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Peripheral T-cell and NK-cell lymphomas and their mimics; taking a step forward - report on the lymphoma workshop of the XVIth meeting of the European Association for Haematopathology and the Society for Hematopathology

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Abstract

Mature T-cell and T/NK-cell neoplasms are both uncommon and heterogeneous, among the broad category of non-Hodgkin lymphomas. Owing to the lack of specific genetic alterations in the vast majority, most currently defined entities show overlapping morphological and immunophenotypic features, and therefore pose a challenge to the diagnostic pathologist. In the light of recent immunophenotypic, cytogenetic and molecular genetics advances in the field of T-cell and T/NK-cell lymphomas, the focus of the lymphoma workshop of the European Association for Haematopathology/Society for Hematopathology meeting in Lisbon, Portugal, in October 2012 was to refine existing diagnostic criteria and clarify the borders between overlapping entities. The panel reviewed over 200 submitted cases, which were grouped into five categories: (i) angioimmunoblastic T-cell lymphoma and T-follicular-helper-cell-associated lymphomas; (ii) CD30-positive T-cell lymphomas/ lymphoproliferative diseases; (iii) extranodal T-cell and NK-cell neoplasms; (iv) EBV-associated T-cell/NK- cell lymphomas/lymphoproliferative diseases; and (v) peripheral T-cell lymphoma, not otherwise specified, post-transplant lymphoproliferative disorders, and mimics. This report summarizes the discussions and conclusions of the workshop,

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which question current diagnostic criteria and provide recommendations for refining existing classifications.

Introduction

Mature T-cell and T/NK-cell neoplasms comprise a heterogeneous group of diseases that present a challenge for the diagnostic pathologist: they are uncommon, specific genetic alterations have not been identified in most entities, and they often show overlapping morphological and immunophenotypic features.

Mature T-cell and T/NK-cell neoplasms account for <15% of non-Hodgkin lymphomas worldwide. They are more prevalent in Asia and Central and South America, owing to the high incidence of virus-related lymphoproliferations, which are relatively uncommon in the West.[1,2] Except for a few lymphomas that have disease-defining genetic alterations, such as ALK-positive anaplastic large-cell lymphoma (ALCL), most are diagnosed by integrating clinical features (including site of involvement), morphology, immunoprofile and genetic abnormalities that are not entirely specific to a given tumour type. Therefore, although archetypical cases are often straightforward, many show considerable morphological and immunophenotypic overlap between entities, making diagnosis of these uncommon neoplasms very challenging.

In the past few years, genomic techniques have been applied to both normal and neoplastic T cells, leading to the recognition of distinctive functional subsets, such as follicular T-helper cells (T_{FH}), that also have counterparts among the T-cell lympho- mas.[3,4] In addition, advances in DNA sequencing have led to the recognition of recurrent genetic alterations associated with some subsets of T-cell malignancy.[5,6] These new data are leading to reassessment of traditional histological groupings, and offer promise for the recognition of clinically and biologically validated subtypes of T-cell lymphoma in the future.

Angioimmunoblastic T-cell lymphoma (AITL) best exemplifies these advances. AITL has been shown to have the molecular signature and phenotype of T_{FH}, a recently described distinct subset of T cells.[3] Although AITL is the prototype of these T_{FH}-derived neoplasms, there is much debate about its relationship with the follicular variant of peripheral T-cell lymphoma, not otherwise specified, and other peripheral T-cell lymphomas with a T_{FH} phenotype.[7] The identification of recurrent genetic mutations may help to resolve these questions.

ALK-positive ALCL has been clearly defined by the presence of a rearranged *ALK* gene.[2] However, in the absence of a specific genetic marker, the demarcation between ALK-negative ALCL and CD30-positive peripheral T-cell lymphoma, not otherwise specified (PTCL NOS), is less clear. Although the recent demonstration of distinct cytogenetic

abnormalities in a proportion of the former validates classifying it as a distinct entity separate from PTCL NOS, these abnormalities are not universal.[6]

Another area of controversy in recent years has been the relevance of an αβ versus a γδ phenotype in defining T-cell lymphomas in a variety of sites.[8] Other areas of uncertainty include the spectrum of Epstein-Barr virus (EBV)-positive T-cell and NK-cell lymphomas, for which diseases EBV expression is a defining feature, and how many categories should be recognized. Finally, it has become apparent that not all T-cell and NK-cell lymphomas are clinically aggressive, but the criteria for recognizing such cases are not yet fully established. [9] The European Association of Haematopathology (EAHP) recognized the challenges and the recent phenotypic and genetic advances in the field of T-cell lymphoma diagnosis and research, and felt that there was a need to refine diagnostic criteria and clarify the borders between overlapping entities, and also to recognize potentially new entities. Therefore, a call was made for submission of cases for the lymphoma workshop of the XVIth meeting of the EAHP in association with the Society for Hematopathology (SH), Lisbon, 18–25 October 2012, under the title 'Peripheral T- and NK-cell lymphomas and their mimics; taking a step forward'. Over 200 cases were submitted by participants worldwide, including a wide range of mature T-cell and T/NK-cell neoplasms/lymphoproliferations and their mimics. The cases were reviewed prior to the meeting by a panel of haematopathologists, using the submitted clinical and genetic information and available biopsy material. On the basis of this review, all submitted lymphoproliferations were grouped into five categories and presented in corresponding sessions at the meeting:

1. AITL and T-follicular-helper-cell-associated lymphomas.

2. CD30-positive T-cell lymphomas/lymphoproliferative diseases.

3. Extranodal T-cell and NK-cell neoplasms.

4. EBV-associated T-cell/NK-cell lymphomas/lympho- proliferative diseases.

5. PTCL NOS, post-transplant lymphoproliferative disorders, and mimics.

On the basis of the reviewed cases and the discussions at the EAHP/SH meeting, this article describes the diagnostic challenges, general conclusions and open issues in the field of peripheral T-cell and NK-cell lymphomas.

Session 1: Angioimmunoblastic T-cell lymphoma and T-follicular-helper-cell- associated lymphomas

AITL is an aggressive nodal peripheral T-cell lymphoma that usually presents with systemic symptoms, advanced-stage disease with generalized lymphadenopathy, frequent hepatosplenomegaly, and a pruritic skin rash, and is characteristically associated with immune dysregulation.[2,10] Histologically, AITL shows effacement of nodal architecture by a polymorphous infiltrate, together with proliferation of high endothelial venules (HEVs) and follicular dendritic cell (FDC) meshworks, and frequent expansion of EBV-infected B-blasts.[2] AITL may show three overlapping histological patterns (I, II, and III), with hyperplastic follicles, regressed follicles, and no identifiable follicles, respectively.[11] Pattern

I represents a perifollicular pattern of involvement, whereas patterns II and III are considered to be 'typical' histology for AITL.

For many years, the characteristic expansion of FDCs emphasized the importance of the follicular microenvironment in AITL. However, it is only in the last decade that gene expression profiling and phenotypic studies have shown that the neoplastic T cells of AITL are derived from T_{FH} cells, a recently described distinct functional subset of mature T cells.[3] The markers that are characteristic, but not always specific, for the T_{FH} phenotype include PD1, ICOS, CXCL13, CXCR5, CD200, c-MAF, SAP, and bcl-6.[12,13] CD10, which is expressed by a subset of normal T cells, is frequently positive in AITL.[11,12,14,15]

The T_{FH} phenotype is also a feature of the follicular variant of peripheral T-cell lymphoma, not otherwise specified (PTCL-F), and the rare primary cutaneous CD4-positive small medium T-cell lymphoma (a provisional entity in the 2008 WHO classification). The 2008 WHO classification considers PTCL-F to be distinct from AITL, as (in contrast to AITL) these cases typically present at an early clinical stage, show partial nodal involvement, lack the proliferation of HEVs and FDCs, and may harbour t(5;9).[2,16] Nevertheless, cases of PTCL-F reported in the literature appear to show definite clinico-pathological overlap with AITL.[7,17] In addition to these neoplasms, there remain a small number of mature T-cell neoplasms that express a range of T_{FH} markers; they may show some overlap, but do not fulfil the accepted defining criteria for AITL or PTCL-F.[3,18] Recent studies have shown the frequent occurrence of recurrent *TET2* mutations in AITL and in a subset of PTCL NOS that express the T_{FH} phenotype and/or show overlapping morphological features with AITL.[5] How should these latter lymphomas be classified - is the spectrum of AITL broader than is currently recognized?

The aim of session 1 was to define the borders of AITL and determine the minimum criteria required for diagnosis. The report is based on the 42 cases assigned to this session, and will focus on: (i) interesting observations in cases of AITL (typical and pattern 1); (ii) cases that deviate from currently accepted diagnostic criteria, but nevertheless fall within the spectrum of AITL; (iii) PTCL-F and its relationship with AITL; (iv) the specificity and role of T_{FH} markers (in distinguishing AITL from PTCL NOS); and (v) the spectrum of B-cell proliferations in AITL/PTCL-F.

AITL - TYPICAL AND PARTIAL/EARLY NODAL INVOLVEMENT (PATTERN 1)

Manifestations of immune dysregulation (e.g. polyclonal hypergammaglobulinaemia and Coomb's positive haemolytic anaemia) that are considered to be typical of AITL are frequent but not universal, and are therefore not mandatory for diagnosis.[10] They were absent in two of five workshop cases of typical AITL where this information was available.

Diagnosis of 'typical' AITL is straightforward, and CD21 is usually a reliable marker to demonstrate FDC hyperplasia.[19] However, as observed in the workshop (Figure 1A,B), in a few cases this is better detected by CD23 staining, and its use is therefore recommended when staining for CD21 fails to show significant FDC expansion.

The pattern of partial nodal involvement (pattern I) is characterized by hyperplastic follicles[20] and a perifollicular neoplastic T-cell infiltrate, and shows morphological overlap with follicular hyperplasia and also, in some cases, the perifollicular/marginal zone pattern of PTCL-F (Figure 1C,D).[21] Although sometimes mistakenly thought to represent early-stage disease, it is merely early/partial involvement of a lymph node in otherwise disseminated disease.[22,23] Frequently, as in all three workshop cases, AITL pattern I presents with typical clinical and immune manifestations. One of the workshop cases was in a 27-year-old female; although it has previously reported at this age, presentation at age <30 years is very rare.[22] The distribution of the neoplastic CD10-positive/T_{FH} cells - spilling out into the interfollicular area from the outer zone of the follicle (Figure 1D), rather than being predominantly intrafollicular - is useful for distinguishing it from follicular hyperplasia.[23,24] As seen in some of the workshop cases, it is also useful to note that clo-nality analysis may be misleading in some reactive mimics of AITL, especially EBV-related reactive clonal T-cell proliferations. Interestingly, one case with this pattern showed florid proliferation of medium-sized tumour cells without polymorphism (Figure 1C,D). However, advanced-stage disease, typical biological manifestations, subtle expansion of FDCs and proliferation of HEVs in the paracortex favoured AITL. It is of note that the case was positive for t(5;9) by FISH, a feature reported to be associated with PTCL-F.

CASES THAT DEVIATE FROM CURRENT DIAGNOSTIC CRITERIA BUT FALL WITHIN THE SPECTRUM OF AITL: TUMOUR CELL-RICH AITL

There were five workshop cases in which the lymph node was effaced by a monomorphous infiltrate of atypical T cells with a T_{FH} phenotype (Figure 1E). There was no significant HEV proliferation in three of five cases. On morphology alone, these would be classified as PTCL NOS. However, there was florid proliferation of FDCs in all cases, which, taken together with the T_{FH} phenotype of the neoplastic cells, out-weighed the lack of defining WHO criteria - i.e. a polymorphous infiltrate and (in three cases) proliferation of HEVs - and a panel diagnosis of tumour cell-rich AITL was made. In further support of this diagnosis, two cases had previous lymph node biopsies. One showed 'typical' AITL (Figure 1F). The other was recorded as showing a plasmacytic proliferation (not reviewed) with an underlying T-cell clone identical to that detected in the later biopsy (having the features of tumour cell-rich AITL), suggesting a possible AITL masked by the plasmacytic proliferation in the initial biopsy. Although PTCL NOS has rarely been reported on follow-up biopsy,[22] the evidence suggests that, at least in some cases, a tumour cell-rich pattern is likely to represent histological progression (with tumour cell enrichment and a reduction/lack of polymorphic environment), and could be regarded as a tumour-cell rich variant of AITL.

CASES THAT DEVIATE FROM CURRENT DIAGNOSTIC CRITERIA BUT FALL WITHIN THE SPECTRUM OF AITL: UNUSUAL MORPHOLOGY WITH PRIMARY FOLLICLES AND NO FDC EXPANSION

For many years, FDC expansion has been considered to be mandatory for the diagnosis of AITL. However, the more recently recognized pattern I AITL lacks significant FDC expansion. Although FDC expansion remains an essential diagnostic criterion for 'typical' AITL, there have also been some cases reported as showing limited or no detectable CD21/CD23 FDC expansion, despite an otherwise typical appearance of AITL.[14] One of the cases

did not fall into any of the recognized patterns of AITL (Figure 1G,H): the node was partially effaced by paracortical clusters of clear T_{FH}-type cells amidst hyperplastic HEVs in a background of IgD-positive small B cells without expansion of FDCs. Despite the difference from any of the recognized patterns, the panel was unanimous in its diagnosis of AITL, albeit an unusual morphological variant. In further support of this, one of the panellists (P.G.) demonstrated a case (not in the workshop) of typical AITL where the follow-up biopsy showed a very similar appearance to the biopsy under discussion.

CASES THAT DEVIATE FROM CURRENT DIAGNOSTIC CRITERIA BUT FALL WITHIN THE SPECTRUM OF AITL: EPITHELIOID CELL-RICH AITL

Epithelioid cell-rich AITL is uncommon but well recognized, and should be considered in the differential diagnosis of lymphomas with confluent clusters of epithelioid histiocytes. [10,14] As seen in the workshop cases, the abundance of epithelioid histiocytes masks typical morphological features of AITL (resulting in limited polymorphism and only mild proliferation of HEVs) and resembles PTCL NOS, lympho-epithelioid variant (Lennert lymphoma). However, in contrast to the latter, epithelioid cell-rich AITL shows definite FDC expansion, and the neoplastic T cells have a T_{FH} phenotype.

