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Early lesions in lymphoid neoplasia:

Conclusions based on the Workshop of the XV. Meeting of the European Association of Hematopathology and the Society of Hematopathology, in Uppsala, Sweden

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Abstract

The increasing use of immunophenotypic and molecular techniques on lymphoid tissue samples without obvious involvement by malignant lymphoma has resulted in the increased detection of “early” lymphoid proliferations, which show some, but not all the criteria necessary for a diagnosis of malignant lymphoma. In most instances, these are incidental findings in asymptomatic individuals, and their biological behaviour is uncertain. In order to better characterize these premalignant conditions and to establish diagnostic criteria, a joint workshop of the European Association for Haematopathology and the Society of Hematopathology was held in Uppsala, Sweden, in September 2010. The panel reviewed and discussed more than 130 submitted cases and reached consensus diagnoses. Cases representing the nodal equivalent of monoclonal B-cell lymphocytosis (MBL) were discussed, as well as the “in situ” counterparts of follicular lymphoma (FL) and mantle cell lymphoma (MCL), topics that also stimulated discussions concerning the best terminology for these lesions. The workshop also addressed the borderland between reactive hyperplasia, and clonal proliferations such as pediatric marginal zone lymphoma and pediatric FL, which may have very limited capacity for progression. Virus-driven lymphoproliferations in the grey zone between reactive lesions and manifest malignant lymphoma were covered. Finally, early manifestations of T-cell lymphoma, both nodal and extranodal, and their mimics were addressed. This workshop report summarizes the most important conclusions concerning diagnostic features, as well as proposals for terminology and classification of early lymphoproliferations and tries to give some practical guidelines for diagnosis and reporting.

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Introduction

In the last years, it has become evident that the widespread up-front use of immunohistochemistry, multicolour flow cytometry and molecular techniques on biopsy specimens without morphologically evident lymphoid malignancy has resulted in an increased detection of “early” lymphoid proliferations of unknown biological potential. These proliferations, which carry at least some immunophenotypic and/or molecular criteria of malignant lymphoma, commonly occur in clinically healthy individuals, and the risk for progression to overt lymphoma is often unknown.

With this in mind, the organizers of the lymphoma workshop of the XVth Congress of the European Association for Haematopathology (EAHP) and the Society of Hematopathology (SH) held in Uppsala, Sept. 25th–30th 2010, called for the submission of cases under the general heading of “Early lesions in lymphoid neoplasia”. More than 130 cases were received from international participants, and most cases fit well into the general topic of the workshop, representing “early lesions” either in a morphological, biological or clinical sense, or representing cases in the difficult borderline between atypical lymphoproliferations and early malignant lymphoma.

For several reasons, this workshop travelled uncharted waters. Most previous workshops aimed primarily at refining criteria for existing entities and exploring the spectrum of malignant lymphoproliferations, including “grey zone” lesions difficult to classify within established lymphoma subtypes [1,2]. In contrast, many of the “early” lesions encountered in the 2010 workshop do not represent clinically manifest malignancy, but rather an incidental finding of uncertain clinical relevance. Therefore, with the exception of well-known lymphoma precursor lesions such as monoclonal gammopathy of unknown significance (MGUS) or monoclonal B-cell lymphocytosis (MBL), no universally accepted terminology exists. Due to the uncertain risk of progression of these proliferations, many lesions defy a black-and-white separation into “benign” and “malignant” categories. As such, discussions related to terminology proved to be both difficult and controversial. A goal of the workshop was to develop diagnostic terms that are both biologically correct, as well as indicative of expected clinical behaviour, and risk for progression.

Based on the initial review by the expert panel, the submitted cases were grouped into 5 sessions.

- Progressively transformed germinal centers, follicular hyperplasia, and marginal zone hyperplasia
- Monoclonal B-cell lymphocytosis, indolent mantle cell lymphoma and early/indolent plasma cell proliferations: diagnosis in peripheral blood, bone marrow, and other sites
- *In situ* follicular lymphoma and *in situ* mantle cell lymphoma: definitions and boundaries
- Early T-cell and NK-cell lymphoproliferative lesions
- Virus-related lymphoproliferative lesions

