in Table 3.

4.1. Langerhans cell histiocytosis

Langerhans cell histiocytosis (LCH) is a rare, benign disorder characterized by a clonal proliferation of Langerhans cells expressing CD1a, langerin, and S100 [96]. The clinical presentation is widely variable, but the bones (>80%), skin (33%), and pituitary gland (25%) are frequently involved [96,97]. LCH with systemic involvement is referred to as Letterer–Siwe disease and presents with fever, hepatosplenomegaly, liver dysfunction, hematopoietic failure, and visceral involvement [98]. Genetics are discussed below.

4.2. Erdheim–Chester disease

Erdheim–Chester disease (ECD) is a rare, multi-organ, non-Langerhans cell histiocytic disorder that occurs predominantly in the 40–70-year-old age range with a male to female ratio of about 3:1 [96,99]. Pathologic changes include osteosclerotic lesions of the long bones with infiltration of foamy histiocytes and fibrosis (90% of patients), central nervous system involvement (20–50%), infiltration of the orbits (25%), retroperitoneal involvement (including the so-called ‘hairy kidney’; 30%), skin lesions (xanthelasma; 30%), cardiovascular involvement (with a ‘coated aorta’ appearance on imaging studies), and pulmonary changes (50%) [96,99–104]. The abnormal cells express CD68, CD163, and Factor XIIIa and are negative for CD1a, langerin, and S100 [96]. Patients typically have elevated levels of interferon-α, IL12, and monocyte chemotactic protein-1 and decreased levels of IL4 and IL7 [96,105]. The cells in ECD are identical to those in juvenile xanthogranuloma (JXG), but JXG usually does not present with multisystem involvement

[96]. Positron emission tomography-computed tomography imaging is recommended for initial assessment of the overall disease burden in ECD due to its sensitivity for detecting extraosseous lesions [106]. Treatment with interferon-α has improved OS in ECD patients [107]. Anakinra, a recombinant IL1 receptor antagonist, also has shown efficacy [103].

Recent studies have identified a *BRAF* V600E mutation in over 50% of patients with ECD and LCH, suggesting a critical role of mitogen-activated protein (MAP) kinase signaling in the pathogenesis of both disorders [108,109]. Whole-exome and transcriptome sequencing has revealed recurrent mutations involving *BRAF*, *ALK*, and *NTRK1*, and in *MAP2K1* and *ARAF* in non-Langerhans cell histiocytic tumors with wild-type *BRAF*, including ECD, JXG, and Rosai–Dorfman disease [96,110]. The BRAF inhibitor, vemurafenib, has resulted in dramatic clinical and radio-graphic responses in LCH and ECD and is recommended in refractory patients carrying the *BRAF* V600E mutation [111].

5. Expert commentary

Lymphoma classification is a continually evolving field that needs to be responsive to new clinical, pathological, and molecular understanding of lymphoid neoplasia. The 2016 revisions in the WHO classification of mature T-cell neoplasms, Hodgkin lymphomas, and HDC neoplasms include significant changes that impact the diagnosis, prognosis, and management of these diseases. The 2016 revision particularly impacts PTCLs and sees a reorganization of current categories and distinction of new provisional entities. The grouping of TFH-derived PTCLs into a new umbrella category represents a general example of how biologic and molecular features can help group diseases with similar characteristics, and a specific example of how discrete entities can be dissociated from the ‘wastebasket’ diagnosis of PTCL, NOS. Another major advance is the evolving recognition of indolent T-cell lymphomas and lymphoproliferative disorders, which are particularly important to distinguish, given the clinically aggressive nature of most PTCLs.

6. Five-year view

We anticipate that the future of T-cell lymphoma classification lies in molecular characterization of subgroups that will allow selection of appropriate targeted therapies and inclusion into clinical trials accordingly. These molecular tools are likely to include not only genomics but also other high-throughput technologies such as epigenomics, proteomics, and metabolomics. We expect these advances will continue to identify new entities with distinct clinical, pathological, and molecular features that will reclassify cases out of the heterogeneous and relatively common PTCL, NOS category. Advances in Hodgkin lymphoma are likely to arise from an increasing understanding of the relationship between the neoplastic cells and the rich microenvironment long recognized to be a critical component of this group of diseases. Finally, management of HDC neoplasms will be facilitated by ongoing genomic studies that are uncovering a spectrum of targetable alterations involving kinase signaling in this group of tumors.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1••. Swerdlow, S.Campo, E.Harris, N., et al., editors. WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon: International Agency for Research on Cancer; 2008. Pending release of the 2016 WHO revision, this 2008 edition remains the current published edition of the WHO classification at the time of this writing.

2••. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016; 127(20):2375–2390. A comprehensive overview of the 2016 WHO revision, published prior to release of the revision itself and outlining major changes from the 2008 edition. [PubMed: 26980727]

3. The non-Hodgkin's lymphoma classification project: a clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. Blood. 1997; 89(11):3909–3918. [PubMed: 9166827]

4•. Vose J, Armitage J, Weisenburger D. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol. 2008; 26(25):4124–4130. An important study of the frequencies, geographic distribution, and outcomes of T-cell lymphoma subtypes. [PubMed: 18626005]

5. Armitage JO. The aggressive peripheral T-cell lymphomas: 2015. Am J Hematol. 2015; 90(7):665–673. [PubMed: 26031230]

6. Jaffe ES. Anaplastic large cell lymphoma: the shifting sands of diagnostic hematopathology. Mod Pathol. 2001; 14(3):219–228. [PubMed: 11266530]

7. Webb TR, Slavish J, George RE, et al. Anaplastic lymphoma kinase: role in cancer pathogenesis and small-molecule inhibitor development for therapy. Expert Rev Anticancer Ther. 2009; 9(3):331–356. [PubMed: 19275511]

8. Morris SW, Kirstein MN, Valentine MB, et al. Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma. Science. 1995; 267(5196):316–317.