PTCL-F AND ITS RELATIONSHIP WITH AITL

The workshop had three cases that showed an overlap between PTCL-F and AITL, and none that could be classified as 'pure' PTCL-F. Two cases had a predominantly follicular growth pattern resembling follicular lymphoma (Figure 2A-D), and one case had a perifollicular pattern of involvement. In one of the cases (Figure 2A,B) with a predominantly follicular growth pattern but with many morphological features of AITL (including focal regressed follicles, HEV hyperplasia, and focal FDC expansion), a proportion of neoplastic T_{FH} cells were positive for t(5;9) by FISH, raising the possibility that this may be a secondary event in this case. The identification of t(5;9) in AITL (in pattern I AITL in the workshop, and another case of typical AITL[25] mentioned during the workshop, but not part of the workshop) suggests that it may not help to distinguish PTCL-F from AITL. In the other case with a follicular growth pattern, there was focal FDC expansion (Figure 2C,D). A follow-up biopsy (submitted after the workshop) showed a diffuse tumour cell-rich monotonous infiltrate of larger, more atypical T cells associated with prominent HEV hyperplasia and scattered residual (predominantly primary) follicles, but with no significant FDC expansion (Figure 2D). The transformed CD4-positive neoplastic T-cell infiltrate, which no longer had a follicular microenvironment, showed some down-regulation of the T_{FH} phenotype, being positive only for PD1.

In accordance with many of the reports in the literature, the proceedings of this workshop support the concept that PTCL-F may not be a distinct entity, but may represent part of the spectrum of AITL. However, the question remains: why, in most cases, does the neoplastic T_{FH} infiltrate spread outward in an in- terfollicular/perifollicular distribution (AITL), whereas in a small minority of cases it is folliculotropic (PTCL- F)?

THE SPECIFICITY AND ROLE OF T$_{FH}$ MARKERS

The expression of T$_{FH}$ markers is a useful adjunct for the diagnosis of AITL. However, the varying sensitivity and specificity in workshop cases confirmed the reports in the literature that PD1 and ICOS are sensitive but less specific, and CXCL13 and CD10 are more specific but less sensitive.[12,14,18,26,27] As previously reported, the success of PD1 staining is fixation-dependent, being weak/negative in poorly fixed/archival tissues.[24] Therefore, although PD1 is strongly expressed by neoplastic T cells in most cases of AITL, comparison with a positive internal control (e.g. strongly PD1-positive T$_{FH}$ cells) helps in the interpretation of weak/negative staining as genuine.

In addition to recognized T$_{FH}$-derived subtypes of T- cell lymphoma, there is a small group of PTCL NOS that express T$_{FH}$ markers.[3,18] Many of these show some morphological and genetic overlap with AITL. However, it is useful to note that some of the so- called T$_{FH}$ markers may also rarely be expressed by other subtypes of PTCL. One case in the workshop of nodal involvement by mycosis fungoides/Sézary syndrome (MF/SS) highlighted the importance of morphology and clinical correlation, and the potential pitfalls if the focus is solely on the immunoprofile of the neoplastic T cells. The involved node showed a monotonous paracortical infiltrate of medium-sized cerebriform T cells with no associated HEV or FDC hyperplasia. The neoplastic T cells showed weak/focal expression of CD10, were positive for PD1 and ICOS (but with weaker expression than reactive T$_{FH}$ cells), and were negative for CXCL13. Although it is rare, expression of CD10 and T$_{FH}$ markers has been reported in MF/SS.[28]

THE SPECTRUM OF B-CELL PROLIFERATIONS IN AITL/PTCL-F

For many years, the expansion of B cells, including plasma cells and B-immunoblasts, a frequent feature in AITL, was thought to be a result of secondary immunodeficiency, but more recently it has been attributed to functional properties of neoplastic T$_{FH}$ cells.[12] Expansion of EBV-positive B-immunoblasts is present in up to 95% of cases of AITL.[29] This may be in the form of a sparse or prominent infiltrate of polyclonal/polytypic EBV-positive B cells, or a clonal proliferation of large B cells that may amount to secondary diffuse large B-cell lymphoma (DLBCL), sometimes obscuring the underlying AITL.[22,30]

Expansion of EBV-negative large B cells may also be noted, and EBV-negative DLBCL has rarely been reported. There have also been rare reports of clonal EBV-positive and negative plasmacytic proliferations in relation to AITL.[30,31] The large EBV-positive B-immunoblasts seen in AITL/PTCL-F may have the morphology of Hodgkin/Reed-Sternberg (HRS) cells.[32,33] If these are prominent, they may lead to a mistaken diagnosis of classical Hodgkin lymphoma (cHL). More recently, HRS-like B cells negative for EBV have been reported in AITL/PTCL-F.[34]

The workshop included AITL cases with a wide spectrum of B-cell proliferations that included polyclonal/clonal EBV-positive large B-cell proliferations, EBV-positive DLBCL, and EBV-positive clonal plasmacytic proliferation. There were also two cases of AITL and one case of AITL that overlapped with PTCL-F that contained EBV-negative HRS-like cells (Figure 2F). EBV-positive HRS-like B cells are frequent in AITL, but EBV-negative HRS

cells have been observed rarely; one such case from the workshop was included in a recent series.[34] The potential pitfall is misdiagnosing cHL or composite cHL/AITL. The polymorphous infiltrate with atypical CD10-positive T_{FH} cells, hyperplastic HEVs and FDCs supports the diagnosis of AITL. The rosetting of HRS-like cells by neoplastic (CD10-positive) T cells rather than reactive T cells, and the absence of any demarcation between the areas containing HRS-like cells and the underlying AITL, are against cHL or a composite tumour (Figure 2F). In one of the cases, the CD30-positive, CD15-positive HRS-like cells were CD20-positive, weakly CD79a-positive, and kappa restricted, but in the other they had a more typical HRS phenotype, being CD20-negative, CD79a-negative, Pax5-positive, OCT2-negative, and BOB-1-negative, and lacking light chain expression. Lack of expression of B-cell- associated transcription factors and light chains (observed in the latter case) has recently been reported in HRS-like cells in the context of AITL/ PTCL-F.[33,34] These observations are in concordance with the findings of Brauninger *et al.*,[35] who demonstrated the expansion of immunoglobulin-receptor- deficient EBV-infected B cells in the context of AITL. It should be noted that the presence of HRS-like cells is not unique to AITL, and this phenomenon was observed in three cases diagnosed as peripheral T-cell lymphoma, NOS (session 5). Of these, two were EBER-negative and one was EBER-positive (Figure 7G,H).

A summary of the take home messages from session 1 is shown in Table 1.

Session 2: CD30-positive T-cell lymphomas/lymphoproliferative diseases

Session 2 summarizes diagnostic issues related to CD30-positive T-cell lymphomas. The expression of CD30 in PTCL NOS is discussed in session 5.

ALK-POSITIVE ANAPLASTIC LARGE-CELL LYMPHOMA

ALK-positive ALCL can reliably be identified by strong expression of CD30 and ALK.[2] Thus, ALK-positive ALCL does not seem to present a diagnostic challenge. At the workshop, cases of ALK-positive ALCL were presented that occurred as localized extranodal lesions without any dissemination beyond the pri-mary lesion in the central nervous system (Figure 3) or the skin.[36] These observations have practical implications. Although extranodal tissue involvement is considered to be an unfavourable prognostic feature in systemic ALK-positive ALCL in children, the group of patients that has been best studied so far,[37] the cases of localized disease involving extranodal sites presented at the workshop were associated with a favourable outcome. ALK expression in a primary cutaneous ALCL (restricted to the skin) does not necessarily indicate the presence of disseminated dis-ease.[36] Analysis of all primary cutaneous CD30-positive lymphoproliferative disorders for ALK expression might thus be recommended, even if the clinical staging suggests primary cutaneous disease. One might speculate that the extranodal manifestation in these localized variants of ALK-positive ALCL is induced by an inflammatory microenvironment at these sites.

CD30-POSITIVE PRIMARY CUTANOUS LYMPHOPROLIFERATIVE DISEASE WITH NODAL INVOLVEMENT

CD30-positive primary cutaneous lymphoproliferative disease (pcLPD) comprises two groups of disorders, lymphomatoid papulosis with its variants, and primary cutaneous anaplastic large-cell lymphoma, both being negative for ALK expression.[2] Older studies reported on accompanying lymphomas of other types in patients with CD30-positive pcLPD, such as peripheral T-cell lymphomas or classical Hodgkin lymphoma (cHL). One case that was recently reported in a case series indicates that most of the Hodgkin-like lymphoproliferations in draining lymph nodes of CD30-positive pcLPD represent nodal dissemination of the CD30-positive pcLPD rather than a second neoplasm (Figure 3).[38] Lymph node involvement by CD30-positive neoplastic cells in lymph nodes of patients with CD30-positive pcLPD presents a kind of dissemination beyond the skin, but does not necessarily indicate an aggressive clinical course. For diagnostic purposes, CD30-positive pcLPD with nodal involvement should be considered in any ALK-negative ALCL or other CD30-positive T-cell lymphoma if only a single lymph node is involved. As the nodal manifestation might precede or follow the cutaneous lesion, obtaining a detailed clinical history of skin disorders is vital. This is of importance to prevent overtreatment of patients with nodal involvement in CD30-positive pcLPD, which mimics other CD30-positive lymphomas.

Just as CD30-positive pcLPD might mimic nodal lymphomas, other lymphoma entities might mimic CD30-positive pcLPD in the skin. Most importantly, transformed mycosis fungoides and adult T-cell leukaemia/ lymphoma might be morphologically and immunophe- notypically indistinguishable from CD30-positive pcLPD, as highlighted by several cases submitted to the workshop. Again, knowledge of the patient history, including previous biopsies, is crucial for the correct diagnosis.

DIAGNOSTIC CRITERIA OF ALK-NEGATIVE ANAPLASTIC LARGE-CELL LYMPHOMA

The majority of the difficult cases were lymphomas in the grey zone of ALK-negative ALCL and classical Hodgkin lymphoma. A few were examples of PTCL NOS with some features raising the possibility of ALK-negative ALCL.

ALK-negative ALCL is, according to the WHO definition, 'a CD30+ T-cell neoplasm that is not reproducibly distinguishable on morphological grounds from ALCL, ALK+, but lacks anaplastic lymphoma kinase protein (ALK)'.[2] Recognition is important, as its clinical behaviour seems to be different, and patients have an overall survival rate intermediate between those of patients with PTCL NOS and ALK-positive ALCL.[39] Although no specific genetic alterations have been consistently found in this entity, t(6;7)(p25.3;q32.3) involving the *DUSP22/IRF4* locus phosphatase gene on 6p25.3 and the *FRA7H* fragile site on 7q32.3 seems to be promising, but its role is yet to be determined.[6]

The most helpful features for the diagnosis of ALK-negative ALCL at the current stage of knowledge were considered to be as described in the WHO classification: a morphology indistinguishable from that of ALK-positive ALCL, especially a sinusoidal growth pattern, cytology showing hallmark cells, and cohesive architecture, in conjunction with strong and

abundant CD30 expression (in almost all cells). Other features that should favour the diagnosis are the absence of a B-cell program, as demonstrated by the lack of Pax5 expression (with the exception of cases with *PAX5* gene amplification),[40] loss of T-cell markers, expression of EMA, a cytotoxic phenotype, and lack of T-cell receptor (TCR) expression. Cases not showing these features were classified as PTCL NOS. However, the panel felt that a cytotoxic phenotype is not mandatory for ALCL. One case diagnosed in a small fragment with architectural features lacking was especially problematic, owing to the difficulty in applying the above criteria.

Five of the cases submitted to the workshop were challenging with respect to the differential diagnosis between ALK-negative ALCL and cHL. One of these cases is presented in Figure 3. The major difficulties were attributable to the following features occurring in a molecularly proven clonal T-cell lymphoproliferation with scattered large CD30-positive blasts: nodularity, EBV detection in the lymphoma cells by *EBER in-situ* hybridization, partial expression of B-cell markers such as PAX5, BOB-1, and OCT2, or the lack of a cytotoxic phenotype (TIA-1, granzyme B, and perforin). The panel felt that a careful morphological review for HRS cells (favouring cHL) or hallmark cells (favouring ALCL), and the presence of a polymorphous inflammatory (favouring cHL) or a lymphocytic microenvironment (favouring ALCL/PTCL NOS) or a gap in cell size between the large neoplastic cells and the background (favouring cHL) were the most useful features for discriminating between cHL and ALK-negative ALCL/PTCL NOS. It was also concluded that, if cHL is excluded according to the above, many of the remaining lymphomas in this group lack defining criteria of ALCL, such as cohesive or intrasinusoidal growth (see above), and might be better classified as PTCL NOS.

Conversely, one of the workshop cases was a typical case of nodular sclerosis Hodgkin lymphoma, with the expression of T-cell antigens (CD2 and CD4). These are true classical Hodgkin lymphoma cases, but may have a more aggressive prognosis.[41] The occurrence of true T-cell Hodgkin lymphoma remains controversial.

IMPLANT-ASSOCIATED ANAPLASTIC LARGE-CELL LYMPHOMA

Breast implant-associated ALCL is rare; it was initially described by Keech and Creech in 1997,[42] and was recently reviewed by Aladily *et al*.[43,44] In the workshop, a number of implant-associated lesions were reviewed. These covered a wide spectrum of histological presentations, ranging from the classical seroma-located prototypic lesion to cases with nodal and systemic dissemination. All cases shared a similar morphology in the serous fluid, and in two of the cases the same large anaplastic cells were present in regional lymph nodes. The workshop cases expand the histological spectrum of this variant of ALK-negative ALCL to nodal variants with systemic dissemination.

In the seroma-like cases, the prognosis was good, but it seems to be variable if regional lymph node involvement is detectable at presentation. In the cases with seroma-like ALCL and regional lymph node involvement, the patients were in remission at the time of submission to the workshop, but the other case followed an aggressive course, killing the patient within 5 months. In one case, there was unverified stage III disease because of abdominal lymphadenopathy; however abdominal lymph nodes were not sampled. The

patients with dissemination presented at the workshop were all treated with chemotherapy and/or radiation therapy in addition to capsulectomy and implant removal.

A summary of the take home messages from session 2 is shown in Table 2.

