Pathobiology of nodal peripheral T-cell lymphomas: current understanding and future directions

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Abstract

Predominantly nodal is the most common clinical presentation of peripheral T- (and NK-) cell lymphomas (PTCL), which comprise three main groups of diseases: (i) systemic anaplastic large cell lymphomas (ALCL), whether positive or negative for anaplastic lymphoma kinase (ALK); (ii) follicular helper T-cell lymphomas (TFHL); and (iii) PTCL, not otherwise specified (NOS). Recent advances in the genomic and molecular characterization of PTCL, with enhanced understanding of pathobiology, have translated into significant updates in the latest 2022 classifications of lymphomas. ALK-negative ALCL is now recognized to be genetically heterogeneous, with identification of *DUSP22* rearrangements in approximately 20-30% of cases, correlated with distinctive pathological and biological features. The notion of cell-of-origin as an important determinant of the classification of nodal PTCL is best exemplified by TFHL, considered as one disease or a group of related entities, sharing oncogenic pathways with frequent recurrent epigenetic mutations as well as a relationship to clonal hematopoiesis. Data are emerging to support that a similar cell-of-origin concept might be relevant to characterize meaningful subgroups within PTCL, NOS, based on cytotoxic and/or Th1 *versus* Th2 signatures. The small group of primary nodal Epstein-Barr virus-positive lymphomas of T- or NK-cell derivation, formerly considered PTCL, NOS, is now classified separately, due to distinctive features, and notably an aggressive course. This review summarizes current knowledge of the pathology and biology of nodal-based PTCL entities, with an emphasis on recent findings and underlying oncogenic mechanisms.

Introduction

Peripheral T-cell lymphomas (PTCL) collectively refer to neoplasms of mature NK or T cells. They constitute approximately 10% of all lymphomas in the Western world and up to 20% in Asia. PTCL exhibit significant clinical and biological diversity, leading to the recognition of over 30 distinct entities in the latest classification proposals.[1,2] These entities can be categorized into three groups based on their typical clinical presentation: involvement of lymph nodes, skin and other extranodal organs, or dissemination/leukemic manifestations. This clinical grouping reflects, to some extent, the distinct cell of origin for each entity, characterized by specific functional, homing, or trafficking properties, as well as varying oncogenic mechanisms. The nodal-based PTCL entities represent the large majority of PTCL cases. They include anaplastic large cell lymphomas (ALCL), categorized as positive or negative for anaplastic lymphoma kinase (ALK^+ and ALK^-, respectively), lymphomas originating from T-follicular helper (TFH) cells, primary nodal Epstein-Barr virus (EBV)-associated PTCL, and PTCL, not otherwise specified (PTCL, NOS) (Figure 1, Tables 1 and 2).

The two proposed classifications emanated in 2022, the International Consensus Classification (ICC) of mature lymphoid neoplasms[1] and the 5th edition of the World Health Organization classification of lymphoid neoplasms (WHO-HAEM5),[2] represent updates of the former 2017 revised 4th edition of the World Health Organization classification (WHO-HAEM4R),[3] and both maintain the principle of a multiparametric definition of lymphoma entities adopted since 1994. Morphology, immunophenotype, genetic and clinical features as well as the putative normal cellular counterpart are all taken into account for the classification. Research advances elucidating the genomic landscape and molecular characterization of many PTCL, in addition to enhanced understanding of the pathobiology and pathogen-

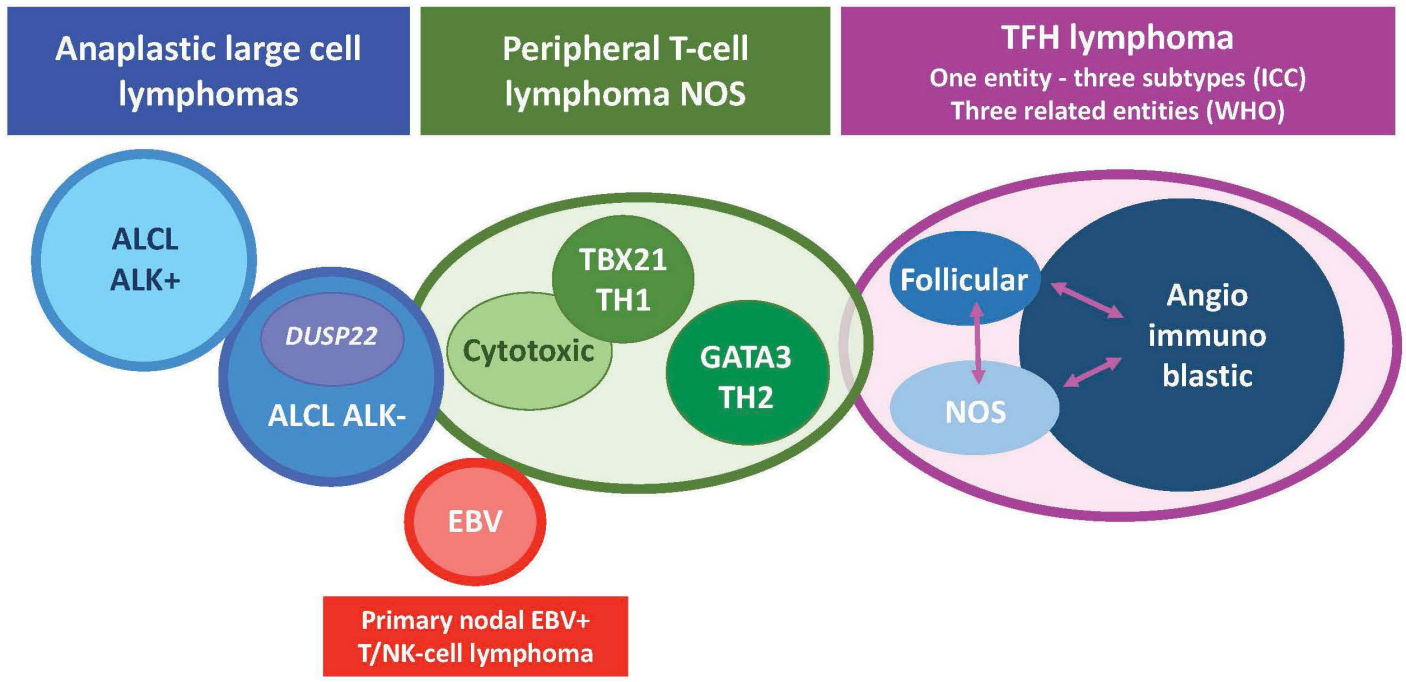

Figure 1. Representation of nodal T- and NK-cell lymphoma entities according to the 2022 classifications. NOS: not otherwise specified; TFH: T follicular helper cell; ICC: International Consensus Classification; WHO: World Health Organization; ALCL: anaplastic large cell lymphoma; ALK: anaplastic lymphoma kinase; EBV: Epstein-Barr virus.

esis with information derived from both clinical and experimental models, have translated into significant updates in both classifications. The main adjustments and changes introduced in both proposals reflect similar conceptual shifts. Here, we present a review of our current knowledge of the pathology and biology of nodal-based PTCL, the understanding of oncogenic mechanisms, and discuss future directions.

Anaplastic large cell lymphomas

ALCL encompass four entities having in common large pleomorphic tumor cells with strong expression of CD30, but being distinct in their pathogenesis, clinical presentation and outcome. The two systemic entities, ALK$^+$ and ALK$^-$ ALCL, most often present as nodal-based disease and are considered nodal PTCL, but may show the involvement of a variety of extranodal sites. The other two ALCL entities are extranodal and site-specific. Although not a nodal PTCL entity, breast implant-associated (BIA)-ALCL is described here to highlight both overlapping and distinguishing features compared with ALK$^-$ ALCL, and the fact that it may disseminate to lymph nodes.[4] Primary cutaneous ALCL (ALK$^-$), classified with other primary cutaneous CD30$^+$ T-cell lymphoproliferative disorders, is not included in this review.[1,2]

The classification and diagnostic criteria of ALCL entities is essentially identical in the two 2022 classifications (Table 1). Provisional in WHO-HAEM4R, BIA-ALCL is now a definitive entity. Among ALK$^-$ ALCL, *DUSP22*-rearranged (*DUSP22*-R) cases constitute a distinct genetic subtype according to the ICC 2022, but not in WHO-HAEM5, as discussed below.[1,2]

Anaplastic large cell lymphomas, ALK-positive

In ALK$^+$ ALCL, there is aberrant expression of the ALK protein secondary to rearrangements involving the *ALK* gene.[3] ALK$^+$ ALCL accounts for 7-9% of (non-cutaneous) PTCL worldwide,[5,6] most commonly affects young male patients (median age, 30-35 years), but may occur at any age including in children.[7,8] ALK$^+$ ALCL usually presents at an advanced stage, and frequently involves lymph nodes and/or various extranodal sites, including bone, skin and lung.[7,8] Rare cases, mostly of the small cell variant, present as leukemia.[9] ALK$^+$ ALCL has the most favorable prognosis among systemic PTCL, with a long-term overall survival reaching 70-90% in adults and up to 95% in children. This is in part related to the younger age at diagnosis.[6-8]