9. Marzec M, Kasprzycka M, Liu X, et al. Oncogenic tyrosine kinase NPM/ALK induces activation of the rapamycin-sensitive mTOR signaling pathway. Oncogene. 2007; 26(38):5606–5614. [PubMed: 17353907]

10. Ma Z, Cools J, Marynen P, et al. Inv(2)(p23q35) in anaplastic large-cell lymphoma induces constitutive anaplastic lymphoma kinase (ALK) tyrosine kinase activation by fusion to ATIC, an enzyme involved in purine nucleotide biosynthesis. Blood. 2000; 95(6):2144–2149. [PubMed: 10706887]

11. Feldman AL, Vasmatzis G, Asmann YW, et al. Novel TRAF1-ALK fusion identified by deep RNA sequencing of anaplastic large cell lymphoma. Genes Chromosomes Cancer. 2013; 52(11):1097–1102. [PubMed: 23999969]

12. Falini B, Pileri S, Zinzani PL, et al. ALK+ lymphoma: clinico-pathological findings and outcome. Blood. 1999; 93(8):2697–2706. [PubMed: 10194450]

13•. Parrilla Castellar ER, Jaffe ES, Said JW, et al. ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes. Blood. 2014; 124(9):1473–1480. Identification of the prognostic significance of chromosomal rearrangements within ALK-negative anaplastic large-cell lymphoma. [PubMed: 24894770]

14. Feldman AL, Dogan A, Smith DI, et al. Discovery of recurrent t(6;7) (p25.3;q32.3) translocations in ALK-negative anaplastic large cell lymphomas by massively parallel genomic sequencing. Blood. 2011; 117(3):915–919. [PubMed: 21030553]

15. Huang CY, Tan TH. DUSPs, to MAP kinases and beyond. Cell Biosci. 2012; 2(1):24. [PubMed: 22769588]

16. Melard P, Idrissi Y, Andrique L, et al. Molecular alterations and tumor suppressive function of the DUSP22 (dual specificity phosphatase 22) gene in peripheral T-cell lymphoma subtypes. Oncotarget. 2016; 7(42):68734–68748. [PubMed: 27626696]

17. Vasmatzis G, Johnson SH, Knudson RA, et al. Genome-wide analysis reveals recurrent structural abnormalities of TP63 and other p53-related genes in peripheral T-cell lymphomas. Blood. 2012; 120(11):2280–2289. [PubMed: 22855598]

18. Graziano V, De Laurenzi V. Role of p63 in cancer development. Biochim Biophys Acta. 2011; 1816(1):57–66. [PubMed: 21515338]

19•. Crescenzo R, Abate F, Lasorsa E, et al. Convergent mutations and kinase fusions lead to oncogenic STAT3 activation in anaplastic large cell lymphoma. Cancer Cell. 2015; 27(4):516–532. Identification of STAT3 activation as a common result of varied genetic alterations in anaplastic large-cell lymphoma. [PubMed: 25873174]

20•. Laurent C, Delas A, Gaulard P, et al. Breast implant-associated anaplastic large cell lymphoma: two distinct clinicopathological variants with different outcomes. Ann Oncol. 2016; 27(2):306–314. Characterization of correlation between extent of disease and outcome in breast implant-associated anaplastic large-cell lymphoma. [PubMed: 26598546]

21. Aladily TN, Medeiros LJ, Amin MB, et al. Anaplastic large cell lymphoma associated with breast implants: a report of 13 cases. Am J Surg Pathol. 2012; 36(7):1000–1008. [PubMed: 22613996]

22•. Clemens MW, Medeiros LJ, Butler CE, et al. Complete surgical excision is essential for the management of patients with breast implant-associated anaplastic large-cell lymphoma. J Clin Oncol. 2016; 34(2):160–168. Characterization of correlation between extent of disease and outcome in breast implant-associated anaplastic large-cell lymphoma. [PubMed: 26628470]

23. Miranda RN, Aladily TN, Prince HM, et al. Breast implant-associated anaplastic large-cell lymphoma: long-term follow-up of 60 patients. J Clin Oncol. 2014; 32(2):114–120. [PubMed: 24323027]

24. Hapgood G, Pickles T, Sehn LH, et al. Outcome of primary cutaneous anaplastic large cell lymphoma: a 20-year British Columbia Cancer Agency experience. Br J Haematol. 2017; 176(2): 234–240. [PubMed: 27766622]

25. Wieser I, Oh CW, Talpur R, et al. Lymphomatoid papulosis: treatment response and associated lymphomas in a study of 180 patients. J Am Acad Dermatol. 2016; 74(1):59–67. [PubMed: 26518172]

26. Karai LJ, Kadin ME, Hsi ED, et al. Chromosomal rearrangements of 6p25.3 define a new subtype of lymphomatoid papulosis. Am J Surg Pathol. 2013; 37(8):1173–1181. [PubMed: 23648461]

27. Wada DA, Law ME, Hsi ED, et al. Specificity of IRF4 translocations for primary cutaneous anaplastic large cell lymphoma: a multicenter study of 204 skin biopsies. Mod Pathol. 2011; 24(4): 596–605. [PubMed: 21169992]