Session 3: Extranodal T-cell and NK-cell neoplasms

Session 3 encompassed three somewhat unrelated topics, which will be dealt with separately in this report: extranodal T-cell or NK-cell proliferations involving (i) the gastrointestinal tract, (ii) the skin and subcutaneous tissue, and (iii) the spleen. T-cell and NK-cell proliferations associated with EBV are largely dealt with in session 4. Relatively few cases were submitted in the category of cutaneous neoplasms, and, as this was the subject of another recent workshop devoted to cutaneous lymphomas, this topic will be dealt with only briefly.[45–48]

Two variants of enteropathy-associated T-cell lymphoma (EATL) are included in the 2008 WHO classification, referred to as EATL type I and type II.[2] Type I is associated with either overt or clinically silent gluten-sensitive enteropathy, and is mainly seen in patients of European extraction, whereas the type II form has a more worldwide distribution, and is not clearly linked to coeliac disease. In recent years, with the acquisition of more epidemiological and molecular data, EATL type II has come to be regarded as largely a separate entity, and not a variant of EATL type I.[8] However, the 25 cases submitted to the workshop encompassed an even broader spectrum of disease, and included a number of cases that the panel classified as PTCL NOS. Also submitted were two examples of indolent T-cell or NK-cell lymphoproliferative disease (LPD). Finally, there was a single case of an EBV-positive T-cell lymphoma in a patient from Singapore. The small bowel mucosa was involved without significant epitheliotropism, and there was widespread involvement of lymph nodes and bone marrow. The tumour cells did show clonal *TCR* gene rearrangement, and expressed the αβ TCR. The infiltrate was relatively monomorphic, resembling the nodal EBV-positive T-cell lymphomas encountered in session 4. The workshop did confirm that nearly all of the cases presenting with gastrointestinal tract involvement had a cytotoxic phenotype, even if they did not conform to EATL type I or II.

EATL TYPE I AND TYPE II, AND REFRACTORY COELIAC DISEASE

Seven of the workshop cases were classified as EATL type I, and six as EATL type II. EATL type I usually had a polymorphous cellular composition, sometimes with Hodgkin-like cells, and variable CD30 expression (Figure 4A-C).[49] In contrast, the type II cases had the expected monomorphic appearance with striking epitheliotropism (Figure 4D-E).[8,50] Interestingly, all cases of EATL showed considerable variability in TCR expression. Whereas it has been suggested in the literature that EATL type I is usually of αβ T-cell origin, two cases submitted for the workshop expressed γδ TCR (Figure 4C), and one was TCR silent. Supporting the diagnosis of EATL type I was absent expression of CD56, and the absence of megakaryocyte-associated tyrosine kinase (MATK) shown in one case.[51] Variability in the pattern of TCR expression was also seen in EATL type II, which otherwise had the expected CD8-positive/CD56-positive immunophenotype. Three cases were positive for TCRγ, two were positive for pF1, and one case was TCR silent. Aberrant expression of

CD20 or CD79a was observed in occasional cases, an issue discussed in session 5. Although there is immunophenotypic overlap between some cases of EATL types I and II, consensus is emerging that EATL type II is a distinctive entity, with characteristic epidemiological, histological and clinical features, and is unrelated to coeliac disease in the vast majority of cases.[8,50–52] In two cases, the issue of refractory coeliac disease (RCD) type 2, which is regarded as an incipient form of EATL, was also examined.[53] Both were clonal according to PCR studies, and one progressed to EATL type I, but, interestingly, both cases also expressed CD8, which is said to be absent in RCD type 2, often aiding in the differential diagnosis between RCD type 1 and uncomplicated coeliac disease.[54]

PERIPHERAL T-CELL LYMPHOMA, NOT OTHERWISE SPECIFIED (PTCL NOS)

Six cases submitted to the workshop were classified as PTCL NOS, lacking the necessary criteria for EATL. None presented in patients with a history of coeliac disease, and, histologically, all lacked significant epitheliotropism. However, to some extent the diagnosis of PTCL NOS was a diagnosis of exclusion, as the panel did not have complete clinical (e.g. HLA) or pathological (limited access to primary gastrointestinal lesion) data. Only one case presented in the small bowel, whereas three presented in the colon, and two in the stomach. Interestingly, four of five cases with evaluable data were TCR silent, whereas only one case had an $\alpha\beta$ phenotype.[55] The cases of PTCL NOS were variable in their cytological composition. One case presented in a patient with hypereosinophilia (Figure 4F), and was also CD30-positive. There is an increased incidence of clonal T-cell disorders in patients with hypereosinophilic syndrome,[56,57] and this particular patient had widespread disease involving multiple extranodal sites. Clinically, PTCL NOS was aggressive.

INDOLENT T-CELL OR NK-CELL LYMPHOPROLIFERATI VE DISEASE

The workshop highlighted excellent examples of indolent T-cell or NK-cell lymphoproliferations that may be mistaken for T-cell or NK-cell lymphomas, but require minimal if any therapeutic intervention. One case represented an example of NK-cell enteropathy,[58] presenting with colonic lesions showing superficial ulceration. The initial biopsy in 2005 was interpreted as cytotoxic T-cell lymphoma. However, the patient refused chemotherapy, and remained well following surgical resection. A recurrent colonic lesion was detected in 2008, but the patient has been asymptomatic without further intervention since then. Histologically the biopsy resembled the previously published cases, containing medium-sized to large irregular cells confined to the lamina propria.

A condition with somewhat similar clinical and pathological features is indolent T-cell LPD of the gastrointestinal tract.[9] This condition, also discussed during the Lymphoma Symposium, is characterized by superficial, somewhat polypoid lesions that can affect the entire gastrointestinal tract. The presenting symptoms often include diarrhoea and abdominal pain. The infilrates are composed of small, monotonous lymphoid cells, most often with a CD8-positive/CD4- negative phenotype. The cells have a very low proliferative rate, although the process is clonal according to *TCR* gene rearrangement. This condition is also associated with marked chronicity; patients have been followed for many years, with persistence of intestinal lesions, but without progression (Figure 4H, I).

The complexity of T-cell lymphomas affecting the gastrotintestinal tract reflects the complexity of the intestinal T-cell system. Two main types of intestinal T cell have been characterized.[59] Type a mucosal T cells are mainly found in the lamina propria, and are mainly CD8-positive αβ T cells, similar to those seen in the indolent T-cell LPDs. Type b T cells are mainly intraepithelial, can be of either αβ or γδ derivation, and typically express a CD8 $\alpha\alpha$ homodimer. These cells have some unique functional attributes, and show a high degree of reactivity to self-antigens. They are felt to be involved in immune regulation. Some cells fail to express the CD8 $\alpha\alpha$ homodimer, and have a double-negative phenotype. Thus, this population appears to correspond to the phenotypes encountered in both type I and type II EATL, and helps to explain the complexity of TCR expression encountered in these lymphomas.

CYTOTOXIC T-CELL LYMPHOMA OR LYMPHOPROLIFERATION IN THE SKIN

According to the WHO-EORTC classification of cutaneous lymphomas and the 2008 WHO classification,[2,60] cytotoxic lymphomas infiltrating the subcutaneous tissue encompass two distinct entities with clinical and pathological differences, i.e. subcutaneous panniculitis-like T-cell lymphoma (SPTCL) - restricted to cases with an αβ phenotype - and primary cutaneous γδ T-cell lymphoma (PCGD-TCL). The characteristics of these two entities are described in the report of the 2011 Society for Hematopathology/European Association for Haematopathology workshop, and will therefore be only briefly mentioned.[61]

SPTCL shows selective infiltration of the subcutis by atypical CD8-positive, CD56-negative, CD3-positive, αβ T cells with expression of cytotoxic proteins surrounding adipocytes. The disease has a good prognosis, in particular if it is not associated with haemo-phagocytic syndrome (HPS). In contrast, PCGD-TCL is a lymphoma composed of neoplastic CD4-negative, CD8-negative, CD56-positive γδ T cells. A panniculitis-like pattern may be seen in the subcutis, but involvement of the dermis and/or epidermis is usually present. The prognosis is generally poor.[60,62] Whereas dissemination to extracutaneous sites has rarely been reported in SPTCL, two cases submitted to the workshop showed 'lipotropic' involvement in organs other than the skin: one involving the mesentery - revealed by abdominal pain - in a patient with other typical subcutaneous lesions,[63] and another in a patient with bone marrow involvement and HPS showing the typical rimming of atypical CD8-positive cells around adipocytes in the marrow (Figure 5A,B). Both underwent rapid or initial dissemination to spleen and lymph nodes, and showed poor response to chemotherapy. Another case presenting with isolated painful subcutaneous plaques associated with HPS also showed an aggressive course. Altogether, the three submitted SPTCL cases highlighted the fact that association with HPS and/or dissemination to ex-tracutaneous sites are indicators of aggressiveness and poor outcome, and may indicate a requirement for systemic chemotherapy. Two cases of PCGD-TCL submitted to the workshop showed some variation from the classical clinical and pathological presenta-tion. Disease was confined to the subcutaneous tissue, as is more typically seen in SPTCL, and one of these two patients responded well to CHOP chemotherapy, with a complete response being maintained 3 years after diagnosis. These findings highlight some overlapping features between SPTCL and PCGD-TCL

The workshop cases also included a single case of indolent CD8-positive T-cell LPD of the ear. This case illustrated the distinctive features of this entity, recently described by Petrella *et al.,*[64] involving the dermis without epidermotropism and composed of αβ CD8-positive, CD56-negative cells. This lesion occurs most often on the ear, but more rarely on the nose or other acral sites.[65] It has an indolent clinical course, and tends to remain localized, without a need for systemic therapy. Such lesions should be distinguished from more aggressive CD8-positive T-cell lymphomas involving the skin, including aggressive epidermotropic cytotoxic CD8-positive T-cell lymphomas, SPTCL, and uncommon variants of CD8-positive MF. It may belong to a wider spectrum of indolent T-cell or NK-cell LPD arising in skin or mucosa (see above). However, the term indolent cutaneous CD8-positive T-cell lymphoid proliferation disease (ear type) seems to be appropriate.

CYTOTOXIC T-CELL LYMPHOMA OR LYMPHOPROLIFERATION IN THE SPLEEN

Eleven cases in the workshop dealt with the issue of T-cell LPD with splenic involvement, mostly illustrating cases of T-cell large granular lymphocytic leukaemia (T-LGL) and hepatosplenic T-cell lymphoma (HSTL). Both diseases are derived from subsets of cytotoxic cells, usually CD8-positive αβ T cells for T-LGL, and CD4-negative, CD8-negative γδ T cells for HSTL.[2] Recent data have emphasized plasticity in terms of cell derivation in both entities. As an illustration, a category of indolent NK-cell lymphoprolifer- ative disorder (NK-LPD) was recognized in the 2008 WHO classification. It has similar clinicopathological features to T-LGL, and the recent discovery of *STAT3* somatic mutations in both T and NK forms unifies the pathogenesis of chronic NK-LPD and T-LGL.[66] The diagnosis of T-LGL and HSTL is usually straight-forward, and is clinically highly relevant, as T-LGL is indolent whereas HSTL is aggressive, with a fatal outcome in most patients.[67] However, the two diseases can share some features, such as a common presentation with splenomegaly (mild and inconstant in T- LGL; large and constant in HSTL), cytopenias, and the pattern of infiltration in the splenic red pulp, without gross lesions. The workshop highlighted the clinicopathological spectrum of both entities with cases that deviated from the prototypic clinical presentation (with an initial indolent phase in some HSTL cases), also illustrating the limited diagnostic value of αβ or γδ determination, and the critical importance of evaluation of the bone marrow trephine for the diagnosis of HSTL.

T-CELL LARGE GRANULAR LYMPHOCYTIC LEUKAEMIA (T-LGL)

T-LGL is an indolent, often asymptomatic, disorder defined by a clonal expansion of mature lymphocytes containing cytoplasmic azurophilic granules in the peripheral blood ($>0.5 \times 10^9$/l) with, usually, an αβ, activated cytotoxic phenotype. T-LGL may be associated with neutropenia, mild splenomegaly (50%), and autoimmune manifestations. The diagnosis is based on examination of blood and/or marrow smears, and flow cytometry (FCM) and PCR analysis, allowing the demonstration of a clonal LGL expansion with a CD8- positive, CD57-positive phenotype [killer cell immunoglobulin-like receptor (KIR) restriction is especially useful in NK-LPD]. Examination of the core biopsy is usually not needed, but may be helpful in cases without significantly increased LGLs. The bone marrow core shows a relatively sparse interstitial lymphocytic infiltrate of CD8-positive, TIA1-positive, granzyme B-positive cells with minimal to absent involvement of the sinuses.[68]

Although histopathology is not required in the great majority of cases, three submitted cases highlighted atypical situations where splenectomy or lymph node biopsy was performed for diagnostic purposes. The indications for biopsy were related to: a γδ phenotype of the circulating cells (as reported in a minority of T-LGL cases[69]); absent or a minimal number of LGLs at presentation; and/or first manifestation of the disease as abdominal adenopathy in one peculiar case. In the last of these cases, these manifestations preceded the appearance of LGLs in the peripheral blood 2 years later. These cases illustrated the typical histopathological features of T-LGL, with a sparse and minimal lymphocytic infiltration of the splenic red pulp (with preservation of the white pulp) comprising small CD8-positive, granzyme B-positive lymphocytes without significant cytological atypia (Figure 5C,D). Lymph nodes showed a similar monotonous infiltrate in the interfollicular region (Figure 5E,F). These cases were characterized by an indolent clinical course. In agreement with the reported variability in CD57 expression, CD57 was negative (one case) or partially expressed (two cases). It is noteworthy that one of the two γδ T-LGL cases had a CD4-negative, CD8-negative, CD56-positive (dim) immunophenotype that might point towards γδ HSTL. However, the characteristic appearance of the splenic red pulp infiltrate with an activated cytotoxic granzyme B-positive phenotype, the detection of a similar lymphoid population in the peripheral blood and the indolent presentation and outcome were consistent with γδ T-LGL.

HEPATOSPLENIC T-CELL LYMPHOMA (HSTL)

HSTL is an aggressive disease characterized by splenomegaly, often hepatomegaly without lymphadenopathy, B symptoms, cytopenias, an infiltration of the sinuses (almost exclusively) of the bone marrow, the sinusoids of the liver and the cords and sinuses of the spleen by small/medium-sized lymphoid cells with a CD3-positive, CD4-negative, CD8-negative, CD5- negative, CD56-positive phenotype and a non-activated cytotoxic profile, and isochromosome 7q in 50–60% of cases. Most cases are γδ, but cases with similar clinicopathological features and an αβ phenotype have been reported. Four of the workshop cases were classified as HSTL by the panel: one αβ HSTL, and three γδ HSTL. All cases showed the typical dense, mainly sinusoidal, infiltration of the splenic red pulp by medium-sized lymphoid cells (Figure 5G). Slight pleomorphism was noted in two cases. Importantly, three cases with available bone marrow trephine all showed selective involvement of sinuses, which were dilated by an infiltrate of medium-sized CD3-positive, CD5-negative T-cells (Figure 5H), reinforcing the critical value of bone marrow trephine, as previously reported.[70] It is of note that one case with supraclavicular lymph node involvement occurred in a setting of sarcoidosis, perhaps emphasizing the reported context of dysimmune conditions or chronic antigen stimulation in HSTL.[67] Only one of the four cases, of the γδ subtype, showed isochromosome7q, reinforcing the inconstancy of this alteration (in HSTL), which is also not specific (see Session 5).[71] Interestingly, one case was initially diagnosed as γδ CD56-positive T-LGL, in view of an 'indolent' 2-year phase with cytopenias prior to a more aggressive disease with splenomegaly, hepatomegaly, and B symptoms. The panel favoured a diagnosis of γδ HSTL, in view of the prototypic appearances in the spleen with a dense infiltrate of medium-sized cells, the non-activated cytotoxic phenotype (granzyme B only partially positive), and the selective sinusoidal infiltration in the marrow. This case illustrates the presence of an indolent initial phase in some HSTL cases, as previously reported.[72]

Another case remained unclassified by the panel in the absence of bone marrow trephine, emphasizing the need to integrate clinical, pathological and genetic data in difficult cases.[69]

Also submitted was one example of a transient reactive clonal expansion of γδ T cells in the peripheral blood and in the spleen of an adult with haemolytic anaemia, in agreement with the reported expansion of benign γδ T cells in infections and autoimmune diseases[73]; these can be oligoclonal/clonal in some cases.[74] This emphasizes that clonality and expansion of γδ T cells may be misleading as HSTL mimics.