In the first session, the borderlines between atypical marginal zone hyperplasia and early marginal zone B-cell lymphoma, and between follicular hyperplasia with clonal B-cells versus follicular lymphoma, especially of pediatric type, constituted the bulk of the sometimes very difficult cases. The most prominent topics in the second session were minor tissue-based infiltrates of clonal B-cells of CLL type, which usually did not pose major diagnostic difficulties, but raised important terminology issues, and the features and

definition of indolent mantle cell lymphoma. In addition to describing the spectrum of FL and MCL “*in situ*” and their separation from partial involvement by FL and MCL, respectively, cases of composite lymphomas consisting of an overt lymphoma with an “*in situ*” component of different subtype were the main topics of session three. Sessions four and five provided the broadest spectrum of cases. Among the T-cell proliferations, the submitted cases of “early” angioimmunoblastic T-cell lymphoma documented the fact that morphologically “early” lesions may well be observed in patients with clinically advanced disease. A number of instructive cases of EBV-associated lymphoproliferations in different settings of immunocompetence and with a broad range of clinical severity and morphological features formed the bulk of session five, which aimed at discerning self-limited, benign virus-driven proliferations from aggressive and potentially fatal disease.

The wealth of difficult and interesting cases submitted to the workshop, supplemented by related presentations by experts, provided the basis for fruitful and sometimes animated discussions between the submitters, the panel and the workshop participants and highlighted problem zones concerning both the diagnosis and the clinical management of these cases, as well as more general issues including the extent of workup of morphologically reactive lymphoid tissues. In addition, the panel sought to define diagnostic criteria for some of the early lesions, such as follicular lymphoma “*in situ*”, and to reach consensus on matters of terminology. The following report summarizes the proceedings of the workshop, providing both diagnostic guidelines and suggestions for terminology that reflect the discussions at the workshop, as well as the opinions of the expert panel.

Session 1

Progressively transformed germinal centers (session 1.1)

Progressively transformed germinal centers (PTGC) were initially reported in 1975 by Lennert and Müller-Hermelink [3] and have since been observed mainly in connection with reactive follicular hyperplasia in up to 10 % of cases [4]. A syndrome of persistent lymphadenopathy with florid PTGC in young males has subsequently been described [4,5]. A relation to nodular lymphocyte predominant Hodgkin’s lymphoma (NLPHL) has been noted in several reports, but although a causal connection has been suggested [6–9] it has not been definitely proven. PTGC may be seen in the same node as NLPHL, precede the lesion, or be found in a subsequent node biopsy. A further relationship between PTGC and NLPHL was the observation that both lesions contain an increased proportion of double-positive CD4+CD8+ T-cells [10]. The follicles in PTGC are enlarged, mainly by expansion of the mantle zones. IgD-positive B-cells infiltrate and disrupt the germinal centers, which are fragmented and partially destroyed [11]. PTGC and NLPHL have many features in common causing differential diagnostic problems, but morphological and immunohistochemical differences are also present, e.g. rosetting of CD3+CD57+/PD1(CD279)+ T_{FH}-cells around LP (lymphocyte predominant) cells being one characteristic of NLPHL [12]. A florid variant of PTGC may cause differential diagnostic problems with regards to FL, particularly to the floral variant. Changes reminiscent of PTGC also have been associated with marginal zone hyperplasia and marginal zone lymphomas in the pediatric age group (*see session 1:3–4*) [13].

Workshop cases

The workshop started with case 71 (Dr. Koreishi) of a young male with a history of seminoma and concomitant, PET-positive lymphadenopathy demonstrating florid hyperplasia and classical PTGCs with increasing ‘degree of progression’ as reflected by decreased proliferation and CD10 positivity. Dr. Zhang demonstrated a case (case 12) of persistent lymphadenopathy in a young boy with initial follicular hyperplasia (FH), one year

later with FH and PTGC and 5 years later with FH, PTGC and focal NLPHL with CD3 & CD57-positive T-cells rosetting around LP cells. The case illustrated the progression from FH → PTGC → NLPHL that is occasionally observed, and further cases submitted illustrated the association between PTGC and FH and/or NLPHL and the occasionally difficult differential diagnosis between early NLPHL and PTGC.

In summary, the workshop cases illustrated that differential diagnostic problems between PTGC and NLPHL may arise under certain clinical circumstances and in cases with limited involvement by NLPHL. However, the use of immunohistochemical markers such as BCL6 and OCT-2 help in the recognition of LP cells by highlighting their abnormal nuclear contours. Additionally, the identification of the appropriate cellular environment including rosettes of CD57- and PD1-positive T-cells further helps to resolve these cases[14].