28. Dogan A, Attygalle AD, Kyriakou C. Angioimmunoblastic T-cell lymphoma. Br J Haematol. 2003; 121(5):681–691. [PubMed: 12780782]

29. Jaffe ES, Nicolae A, Pittaluga S. Peripheral T-cell and NK-cell lymphomas in the WHO classification: pearls and pitfalls. Mod Pathol. 2013; 26(Suppl 1):S71–S87. [PubMed: 23281437]

30. de Leval L, Rickman DS, Thielen C, et al. 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. 2007; 109(11):4952–4963. [PubMed: 17284527]

31. Sakata-Yanagimoto M, Enami T, Yoshida K, et al. Somatic RHOA mutation in angioimmunoblastic T cell lymphoma. Nat Genet. 2014; 46(2):171–175. [PubMed: 24413737]

32. Cairns RA, Iqbal J, Lemonnier F, et al. IDH2 mutations are frequent in angioimmunoblastic T-cell lymphoma. Blood. 2012; 119(8):1901–1903. [PubMed: 22215888]

33. Lemonnier F, Couronné L, Parrens M, et al. Recurrent TET2 mutations in peripheral T-cell lymphomas correlate with TFH-like features and adverse clinical parameters. Blood. 2012; 120(7): 1466–1469. [PubMed: 22760778]

34. Tan BT, Warnke RA, Arber DA. The frequency of B- and T-cell gene rearrangements and Epstein–Barr virus in T-cell lymphomas: a comparison between angioimmunoblastic T-cell lymphoma and peripheral T-cell lymphoma, unspecified with and without associated B-cell proliferations. J Mol Diagn. 2006; 8(4):466–475. quiz 527. [PubMed: 16931587]

35. Balagué O, Martínez A, Colomo L, et al. 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. 2007; 31(9):1310–1322. [PubMed: 17721185]

36. Nicolae A, Pittaluga S, Venkataraman G, et al. 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. 2013; 37(6):816–826. [PubMed: 23598959]

37. Moroch J, Copie-Bergman C, de Leval L, et al. Follicular peripheral T-cell lymphoma expands the spectrum of classical Hodgkin lymphoma mimics. Am J Surg Pathol. 2012; 36(11):1636–1646. [PubMed: 23073322]

38•. Iqbal J, Wright G, Wang C, et al. Gene expression signatures delineate biological and prognostic subgroups in peripheral T-cell lymphoma. Blood. 2014; 123(19):2915–2923. Analysis of utility of gene expression profiling in classification of peripheral T-cell lymphomas. [PubMed: 24632715]

39. Chang H-D, Helbig C, Tykocinski L, et al. Expression of IL-10 in Th memory lymphocytes is conditional on IL-12 or IL-4, unless the IL-10 gene is imprinted by GATA-3. Eur J Immunol. 2007; 37(3):807–817. [PubMed: 17304625]

40. Cook KD, Miller J. TCR-dependent translational control of GATA-3 enhances Th2 differentiation. J Immunol. 2010; 185(6):3209–3216. [PubMed: 20696860]

41. Shoemaker J, Saraiva M, O'Garra A. GATA-3 directly remodels the IL-10 locus independently of IL-4 in CD4+ T cells. J Immunol. 2006; 176(6):3470–3479. [PubMed: 16517715]

42. Wang T, Feldman AL, Wada DA, et al. GATA-3 expression identifies a high-risk subset of PTCL, NOS with distinct molecular and clinical features. Blood. 2014; 123(19):3007–3015. [PubMed: 24497534]

43. Palomero T, Couronné L, Khiabanian H, et al. Recurrent mutations in epigenetic regulators, RHOA and FYN kinase in peripheral T cell lymphomas. Nat Genet. 2014; 46(2):166–170. [PubMed: 24413734]

44. Deleeuw RJ, Zettl A, Klinker E, et al. Whole-genome analysis and HLA genotyping of enteropathy-type T-cell lymphoma reveals 2 distinct lymphoma subtypes. Gastroenterology. 2007; 132(5):1902–1911. [PubMed: 17484883]

45. Delabie J, Holte H, Vose JM, et al. Enteropathy-associated T-cell lymphoma: clinical and histological findings from the international peripheral T-cell lymphoma project. Blood. 2011; 118(1):148–155. [PubMed: 21566094]

46. Tan S-Y, Ooi A-S, Ang M-K, et al. Nuclear expression of MATK is a novel marker of type II enteropathy-associated T-cell lymphoma. Leukemia. 2011; 25(3):555–557. [PubMed: 21233830]

47. Tomita S, Kikuti YY, Carreras J, et al. Genomic and immunohisto-chemical profiles of enteropathy-associated T-cell lymphoma in Japan. Mod Pathol. 2015; 28(10):1286–1296. [PubMed: 26226842]

48. Zettl A, Ott G, Makulik A, et al. Chromosomal gains at 9q characterize enteropathy-type T-cell lymphoma. Am J Pathol. 2002; 161(5):1635–1645. [PubMed: 12414511]

49. Chan JK, Chan AC, Cheuk W, et al. Type II enteropathy-associated T-cell lymphoma: a distinct aggressive lymphoma with frequent gammadelta T-cell receptor expression. Am J Surg Pathol. 2011; 35(10):1557–1569. [PubMed: 21921780]

50•. Küçük C, Jiang B, Hu X, et al. Activating mutations of STAT5B and STAT3 in lymphomas derived from gammadelta-T or NK cells. Nat Commun. 2015; 6:6025. Identification of STAT3 and STAT5B mutations in γδ T-cell lymphomas. [PubMed: 25586472]