Finally, in addition to cases of T-LGL, HSTL, PCGD- TCL and EATL (mainly type II) with a γδ phenotype that were submitted, the wide spectrum of γδ PTCL was emphasized by two additional cases that presented as extranodal large-cell tumours in the omentum or pleura. Both patients were rapidly refractory to polychemotherapy, and died within months after diagnosis. By exclusion, these cases are referred as PTCL NOS.

A summary of the take home messages from session 3 is shown in Tables 3A,B.

Session 4: EBV-associated T/NK lymphomas/lymphoproliferative diseases

EBV-associated T-cell or NK-cell LPDs encompass several disease entities with diverse clinical and pathological findings. In the WHO classification, aggressive NK-cell leukaemia (ANKL) and extranodal NK-cell/T- cell lymphoma (ENKTCL), nasal type, have been described as prototypes of EBV-positive NK-cell or, more rarely, T-cell neoplasms. In addition, EBV infection of T cells or NK cells can sometimes follow acute EBV infection, leading to indolent or severe disease, depending on the immunological response of the individual, and the viral load. The term 'chronic active EBV infection (CAEBV) of T-cell or NK-cell type' has been used in the literature to encompass a very broad spectrum of diseases, with either systemic or cutaneous manifestations. The systemic form may be polyclonal, but, in severe cases, monoclonality may be identified, and severe CAEBV overlaps with systemic EBV-positive T-cell LPDs in the WHO classification. Hydroa vacciniforme (HV) is a chronic relapsing form of T-CAEBV with mainly cutaneous manifestations, whereas mosquito bite allergy is usually of NK-cell origin. Precise criteria for the prediction of clinical outcome in CAEBV are difficult to define, although adverse prognostic factors are T-cell lineage, cytologi- cal atypia, and monoclonality.[2,75]

Session 4 included 40 cases of EBV-associated T- cell or NK-cell LPD, which highlighted a broader spectrum of T-cell/NK-cell neoplasms than are classically defined in the WHO classification, identifying both unusual histological patterns or sites, and unusual clinical presentations. The distinction between benign and malignant was sometimes ambiguous. The observations provide a basis for possible future revisions of the WHO classification.

AGGRESSIVE NK-CELL LEUKAEMIA AND EXTRANODAL NK-CELL/T-CELL LYMPHOMA, NASAL TYPE

The workshop cases include prototypic examples of ANKL and ENKTCL, nasal type (Figure 6A-C). Whereas ANKL is a fulminant systemic malignancy, the cases of ENKTCL illustrated the spectrum of anatomical sites commonly involved by this tumour. Well

represented were cases with nasal, gastrointestinal, cutaneous and testicular involvement. Other, more uncommon, clinical sites included bone and soft tissue, the central and peripheral nervous systems, and the adrenal gland. Two cases presented with breast involvement in patients who had previously received breast implants, suggesting the possibility of an asso- ciation.[44] One of these had a T-cell phenotype, and the second was of NK-cell origin. Among workshop cases of ENKTCL with analysis of *TCR* gene rearrangement, three of four were of the expected NK-cell lineage, one showing clonal T-cell gene rearrangement. Two primary cutaneous ENKTCL cases were also of the T-lineage.

The workshop encountered four cases of EBV-positive T-cell lymphoma that did not conform to ENKTCL as classically defined. All were relatively monomorphic, in comparison with ENKTCL, and all had lymph node involvement at presentation. Interestingly, three of the four were associated with immunodeficiency; one was HIV-associated, one occurred post-transplant, and the third occurred in an elderly patient, aged 80 years (Figure 6D-F). The literature also includes a number of reports of transplant-associated EBV-positive T-cell lymphomas, further supporting an association with immunodeficiency that is generally lacking in EBV-positive NK-cell lymphomas.[76] Two of the EBV-positive T-cell cases had a prominent intravascular component, involving the central nervous system and the skin, respectively. These observations confirm that not all EBV-positive T-cell lymphomas should be classified as ENKTCL, but whether they represent a distinct entity remains to be determined. Like most other EBV-positive T-cell/NK-cell lymphomas, they had a cytotoxic phenotype. In the workshop cases studied, CD56 staining was negative, helping to distinguish them from nasal-type T-cell/NK-cell lymphoma. However, the literature includes some cases that were positive for this marker.[77] Expression of CD5 was variable. The term 'nodal T-cell/NK-cell lymphoma' was proposed for this group of cases.

CHRONIC ACTIVE EBV INFECTION (CAEBV)

CAEBV was defined as a systemic EBV-associated illness characterized by fever, lymphadenopathy and splenomegaly developing after primary virus infection in patients without known immunodeficiency (Figure 6G-I). Affected patients have high levels of EBV DNA in the blood, histological evidence of organ disease, and elevated levels of EBV RNA or viral proteins in affected tissues.[78,79] CAEBV was conceived of as being related to persistent EBV infection of either B cells or T/NK cells, but most of the reported cases involve T cells or NK cells, as is more commonly seen in Asia. The severity of CAEBV is probably related to the immunological response of the individual and the EBV viral load.

Clinical symptoms are usually systemic, and include fever, lymphadenopathy, abnormal liver function test results, and splenomegaly. Both HV and mosquito bite allergy are cutaneous forms of CAEBV, but can progress to systemic involvement and more fulminant disease. [80–82] The spectrum of HV to HV- like T-cell lymphoma is somewhat of a continuum, but clinical, histological and molecular features are all useful in classification (Table 4).

The workshop cases included three cases classified as CAEBV, one accompanied by mosquito bite hypersensitivity, one with features of HV, and a third with unusual chronic cutaneous manifestations, lacking sensitivity to light or exposure to insect bites. The patient

with mosquito bite hypersensitivity developed intestinal perforation secondary to gastrointestinal tract involvement.

The EBV-infected T or NK cells in CAEBV frequently lack histological evidence of malignancy, and range from polyclonal, to oligoclonal, to monoclonal. Because CAEBV constitutes a continuous spectrum of EBV-infected T-cell/NK-cell proliferation, a threetiered classification based on the morphology of infiltrating lymphocytes and clonality was proposed by the CAEBV study group, to aid in prediction of the clinical course and aggressiveness.[83] Most patients with CAEBV have a waxing and waning clinical course, sometimes with spontaneous regression. However, a substantial proportion of patients die from the disease, the main causes of death being HPS and progression to overt T-cell or NK-cell lymphoma.

Atypical T-cell proliferations can sometimes be encountered during the course of infectious mononucleosis, and must be distinguished from CAEBV. It was demonstrated some years ago that the cytotoxic T-cell response to EBV following acute infection can be clonal.[84,85] Three cases were presented at the workshop involving atypical cytotoxic T-cell responses in the setting of infectious mononucleosis. In one case, T-cell clonality was demonstrated in liver and bone marrow. Importantly, the T cells in this type of immune reaction are negative for EBV, aiding correct diagnosis. All patients had a self-limited course.

SYSTEMIC EBV-POSITIVE T-CELL LPD (SEBV-T)

SEBV-T is an aggressive EBV-driven process that overlaps with severe CAEBV of T-cell type 2.[83] The cells may show varying degrees of cytological atypia, but clonality is usually evident from PCR studies of *TCR* gene rearrangement. Most cases present in childhood as a fulminant systemic illness, frequently associated with HPS. Five cases presented at the workshop were classified as SEBV-T: four in children, and one in an adult. The workshop cases reflected the known epidemiological patterns; two were diagnosed in Hispanic or Mexican children, one in an Asian child, and two in Caucasians. The clinical course was fulminant in most cases, with three patients dying within 6 months. Two patients had a good response to therapy, one of whom had undergone allogeneic bone marrow transplantation. The workshop cases high-lighted the clinical overlap with ANKL, in terms of both epidemiology and aggressive clinical course.

CONCLUSIONS

On the basis of the spectrum of cases reviewed at the workshop, and additional data from the literature, an alternative classification of EBV-positive T-cell and NK-cell lymphoproliferative disorders was considered by the panel (Table 5). CAEBV can involve either T cells or NK cells, and mainly affects children. It most commonly follows acute EBV infection. It can be associated with systemic disease, but also includes the novel cutaneous conditions HV and mosquito bite allergy, derived from T cells and NK cells, respectively. CAEBV has an uncertain clinical course - it may be self-limiting, undergoing spontaneous resolution, or progress to fulminant disease associated with HPS or overt T-cell/NK-cell malignancy. Both cytology and clonality are useful in predicting the clinical evolution, but precise criteria are lacking.

ANKL and systemic EBV-positive T-cell LPD can be considered together as aggressive, systemic neoplasms that may supervene on a background of CAEBV. They both tend to occur in children or young adults, but presentation in older adults can be seen. They have an aggressive, often fulminant, clinical course complicated by HPS. They show widespread involvement of the liver, bone marrow, spleen, and lymph nodes, but lymphade- nopathy is usually not a conspicuous feature.

ENKTCL affects mainly adults, and is generally not associated with CAEBV. It is usually of NK-cell derivation, although T-cell cases exist. The nasal form is the prototype, but a variety of extranodal sites can be involved. Nodal T-cell/NK-cell lymphomas also present in adults, but are often associated with immunodeficiency. They are usually of T-cell derivation, and have a more monomorphic cellular composition than ENKTCL.

A summary of the take home messages from session 4 is shown in Table 6.

Session 5: Peripheral T-cell lymphoma, not otherwise specified, post-transplant lymphoproliferative disorders, and mimics

Session 5 included benign mimics of T-cell lymphomas, borderline and unclassifiable cases, T-cell posttransplant lymphoproliferative disorders (PTLD), adult T-cell lymphoma leukaemia (ATLL), and PTCL NOS.

MIMICS OF T-CELL LYMPHOMAS

In addition to benign mimics of T-cell lymphoma, the workshop cases included a spectrum of borderline lesions indeterminate for malignancy, as well as T-cell proliferations that were difficult to characterize. These frequently involved extranodal sites, and occurred in patients of all ages, from childhood to 70 years. Many of the patients had an abnormal immune background, either congenital (as in the case of autoimmune lymphoproliferative syndrome, ALPS), autoimmune disease including myasthenia and Hashimoto's thyroiditis (Figure 7A,B), or iatrogenic immunosuppression.

Acute EBV infection can easily mimic lymphoma with architectural distortion caused by a polymorphous cellular proliferation.[86] Particular caution in diagnosing T-cell malignancy should be exercised when evaluating localized lesions at extranodal sites, and clinical history is a critical part of the evaluation. Most of the cases were CD4-positive, and benign cases included those with a T_{FH} cell phenotype. Clonal T-cell gene rearrangements were occasionally identified in cases that the panel considered to be benign, including one case of HPS in the spleen, and one of indolent small lymphocytic infiltration of the central nervous system.

T-cell lymphoma should be diagnosed with caution in children or young adults, and Kikuchi-Fujimoto disease (histiocytic necrotizing lymphadenitis) may be particularly problematic in the proliferative phase, in which there is paracortical expansion with immuno- blasts, histiocytes, and plasmacytoid dendritic cells (PDCs) (Figure 7C,D). Stains for CD123 and CD68 highlight PDCs, and macrophages stain for myeloperoxidase, despite the absence of a neutrophilic infiltrate.

POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS (T-PTLDS)

T-cell PTLDs are relatively uncommon, and constitute <15% of PTLD cases in most series. In addition to PTCL NOS, cases of HSTL, ALCL and ENKTCL, nasal type, have been reported. They tend to occur late after transplantation, and the majority are extranodal and not associated with EBV. Persistent T-cell large granular lymphocytic expansion can be seen after allogeneic haematopoietic stem cell transplantation, and is frequently monoclonal, resembling T-LGL. This appears to be a reactive immune response to autologous stem cell transplantation, and is not associated with neutropenia or splenomegaly.[87] A restricted T-cell repertoire during immune reconstitution can also lead to the detection of clonal T-cell populations in the absence of malignancy.[88]

ADULT T-CELL LYMPHOMA/LEUKAEMIA (ATLL)

ATLL is a generally aggressive form of lymphoma associated with human T-lymphotropic virus type I (HTLV-I). It is derived from post-thymic T-helper cells positive for CD4 and CD25, and comprises T cells with variable expression of FOXP3, suggesting an origin from T-regu- latory cells.[89] PD1 expression is elevated, and the PD1/ PD-L1 pathway is thought to play a role in fostering persistent HTLV-I infection.[90] Cases of ATLL were well represented in the workshop, and occurred over a broad age range (24–57 years). Most workshop cases were from the Caribbean basin or Brazil, and had a non-leukaemic presentation with lymphadenopathy. Systemic findings in some patients included fatigue, hypercalcaemia, and lytic bone lesions. The common phenotype was CD4-positive/CD25-positive, but there was variable expression of FOXP3, ICOS, and PD1. Aberrant phenotypes included expression of CD8 and CD20. Several cases showed expression of CD30 with a characteristic Golgi and membrane pattern, and these cases should not be confused with ALCL (Figure 7E,F).[91] One case showed co-infection with HIV and HTLV-I.