ALK$^+$ ALCL comprises several morphological variants,[10] all containing “hallmark cells”, with a large, often kidney-shaped nucleus, abundant cytoplasm and a prominent Golgi zone, although in variable proportions.[3] In the classic form (common pattern) (Figure 2A-G), hallmark cells are numerous and form cohesive sheets. Nodal infiltration typically shows an intrasinusoidal growth pattern. The small cell and lymphohistiocytic patterns, which are characterized by smaller hallmark cells with a preferential perivascular distribution and a dominant infiltrate of reactive histiocytes, respectively,[3] are often encountered together, and have been associated with an adverse prognosis in the pediatric population, but not in adults.[11] A rare pattern mimicking nodular sclerosis classic Hodgkin lymphoma (Hodgkin-like pattern) may be diagnostically challenging.[12]

CD30 expression is strong and diffuse in the classic and Hodgkin-like variants, but may be more focal in the other patterns.[3,10] Chimeric ALK protein is by definition expressed, but its subcellular location depends on the translocation partner. The most common t(2;5)(p23;q35) translocation

Table 1. List of nodal mature T and NK-cell neoplasms in the International Consensus Classification (ICC) and the World Health Organization (WHO)-HAEM5 classification (2022) in reference to the WHO-HAEM4R scheme (2017) (adapted from Campo *et al.*[1] and Alaggio *et al.*[2])

WHO-HAEM4R	ICC 2022	WHO-HAEM5
Anaplastic large cell lymphoma, ALK-positive	Anaplastic large cell lymphoma, ALK-positive	ALK-positive anaplastic large cell lymphoma
Anaplastic large cell lymphoma, ALK-negative	Anaplastic large cell lymphoma, ALK-negative	ALK-negative anaplastic large cell lymphoma
Nodal lymphomas of T follicular helper origin	Follicular helper T-cell lymphoma	Nodal T-follicular helper (TFH) cell lymphoma
Angioimmunoblastic T-cell lymphoma	Follicular helper T-cell lymphoma, angio-immunoblastic type (angioimmunoblastic T-cell lymphoma)	Nodal TFH cell lymphoma, angioimmunoblastic type
Follicular T-cell lymphoma	Follicular helper T-cell lymphoma, follicular type	Nodal TFH cell lymphoma, follicular type
Nodal peripheral T-cell lymphoma with T follicular helper phenotype	Follicular helper T-cell lymphoma, NOS	Nodal TFH cell lymphoma, NOS
Not listed as an entity, subtype of peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS)	*Primary nodal EBV⁺ T-cell/NK-cell lymphoma*	EBV⁺ nodal T- and NK-cell lymphoma
Peripheral T-cell lymphoma, NOS	Peripheral T-cell lymphoma, NOS	Peripheral T-cell lymphoma, NOS

The entities are listed according to the order in which they appear in the International Consensus Classification 2022. Italics indicate provisional entities. WHO: World Health Organization; HAEM4R: revised 4th edition of the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues; ICC: International Consensus Classification of lymphoid neoplasms; HAEM5: the 5th edition of the WHO Classification of Lymphoid Neoplasms; ALK: anaplastic lymphoma kinase; TFH: T-follicular helper; PTCL: peripheral T-cell lymphoma; NOS: not otherwise specified; EBV: Epstein-Barr virus.

(80% of the cases) results in a *NPM1::ALK* fusion that shuttles between the nucleus and the cytoplasm, due to the preserved N-terminal portion of NPM1, and is detected by ALK immunohistochemistry in both compartments.[13] With alternative partners, ALK staining may be purely cytoplasmic (e.g., *ATIC::ALK*), membranous (*MSN::ALK*), or both (*TPM3::ALK*).[14,15] Epithelial membrane antigen (EMA) is typically positive and EBV is always negative. The neoplastic cells often show loss of T-cell receptor (TCR) molecules ("null" immunophenotype) and of several T-cell antigens (typically CD3, CD5 and CD7 commonly negative), while CD2, CD4 and CD43 are more frequently preserved. CD8 is usually negative. Cytotoxic markers (granzyme B, perforin, T-cell intracellular antigen 1 [TIA-1]) are generally expressed.[3]

The ALK fusion proteins have constitutive tyrosine kinase activity which activates multiple signaling cascades involved in oncogenesis, including the JAK-STAT3 pathway.[15,16] Accordingly, nuclear phospho-STAT3 (pSTAT3) is detected by immunohistochemistry in nearly all cases.[16,17] In relation to the crucial driver role of ALK fusions, ALK inhibitors have demonstrated high response rates in pediatric and young adult patients with relapsed/refractory ALK⁺ ALCL.[8] Nevertheless, as for *ALK*-rearranged lung carcinomas, mechanisms of resistance may develop, including acquired *ALK* mutations.[18]

Mutational profiling of ALK⁺ ALCL has revealed *NOTCH1* mutations in 20% of the cases. NOTCH1 expression is also induced via STAT3 activation mediated by the ALK fusion protein. In line with these observations, inhibition of the NOTCH1 pathway by γ-secretase inhibitors is effective *in vitro* and a promising treatment target to be further explored.[19] Other recurrently mutated genes in ALK⁺ ALCL include *LRP1B* (19%) and *TP53* (11%), as well as epigenetic modifier genes such as *EP300, KMT2C* and *KMT2D*. *TP53* mutations have been associated with an inferior outcome.[20]

Anaplastic large cell lymphomas, ALK-negative

ALK⁻ ALCL account for 6-15% of PTCL[5,6,21] and occur later in life than ALK⁺ ALCL (median age, 54 years), with a slight male predominance.[21] Most patients present with advanced stage disease, and extranodal sites of involvement (50%) include lung, liver and bone.[7,22] The 5-year overall survival is, as a whole, worse (~50% with CHOP-like chemotherapy) for ALK⁻ ALCL patients than for ALK⁺ patients.[7,21]

The diagnosis of ALK⁻ ALCL requires typical morphology, with hallmark cells identical to the classic form of ALK⁺ ALCL, uniformly strong CD30 expression, negativity for ALK expression or *ALK* rearrangement, and absence of EBV. Tumor cells frequently show loss of T-cell antigens,

Table 2. Usual features of the main nodal peripheral T-cell lymphoma entities.

PTCL entities	Immunophenotype	Cell of origin	Genes altered, cytogenetic features
TFH lymphoma Small to medium atypical neoplastic cells with clear cytoplasm and often prominent polymorphous environment	CD4⁺; TFH cell markers (BCL6, CD279 [PD1], ICOS, CXCL13, CD10); expanded CD21⁺ follicular dendritic cell meshworks in angioimmunoblastic type; CD20⁺ B immunoblasts, often EBV⁺	CD4 TFH cell	*TET2, DNMT3A, IDH2, RHOA, CD28, FYN, LCK, PLCG1, VAV1*
ALCL, ALK-positive Large pleomorphic cells, cohesive	CD30⁺, ALK⁺, often extensive loss of pan-T-cell antigens, frequently cytotoxic (TIA-1, granzyme B, perforin), EBV⁻	CD4 αβ T cell	*ALK* fusions *NOTCH1, TP53*
ALCL, ALK-negative Large pleomorphic cells, cohesive	CD30⁺, ALK⁻, variable expression of pan-T-cell antigens and of cytotoxic markers (TIA-1, granzyme B, perforin), EBV⁻	CD4 αβ T cell	*JAK1, JAK3, STAT3, MSC* Rearrangements: *DUSP22, TP63, JAK2*
PTCL, NOS Variable cytology of the neoplastic cells and variable microenvironment	Variable	CD4 > CD8, αβ > γδ, Th1 or Th2 subsets	*TP53, PRDM1, TET1, TET3, DNMT3A, ATM, PTEN, RB1*…
Primary nodal EBV⁺ T/NK-cell lymphoma Large cells, monomorphic, no angiocentricity	EBV⁺, CD8⁺ and CD56⁻, cytotoxic (TIA-1, granzyme B, perforin)	CD8 T cell > NK cell	*TET2, PIK3CD, STAT3*

PTCL: peripheral T-cell lymphoma; TFH: T follicular helper; EBV: Epstein-Barr virus; ALCL: anaplastic large cell lymphoma; ALK: anaplastic lymphoma kinase; TIA-1: T-cell intracellular antigen 1; NOS: not otherwise specified.