51. Roberti A, Dobay MP, Bisig B, et al. Type II enteropathy-associated T-cell lymphoma features a unique genomic profile with highly recurrent SETD2 alterations. Nat Commun. 2016; 7:12602. [PubMed: 27600764]

52. Pfister SX, Markkanen E, Jiang Y, et al. Inhibiting WEE1 selectively kills histone H3K36me3-deficient cancers by dNTP starvation. Cancer Cell. 2015; 28(5):557–568. [PubMed: 26602815]

53•. Perry AM, Warnke RA, Hu Q, et al. Indolent T-cell lymphoproliferative disease of the gastrointestinal tract. Blood. 2013; 122(22):3599–3606. Analysis of clinicopathologic features of indolent T-cell lymphoproliferative disease of the gastrointestinal tract. [PubMed: 24009234]

54. Virmani P, Jawed S, Myskowski PL, et al. Long-term follow-up and management of small and medium-sized CD4+ T cell lymphoma and CD8+ lymphoid proliferations of acral sites: a multicenter experience. Int J Dermatol. 2016; 55(11):1248–1254. [PubMed: 27369070]

55. Garcia-Herrera A, Colomo L, Camos M, et al. Primary cutaneous small/medium CD4+ T-cell lymphomas: a heterogeneous group of tumors with different clinicopathologic features and outcome. J Clin Oncol. 2008; 26(20):3364–3371. [PubMed: 18541895]
56. Beltraminelli H, Leinweber B, Kerl H, et al. 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. 2009; 31(4):317–322. [PubMed: 19461234]
57. Petrella T, Maubec E, Cornillet-Lefebvre P, et al. Indolent CD8-positive lymphoid proliferation of the ear: a distinct primary cutaneous T-cell lymphoma? Am J Surg Pathol. 2007; 31(12):1887–1892. [PubMed: 18043044]
58. Bajor-Dattilo EB, Pittaluga S, Jaffe ES. Pathobiology of T-cell and NK-cell lymphomas. Best Pract Res Clin Haematol. 2013; 26(1):75–87. [PubMed: 23768642]
59. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. Blood. 2005; 105(10):3768–3785. [PubMed: 15692063]
60. Guitart J, Weisenburger DD, Subtil A, et al. Cutaneous γδ T-cell lymphomas: a spectrum of presentations with overlap with other cytotoxic lymphomas. Am J Surg Pathol. 2012; 36(11): 1656–1665. [PubMed: 23073324]
61. Toro JR, Liewehr DJ, Pabby N, et al. Gamma-delta T-cell phenotype is associated with significantly decreased survival in cutaneous T-cell lymphoma. Blood. 2003; 101(9):3407–3412. [PubMed: 12522013]
62. Quintanilla-Martinez L, Kumar S, Fend F, et al. Fulminant EBV(+) T-cell lymphoproliferative disorder following acute/chronic EBV infection: a distinct clinicopathologic syndrome. Blood. 2000; 96(2):443–451. [PubMed: 10887104]
63. Quintanilla-Martinez L, Ridaura C, Nagl F, et al. Hydroa vacciniforme-like lymphoma: a chronic EBV+ lymphoproliferative disorder with risk to develop a systemic lymphoma. Blood. 2013; 122(18):3101–3110. [PubMed: 23982171]
64. Yang Y-Q, Fan L, Wang L, et al. Systemic lymphoma arising from hydroa vacciniforme-like lymphoma: report of two cases with review of literature. Int J Clin Exp Pathol. 2014; 7(9):6403–6408. [PubMed: 25337300]
65. Loughran TP Jr. Clonal diseases of large granular lymphocytes. Blood. 1993; 82(1):1–14. [PubMed: 8324214]
66. Sokol L, Loughran TP Jr. Large granular lymphocyte leukemia. Oncologist. 2006; 11(3):263–273. [PubMed: 16549811]
67. Zhang D, Loughran TP Jr. Large granular lymphocytic leukemia: molecular pathogenesis, clinical manifestations, and treatment. Hematol Am Soc Hematol Educ Program. 2012; 2012:652–659.
68•. Koskela HL, Eldfors S, Ellonen P, et al. Somatic STAT3 mutations in large granular lymphocytic leukemia. N Engl J Med. 2012; 366(20):1905–1913. Identification of STAT3 and mutations in T-cell large granular lymphocytic leukemia. [PubMed: 22591296]
69. Jerez A, Clemente MJ, Makishima H, et al. STAT3 mutations unify the pathogenesis of chronic lymphoproliferative disorders of NK cells and T-cell large granular lymphocyte leukemia. Blood. 2012; 120(15):3048–3057. [PubMed: 22859607]
70. Rajala HL, Eldfors S, Kuusanmäki H, et al. Discovery of somatic STAT5b mutations in large granular lymphocytic leukemia. Blood. 2013; 121(22):4541–4550. [PubMed: 23596048]
71. Nicolae A, Xi L, Pittaluga S, et al. Frequent STAT5B mutations in gammadelta hepatosplenic T-cell lymphomas. Leukemia. 2014; 28(11):2244–2248. [PubMed: 24947020]
72. Loughran TP Jr, Zickl L, Olson TL, et al. Immunosuppressive therapy of LGL leukemia: prospective multicenter phase II study by the Eastern Cooperative Oncology Group (E5998). Leukemia. 2015; 29(4):886–894. [PubMed: 25306898]
73. Diehl V, Sextro M, Franklin J, et al. Clinical presentation, course, and prognostic factors in lymphocyte-predominant Hodgkin's disease and lymphocyte-rich classical Hodgkin's disease: report from the European Task Force on Lymphoma Project on Lymphocyte-Predominant Hodgkin's Disease. J Clin Oncol. 1999; 17(3):776–783. [PubMed: 10071266]