PERIPHERAL T-CELL LYMPHOMA, NOT OTHERWISE SPECIFIED (PTCL NOS)

PTCL NOS is a heterogeneous category that consists of cases that lack diagnostic criteria for other entities, and is therefore a 'wastebasket' category without specific pathological and clinical features. The workshop addressed three major questions:

1.   Can we recognize meaningfully biologically defined subgroups within PTCL NOS?

2.   Can we define clinicopathological entities that merit separation from PTCL NOS?

3.   Can we identify the borders between PTCL NOS and the better-defined T-cell lymphomas?

IMMUNOPHENOTYPIC CLASSIFICATION OF PTCL NOS

As a strategy to classify T-cell lymphomas, a two-step approach using a formalized panel of antibodies, as proposed by Hsi *et al.*,[92] has proven to be useful. A modified panel of antibodies was applied to all potential cases of PTCL NOS in the workshop where material was available, in order to exclude entities such as AITL, ENKTCL and ALCL (Figure 8A) as defined by the WHO. Expression of only some of the defining aspects of an entity may

not be diagnostic. For example, the presence of a component of CD30-positive anaplastic tumour cells was not necessarily diagnostic for ALCL. On the other hand, with appropriate morphology and uniform expression of CD30, the absence of cytotoxic markers was not regarded as a diagnostic prerequisite. Similarly, when the immunohistochemi- cal protocol was used in all submitted cases, PD1 expression was noted in five of 25 cases tested, including one case in an 11-year-old child. Of these, only two cases had strong and uniform expression of PD1 (Figure 8B-F). Absence of the clinical syndrome of AITL and/or other characteristic features such as FDC proliferation precluded a diagnosis of AITL. It is also uncertain whether PD1 expression in PTCL is an indicator of a TFH phenotype and therefore supportive of a 'cell-of-origin' stratification of PTCL. Expression of PD1 may occur in the absence of other T_{FH} markers, such as ICOS or CXCL13, and may vary in follow-up biopsies, as was demonstrated by one case in the workshop. Similarly, FOXP3 with or without CD25 expression, suggestive of a Treg immunopheno- type, may rarely be seen in PTCL NOS outside the context of ATLL,[93] precluding the use of this as a classifying marker (Figure 8I,J).

A relatively high percentage of extranodal PTCL NOS cases show expression of cytotoxic markers (granzyme B, TIA1, and perforin), most often with coexpression of CD8 and/or CD56. A diagnosis of PTCL NOS is most fitting in cases that are EBER-negative and lack further morphological features of EN- KTCL. In the workshop cases, PTCL NOS with a cytotoxic phenotype occurred most often at extranodal sites (testis and central nervous system), although the possibility cannot be excluded that this observation is actually based on selection bias of the submitted cases. Also, the cytotoxic phenotype in PTCL may not be stable in sequential biopsies.

The expression of aberrant markers such as CD20 is not a class-specific feature in T-cell lymphomas. Eleven such cases were identified, including three AITL, five PTCL NOS, one EATL type 2 and one ATLL (Figure 8B,C). Coexpression of CD20 on malignant T cells needs to be differentiated from the presence of monoclonal or polyclonal blastic B cells, which are commonly seen in AITL, and rarely in PTCL NOS. As in AITL, these clonally unrelated blastic B-cell proliferations are often, but not always, EBV-driven.[30,34]

Loss of TCR protein expression in the presence of *TCR* rearrangement is frequently encountered in PTCL NOS of the intestinal tract (see Session 3), where there appears to be an overrepresentation of cases with a cytotoxic phenotype. In the workshop cases of PTCL NOS, loss of TCR expression was seen in seven of 24 cases, including one case with a cytotoxic phenotype.

The above considerations show that, as yet, there is no formal stratification of PTCL NOS by 'cell of origin', and no single marker other than ALK is class- restricted. With the identification of novel molecular alterations, this may change in the future.

MOLECULAR CLASSIFICATION OF PTCL NOS

Molecular studies, including next-generation sequencing, have been successful in identifying novel genetic alterations in T-cell lymphoma. Of these, some may indeed be specific and therefore defining for certain clinicopathological entities. In PTCL NOS and

morphologically related diseases, the most challenging alterations may be the various translocations involving 6p25.[6] Two such cases were submitted, of which one was diagnosed as PTCL NOS and the other as ALK-negative ALCL. In 12 cases, complete karyotypic information was submitted. Three cases showed the presence of isochromosome 7q (i7q10), which is generally considered to be characteristic for HSTL. One of these cases did indeed represent HSTL, but the other two were PTCL NOS (with features reminiscent of EN-KTCL) and EATL type II. Similarly, deletions involving 6q24 were a recurrent finding, but in different entities (ENKTCL and PTCL NOS with features reminiscent of AITL). Therefore, it can be concluded that, at present, insufficient data are available for a molecular or cytogenetic classification of T-cell lymphomas and PTCL NOS.

A summary of the take home messages from session 5 is shown in Table 7.

Acknowledgements

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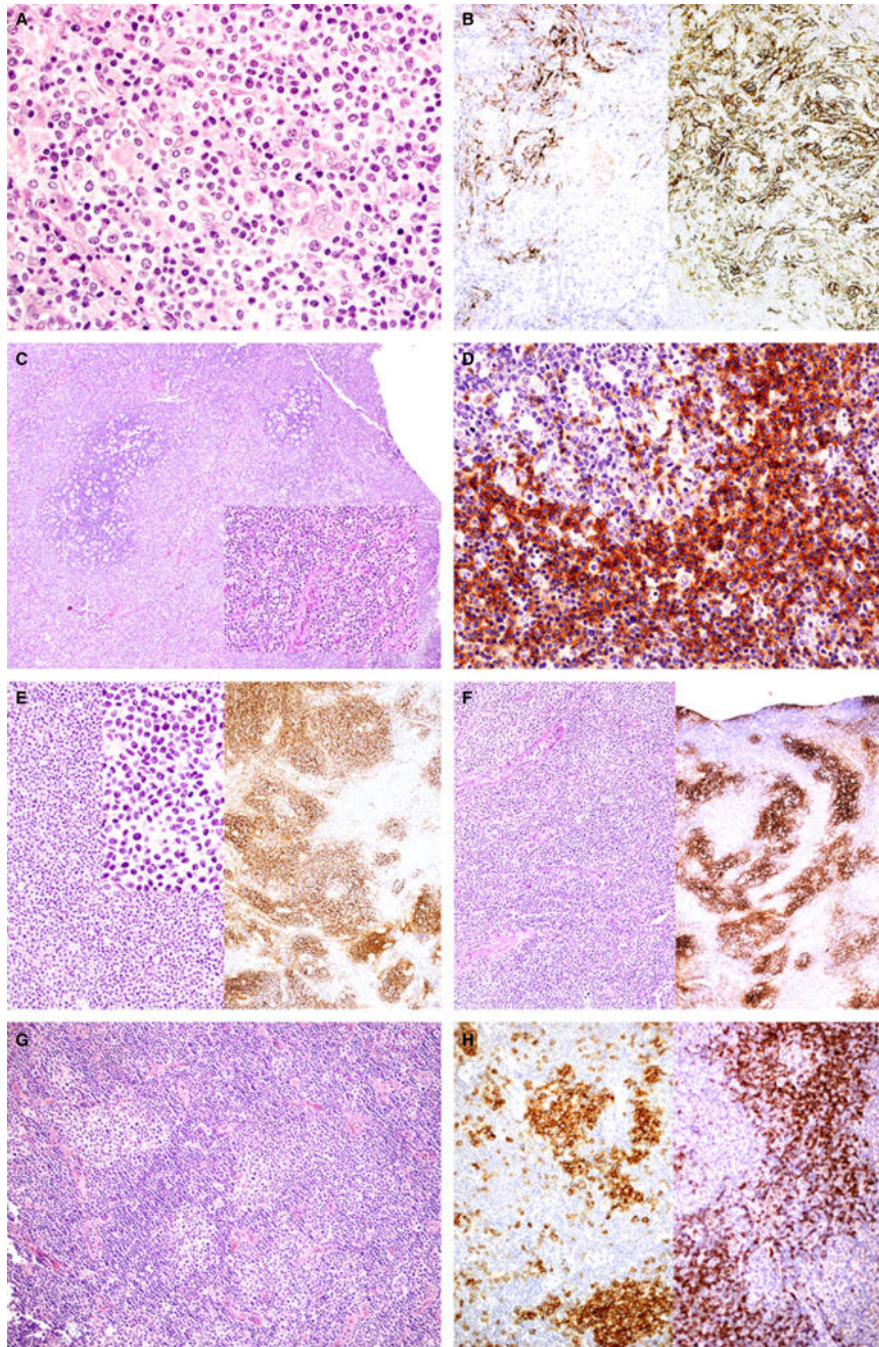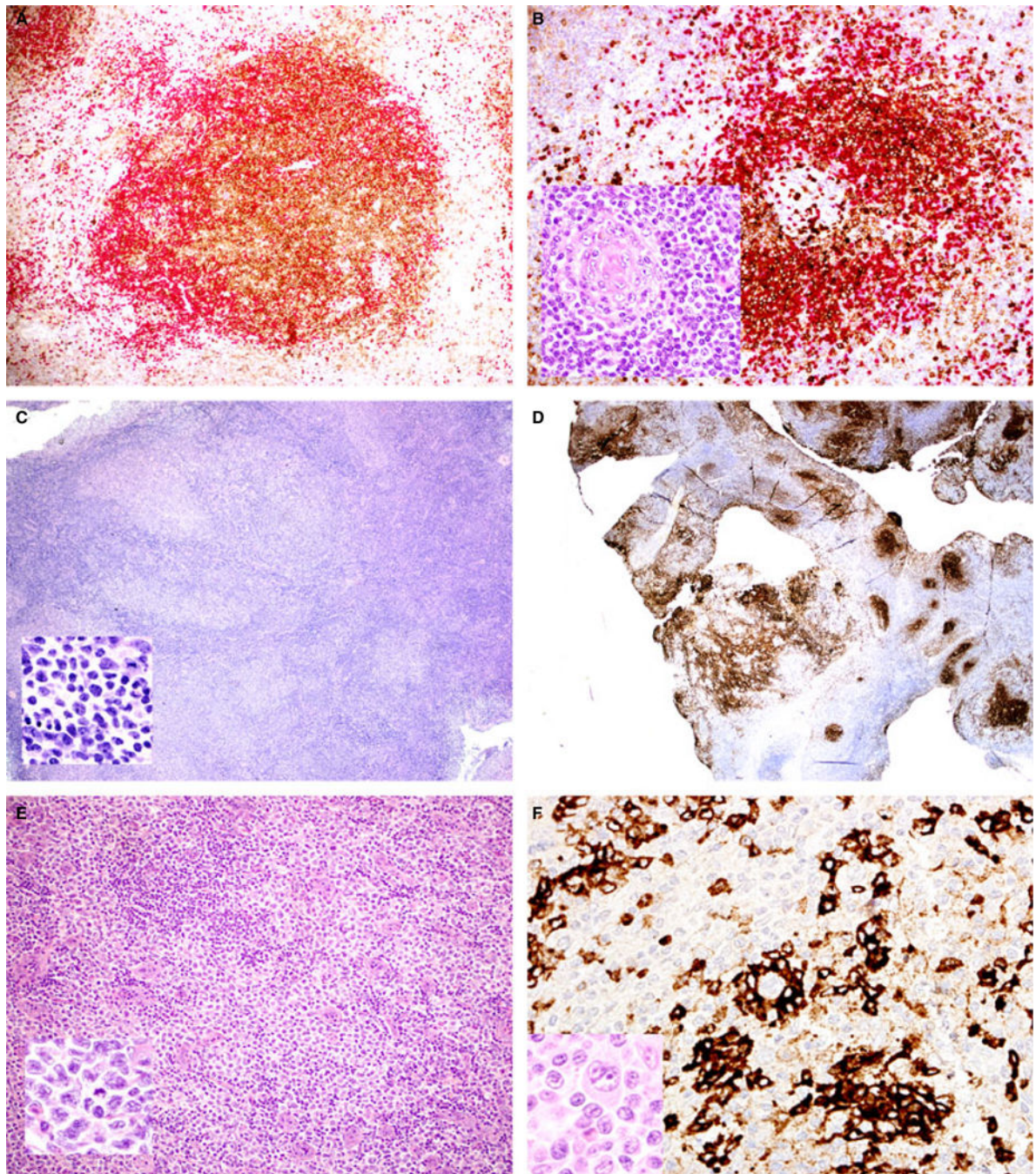
Figure 1.
A, B. A case of 'typical' angioimmunoblastic T-cell lymphoma (AITL) (case 337, Dr Vornanen, Fimlab, Finland). **A,** H&E shows a polymorphous infiltrate with clear cells amidst hyperplastic high endothelial venules (HEVs). **B,** CD21 staining (left panel) fails to show significant expansion of follicular dendritic cell (FDC) meshworks, whereas CD23 staining (right panel) shows florid FDC hyperplasia. **C, D,** A case of AITL, pattern I (case 328, Dr Nelson, Caris Diagnostics, USA). A 73-year-old female presented with systemic symptoms, generalized lymphadenopathy, and skin changes, and had polyclonal

hypergammaglobulinaemia. **C,** H&E shows florid perifollicular monomorphous proliferation of medium-sized lymphoid cells. The inset shows the paracortex with a prominence of HEVs. **D,** The perifollicular neoplastic T cells express PD1. **E, F,** A case that showed typical AITL on initial biopsy and a tumour cell-rich pattern of AITL on follow-up biopsy (case 55, Dr Tzankov, University Hospital Basel, Switzerland). **E,** Second biopsy showing a tumour cell-rich morphology (left panel) with florid FDC expansionon CD21 staining (right panel). **F,** First biopsy showing 'typical' AITL (left panel) with florid FDC expansion on CD21 staining (right panel). **G, H,** A case of AITL with an unusual pattern (case 168, Dr Dogan, Mayo Clinic, USA). A 66-year-old presented with generalized lymphadenopathy, skin rash, and pleural effusion. **G,** H&E shows partial effacement of nodal architecture by paracortical clusters of clear cells amidst hyperplastic HEVs; amidst the clusters, there are many nodules of small lymphoid cells. **H,** left panel, PD1 staining highlights the neoplastic TFH cells corresponding to the clusters of clear cells. **H,** right panel, the nodules of small lymphocytes are IgD-positive

Figure 2.