EMA expression and a cytotoxic phenotype, although not as consistently as observed in ALK⁺ ALCL.[3] Approximately half of all ALK⁻ ALCL express nuclear pSTAT3, as a consequence of translocations or mutations that lead to constitutive JAK-STAT3 activation, including *JAK1* and/or *STAT3* mutations in 20-30% of the samples.[20,22-24] *TP53* mutations are observed in 23% of the cases, and an inferior outcome has been reported for ALK⁻ ALCL with *TP53* or *STAT3* mutations.[20]

Beyond these shared features, the last decade has brought new data that highlight the genetic heterogeneity of ALK⁻ ALCL, with the identification of recurrent structural aberrations, some of which may influence the clinical outcome. The largest genetic subgroup (20-30% of ALK⁻ ALCL) is characterized by the presence of a rearrangement in the *DUSP22* gene,[22,25,26] which induces the downregulation of dual specificity phosphatase, thus preventing its inhibitory effect on various signaling pathways. *DUSP22*-R ALK⁻ ALCL have distinctive biological features, including lack of JAK-STAT3 activation, widespread DNA hypomethylation, expression of the cancer-testis antigens and an immunogenic phenotype.[24] One-third of cases have a musculin (*MSC*) hotspot mutation (E116K), which promotes the CD30–IRF4–MYC axis.[27] *DUSP22*-R ALK⁻ ALCL (Figure 2H-N) frequently demonstrate doughnut-shaped nuclei and, compared to *DUSP22* non-rearranged (NR) cases, are more frequently CD3⁺ but less commonly express EMA and cytotoxic molecules.[22,25,26] Conversely, strong and uniform nuclear expression of lymphoid enhancer binding factor 1 (LEF1) is highly associated with *DUSP22*-R.[28] Clinically, the *DUSP22*-R subgroup has been the subject of a number of recent studies with somewhat disparate results (5-year overall survival: 40%-100%; 5-year progression-free survival: 40-57%), but, although study sizes still remain small, collectively it appears to have a more favorable prognosis, intermediate between ALK⁺ ALCL and *DUSP22*-NR ALK⁻ ALCL.[22,25,26,29] Consequently, *DUSP22*-R ALCL is now considered a genetic subtype among ALK⁻ ALCL in the ICC 2022 – which recommends fluorescence *in situ* hybridization testing if available –, but not in the WHO-HAEM5 classification due to uncertainties around prognosis.[1,2]

The presence of a *TP63*-R characterizes a smaller genetic subgroup of ALK⁻ ALCL, accounting for 2-8% of cases and associated with an adverse prognosis.[25,26,30] A few cases with *JAK2*-R have been described, featuring Reed-Sternberg-like cells in an inflammatory background with eosinophilia, reminiscent of classic Hodgkin lymphoma.[31] A Hodgkin-like morphology has also been observed in a subset of cases expressing truncated *ERBB4* transcripts.[32]

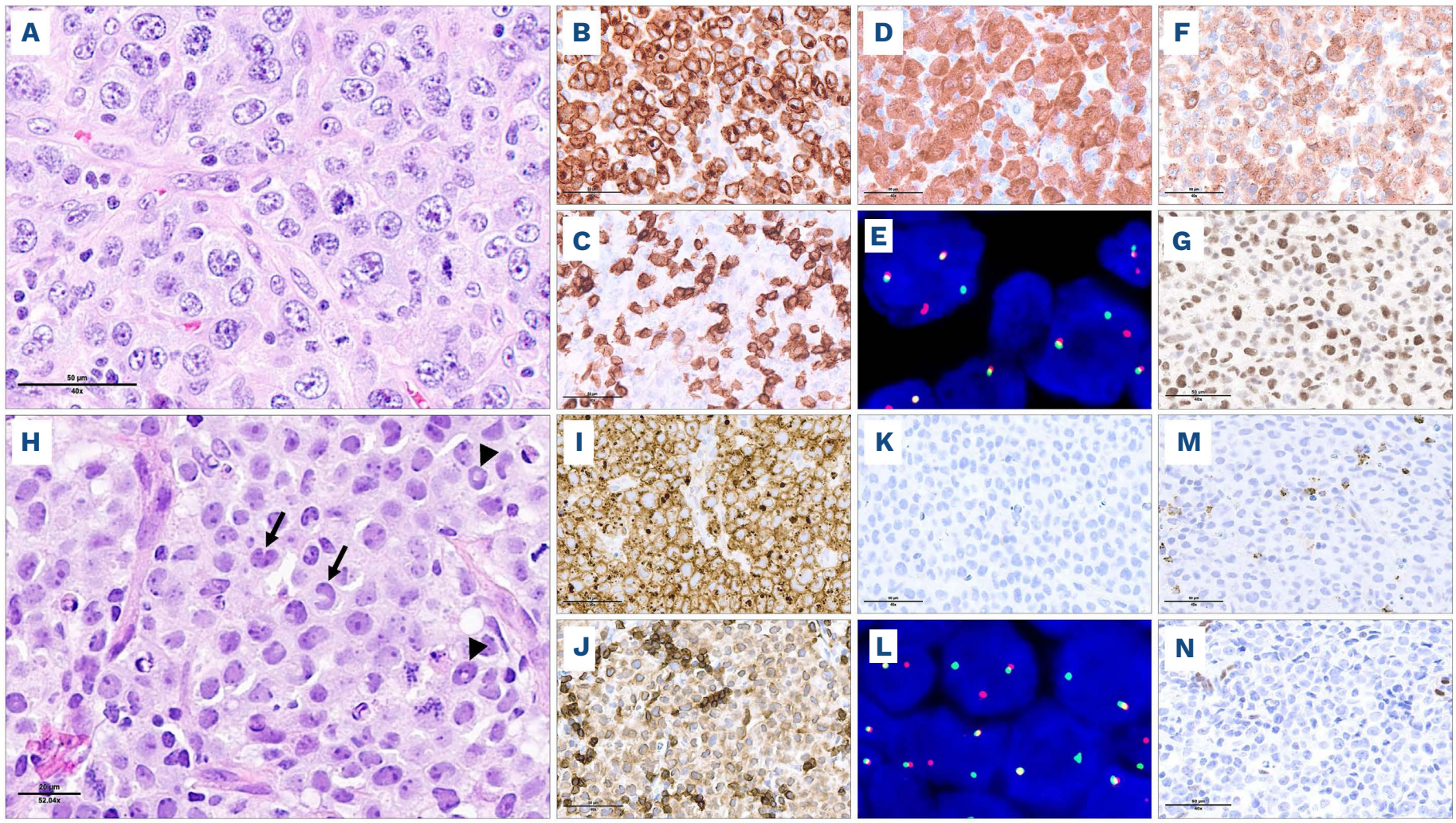

Figure 2. Nodal involvement by systemic anaplastic large cell lymphoma. (A-G) Anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL), classic pattern. This case comprises cohesive sheets of large pleomorphic cells (A, hematoxylin & eosin), shows diffuse strong expression of CD30 (B) and loss of several T-cell antigens including CD3 (C). Nuclear and cytoplasmic expression of ALK protein (D) is indicative of a *NPM1::ALK* fusion. An *ALK* gene rearrangement can be confirmed by break-apart fluorescence *in situ* hybridization (FISH) (E, the rearranged *ALK* allele is represented by split red and green signals). The cells are positive for cytotoxic markers (F, perforin) and nuclear phospho-STAT3 (G). (H-N) ALK-negative ALCL with *DUSP22* rearrangement. This case comprises cohesive sheets of neoplastic cells, including kidney-shaped hallmark cells (H, hematoxylin & eosin, arrows) and cells with doughnut-shaped nuclei (H, arrowheads). The cells are strongly CD30-positive (I), weakly positive for CD3 (J), and ALK-negative (K). Break-apart FISH shows a *DUSP22* locus rearrangement (L, the rearranged *DUSP22* allele is represented by split red and green signals). The cells are negative for cytotoxic markers (M, T-cell intracellular antigen 1 [TIA-1]) and phospho-STAT3 (N).

Other gene fusions reported in ALK⁻ ALCL involve the tyrosine kinase domain of *FRK*, *ROS1* or *TYK2*.[23,33] Nevertheless, these cases represent very small and heterogeneous subsets of patients, and further data are needed before stratifying *DUSP22*-NR ALK⁻ ALCL into further genetic subtypes.

Breast implant-associated anaplastic large cell lymphoma

BIA-ALCL is a rare complication of textured breast implants, with a median of 9 years from implantation to diagnosis, and generally an excellent prognosis.[34] Recent data suggest that germline *BRCA1* or *BRCA2* mutations represent a risk factor for developing BIA-ALCL.[35]

Most often, BIA-ALCL occurs as a peri-prosthetic effusion and is diagnosed on cytological samples.[36] In surgical capsulectomies, lymphoma cell deposits are found along the inner surface of the capsule. In the infiltrative forms, tumor cells extend into the capsule and rarely may form a mass.[36] Regional lymph node involvement may occur, typically with low tumor burden with sinusoidal and perifollicular growth patterns.[37]

Although BIA-ALCL resembles systemic ALK⁻ ALCL morphologically and immunophenotypically,[36] it develops in a peculiar confined microenvironment, in which bacterial infection, chronic inflammation and hypoxia are believed to be distinctive pathogenic determinants.[38] The genetic aberrations acquired in this setting and transformation mechanisms partially overlap with those of systemic ALK⁻ ALCL. The JAK-STAT3 pathway appears to be consistently activated, either by mutations (in 60-90% of cases, most frequently *STAT3* and *JAK1*) or by other mechanisms, as witnessed by the constant pSTAT3 expression.[39] In contrast, *DUSP22* and *TP63* rearrangements have not been found in BIA-ALCL.[34,40] Furthermore, loss of 20q13.13, detected by shallow whole-genome sequencing in 66% of cases in one series, is reportedly highly characteristic of BIA-ALCL

compared to systemic ALK$^+$ or ALK$^-$ ALCL.[38] Other recurrent alterations involve epigenetic modifiers, with frequent mutations in *KMT2C*, *CHD2*, *CREBBP* and *KMT2D* (up to 75% of cases), while *TET2* and *DNMT3A* mutations, typically observed in TFH lymphomas, are uncommonly detected.[39] Altogether, the unique clinical association, peculiar pathogenic background and distinctive pathobiological features of BIA-ALCL support its classification as a separate entity.