Follicular hyperplasia and lymphoma (session 1.2)

The Session 1.2 dealt with the borderland between florid FH and follicular lymphoma of pediatric type. This distinction is made more challenging by the occasional presence of monoclonal B-cell populations detected by flow cytometry or PCR in a lymph node that appears histologically reactive [15]. Pediatric FL has been recognized as a specific subtype of FL in the new WHO classification, usually showing grade 3a/b morphology, mostly lack of BCL2 expression and absence of t(14;18) translocation [16–19]. The distinction between FH and pediatric type FL therefore has to rely more on morphological features, such as distortion of the lymph node architecture, lack of well-defined mantle zones, large confluent follicles and demonstration of light chain restriction or clonality. These cases usually are of limited stage and show an excellent prognosis, even without therapy. One of the questions raised at the workshop was whether cases with similar features exist in adult populations, and how to discern them from clonal follicle center B-cell populations in reactive follicular hyperplasia (see also Session 3.1) [15].

Workshop cases

Dr. Yohe presented a LN from an adolescent male with asymptomatic lymphadenopathy (case 19)(Figure 1A–C). Flow cytometry demonstrated a population of monotypic lambda+ lymphocytes coexpressing CD10 and CD23. The LN contained two types of 'follicles' – ordinary, reactive GCs and neoplastic follicles lacking polarization and expressing CD10 and BCL6 but not BCL2, which were considered to represent a pediatric FL. Further cases documented the role of ancillary studies, such as light chain restriction demonstrated with in situ hybridization or clonal IgH rearrangements. Some cases were considered by the panel to be recapitulating the occasionally difficult differential diagnosis between FH and FL. Case 36.2 showed kappa restriction on CD10+ cells and monoclonality by PCR, but no BCL2 or BCL6 breakpoints by FISH. Although a FH with monotypic B-cells could be considered [15] the morphology was too unusual for FH, and the diagnosis of a BCL2 negative FL was preferred.

Marginal zone lesions (sessions 1.3 and 1.4)

Nodal marginal zone lymphomas (NMZL) first described in 1986 [20], are mostly diagnosed in adult patients. Histologically these lymphomas may show a wide spectrum of lesions, with a follicular, perifollicular, interfollicular or diffuse growth pattern [21]. Follicles may be heavily colonized by neoplastic cells, including monotypic plasma cells or plasmacytoid cells. In other cases germinal centers are atrophic. At the cytological level, one may see centrocyte-like cells, monocytoid B cells, lymphocytes and plasma cells and a variable percentage of blasts.

A specific category according to the 2008 WHO classification is the pediatric nodal marginal zone lymphoma (PNMZL). These rare lymphomas mainly present in boys or male adolescents [13,22–24]. Most patients have localized, unilateral submandibular or cervical disease. PNMZL should be distinguished from a primary extranodal disorder described by Attygale et al [25] with involvement of the tonsil or appendix. The latter cases show expansion of marginal zones with exclusively lambda restricted but on the DNA level polyclonal B cells / plasma cells. At the histological level, PNMZL may look similar to adult type NMZL, but several cases show a peculiar pattern with many, often poorly delineated PTGC that are at the periphery infiltrated by the neoplastic cells. This pattern is very well appreciated by staining for follicular dendritic cells in combination with CD20, CD10 and BCL6, with many cells showing loss of CD10 and BCL6 expression.

Both NMZL and PNMZL must be differentiated from benign hyperplasia of marginal zone B cells / monocytoid B cells. Whereas focal accumulation of monocytoid B cells can be seen in a number of reactive conditions and is easy to recognize, the distinction between a more extensive hyperplasia and MZL can be challenging [26–28]. Clonality analysis is often necessary to make the diagnosis unless there is a convincing monotypic B cell population by flow cytometry (FCM) and / or monotypic plasma cell population. Kojima et al described an unusual type of prominent marginal zone hyperplasia, accompanied by the presence of prominent PTGC in 4 of 6 cases [29]. The patients, aged 24–63 years, presented with isolated cervical lymphadenopathy without any underlying disorder. All cases had polyclonal plasma cells as well as polyclonal IG rearrangements as assessed by PCR. The same author also described the occurrence of marginal zone hyperplasia in approximately 10% of all biopsies with follicular hyperplasia [36]. These data suggests a spectrum of reactive conditions that can mimic both classical NMZL and PNMZL.