A, B, A case of AITL showing overlap with the follicular variant of PTCL NOS (PTCL-F) (case 225, Dr Sabatini, S. Orsola-Malpighi Hospital, University of Bologna, Italy). Pax5 (red) and CD10 (brown) double staining highlights the CD10-positive neoplastic T cells distributed in a follicular pattern (**A**) and also occasionally around a regressed follicle (**B**), **B,** Inset shows the details of the regressed follicle on H&E staining. **C-E,** A case of PTCL-F showing overlap with AITL (case 305, Dr Burke, Alta Bates Summit Medical Center, USA); the follow-up biopsy showed no follicular growth pattern or features of typical AITL. **C,**

H&E of the first biopsy shows a follicular growth pattern. The inset shows the neoplastic lymphoid cells to be of small to medium size. **D**, CD2 3 staining highlights focal FDC expansion. **E, H&E** of the follow-up biopsy shows a monotonous infiltrate of larger atypical lymphoid cells, amidst hyperplastic HEVs. **F,** A case of typical AITL with a prominence of EBV-negative Hodgkin/Reed-Sternberg (HRS) cells (case 35, Dr Vijnovich-Baron, Centro de Patologi'a CEPACIT, Argentina). CD10 staining highlights the neoplastic T cells, which form rosettes around the HRS cells. F inset: **H&E** staining, which shows an HRS cell surrounded by medium-sized neoplastic lymphoid cells.
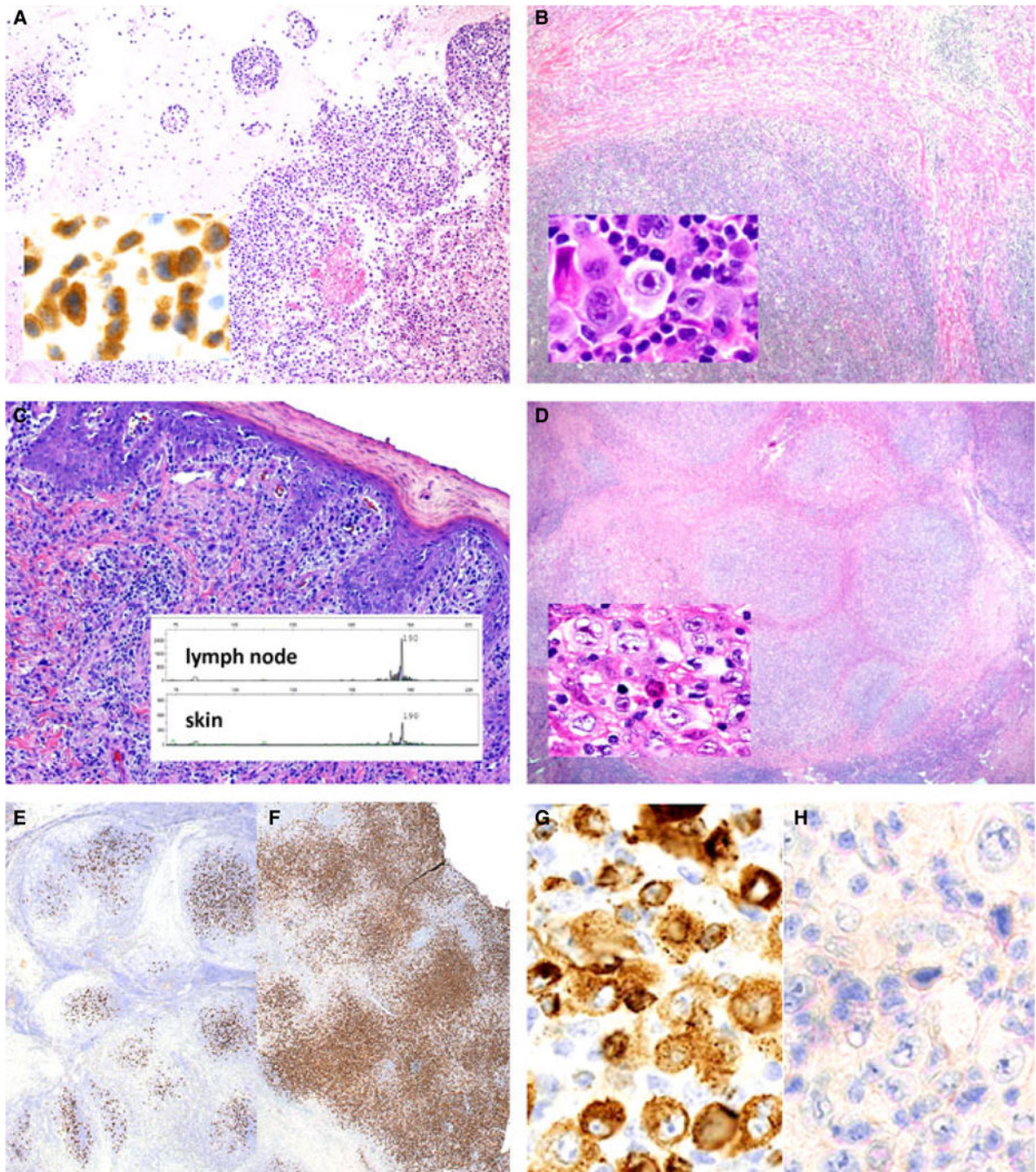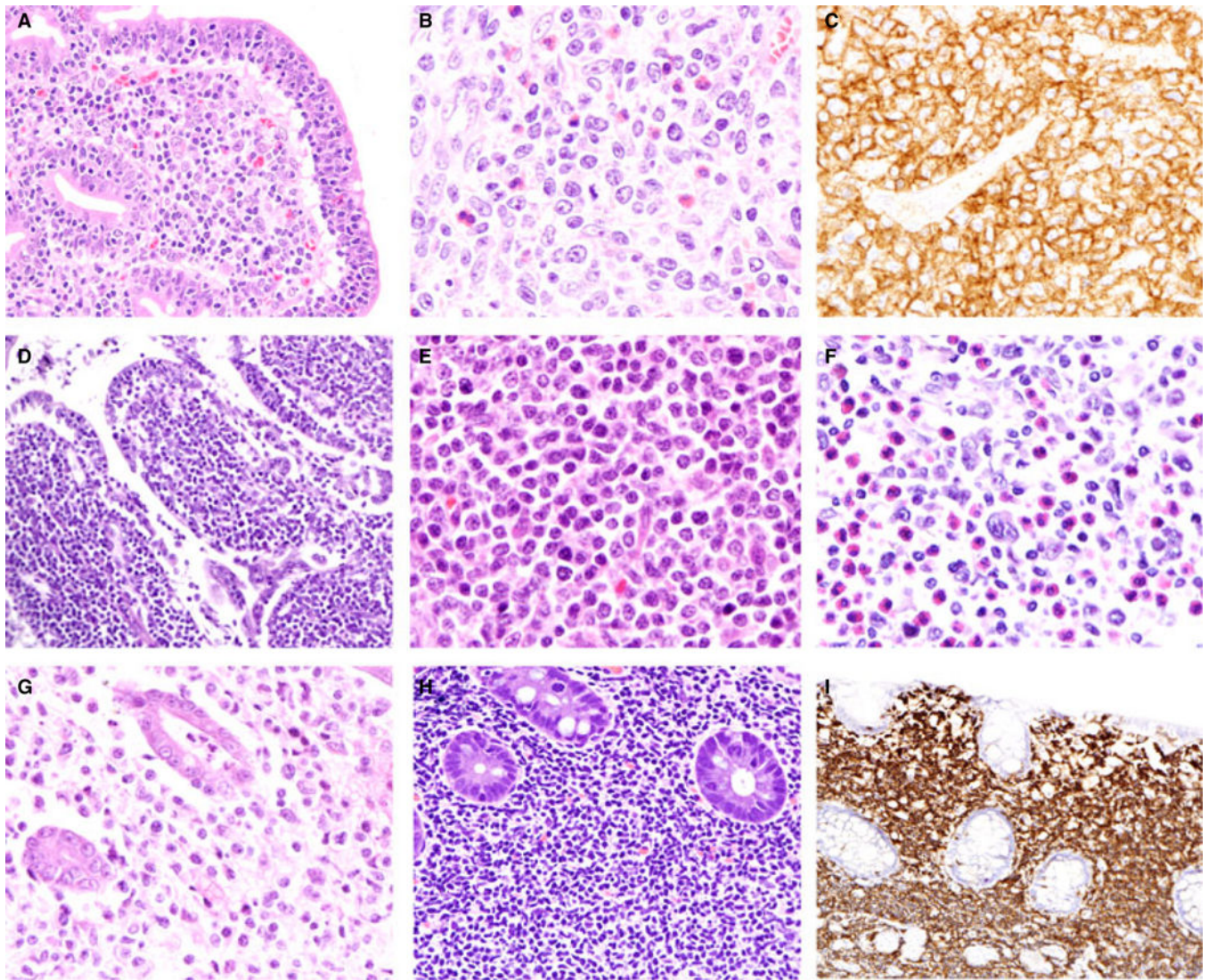
Figure 3.
A, ALK-positive anaplastic large-cell lymphoma confined to the central nervous system (case 256, Dr Park, Gil Medical Centre, South Korea). Staging did not reveal any other manifestation except right-side hemisphere and brainstem (**H&E,** insert ALK1). It is of note that ALK staining was purely cytoplasmic. **B, C,** Involvement of a lymph node by CD30-positive lymphoproliferative disease (case 37, Dr Jaffe, National Institute of Health, USA). This process resembles classical Hodgkin lymphoma, which was the diagnosis originally proposed (**B,** H&E). The patient's skin lesions were not appreciated at the time of initial

diagnosis, and were only recognized some years after treatment for a presumed diagnosis of Hodgkin' lymphoma. The skin lesions were later biopsied and recognized as lymphomatoid papulosis (**C, H&E**). An identical clonal T-cell gene rearrangement was identified in DNA from the lymph node and the subsequent skin biopsies (**C,** inserts according to BIOMED2 protocols). In both biopsies, the blasts were positive for CD30 and CD15 as well as cytotoxic proteins, but lacked Pax5 or detectable EBV. **D-G,** Peripheral T-cell lymphoma mimicking Hodgkin lymphoma (case 253, Dr Bacon, Newcastle upon Tyne Hospitals, UK). The patient was a 60-year-old with left axillary and supraclavicular lymph node swelling, generalized itch, but no B symptoms. After the diagnosis of classical Hodkin lymphoma, the patient was treated accordingly, but relapsed 6 years later. Histologically, nodules separated by fibrous bands harboured varying numbers of large mononuclear Hodgkin-like cells in a background of small lymphocytes, numerous histiocytes, plasma cells, and small numbers of eosinophils (**D, H&E**). In some nodules, the large cells were relatively sparse (**E,** CD30 staining), whereas in others they were more numerous and almost confluent (**F,** CD30 staining). The Hodgkin/Reed-Sternberg-like cells showed expression of CD30 and CD15 in combination with cytotoxic proteins such as perforin (**G**) but no Pax5 (**H**) or LMP1.

Figure 4.

A, EATL type I shows prominent epitheliotropism by atypical lymphocytes (case 100, Dr Ananthanarayanan, University of Chicago, USA) **B,** The infiltrate is polymorphous with admixed eosinophils. The cells show variation in size and shape. **C,** This case was positive for TCRc, and was negative for TCRb (not shown). **D,** This example of EATL type II shows the characteristic prominent epitheliotropism by monomorphic small to medium-sized lymphoid cells (**E**) (case 244, Drs Brar and Jagmohan, UHS Hospitals, USA). Interestingly, the tumour cells were positive for TCRb, and negative for TCRc. **F,** This case was classified as PTCL NOS, and presented in the stomach in a patient with marked eosinophilia (41 000/ mm3). However, the patient had widespread disease, with involvement of multiple extranodal sites. Atypical CD30-positive T cells are associated with numerous eosinophils (case 252, Dr Parrens, Bordeaux University Hospital, France). **G,** NK-cell enteropathy (case 329, Dr Aline-Fardin, Bordeaux University Hospital, France): atypical lymphoid cells with abundant pale cytoplasm within the lamina propria of a colonic biopsy. **H,** Indolent CD8-positive T-cell lymphoproliferative disease can involve multiple sites in the gastrointestinal