Follicular helper T-cell lymphoma

T follicular helper (TFH) cells represent a functional subset of CD4$^+$ lymphocytes that are necessary for the formation and maintenance of germinal centers, interacting with germinal center B cells and aiding their differentiation.[41] In 2007, immunophenotyping and gene expression profiling analyses identified the TFH cell as the cell of origin of angioimmunoblastic T-cell lymphoma (AITL),[42] and this specific cellular derivation has become a cardinal defining feature of the disease. In practice, a TFH phenotype is evaluated by immunohistochemistry by the expression of PD1, ICOS, CXCL13, CD10 and BCL6, which are markers of normal TFH cells, with at least any two positive required for the definition.[3] In 2017, the developing concept that TFH cell derivation represents a unifying feature of a larger group of nodal CD4$^+$ T-cell lymphomas led to the creation of an umbrella term "nodal T-cell lymphoma of T follicular helper origin" to encompass AITL, follicular T-cell lymphoma, and nodal PTCL with a TFH phenotype.[3] The grouping was supported by the fact that these three entities also share a similar genetic landscape, characterized by recurrent mutations in epigenetic modifier genes, *RHOA* and other TCR signaling genes.[42-48] Identification of a TFH phenotype might also be relevant to treatment decisions.[4,49] Therefore the ICC considers one single disease entity, namely follicular helper T-cell lymphoma, with three subtypes, angioimmunoblastic, follicular and NOS (Table 3).[50] This entity by definition applies to CD4$^+$ PTCL, implies significant expression of TFH markers, and excludes primary cutaneous CD4$^+$ T-cell lymphoproliferative disorders with a TFH phenotype. The WHO-HAEM5 proposal considers a family of three related entities of nodal T-follicular helper cell lymphomas, angioimmunoblastic-type, follicular-type and NOS types. Collectively, TFH lymphoma(s) outnumber(s) PTCL, NOS in recent epidemiological studies.[5,51,52]

Follicular helper T-cell lymphoma, angioimmunoblastic type

AITL is the prototypic and most frequent subtype of TFH lymphoma.[42] It manifests as a systemic disease in adults, usually in the elderly. Patients present with generalized lymphadenopathy, often with extranodal involvement (e.g., skin, tonsil, liver, spleen,...), systemic symptoms, and various immune abnormalities. The median survival is <3 years, but a subset of patients experience long-term survival.[53]

Histologically (Figure 3A-F) (for a review, see de Leval *et al.*[54]), AITL comprises a polymorphous infiltrate including variable proportions of neoplastic T cells, typically outnumbered by reactive small lymphocytes, histiocytes, im-

Table 3. Comparison of the three subtypes of follicular helper T-cell lymphoma.

Follicular helper T-cell lymphoma	Angoimmunoblastic type	Follicular type	Not otherwise specified
Epidemiology	Frequent, often accompanied by general symptoms and biological abnormalities	Very rare	20% of PTCL, NOS
Pattern of growth and FDC distribution	Diffuse with FDC expansion OR perifollicular without FDC expansion	Follicular lymphoma-like OR PTGC-like (with IgD$^+$ B cells) FDC restricted to follicles	Diffuse and no FDC expansion OR T-zone pattern No/minimal FDC expansion
Microenvironment	Abundant, polymorphous	Minimal (FL-like) - B cells (PTGC-like)	Minimal
Vascular proliferation	Abundant	Absent or minimal	Absent or minimal
EBV$^{+/-}$ B-cell blasts	Typically present	Often present	May be present
TFH phenotype	Several TFH markers	Several TFH markers, strong	At least 2 (ideally 3) TFH markers

PTCL: peripheral T-cell lymphoma; NOS: not otherwise specified; FDC: follicular dendritic cells; PTGC: progressive transformation of germinal centers; FL: follicular lymphoma; EBV: Epstein-Barr virus; TFH: T follicular helper cell.

munoblasts, eosinophils and plasma cells. The neoplastic lymphoid cells are usually small to medium-sized, with moderately abundant, clear cytoplasm, but may lack significant atypia. Some cases may contain a larger proportion of neoplastic cells or large cells with abundant, clear cytoplasm. Large B-cell immunoblasts, sometimes resembling Hodgkin and Reed-Sternberg cells, represent a typical component of AITL; they are usually scattered, but sometimes numerous. Some cases rich in histiocytes may resemble lymphoepithelioid (Lennert) lymphoma. Plasma cells may be abundant, and some patients may even present with peripheral blood plasmacytosis. A stromal component is typically present, consisting of a marked proliferation of arborizing high endothelial venules, and abnormal extrafollicular expansion of follicular dendritic cells (FDC) best demonstrated by CD21 or CD23 immunostaining. The lymphoproliferation is usually diffuse (pattern III). In less common instances AITL is associated with hyperplastic or regressive follicles (patterns I and II). Transitions between different patterns have been observed in consecutive biopsies, and a combination of patterns may be seen at one time. Patterns I and II correspond to lower tumor cell burden reflecting partial nodal involvement, but do not correlate with lower stage disease.[54-56] Two studies found that a subset of AITL enriched in a B-cell signature was associated with a better outcome,[57,58] and interestingly the favorable significance of a B-cell signature was also found in PTCL, NOS in another study.[59]

The neoplastic cells of AITL consist of mature $CD3^+$ $CD4^+$ $CD8^-$ $TCR\alpha\beta^+$ cells. An aberrant T-cell immunophenotype (most commonly reduced or absent surface CD3, CD5 or CD7) is frequently observed, especially by flow cytometry. The neoplastic cells express several TFH markers, including the CXCL13 chemokine; PD1 (CD279), ICOS, CD10 and CD200 membrane receptors; and BCL6 and cMAF transcription factors.[60,61] Overall, PD1 and ICOS are more sensitive for identifying the neoplastic TFH cells than CXCL13 or CD10, which are more specific.[56] Aberrant co-expression of CD20 and/or partial expression of CD30 by the neoplastic cells is not unusual.[62,63] Reactive $CD8^+$ cells are variably abundant and may outnumber the $CD4^+$ neoplastic cells.[64] The large B-cell immunoblasts are positive for CD20, PAX5 and CD79a, often CD30, and may also sometimes co-express CD15. They are usually, but not always, infected by EBV (positive for EBV-encoded RNA [EBER] and latent membrane protein 1 [LMP-1]).[65] The spectrum of B-cell-derived expansions in AITL also comprises EBV^- large B-cell proliferations, and polytypic (or sometimes monotypic) plasma cell expansions. Up to one-third of cases, particularly those with an increased number of B cells, harbor (oligo)clonal rearrangements of the immunoglobulin genes (IG), in addition to monoclonal or oligoclonal T-cell receptor gene (TR) rearrangements. Some patients develop secondary large B-cell lymphomas.[66]

Most cases demonstrate a characteristic mutational landscape that recapitulates a multi-step oncogenic process derived from underlying clonal hematopoiesis (Figure 4).[67] The profile of AITL alterations typically consists of epigenetic deregulation (*TET2* +/- *DNMT3A* mutations, occurring at early stages in hematopoietic progenitors, present in about 80% and 30-35% of the cases, respectively),[44,46] and second-hit mutations with a more restricted distribution.[68] *TET2* and *DNMT3A* mutations are inactivating, *TET2* mutations are often multiple (2 or 3), and alterations in both genes tend to co-occur. Their global effect is DNA hypermethylation. *DNMT3A* mutations were found in one study associated with a shorter progression-free survival,[69] and in an experimental mouse model of AITL generated by *TET2* inactivation and *RHOA* G17V, addition of *DNMT3A* R882H accelerated the development of the disease.[70] Second-hit mutations include a hotspot *RHOA* G17V mutation encoding a dominant negative variant of the protein in up to 70% of cases, and other gain-of-function mutations targeting the TCR pathway (*PLCG1, CD28, FYN, PIK3* components, *CARD11*, etc.).[45,47,71] RNA fusions involving *CD28* with *ICOS* or rarely *CTLA4*, mutually exclusive with *CD28* mutations, are detected in a small subset of patients.[72] Mouse models have shown that *RHOA* G17V induces TFH differentiation and autoimmunity, and promotes lymphomagenesis in the presence of *TET2* inactivation, indicating the synergistic effect of both mutations.[73-75] AITL harboring the *RHOA* G17V mutation tend to have higher microvessel density, more FDC proliferation and a more pronounced TFH immunophenotype compared to wild-type cases, but no prognostic significance was observed.[76,77] One study showed that sensitive *RHOA* G17V mutation analysis may be valuable for the early diagnosis of TFH lymphoma, as this alteration may be found prior to conclusive histopathological changes.[78] *IDH2* point mutations at the R172 residue, present in about one-third of cases,[79,80] modify IDH2 enzymatic activity resulting in the production of an oncometabolite (2 hydroxyglutarate) ultimately altering DNA and histone methylation.[80,81] *IDH2*-mutated AITL has a characteristic morphology with prominent medium-sized to large clear cells (Figure 3G-H), and tends to show strong CD10 and CXCL13 expression.[82] In an AITL mouse model driven by *IDH2* and *TET2* mutations, the tumors show abundant angiogenesis and plasma cells, and the malignant TFH cells display aberrant transcriptomic and epigenetic programs that impair TCR signaling and alter cross-talk with germinal center B cells, promoting B-cell clonal expansion while decreasing the Fas-FasL interaction and reducing B-cell apoptosis.[83] Gains of chromosomes 5 and 21 are frequent, especially in *IDH2*-mutated cases, and copy number losses in genes regulating the PI3K-AKT-mTOR pathway are enriched in *IDH2*-wild-type cases.[84]