74. Shimabukuro-Vornhagen A, Haverkamp H, Engert A, et al. Lymphocyte-rich classical Hodgkin's lymphoma: clinical presentation and treatment outcome in 100 patients treated within German Hodgkin's Study Group trials. J Clin Oncol. 2005; 23(24):5739–5745. [PubMed: 16009944]

75. Nam-Cha SH, Montes-Moreno S, Salcedo MT, et al. Lymphocyte-rich classical Hodgkin's lymphoma: distinctive tumor and microenvironment markers. Mod Pathol. 2009; 22(8):1006–1015. [PubMed: 19465900]

76. Savage KJ, Mottok A, Fanale M. Nodular lymphocyte-predominant Hodgkin lymphoma. Semin Hematol. 2016; 53(3):190–202. [PubMed: 27496311]

77. Hansmann ML, Stein H, Dallenbach F, et al. Diffuse lymphocyte-predominant Hodgkin's disease (diffuse paragranuloma). A variant of the B-cell-derived nodular type. Am J Pathol. 1991; 138(1): 29–36. [PubMed: 1987769]

78. Braeuninger A, Küppers R, Strickler JG, et al. Hodgkin and Reed– Sternberg cells in lymphocyte predominant Hodgkin disease represent clonal populations of germinal center-derived tumor B cells. Proc Natl Acad Sci U S A. 1997; 94(17):9337–9342. [PubMed: 9256483]

79. Nicholas DS, Harris S, Wright DH. Lymphocyte predominance Hodgkin's disease – an immunohistochemical study. Histopathology. 1990; 16(2):157–165. [PubMed: 2323737]

80. Fan Z, Natkunam Y, Bair E, et al. Characterization of variant patterns of nodular lymphocyte predominant Hodgkin lymphoma with immunohistologic and clinical correlation. Am J Surg Pathol. 2003; 27(10):1346–1356. [PubMed: 14508396]

81•. Hartmann S, Eichenauer DA, Plütschow A, et al. The prognostic impact of variant histology in nodular lymphocyte-predominant Hodgkin lymphoma: a report from the German Hodgkin Study Group (GHSG). Blood. 2013; 122(26):4246–4252. Analysis of the relationship between variant histologic patterns and outcome in nodular lymphocyte predominant Hodgkin lymphoma. [PubMed: 24100447]

82. Rüdiger T, Gascoyne RD, Jaffe ES, et al. Workshop on the relationship between nodular lymphocyte predominant Hodgkin's lymphoma and T cell/histiocyte-rich B cell lymphoma. Ann Oncol. 2002; 13(Suppl 1):44–51.

83. Boudová L, Torlakovic E, Delabie J, et al. Nodular lymphocyte-predominant Hodgkin lymphoma with nodules resembling T-cell/histiocyte-rich B-cell lymphoma: differential diagnosis between nodular lymphocyte-predominant Hodgkin lymphoma and T-cell/histiocyte-rich B-cell lymphoma. Blood. 2003; 102(10):3753–3758. [PubMed: 12881319]

84. Hartmann S, Döring C, Vucic E, et al. Array comparative genomic hybridization reveals similarities between nodular lymphocyte predominant Hodgkin lymphoma and T cell/histiocyte rich large B cell lymphoma. Br J Haematol. 2015; 169(3):415–422. [PubMed: 25644177]

85. Xing KH, Connors JM, Lai A, et al. Advanced-stage nodular lymphocyte predominant Hodgkin lymphoma compared with classical Hodgkin lymphoma: a matched pair outcome analysis. Blood. 2014; 123(23):3567–3573. [PubMed: 24713929]

86. Hartmann S, Döring C, Jakobus C. Nodular lymphocyte predominant Hodgkin lymphoma and T cell/histiocyte rich large B cell lymphoma – endpoints of a spectrum of one disease? PLoS One. 2013; 8(11):e78812. [PubMed: 24244368]

87. Advani RH, Horning SJ, Hoppe RT, et al. Mature results of a phase II study of rituximab therapy for nodular lymphocyte-predominant Hodgkin lymphoma. J Clin Oncol. 2014; 32(9):912–918. [PubMed: 24516013]

88. Ratei R, Hummel M, Anagnostopoulos I, et al. Common clonal origin of an acute B-lymphoblastic leukemia and a Langerhans' cell sarcoma: evidence for hematopoietic plasticity. Haematologica. 2010; 95(9):1461–1466. [PubMed: 20421277]

89. Chen W, Jaffe R, Zhang L, et al. Langerhans cell sarcoma arising from chronic lymphocytic lymphoma/small lymphocytic leukemia: lineage analysis and BRAF V600E mutation study. N Am J Med Sci. 2013; 5(6):386–391. [PubMed: 23923114]

90. Shao H, Xi L, Raffeld M, et al. Clonally related histiocytic/dendritic cell sarcoma and chronic lymphocytic leukemia/small lymphocytic lymphoma: a study of seven cases. Mod Pathol. 2011; 24(11):1421–1432. [PubMed: 21666687]

91•. Feldman AL, Arber DA, Pittaluga S, et al. Clonally related follicular lymphomas and histiocytic/dendritic cell sarcomas: evidence for transdifferentiation of the follicular lymphoma clone.