tract. In this example, the cells infiltrate the colonic mucosa. Note that the glandular epithelium is spared. **I,** Cells are CD8-positive. (**H**) and (**I**) were contributed by Dr Jaffe).
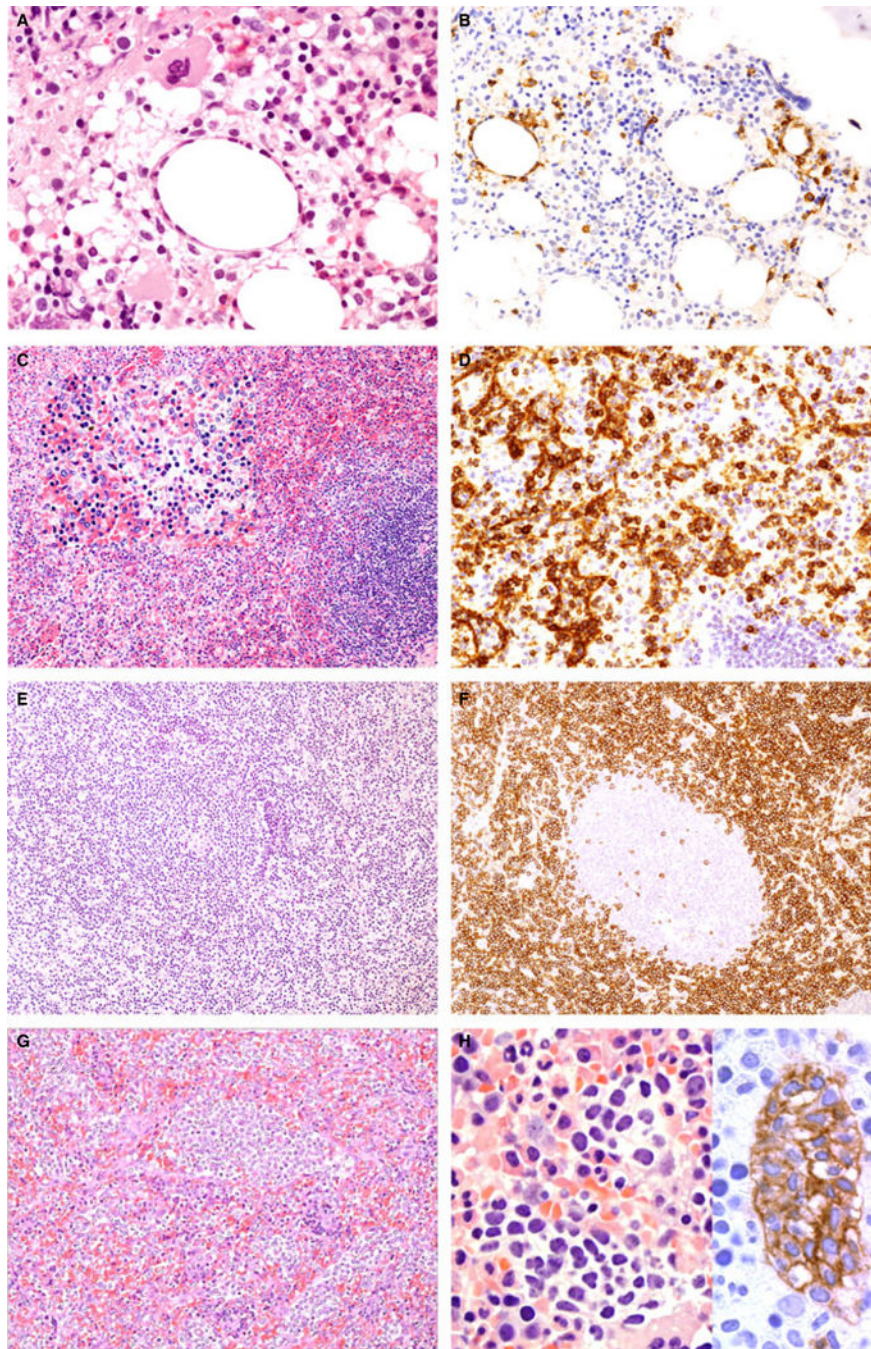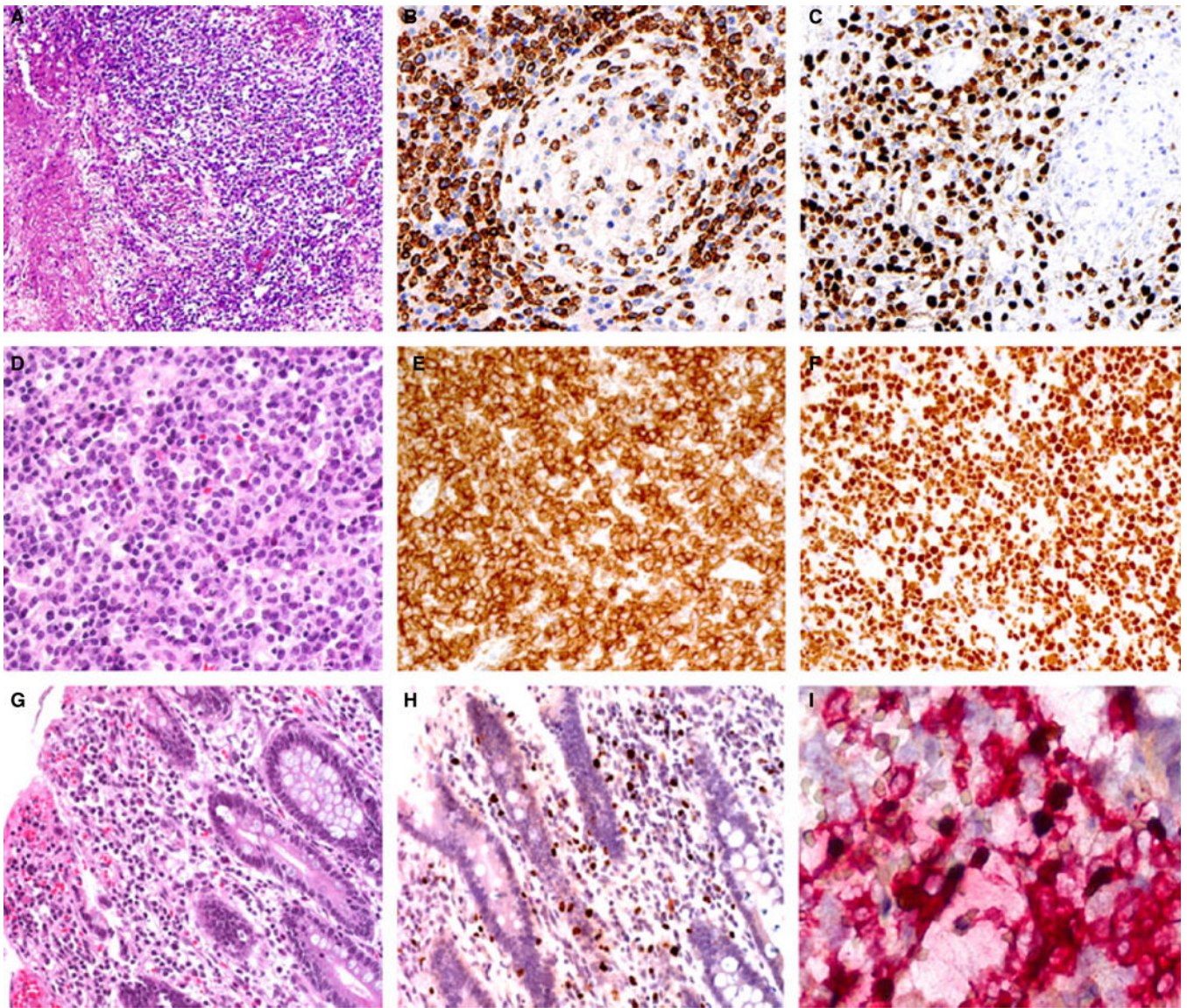
Figure 5.

Subcutaneous panniculitis-like T-cell lymphomas with bone marrow involvement at presentation (case 193, Dr Brown, University of Michigan, USA). This 28-year-old woman presented with subcutaneous nodules associated with adenopathies, splenomegaly, B symptoms, pancytopenia, and haemophagocytic syndrome. **A**, Biopsy of a subcutaneous nodule disclosed typical features of SPTCL. In the concomitant bone marrow biopsy, atypical lymphoid cells with abundant pale cytoplasm surround adipocytes (typical rimming). **B**, Cells are CD8-positive. **C**, This example of γ/δ T-LGL in the spleen (case 61,

Dr Nagendra, Memorial Medical Center, USA) shows the characteristic sparse and minimal infiltrate of the red pulp by small lymphocytes without significant atypia (inset), with remnants of follicles in the white pulp. **D**, Cells are CD8-positive. Note that this case showed restricted expression of a single killer cell immunoglobulin-like receptor (KIR) isoform, CD158b. **E**, Nodal involvement by T-cell large granular lymphocytic leukaemia (case 185, Dr Wotherspoon, Royal Marsden Hospital, UK). A dense monotonous infiltrate of small lymphocytes is seen. **F**, Cells with a CD8-positive phenotype. Note the presence of residual B-cell (CD8-negative) follicles. This 51-year-old man presented with abdominal discomfort, and was found to have mesenteric lymphadenopathy and mild splenomegaly. The lymph node biopsy was initially regarded as PTCL NOS, but was revised to T-LGL when the patient developed lymphocytosis with an excess of clonal large granular lymphocytes 2 years later. The patient was well at last follow-up 38 months after initial presentation, with no treatment. **G**, Hepatosplenic T-cell lymphoma in a 66-year-old man with pancytopenia and splenomegaly (case 313, Dr Oliviera, Mayo Clinic, USA). The spleen shows an expanded red pulp with a dense proliferation of monotonous medium-sized cells with moderately abundant cytoplasm within splenic cords and sinuses. **H**, The bone marrow core with CD3 immunostaining is of critical diagnostic value: there is prominent or exclusive distribution of the neoplastic cells within more or less dilated sinuses (left), and this distribution is emphasized by CD3 staining (right). In this case, cells had an α/β phenotype, and were CD5-negative/CD56-positive, with a non-activated cytotoxic (TIA1-positive, granzyme B-negative) profile.

Figure 6.
A-C, Extranodal NK-cell/T-cell lymphoma, nasal type. **A, H&E**-stained section shows infiltration by atypical lymphocytes with necrosis and haemorrhage (case 32, Dr Goodlad, Western General Hospital & University of Edinburgh, UK). The patient, a 70-year-old Caucasian man, presented with facial swelling and induration. The tumour involved paranasal sinuses, skin, and testis. B, Perforin-positive neoplastic cells show prominent angioinvasive growth. **C,** Almost all tumour cells are EBER-positive. **D-F,** Nodal EBV-positive T-cell/NK-cell lymphoma. **D, H&E** section shows diffuse infiltration by monomorphic small to medium-sized lymphoid cells. The patient was a 53-year-old Asian man who presented with fever, systemic lymphadenopathy, splenomegaly, and haemophagocytosis. **E,** Tumour cells are CD8-positive, and positive for TCRβ and TIA-1 (not shown). **F,** They are also diffusely positive for EBER (**D-F** contributed by Dr Y. H. Ko). **G-I,** Chronic active EBV infection. **G,** Colonic mucosa shows a mixed inflammatory

infiltrate in the lamina propria (case 192, Dr Oh, Hanyang University Hospital, Republic of Korea). The patient was a 5-year-old boy who presented with recurrent bowel perforation and wound dehiscence with fever, abnormal liver function, and NK lymphocytosis (68% of lymphocytes). EBV PCR showed a high viral load (11 450 copies per 5 μl of whole blood). The patient had a waxing and waning clinical course, with subsequent development of mosquito bite hypersensitivity. H, EBER *in-situ* hybridization highlights EBV-infected lymphocytes. **I,** EBER-positive cells of colonic mucosa are positive for CD3 (red, CD3; brown, EBER).
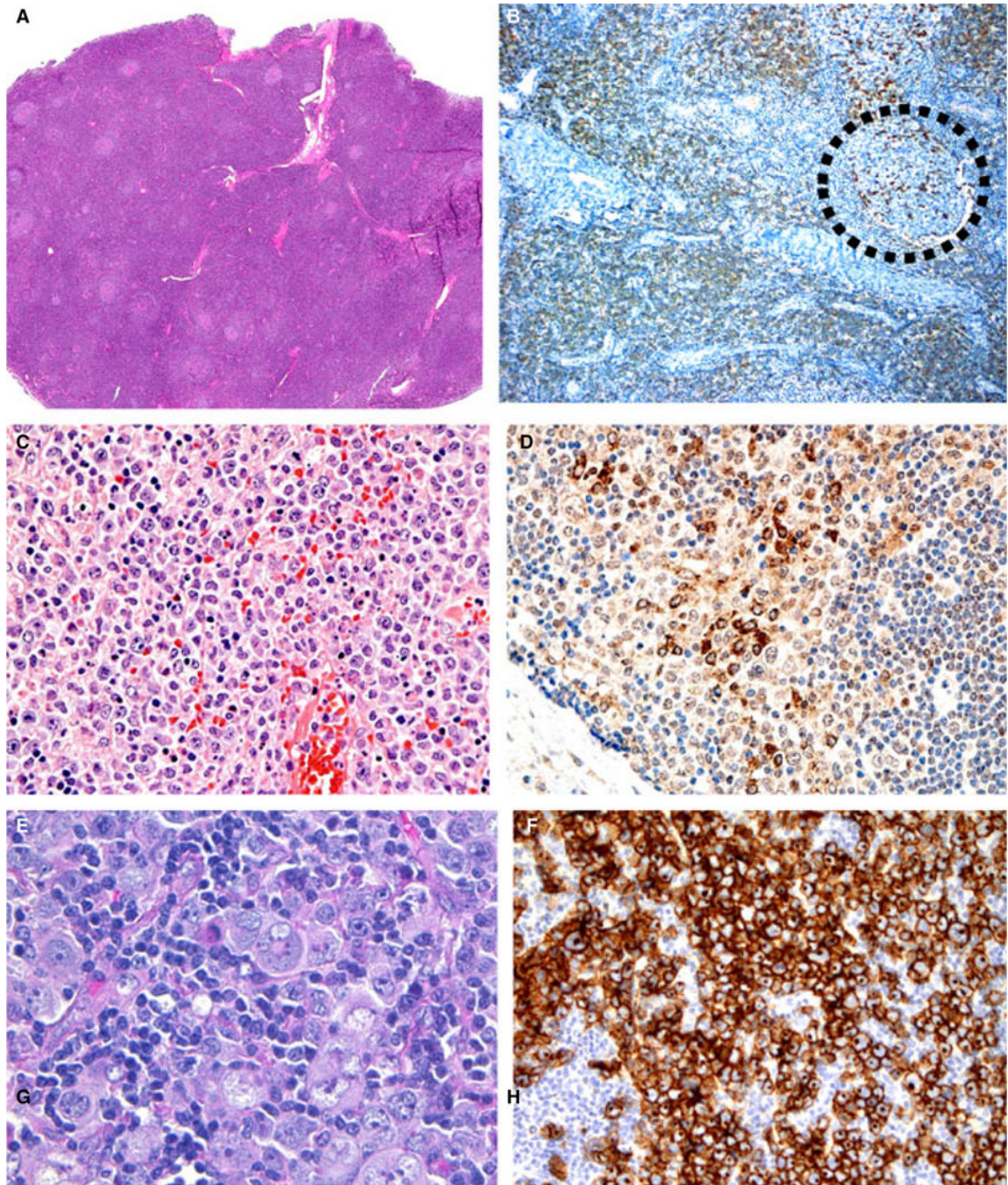
Figure 7.

A, B, Thyroid mass from a 44-year-old male with a 10-year history of Hashimoto's thyroiditis. **A** section shows residual reactive lymphoid follicles and prominent T-zone proliferation. The panel diagnosis was T-lymphoproliferative disorder/indolent peripheral T-cell lymphoma, and illustrates the difficulty in characterizing this type of extranodal T-cell proliferation. **B** shows staining for PD1, suggesting TFH cell proliferation. Note that the staining is less intense than in the hyperplastic germinal centre, which is highlighted (case 314, Dr Sarah Ondrejka, Cleveland Clinic, USA). **C, D,** Lymph node biopsy from a 35-