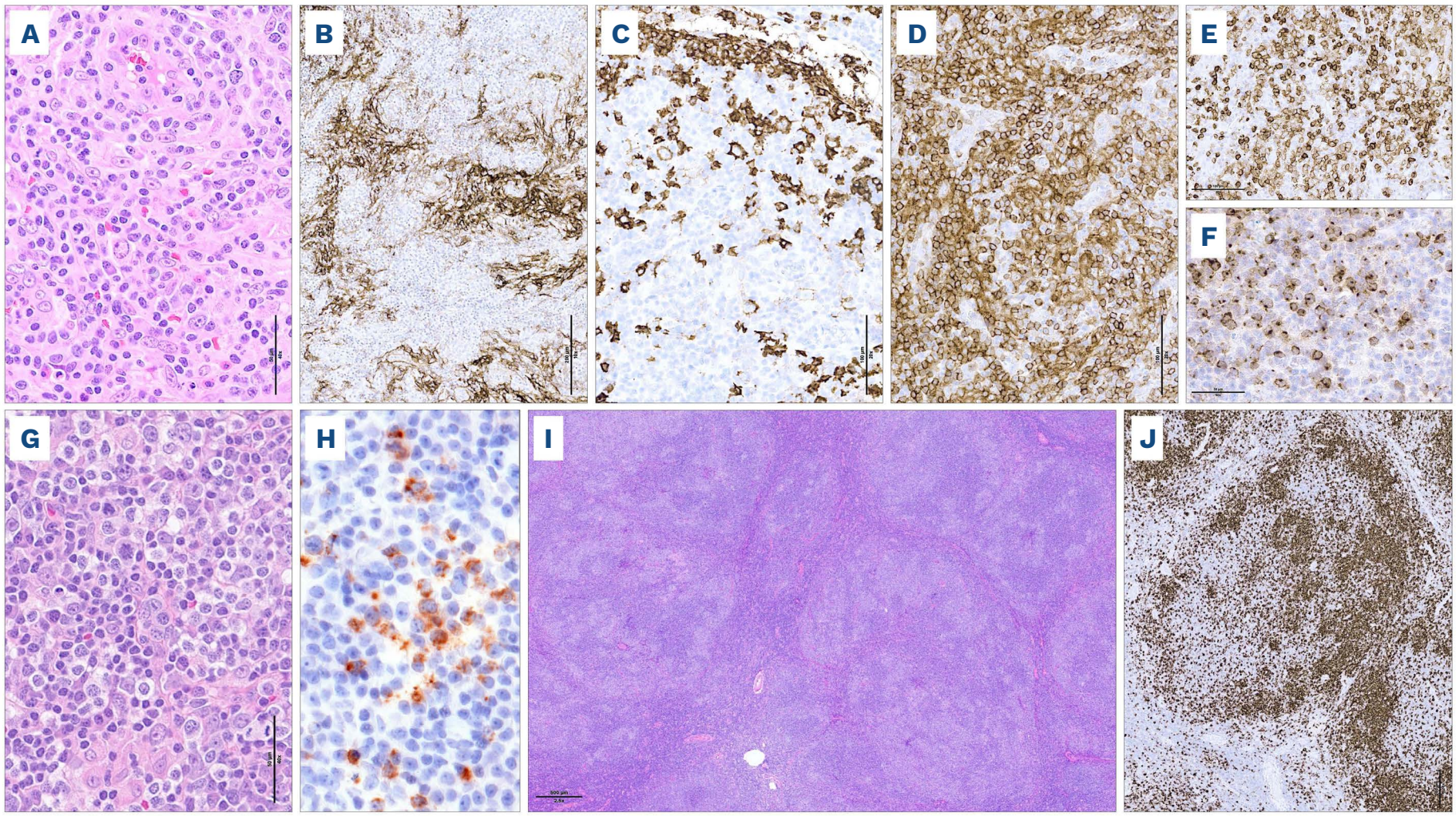

Figure 3. Follicular helper T-cell lymphoma. (A-H) Follicular helper T-cell (TFH) lymphoma, angioimmunoblastic type comprises a polymorphous cellular infiltrate and prominent venules (A, hematoxylin & eosin); immunostains show an irregular proliferation of follicular dendritic cell meshworks (B, CD21), aggregates of small B cells and scattered large blasts positive for CD20 (C), a diffuse infiltrate of CD4$^+$ cells (D), which are positive for TFH markers (E, PD1 and F, CXCL13). In *IDH2*-mutated cases (G, H), large cells with abundant clear cytoplasm are prominent (G, hematoxylin & eosin), and expression of the *IDH2* R172K variant is highlighted by immunohistochemistry (H). (I, J) TFH lymphoma, follicular type is characterized by large nodules resembling progressive transformation of germinal centers at low magnification (I, hematoxylin & eosin), and TFH markers demonstrate aggregates of pale neoplastic cells (J, ICOS).

Detailed genetic analyses of AITL have shown that these lymphomas may contain one or multiple clonal TR gene rearrangements associated with the same *TET2* mutation(s), indicating parallel neoplastic evolution from a common *TET2*-mutant hematopoietic progenitor pool. A biased *TRBV* usage was also found, suggesting the role of antigenic stimulation in promoting T cells to clonal expansion and malignant transformation.[85] Moreover, the study of microdissected T- and B-cell populations has shown that *TET2* mutations of AITL clones are frequently present in the B cells as well, indicating that clonal hematopoiesis also generates a large population of mutated mature B cells and, while *RHOA* and *IDH2* mutations are confined to the T-cell compartment, other mutations, notably in *NOTCH1*, may be identified in the B cells, providing an explanation for the frequently associated B-cell expansions in AITL (Figure 4).[86,87] Clonal hematopoiesis appears to be the source of the observed association with myeloid neoplasms in certain patients[88] and the increased incidence of myeloid neoplasms after TFH lymphoma-directed therapy, through divergent clonal evolution (Figure 4).[4,67]

Follicular helper T-cell lymphoma, follicular type

This least common subtype of TFH lymphoma presents either a truly follicular pattern, mimicking follicular lymphoma (FL-like), or more commonly a pattern resembling progressive transformation of germinal centers (PTGC-like). In FL-like cases, nodular aggregates of neoplastic cells are sustained by a meshwork of FDC. In PTGC-like cases (Figure 3I, J), pale aggregates of medium-sized atypical T cells are distributed within expanded mantle zones in large nodules mostly composed of small IgD$^+$ B cells.[43,89] TFH lymphoma, follicular type lacks both the extrafollicular expansion of FDC and the proliferation of high endothelial venules characteristic of AITL. The clinical presenting features overlap with those of AITL.[89,90] A subset of patients has long-term survival despite sometimes multiple relapses and the prognosis might be slightly better than that of AITL.[89,90]

The neoplastic cells are CD3$^+$ CD4$^+$ and usually show extensive positivity for most TFH markers (PD1, ICOS, CXCL13, BCL6, CD10, and sometimes CD57).[89,91] In one study most cases had at least partial expression of CD30 in the neoplastic cells.[91] A component of large blastic EBV$^+$ or EBV$^-$ B