Blood. 2008; 111(12):5433–5439. Description of clonal relationships between some histiocytic and dendritic cell neoplasms and underlying lymphomas. [PubMed: 18272816]

92. Stoecker MM, Wang E. Histiocytic/dendritic cell transformation of B-cell neoplasms: pathologic evidence of lineage conversion in differentiated hematolymphoid malignancies. Arch Pathol Lab Med. 2013; 137(6):865–870. [PubMed: 23721279]
93. Feldman AL, Minniti C, Santi M, et al. Histiocytic sarcoma after acute lymphoblastic leukaemia: a common clonal origin. Lancet Oncol. 2004; 5(4):248–250. [PubMed: 15050956]
94. Feldman AL, Berthold F, Arceci R, et al. Clonal relationship between precursor T-lymphoblastic leukaemia/lymphoma and Langerhans-cell histiocytosis. Lancet Oncol. 2005; 6(6):435–437. [PubMed: 15925822]
95. West DS, Dogan A, Quint PS, et al. Clonally related follicular lymphomas and langerhans cell neoplasms: expanding the spectrum of transdifferentiation. Am J Surg Pathol. 2013; 37(7):978–986. [PubMed: 23759932]
96. Diamond EL, Dagna L, Hyman DM, et al. Consensus guidelines for the diagnosis and clinical management of Erdheim–Chester disease. Blood. 2014; 124(4):483–492. [PubMed: 24850756]
97. Laurencikas E, Gavhed D, Stålemark H, et al. Incidence and pattern of radiological central nervous system Langerhans cell histiocytosis in children: a population based study. Pediatr Blood Cancer. 2011; 56(2):250–257. [PubMed: 21157893]
98. Hefti F, Jundt G. Langerhans cell histiocytosis. Orthopade. 1995; 24(1):73–81. [PubMed: 7892011]
99. Arnaud L, Hervier B, Néel A, et al. CNS involvement and treatment with interferon-alpha are independent prognostic factors in Erdheim–Chester disease: a multicenter survival analysis of 53 patients. Blood. 2011; 117(10):2778–2782. [PubMed: 21239701]
100. Haroche J, Arnaud L, Cohen-Aubart F, et al. Erdheim–Chester disease. Curr Rheumatol Rep. 2014; 16(4):412. [PubMed: 24532298]
101. Karcioglu ZA, Sharara N, Boles TL, et al. Orbital xanthogranuloma: clinical and morphologic features in eight patients. Ophthal Plast Reconstr Surg. 2003; 19(5):372–381.
102. Pautas E, Chérin P, Pelletier S, et al. Cerebral Erdheim–Chester disease: report of two cases with progressive cerebellar syndrome with dentate abnormalities on magnetic resonance imaging. J Neurol Neurosurg Psychiatry. 1998; 65(4):597–599. [PubMed: 9771797]
103. Killu AM, Liang JJ, Jaffe AS. Erdheim–Chester disease with cardiac involvement successfully treated with anakinra. Int J Cardiol. 2013; 167(5):e115–e117. [PubMed: 23659884]
104. Arnaud L, Pierre I, Beigelman-Aubry C, et al. Pulmonary involvement in Erdheim–Chester disease: a single-center study of thirty-four patients and a review of the literature. Arthritis Rheum. 2010; 62(11):3504–3512. [PubMed: 20662053]
105. Arnaud L, Gorochov G, Charlotte F, et al. Systemic perturbation of cytokine and chemokine networks in Erdheim–Chester disease: a single-center series of 37 patients. Blood. 2011; 117(10): 2783–2790. [PubMed: 21205927]
106. Steňová E, Steňo B, Povinec P, et al. FDG-PET in the Erdheim– Chester disease: its diagnostic and follow-up role. Rheumatol Int. 2012; 32(3):675–678. [PubMed: 21136259]
107. Braiteh F, Boxrud C, Esmaeli B, et al. Successful treatment of Erdheim–Chester disease, a non-Langerhans-cell histiocytosis, with interferon-alpha. Blood. 2005; 106(9):2992–2994. [PubMed: 16020507]
108•. Hervier B, Haroche J, Arnaud L, et al. Association of both Langerhans cell histiocytosis and Erdheim–Chester disease linked to the BRAFV600E mutation. Blood. 2014; 124(7):1119–1126. Identification of BRAF mutations in histiocytic neoplasms. [PubMed: 24894769]
109. Go H, Jeon YK, Huh J, et al. Frequent detection of BRAF(V600E) mutations in histiocytic and dendritic cell neoplasms. Histopathology. 2014; 65(2):261–272. [PubMed: 24720374]
110. Diamond EL, Durham BH, Haroche J, et al. Diverse and targetable kinase alterations drive histiocytic neoplasms. Cancer Discov. 2016; 6(2):154–165. [PubMed: 26566875]
111. Haroche J, Cohen-Aubart F, Emile J-F, et al. Dramatic efficacy of vemurafenib in both multisystemic and refractory Erdheim–Chester disease and Langerhans cell histiocytosis harboring the BRAF V600E mutation. Blood. 2013; 121(9):1495–1500. [PubMed: 23258922]

Key issues

- The 2016 revision of the World Health Organization classification of lymphoid neoplasms includes several critical changes in the classification of T-cell non-Hodgkin lymphomas, Hodgkin lymphomas, and histiocytic/dendritic cell neoplasms that have immediate impact on diagnosis, prognosis, management, and entry criteria for clinical research protocols.
- ALK-negative anaplastic large cell lymphoma has been upgraded to a definite entity, in which genetic markers may have prognostic significance; breast implant-associated cases are considered separately.
- T-cell lymphomas of T follicular helper cell origin share common clinical, pathological, and genetic features and are grouped in a new umbrella category containing 3 distinct entities.
- The classification of T-cell lymphomas of the gastrointestinal tract has been reorganized, and includes an indolent T-cell lymphoproliferative disorder as a new provisional entity.