month-old boy with fever and cervical adenopathy, and referred with an outside diagnosis of PTCL. An H&E photomicrograph (**C**) shows sheets of blasts and plasmacytoid dendritic cells, and the panel diagnosis was Kikuchi-Fujimoto disease. Stain for CD123 (D) highlights plasmacytoid dendritic cells (case 306, Dr Nancy Harris, Massachusetts General Hospital, USA). **E, F,** A 49-year-old Jamaican woman presented with enlarged cervical lymph nodes, fever and weight loss, and positive HTLV-I serology. A lymph node biopsy shows features of ATLL, with numerous large anaplastic cells, staining for CD30 in F. CD30-positive anaplastic cells are not uncommon in ATLL, and should not lead to misclassification as ALCL in the setting of HTLV-I infection (case 41, Dr S. Choi, Hospital of the University of Pennsylvania, USA).
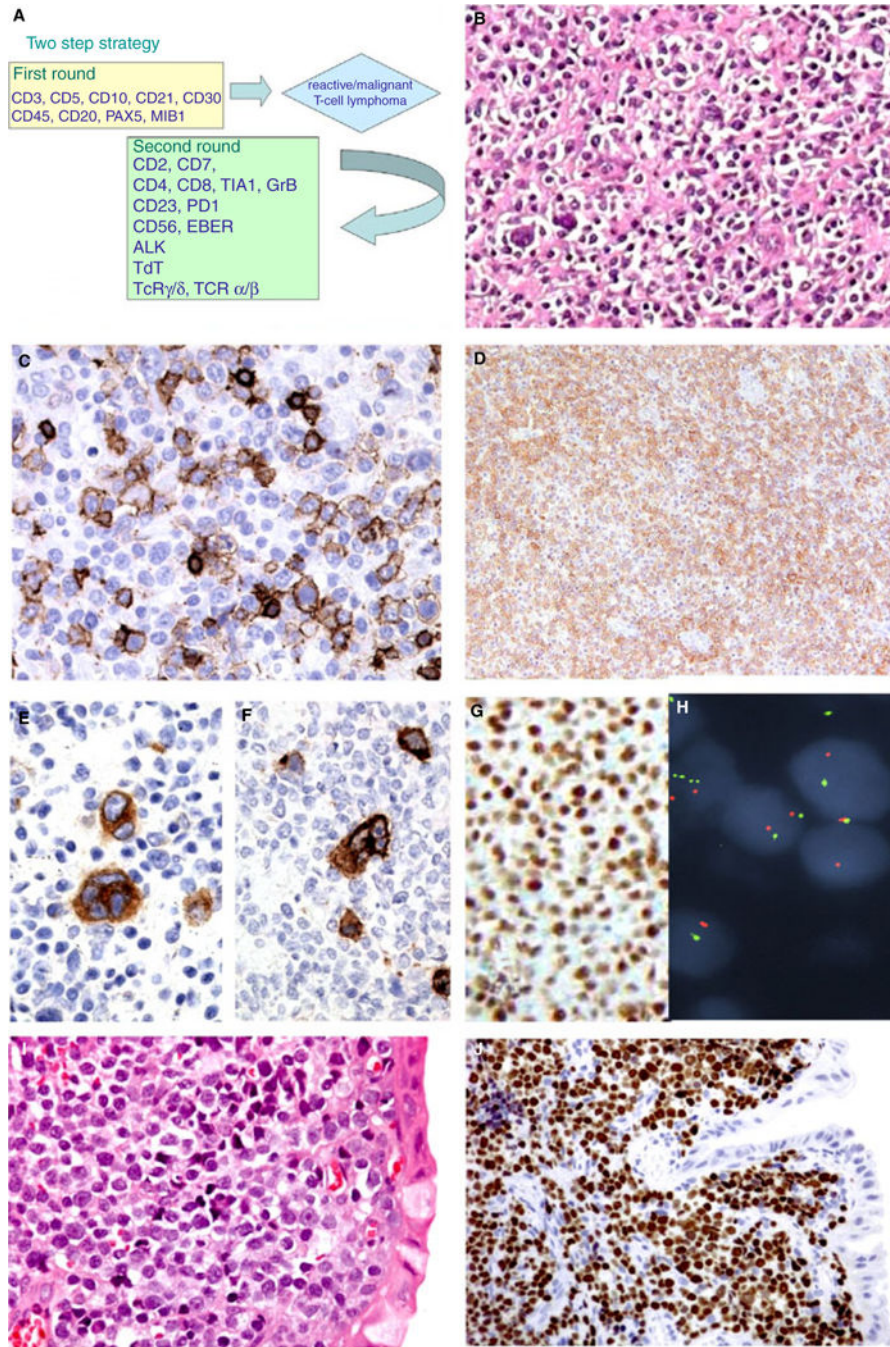
Figure 8.

A, A two-step algorithm for the diagnostic strategy for T-cell lymphoma. The primary staining panel (first round) for all suspected T-cell lymphomas will help to distinguish reactive and neoplastic conditions. In any case of T-cell lymphoma the second round of staining can be used to arrive at a final classification. Regarding the use of CD21 and CD23 for FDC detection, see also Figure 1A,B and the corresponding section in the text. **B-F,** A 76-year-old male presented with generalized lymphadenopathy (case 190, Dr L. Ruco, Dr A. Di Napoli and Dr M. C. Cox, Rome, Italy). The panel diagnosis was peripheral T-cell

lymphoma, NOS (**B**). The case shows varying expression of CD20 (**C**). Moreover, the tumour cells were positive for PD1 (**D**) in the absence of other TFH markers. Moreover, this case illustrates the presence of an EBV-driven population of Hodgkin-like cells positive for CD30 (**E**) and LMP1 (**F**). G,H, The lymph node of a 43-year-old man with submandibular lymphadenopathy after a renal transplant was diagnosed as peripheral T-cell lymphoma, NOS, and showed monoclonal T-cell proliferation with aberrant PAX5 expression (**G**), but in the absence of PAX5 amplification (**H**) (case 364, Dr M. Lew, Boston, USA; FISH performed by Dr A. L. Feldman, Mayo Clinic, USA). **I,J,** The case of a 61-year-old female, presenting with abdominal lymphadenopathy, a jejunal mass and colonic involvement (**I**), was also was diagnosed as peripheral T-cell lymphoma, NOS, and illustrates isolated expression of FOXP3 (J) in the context of a cytotoxic T-cell phenotype (CD3-positive, CD25-positive, CD4-positive, CD8-negative, CD30-negative). There were no signs of enteropathy, and HTLV-I serology was negative (case 151, C. Lome-Maldonado, Mexico).

Table 1.

Session 1 take home messages

In a few cases of typical AITL, CD23 staining may be better than CD21 staining at demonstrating FDC expansion
AITL pattern I represents partial nodal involvement in otherwise disseminated disease; the pattern of CD10-positive/T_{FH} cells, spilling out into the interfollicular area from the outer zone of the follicle rather than being confined to the follicle, helps to distinguish this from reactive hyperplasia
Reactive mimics of AITL – clonality analysis may be misleading
In addition to typical AITL, there are morphological variants that deviate from currently accepted defining criteria, and include the following: (i) hyperplastic follicles (pattern I); (ii) epithelioid cell-rich; (iii) tumour cell-rich/clear cell-rich; (iv) follicular; and (v) rich in IgD-positive small B cells
PTCL-F may not be a distinct entity, but may be part of the spectrum of AITL
t(5;9)(q33;q22) may be seen in AITL, and may not help to distinguish PTCL-F from AITL
CD10 and TFH markers show varying sensitivity and specificity in their expression in TFH-derived neoplasms; they may rarely be expressed by other specific PTCL subtypes
PD-1 is strongly expressed in most cases of AITL, but staining is fixation-dependent; comparison with an internal control, when present, helps to distinguish genuine weak staining from fixation-related poor-quality staining
AITL may be associated with a variety of EBV-positive and EBV-negative B-cell proliferations
EBV-positive or EBV-negative Hodgkin/Reed–Sternberg (HRS)-like cells may be encountered in AITL, and should not be mistaken for classical Hodgkin lymphoma or a composite tumour. Against the latter is the absence of clear demarcation between the areas with HRS-like cells and the underlying AITL

Table 2.

Session 2 take home messages

ALK-positive ALCL
ALK immunohistochemistry is recommended in all T-cell lymphomas with expression of CD30, including primary cutaneous LPD
ALK-positive ALCL might present as localized disease at extranodal sites
In the setting of localized disease, extranodal manifestation might not be a risk factor
Diagnostic criteria for ALK-negative ALCL
Prerequisite
Morphology indistinguishable from ALK-positive ALCL: cytology (hallmark cells) and architecture (cohesive)
CD30 expression, strong and abundant (almost all cells)
Desirable
Reduced T-cell surface markers
Cytotoxic phenotype
EMA positivity
Sinusoidal growth
Genetics – promising, but role to be determined!
CD30-positive cutanous lymphoproliferative disease
CD30-positive clonal cells might be detected in regional lymph nodes accompanying primary cutaneous CD30-positive LPD
CD30-positive transformation of mycosis fungoides to be excluded in any case of cutaneous CD30-positive LPD by assessing patient history and presentation outside nodules
If a single lymph node shows infiltrates of an ALK-negative ALCL or a 'Pax5-negative HL', or any other CD30-positive T-cell lymphoma, ask for a detailed clinical history of skin lesions

Table 3.

Session 3 take home messages (A) Part 1 and (B) Part 2

(A) Part 1
Many T-cell and NK-cell lymphomas can present in the gastrointestinal tract, and nearly all of these have a cytotoxic phenotype
EATL type I
EATL type II
PTCL NOS
Indolent T-cell and NK-cell lymphoproliferative diseases
EBV-positive extranodal NK-cell/T-cell lymphoma
Both EATL type I and EATL type II show epitheliotropism, but have distinguishing features
EATL type I
Evidence of coeliac disease
Usually αβ, but some cases are γδ
Often double-negative for CD4 and CD8
Polymorphous cytological composition
EATL type II (monomorphic intestinal T-cell lymphoma)
Usually no evidence of coeliac disease
Worldwide distribution
Usually γδ, but can be αβ
Monomorphic CD8-positive, CD56-positive
Peripheral T-cell lymphoma, NOS
A diagnosis of exclusion
A variety of anatomical sites: stomach, colon, and also small intestine
Absence of history of coeliac disease
Absence of demonstrable epitheliotropism
Often TCR silent, may be αβ or γδ
Cytotoxic
Indolent T-cell and NK-cell lymphoproliferative disorders of the GI tract
May be mistaken for T-cell or NK-cell lymphoma
Lack epitheliotropism
Superficial, confined to lamina propria and muscularis mucosae
Cytotoxic T-cell or NK-cell phenotype
Relapsing chronic course, without dissemination
(B) Part 2
Cytotoxic cutaneous T-cell lymphoma or lymphoproliferation
CD8-positive T-LPD in the skin ('ear type') is an indolent disorder, to be distinguished from other CD8-positive lymphomas in the skin, such as primary cutaneous
CD8-positive aggressive TCL (epidermotropic),
CD8-positive mycosis fungoides, or even subcutaneous
TCL; may belong to a wider spectrum of indolent
T-cell or NK-cell LPD arising in skin and mucosa

Subcutaneous TCL (αβ) can occasionally involve extracutaneous sites, with a 'lipotropic' pattern (including bone marrow)

Subcutaneous TCL (αβ) may be aggressive when disseminated and/or associated with haemophagocytic syndrome

The spectrum of γδ T-cell lymphoma includes tumours involving other/unusual (non-cutaneous, non-mucosal) extranodal sites; currently they are referred as PTCL NOS

T-LGL

An indolent disease, transformation exceptional (if it exists)

Asymptomatic or mild features (neutropenia)

Presence of LGLs in the peripheral blood, but cases without significant LGLs exist

Often αβ, may be γδ or NK

Activated cytotoxic (i.e. granzyme B-positive/perforin- positive) phenotype

BM trephine required in atypical situations, especially in cases without significant LGLs: infiltrate is sparse and interstitial, with minimal involvement of the sinuses (small clusters of six to eight CD8-positive cells)

STAT3 mutations in approximately one-third of cases (T and NK)

Hepatosplenic T-cell lymphoma

Aggressive, B symptoms, cytopenia

No lymphocytosis

CD4-negative/CD8-negative, CD5-negative, CD56-positive

Usually γδ, may be αβ

Non-activated cytotoxic (TIAI-positive, granzyme B-positive)

BM trephine critical for the diagnosis on bone marrow: sinus pattern (CD3-positive)

Spleen: monomorphic small/medium-sized cells, cords and sinuses of the red pulp

Isochromosome 7q inconstant (50–60%) and non-specific

T-LGL versus HSTL?

γδ versus αβ not helpful

Similar pattern of infiltration in the spleen and the liver; be cautious when dealing with spleen and liver samples

Critical value of bone marrow biopsy for the diagnosis of HSTL: demonstration of a prominent CD3-positive infiltrate in the sinuses is almost mandatory

Atypical features for T-LGL include the absence of significant LGLs, some lymphadenopathy in rare cases, and γδ or NK phenotype

Atypical features for HSTL include an indolent initial phase in some cases, cytological pleomorphism (medium/large cells), granzyme B staining (partial), and possible circulating cells in the late phase (relapses?)

Integration of clinical, pathological and phenotypic data is needed in difficult cases

Table 4.

Session 4 take home messages; criteria for stratifying hydroa vacciniforme (HV)-like T-cell LPD

Findings	HV	HV-like T-cell lymphoma
Photosensitivity	+	+/−
High viral load in peripheral blood	−/+	+
CAEBV symptoms	−/+	+/−
EBV clonality	−/+	+
T-cell clonality	−/+	+
Depth of infiltrates	Dermal	Subcutaneous
EBV-positive cells in skin	+	++
Atypia of T cells	−	+/−

Table 5.

Session 4 take home messages; classification of EBV-positive T-cell and NK-cell LPD

Chronic active EBV infection
Systemic (T or NK)
Hydroa vacciniforme (T cells)
Mosquito bite allergy (NK cells)
Systemic, malignant EBV-positive LPDs
Aggressive NK-cell leukaemia/lymphoma (NK)
Systemic EBV-positive T-cell LPD
Extranodal NK-cell/T-cell lymphoma, nasal type
Nodal T-cell/NK-cell lymphoma

Table 6.

Session 4 take home messages

Chronic active EBV infection (CAEBV)
May involve either T cells or NK cells, usually polyclonal
Mainly in children, rarely in adults
Includes hydroa vacciniforme and mosquito bite hypersensitivity
Uncertain clinical evolution; may have a self-limiting clinical course or progress
Cytological features and clonality are both useful in predicting clinical evolution, but precise criteria are lacking
Aggressive NK-cell leukaemia and systemic EBV-positive
T-LPD of childhood
May arise on a background of CAEBV - but usually have a rapid onset with severe systemic symptoms
Clonal (may be hard to show for NK)
Mainly children and young adults
Aggressive clinical course, often with HPS
Systemic involvement of the 'reticuloendothelial system', including spleen, liver, bone marrow, and lymph nodes
Extranodal NK-cell/T-cell lymphoma, nasal type
Mainly adults
Not associated with prior CAEBV clinically
Usually NK cell, may be T cell
Nodal T-cell/NK-cell lymphoma
Mainly adults, often elderly
Often associated with immunodeficiency
HIV, post-transplant, immune senescence
Usually T cell

Table 7.

Session 5 take home messages

Use caution in diagnosing T-cell lymphoma in children and in patients with localized extranodal disease
Clinical history is essential, particularly with regard to infections (EBV), autoimmune dysfunction, both congenital (ALPS) and acquired, iatrogenic immunosuppression, and drug use
A T_{FH} phenotype with staining for PD1 is not uncommon in benign T-cell proliferations
PTCL NOS should be diagnosed with exclusion of specific entities, which are defined by their clinicopathological findings, histology, immunohistochemistry, and other relevant studies, such as cytogenetic or molecular studies, where indicated. Needle core biopsies are almost always inadequate
Cytogenetic and molecular genetic alterations are promising, but it is too early to base a classification on these, with the exception of ALK alterations
Phenotypic aberrations, including expression of B-cell markers, occur across the entire spectrum of TCL
HTLV-I serology should be performed in all cases where ATLL is in the differential diagnosis. Cases from the Caribbean basin often present with nodal disease in the absence of peripheral blood involvement
Anaplastic large cells staining for CD30 are common in ATLL, and these cases should not be diagnosed as ALCL in the setting of HTLV-I seropositivity