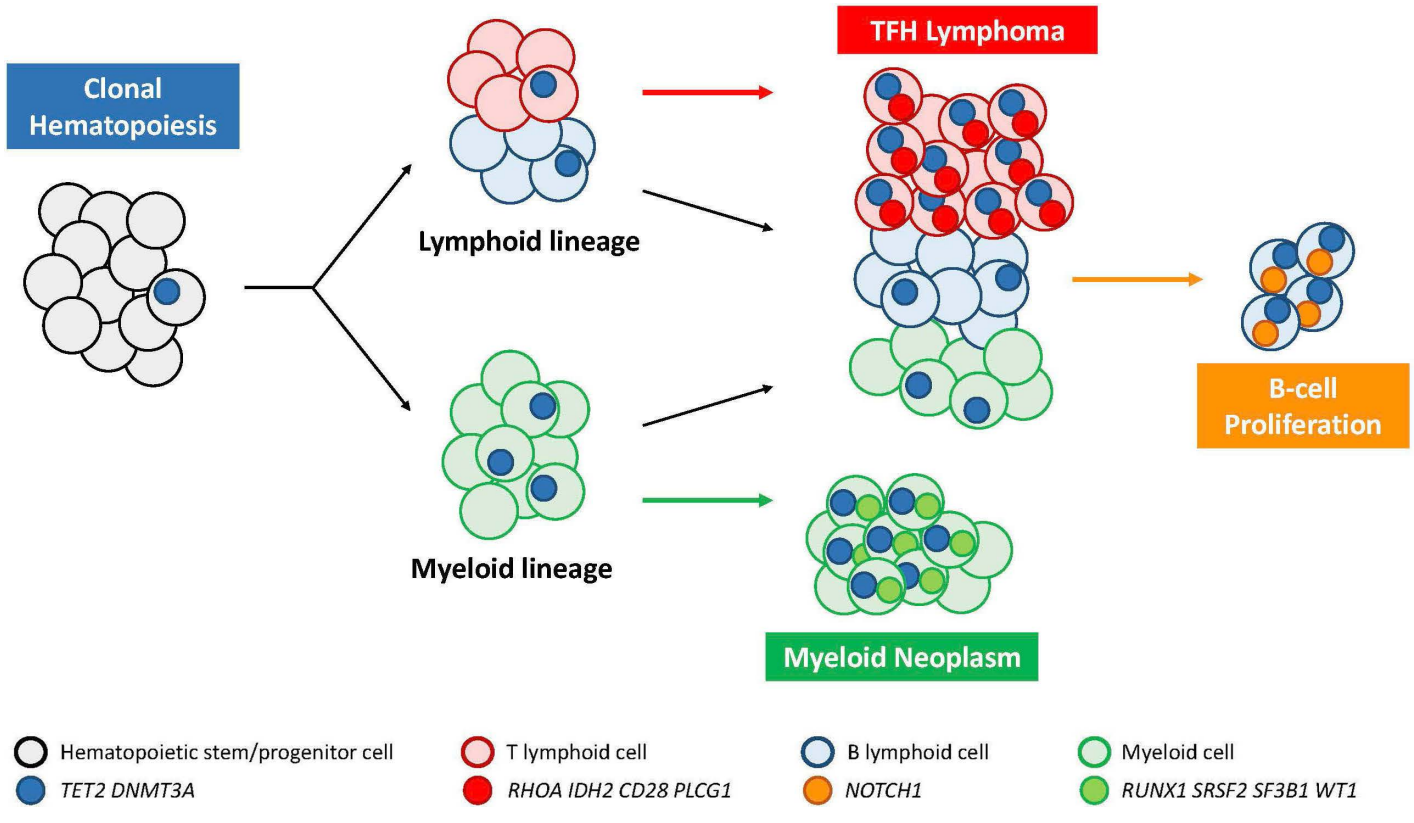

Figure 4. Oncogenic model of follicular helper T-cell lymphoma in relationship to clonal hematopoiesis. TFH: follicular helper T-cell

cells is often identified, frequently with Reed-Sternberg-like morphology and immunophenotype.[65,89,91-93] The t(5;9)(q33;q22) translocation, resulting in an *ITK::SYK* fusion, is found in about 20% of the follicular type, and has been reported thus far in only one case of typical AITL.[89,94] Based on limited data, the mutational pattern of follicular PTCL appears otherwise to overlap with that of AITL.[48]

Follicular helper T-cell lymphoma, not otherwise specified

TFH lymphoma, NOS, formerly nodal T-cell lymphoma with a T follicular helper phenotype,[3] encompasses cases without specific pathological features, but showing imprints of the TFH signature and/or expression of TFH markers, and/or cases exhibiting some characteristics of AITL (e.g., increased vascularity, presence of EBV$^+$ B-blasts).[42,44] According to the WHO-HAEM4R, qualification for a TFH lymphoma required the expression of at least two or ideally three TFH markers (among the 5 recommended for routine testing: PD1, ICOS, CD10, BCL6, CXCL13) by the neoplastic cells, in addition to CD4.[3] This criterion is retained in the current proposals (Table 3). Some cases show perifollicular involvement and may mimic marginal zone lymphoma.[56] A subset of cases may present as what was previously called the "T-zone variant" of PTCL, NOS, in which there is preserved architecture with residual sometimes hyperplastic B-cell follicles, and interfollicular lymphomatous involvement.[95] Since FDC proliferation is generally considered as a typical hallmark of AITL, cases with some FDC expansion are better qualified as tumor-cellrich AITL, but the border between PTCL-TFH and AITL is not well delineated, likely reflecting a biological continuum.[48,56] The genetic background of TFH lymphoma, NOS overlaps with that of AITL, including frequent mutations in *TET2* and *DNMT3A* but less frequent *RHOA* mutations and infrequent *IDH2* mutations.[44-47,58] According to limited data available, the outcome related to TFH lymphoma, NOS, is similar to that of TFH lymphoma of the angioimmunoblastic type but larger studies are needed.[48,96]

Primary nodal Epstein-Barr virus-positive T/NK-cell lymphoma

Primary EBV$^+$ nodal T-cell or NK-cell lymphoma was introduced in the WHO-HAEM4R as a variant of PTCL, NOS.[3] In the light of novel data confirming its distinctive features from extranodal EBV$^+$ NK/T-cell lymphoma, nasal type (ENKTCL), and supporting specific characteristics, this rare disease is a new entity in the 2022 classifications, with slightly different nomenclatures (Table 1).[1,2]

Most cases were described in reports from Asia.[97-99] Primary nodal EBV$^+$ T/NK-cell lymphoma involves lymph nodes and tends to occur in elderly adults who present with generalized lymphadenopathy, frequent dissemination to the liver or spleen but lack of nasal involvement, sometimes in association with human immunodeficiency virus infection or immunodeficient conditions.[56,100] The outcome of patients with primary nodal EBV$^+$ T/NK-cell lymphoma is dismal, being significantly worse than that of patients with ENKTCL or PTCL, NOS.[101] Pathological features distinct from ENKTCL include a usually monomorphic large cell morphology, lack of prominent angiocentricity or necrosis, negativity for CD56, positivity for CD8, and more frequent derivation from T cells than

from NK cells.[100,102] The lymphoma cells are CD3$^+$ CD5$^{-/+}$ with an activated cytotoxic phenotype, with EBV detected in the majority of tumor cells by *in situ* hybridization or expression of LMP-1.

Most cases are of T-cell lineage, carry clonally rearranged TR genes associated with 14q11.2 loss, and variably express the TCR.[100] Compared with ENKTCL, primary nodal EBV$^+$ T/NK-cell lymphoma is characterized by low genomic instability, upregulation of immune pathways (checkpoint protein PD-L1) that promote immune evasion, and downregulation of EBV microRNA.[101] Few cases have been investigated by high-throughput sequencing; recurrent mutations have been found in *TET2, DNMT3A, STAT3, PIK3CD* and *DDX3X*.[101,102]

Peripheral T-cell lymphoma, not otherwise specified

PTCL, NOS remains defined as a diagnosis of exclusion for those cases of PTCL lacking specific features that qualify for another "specific" PTCL entity. While the definition is unchanged from the previous WHO classifications, subsets of cases formerly included in PTCL, NOS, such as those expressing a TFH phenotype or positive for EBV, are now classified into distinct entities, and therefore the boundaries of PTCL, NOS are narrowing.[1-3] Accordingly, while PTCL, NOS has for decades been reported as the most frequent type of PTCL,[6] in recent years the reported prevalence of PTCL, NOS is tending to decrease, accounting for 21-27% of PTCL.[5,51,52]

PTCL, NOS nearly always affects adults.[103,104] The presentation is usually nodal, with frequent concurrent extranodal involvement, especially of the skin. Most patients have disseminated disease, constitutional symptoms, intermediate- to high-risk International Prognostic Index score and sometimes blood eosinophilia.[103] The overall outcome is 20-30% survival at 5 years.[103] A small minority of patients have a preceding lymphoproliferative variant of the hypereosinophilic syndrome[105] or chronic lymphocytic leukemia.[106]

PTCL, NOS is morphologically heterogeneous (Figure 5A-N). Many cases show predominantly medium-sized or large cells with irregular nuclei and prominent nucleoli. Less commonly, others have a predominance of atypical small cells with irregular nuclei.[3] Morphological grading is not recommended for clinical purposes, but tumors with a predominance of large cells have been found to have a worse outcome.[103] Many cases have an admixture of reactive small lymphocytes, eosinophils, histiocytes, B cells and plasma cells. Any of the microenvironmental components can be dominant, obscure the neoplastic cells, and represent a confounding factor to establishing a correct diagnosis. Cases with a prominent infiltrate of epithelioid histiocytes, referred to as lymphoepithelioid lymphoma (Lennert lymphoma), represented less than 10% of PTCL, NOS in historical series and were associated with an overall better prognosis than other PTCL, NOS.[103] In recent years it has turned out that many cases of "Lennert lymphoma" correspond to histiocyte-rich TFH lymphomas.[95,107,108] It is unclear at the present time whether the Lennert/lymphohistiocytic lymphomas remaining categorized as PTCL, NOS, which are often derived from CD8$^+$ cells with a non-activated cytotoxic immunophenotype, should be considered as a distinct subgroup of PTCL, NOS.[109-111]

The neoplastic cells in PTCL, NOS are positive for pan-T-cell antigens (CD3, CD2, CD5, CD7), but one or several of these (most commonly CD5 or CD7) may show reduced or absent expression; they are most commonly CD4$^+$ CD8$^-$, less frequently CD4$^-$ CD8$^+$, uncommonly CD4$^-$ CD8$^-$ or CD4$^+$ CD8$^+$.[110] More than 85% of cases express the αβ TCR, and a minority of cases are either of γδ derivation, or TCR-silent.[112] Loss of BCL2 expression, observed in 45-60% of the cases, can be a useful marker indicative of T-cell malignancy.[113,114] A small proportion of PTCL, NOS (5% or less) express CD20 (or other B-cell markers) in a subset of the neoplastic cells.[115] By definition, the neoplastic cells in CD4$^+$ PTCL, NOS must lack a TFH immunophenotype.[1,2] CD30 expression is frequent (~30%) and variable.[7,62,63] In a study of 141 cases of PTCL, NOS, over 20% of the cases had more than 50% CD30$^+$ tumor cells,[62] and staining extent and intensity were higher in cases with large cell morphology. Strong CD30 expression by a majority of the tumor cells is seen occasionally, and raises the need for a differential diagnosis from ALCL.