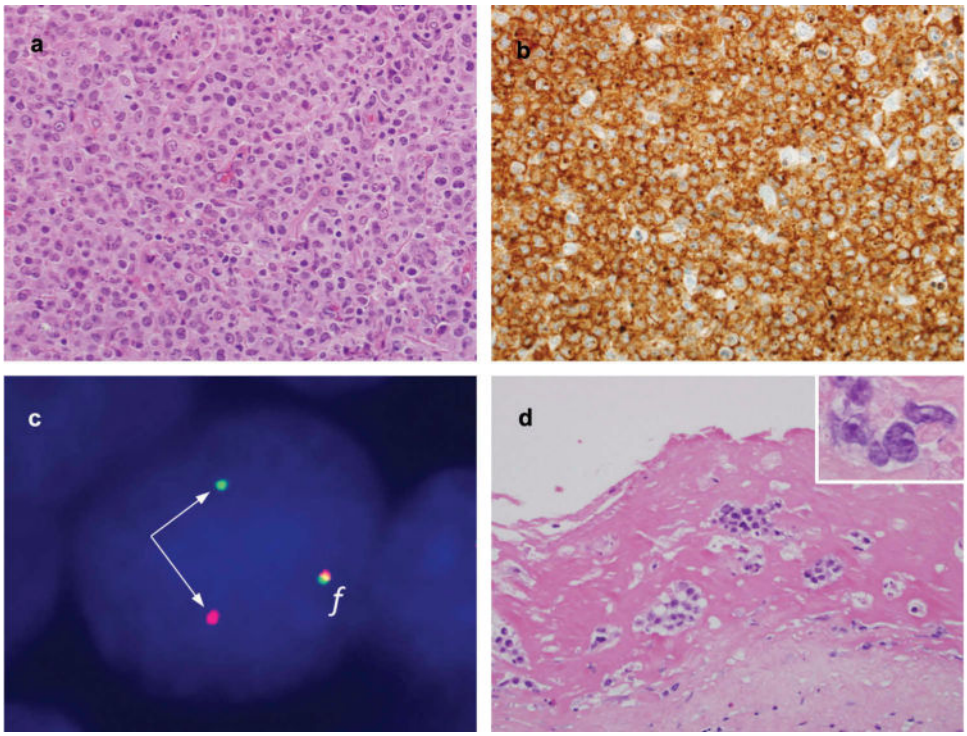

Figure 1.

Systemic and localized ALK-negative anaplastic large cell lymphomas. (a) Systemic ALK-negative anaplastic large cell lymphoma. H&E stain of a lymph node section shows sheets of neoplastic cells. (b) The tumor cells stain strongly and uniformly for CD30 by immunohistochemistry. (c) Fluorescence *in situ* hybridization showed this case to have a *DUSP22* rearrangement, a finding that has been associated with favorable prognosis. The image shows a single tumor cell nucleus (blue). Hybridization with red and green breakapart probes flanking the *DUSP22-IRF4* locus on 6p25.3 show one normal fusion signal (*f*) and abnormal separation of the red and green signals corresponding to the other allele (arrows), indicating a chromosomal rearrangement. (d) Breast implant-associated anaplastic large cell lymphoma involving the seroma cavity and fibrous capsule surrounding a breast implant. H&E stain shows clusters of cells that have pleomorphic nuclear features (inset; high magnification). Full color available online.

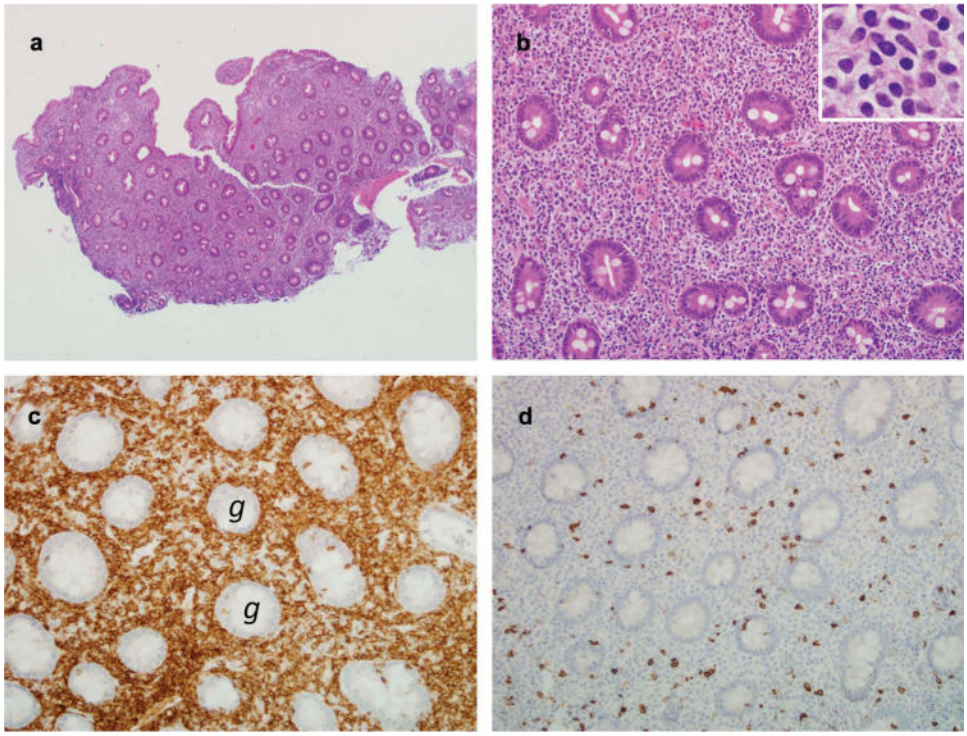

Figure 2.

Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract. (a) Low-power H&E image of fragments of mucosa from an endoscopic duodenal biopsy. (b) A higher power H&E image shows an infiltrate of small lymphocytes with bland cytological features (inset). (c) Nearly all the lymphocytes stain for CD4 by immunohistochemistry, and leave the intervening glands (*g*) relatively unaffected. (d) Staining for CD8 shows only occasional scattered cells. The T cells were shown to be clonal by molecular studies (not shown). This CD4-positive phenotype is less common than a CD8-positive phenotype in this disorder [53].

Table 1

Clinical significance of major 2016 World Health Organization changes for primarily nodal mature T-cell neoplasms.

Disease	Changes	Significance
ALK-negative ALCL	Upgraded from provisional to definite entity	• Must be distinguished both from ALK-positive ALCL and from localized forms of disease, including pcALCL and BIA-ALCL
	Genetic subgroups recognized	• Rearrangements involving *DUSP22-IRF4* on 6p25.3 associated with favorable outcome
	BIA-ALCL	• New provisional entity distinct from systemic ALK-negative ALCL occurring around breast implants • Infiltrative form has more aggressive clinical behavior
T-cell lymphomas of TFH origin	Nodal T-cell lymphoma with TFH phenotype	• New provisional entity for cases with TFH phenotype but not meeting criteria for AITL • Previously would have been classified as PTCL, NOS • Mutational spectrum overlapping other TFH entities
	Follicular T-cell lymphoma	• New provisional entity for cases with TFH phenotype and follicular pattern of involvement • Previously would have been classified as PTCL, NOS • Mutational spectrum overlapping other TFH entities
PTCL, NOS	Remains a ‘wastebasket’ diagnosis for mature T-cell neoplasms not meeting criteria for other, more specific entities	• Subgroups based on GATA3 and TBX21 expression may have clinical significance

AITL: angioimmunoblastic T-cell lymphoma; ALCL: anaplastic large-cell lymphoma; ALK: anaplastic lymphoma kinase; BIA-ALCL: breast implant-associated ALCL; pcALCL: primary cutaneous ALCL; PTCL: peripheral T-cell lymphoma; NOS: not otherwise specified; TFH: T-follicular helper.

Table 2

Clinical significance of major 2016 World Health Organization changes for primarily extranodal and leukemic mature T-cell neoplasms.

Disease	Changes	Significance
T-cell lymphomas of the GI tract	EATL	• Nomenclature to be used only for cases previously called type I EATL (usually associated with celiac disease)
	MEITL	• New nomenclature for non-celiac disease-associated cases previously called type II EATL
	Indolent TLPD of the GI tract	• New provisional entity with indolent clinical behavior • Occasionally may progress
Cutaneous T-cell lymphomas	Primary cutaneous CD4-positive small/medium TLPD	• Name changed from lymphoma to TLPD to reflect indolent behavior
	Primary cutaneous acral CD8-positive T-cell lymphoma	• New provisional entity with indolent clinical behavior • Most common involves ear
	Primary cutaneous γδ T-cell lymphoma	• Excludes cases with γδ T-cell phenotype meeting criteria for other entities such as MF or LyP
EBV-positive NK-/T-cell neoplasms	Systemic EBV-positive T-cell lymphoma of childhood	• Name changed from TLPD to lymphoma to reflect aggressive clinical behavior
	Hydroa vacciniforme-like lymphoproliferative disorder	• Name changed from lymphoma to lymphoproliferative disorder to reflect wide spectrum of clinical behavior

EATL: enteropathy-associated T-cell lymphoma; GI: gastrointestinal; LyP: lymphomatoid papulosis; MEITL: monomorphic epitheliotropic intestinal T-cell lymphoma; MF: mycosis fungoides; TLPD: T-cell lymphoproliferative disorder; EBV: Epstein–Barr virus; NK: natural killer.

Table 3

Clinical significance of major 2016 World Health Organization changes for Hodgkin lymphomas and histiocytic/dendritic cell neoplasms.

Disease	Changes	Significance
Hodgkin lymphomas	LRCHL	• Recognition of features intermediate between CHL and NLPHL
	NLPHL	• Histologic pattern (A–F) should be specified when known; variant patterns associated with more aggressive behavior
		• Cases with THRLBCL-like features should be called THRLBCL-like transformation of NLPHL to distinguish from true THRLBCL
HDC neoplasms	ECD	• Should be distinguished from JXG based on clinical features
		• Recurrent *BRAF* V600E mutations identified
	All subtypes	• Occasional clonal relationship with underlying lymphoid neoplasm

CHL: classical Hodgkin lymphoma; ECD: Erdheim–Chester disease; HDC: histiocytic/dendritic cell; LRCHL: lymphocyte-rich CHL; NLPHL: nodular lymphocyte-predominant Hodgkin lymphoma; THRLBCL: T-cell/histiocyte-rich large B-cell lymphoma; JXG: juvenile xanthogranuloma.