PTCL, NOS is usually positive for LEF1,[63] and negative for BCL6, FOXP3 and TCL1 transcription factors which are, respectively, critical for TFH differentiation and function, related to regulatory T cells, and overexpressed in T-cell prolymphocytic leukemia.[116,117] A few cases of FOXP3$^+$ PTCL, NOS have been described in patients negative for HTLV1 infection; these cases were composed of large cells, some had EBV reactivation in bystander cells and the clinical course was aggressive.[118]

The presence of EBV$^+$ (or EBV$^-$) B cells and plasma cell expansions typical of TFH lymphomas, has been described in PTCL, NOS as well, albeit less frequently; several of these reports, however, antedate the recognition of nodal PTCL of TFH derivation, and therefore their significance is uncertain in the light of the current definition of PTCL, NOS.[119,120]

Conventional cytogenetics and array-based studies have documented many aberrations and complex patterns of imbalances.[121] A whole-genome sequencing study showed that *CDKN2A* and *PTEN* deletions are frequent (46% and 26% of the cases, respectively), and may co-occur; this event is specifically associated with PTCL, NOS and never observed in AITL or ALCL.[122] *CDKN2A* deletions, which were associated with shorter survival in that study, are recurrent

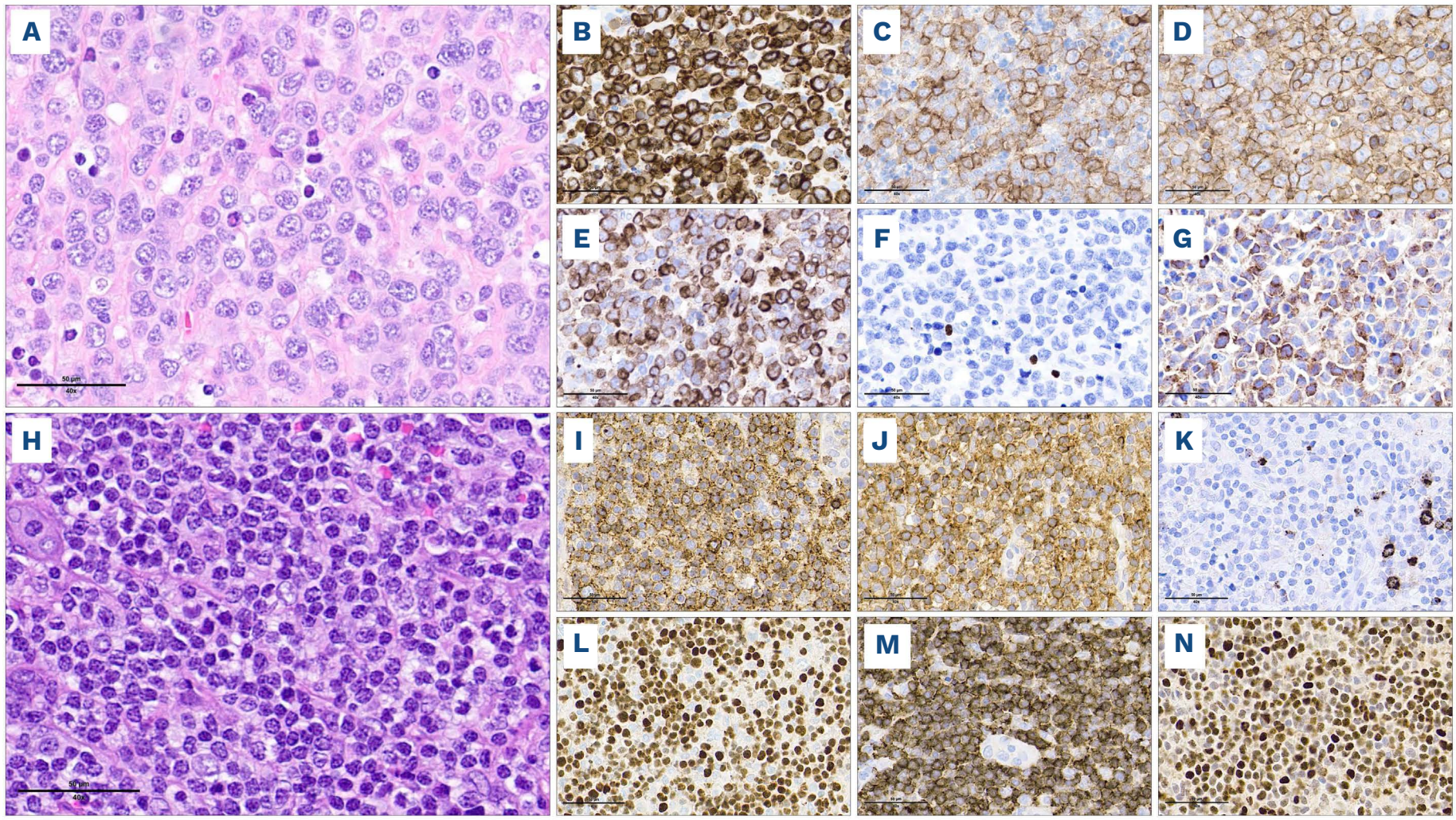

Figure 5. Heterogeneity of peripheral T-cell lymphoma, not otherwise specified. (A-G) Cytotoxic peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS) with large cell morphology and TBX21 (Th1) phenotype. This PTCL, NOS is composed of large pleomorphic cells, with numerous apoptotic bodies (A, hematoxylin & eosin), expresses pan-T-cell markers (B, CD3 and C, CD5), CD4 (D) and cytotoxic markers (E, perforin). Although TBX21 (F) is negative, diffuse expression of CXCR3 (G) subclassifies this lymphoma as PTCL-TBX21. CD30, EBV, GATA3 and CCR4 are also negative (not shown). (H-N) PTCL, NOS with small to medium-sized cells and a GATA3 (Th2) phenotype. This PTCL, NOS comprises diffuse sheets of small to medium-sized cells, with irregular nuclei and occasionally an abundant clear cytoplasm (H, hematoxylin & eosin), is positive for pan-T-cell markers including CD2 (I), and $CD4^+$ (J), and is negative for cytotoxic markers (K, TIA-1). In the absence of TBX21 and CXCR3 expression (not shown), diffuse positivity for GATA3 (L) and CCR4 (M) subclassifies this lymphoma as PTCL-GATA3. P53 protein is diffusely overexpressed (N), reflecting a mutated *TP53* gene status (confirmed by sequencing).

in the GATA3 molecular subgroup of PTCL, NOS (see below).[84]

Few recurrent translocations and several fusion transcripts have been characterized. Overall, their individual prevalence is low, and they are not specific to PTCL, NOS, as they also occur in other entities, in particular ALK^- ALCL and TFH lymphomas.[72,123-125] The t(6;14)(p25;q11.2) involving the *IRF4* locus, has been reported in clinically aggressive cytotoxic PTCL.[126,127] *TP63* rearrangements with *TBL1XR1* or other partner genes, are associated with an aggressive clinical course and bad outcome, as observed in ALK^- ALCL.[30] Fusions involving *VAV1* (*VAV1::MYOF1, VAV1::THAP4, VAV1::S100A7*) result in increased activation of VAV1 effector pathways and the oncogenic properties of *VAV1::MYOF1* were demonstrated in mice *in vivo*.[128] The *FYN::TRAF3IP2* fusion, found in PTCL, NOS and TFH lymphomas, activates the NF-κB pathway.[125,129] Fusions involving *CD28* (*CD28::CTLA4* and *CD28::ICOS*) occur in PTCL, NOS but are more common in TFH lymphomas and adult T-cell leukemia/lymphoma.[72]

PTCL, NOS harbors recurrent mutations in epigenetic modifiers, most often *TET2* or *DNMT3A*,[130] less commonly *SMARCA4* or *KMT2D*, and in genes related to the TCR signaling pathway, notably activating mutations in *PLCG1*, *CD28* and *VAV1*.[71,102,123,131] Mutations in *RHOA* and *IDH2*, recurrent in TFH lymphomas, are essentially absent. Alterations in *TP53* (mutations and/or deletions, often biallelic) are detected in 40% of the cases, and portend an adverse prognostic significance.[84,132] One study found that alterations in *TP53* and/or *CDKN2A* delineate a group of PTCL, NOS characterized by marked genomic instability, mutations in genes related to immune surveillance and immune evasion (*HLA-A, HLA-B, CIITA, CD58, CD274*), mutations in transcriptional and post-transcriptional regulators, and a worse outcome.[132]

As outlined below, research continues into the identification of meaningful subgroups of PTCL, NOS.

Cytotoxic molecule-positive PTCL, NOS. A subset of PTCL, NOS, ranging from 15% to 30-40% of the cases in various series, express one or several cytotoxic granule-associated

molecules (TIA-1 and/or granzyme B and/or perforin) indicative of a resting or more commonly activated cytotoxic immunophenotype.[109,110,133] Of note, most series of cytotoxic PTCL, NOS have been reported from Asia, and often contained EBV$^+$ cases, which are now classified separately (see above).[1,2] In a recently published European cohort of 45 EBV$^-$ nodal cytotoxic PTCL,[102] the disease affected predominantly males at a median age of 60 years and one-fifth of the patients had a previous history of B-cell lymphoma, solid tumor or underlying immune disorder. Besides a primary nodal presentation, most patients had extranodal disease, and the median survival was only 13 months. Comparison with non-cytotoxic PTCL, NOS in another study demonstrated an inferior overall survival for cytotoxic PTCL, NOS.[133] The morphology of these tumors is variable, with predominantly medium-sized to large neoplastic cells and a more or less abundant microenvironment. The neoplastic cells are most commonly CD8$^+$ or CD4$^-$ CD8$^-$, less commonly CD4$^+$ or CD4$^+$ CD8$^+$, and in most cases TCRβF1$^+$ or TCR-silent, rarely TCRγδ$^+$.[102,110,133] PTCL, NOS with a cytotoxic phenotype express Th1-associated markers, TBX21 or CXCR3, accounting for a subset of PTCL-TBX21 with a more aggressive course (see below); they harbor frequent mutations in epigenetic modifiers, notably in *TET2* and *DNMT3A*, recurrent alterations affecting the TCR and JAK/STAT signaling pathways, including fusions involving *VAV1* and *CD28*, and *TP53* mutations in 18% of the cases.[102]

Cell-of-origin subgroups. Earlier studies suggested that subclasses of PTCL, NOS might be delineated by their immunological profile according to the expression markers associated with Th1 (CXCR3, CCR5, CD134/OX40, CD69, T-bet) or Th2 (CCR4, CXCR4, ST2[L]) differentiation.[134,135] These classifiers have not been widely applied due to technical difficulty in assessing the markers, often requiring fresh-frozen tissue, and are lacking validation studies.

Two molecular subgroups of PTCL, NOS, PTCL-TBX21 and PTCL-GATA3, were identified by transcriptome profiling (Table 4), based on signatures similar to those regulated by the transcription factors TBX21 (T-bet) and GATA3, which are master regulators of Th1 and Th2 differentiation pathways, respectively.[136] The TBX21 subgroup shows high expression of TBX21 and its target genes (*CCL3, CXCR3, EOMES, IFNG, ILR2B*), and enrichment of the NF-κB pathway; conversely the GATA3 subgroup is characterized by high expression of GATA3 and its target genes (*CCR4, CXCR7, IL18RA*), high MYC and proliferation signatures.[136] Histologically, PTCL-TBX21 (Figure 5A-G) tends to be polymorphic with a background of reactive inflammatory cells, including cases of lymphoepithelioid (Lennert) lymphoma, while PTCL-GATA3 (Figure 5H-N) tends to lack a prominent inflammatory microenvironment and shows sheets of medium-sized tumor cells with abundant clear cytoplasm or clusters or sheets of large tumor cells.[137] Furthermore, GATA3$^+$ PTCL, NOS and cases with a cytotoxic phenotype (clustered within the TBX21 subgroup) were found to have a worse outcome than non-cytotoxic TBX21$^+$ tumors.[136,138] In addition, subsequent studies showed distinctive genetic features. PTCL-TBX21 has fewer copy number aberrations, and a higher frequency of mutations in epigenetic modifying genes, especially those involved in DNA methylation (*TET1, TET3, and DNMT3A*). PTCL-GATA3 has greater genomic complexity; frequent losses of *TP53, PTEN, RB1, CDKN2A/B*, and *PRDM1*; gains of *STAT3* and *MYC*; and recurrent mutations of *TP53* and *PRDM1*.[84] An immunohisto-

Table 4. Comparison of TBX21 and GATA3 subgroups of peripheral T-cell lymphoma, not otherwise specified.

Feature	TBX21	GATA3
Frequency	50-60% of PTCL, NOS	30-40% of PTCL, NOS
Defining signature	High expression of TBX21 and its target genes (*CCL3, CXCR3, EOMES, IFNG, ILR2B*)	High expression of GATA3 and its target genes (*CCR4, CXCR7, IL18RA*)
Morphology	Polymorphous	Medium-sized to large tumor cells Little environment
Immunohistochemistry	Cytotoxic subset TBX21$^+$ and/or CXCR3$^+$	TBX21$^-$ and CXCR3$^-$ GATA3$^+$ and/or CCR4$^+$
Pathways	Enrichment of the NF-κB pathway	High MYC and proliferation signatures
Genetics	Relatively lower genomic complexity, mutations in epigenetic modifiers frequent	Higher genomic complexity, recurrent *TP53* alterations, *CDKN2A* and *PTEN* deletions
Outcome	Better than GATA3 except for the subset of cytotoxic cases	Worse than TBX21

PTCL: peripheral T-cell lymphoma; NOS: not otherwise specified.

chemical algorithm has been developed as a surrogate to the gene expression profiling-based classification. The algorithm uses four antibodies to TBX21, CXCR3 (a TBX21 transcriptional target), GATA3, and CCR4 (a GATA3 transcriptional target), which are interpreted sequentially.[137] Positivity for TBX21 or CXCR3 in 20% or more of the neoplastic cells defines the TBX21 subgroup (Figure 5A-G). Lymphomas negative or below the threshold for TBX21 markers are classified as GATA3 if 50% or more of the neoplastic cells are GATA3$^+$ or CCR4$^+$ (Figure 5H-N). The GATA3 group identified by immunohistochemistry was similarly associated with an inferior overall survival. Other cases remain unclassified. More recently, a simplified transcriptomic assay based on quantification of 153 selected transcripts dedicated for the molecular diagnosis of the major PTCL entities, including the two subtypes of PTCL, NOS, has been implemented on a digital gene expression profiling platform for routinely processed biopsies.[139] The identification of the TBX21 and GATA3 subgroups currently does not have an impact on frontline clinical management of the patients and it remains unclear whether there is differential sensitivity to novel therapies. Thus, it is still considered a research tool and not currently required in standard diagnostic practice.

Conclusions and future directions

The current schemes for nodal PTCL classification (Figure 1), in continuity with the previous model, emphasize the role of distinct genetic drivers in the definition of PTCL entities or subtypes, and reinforce the concept of cellular derivation being an important determinant of PTCL biology and of clinical relevance. Advances in the genetic characterization of nodal PTCL have added more or less specific defining features of distinct entities (Table 2). Accordingly, genetic testing is increasingly used for diagnostic purposes, and its role as an aid to clinical decision-making is likely to expand in the near future.[140]

Among ALCL, the ALK$^-$ entity is no longer simply "negative for ALK" but a set of genetically distinct subgroups, which require further characterization to assess their clinical and biological relevance. Gray zones remain around the demarcation between CD30$^+$ PTCL, NOS and ALK$^-$ ALCL with, interestingly, some overlap at the genetic level. For example, recurrent *JAK2* rearrangements were recently described in PTCL, which had anaplastic features, sometimes Reed-Sternberg-like cells, frequent CD15 positivity (80%),[31] and had been diagnosed in some cases as CD30$^+$ PTCL, NOS and in other cases as ALK$^-$ ALCL. Features overlap with cases of PTCL, NOS co-expressing CD30 and CD15 reported earlier.[141] While it seems premature to jump to definitive conclusions without collecting additional cases, the question is whether genetics will supersede classic morphological and phenotypic criteria to define ALK$^-$ ALCL boundaries. While there are multiple lines of evidence in support of the concept of TFH lymphoma(s), the consideration of one entity *versus* a group of related disorders differs between the two 2022 classifications, and the distinction between the three types, relying essentially on morphology and immunoarchitecture, may be difficult to apply to a significant fraction of cases showing overlapping features. It is felt that the current definition of the TFH phenotype might be insufficient to capture TFH lymphoma, NOS precisely and distinguish it from PTCL, NOS, and additional criteria, possibly including genetic features, require further research. PTCL, NOS is still viewed as a heterogeneous group of neoplasms that likely do not constitute a single entity, awaiting further identification of meaningful subgroups and substratification. While recent efforts have been made in that direction, and there is growing evidence to substantiate the rationale for molecular or functional subgrouping among PTCL, NOS, there is still a lack of large-scale studies and, at present, these are not recognized as new diagnostic subtypes.

Disclosures

KJS has received honoraria from and provided consulting for BMS, Merck, Seagen, and Janssen; has sat on a steering committee for Beigene; has received research funding from BMS; has received institutional research funding from Roche; and sat on a Data Safety and Monitoring Committee for DSMC. BB and LdeL have no conflicts of interest to disclose.

Contributions

BB and LdL conceived the content of the paper, wrote the manuscript and prepared the figures. KS edited the manuscript.

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