In many reactive conditions small monoclonal B cell populations can be encountered. These include autoimmune disorders like idiopathic thrombocytopenia (ITP), Sjögren's disease, hepatitis C virus infection, mixed cryoglobulinemia, cold agglutinin disease, but also immunodeficiency states and Epstein Barr virus infections. In HCV positive patients an increased incidence of lymphomas, in particular marginal zone lymphomas is well appreciated [30]. As can be expected, oligo- and monoclonal B cell expansions can be detected in many HCV patients without overt lymphoma as well [31]. In addition and relevant to workshop cases there are also reports on polyclonal expansion of CD5+ B cells in these patients [32,33]. Atypical hyperplasia with a (partial) disruption of the architecture and expansion of perifollicular or marginal zones with polyclonal or monoclonal B cells also has been described in common variable immunodeficiency (CVID). In a report on 30 biopsies from 17 patients with CVID, 8 samples showed atypical follicular hyperplasia and 14 a more regular type of (follicular) hyperplasia [34]. In the atypical hyperplasia cases, largely expanded germinal centers were described. However, in several of these patients the lymphadenopathy was widespread, opposite to the situation in PNMZL.

Workshop cases

In the workshop, Dr. Bob presented an intriguing adult patient with persistent cervical lymphadenopathy which exhibited both PTGC's and prominent marginal zone hyperplasia (case 76.2)(Figure 1D–F). The presence of such a combined hyperplasia was further supported by the presence of numerous PD-1 (CD279) positive T cells as well as the staining for IRTA1 in the marginal zone component. The lesion was polyclonal both by immunohistochemistry and PCR analysis.

Five cases of marginal zone lesions with monotypic B cells (mostly also proven by FCM) were submitted, eliciting intense discussions about their final classification. Interestingly, all cases were found in conditions associated with an increased risk for development of B cell

lymphoma: two in HCV infection, two cases in CVID patients and one in a patient with rheumatoid arthritis. An example of an otherwise normal lymph node with a small monotypic B cell population in a HCV positive patient was provided by Dr. Song and colleagues (case 73). The localized parotid mass contained 16% monotypic B cells as assessed by FCM. Most importantly, there were no architectural alterations in favour of lymphoma in this case. Two cases of atypical hyperplasia or early lymphoma in CVID patients were submitted to the workshop. Dr. Salama presented a 41-year-old patient with a nine-year history of CVID with worsening lymphadenopathy, showing florid follicular hyperplasia with monocytoid B-cell clusters without evidence of overt lymphoma. All adenopathy spontaneously regressed within six months. Eighteen months later the patient presented with progressive extensive lymphadenopathy and hepatosplenomegaly. A lymph node biopsy again showed atypical follicular hyperplasia. FCM revealed a monotypic CD10+ B cell population in the absence of monotypic plasma cells and monoclonality by IGH PCR.

Two cases of marginal zone hyperplasia without any gross disruption of the architecture, but in addition to the monotypic IG expression, co-expression of CD5 on these cells were submitted. Dr. Garcia et al presented a 62-year-old female (case 30) with rheumatoid factor-positive rheumatoid arthritis and cervical lymphadenopathy. The biopsy showed a moderate expansion of CD5+ marginal zone B cells that were monotypic and monoclonal upon DNA analysis (Figure 2).

There were two good examples of primary extranodal lesions in children with monotypic B cells / plasma cells as described by Attygale in 2004 [25], arising in the tonsil and appendix, respectively. Dr. Colomo submitted a 4-year-old patient (case 78.3) with clinically acute appendicitis and follicular and marginal zone hyperplasia, with monotypic plasmacytoid cells being identifiable by immunohistochemistry, but lack of a clonal B-cell rearrangement by PCR (Figure 3).

Finally there were several cases of non-marginal zone like hyperplastic conditions with evidence of monoclonality. Dr. Chow submitted a splenectomy (case 22.2) from a patient with ITP without any evidence of lymphoma, in which a t(3;22)(q27;q11) involving the BCL6 gene was found in 7 of 20 metaphase cells. Interestingly, clonal and non-clonal breakpoints at 3q27 have been repeatedly reported in hyperplastic lymphoid tissues [35,36], clonal abnormalities being associated with later malignancy.

Summary of Session 1

In summary, part 1 of the workshop highlighted the difficult area of marginal zone expansions in various clinical settings such as HCV infection and CVID, atypical follicular lesions raising a differential diagnosis of follicular lymphoma, especially of “pediatric type” also arising in adult patients, and the problems of using ancillary techniques such as FCM and PCR that might uncover small cell clones with an unpredictable but often benign behaviour. In general, it was felt that a diagnosis of malignant lymphoma requires a combination of both a monoclonal B cell population with or without aberrant marker profile and a distinct architectural distortion.

Session 2

Persistent polyclonal B-lymphocytosis (session 2.1)

In 1982 Gordon et al. were the first to describe a condition of persistent polyclonal lymphocytosis of B-lymphocytes (PPBL, also known as chronic B lymphocytosis with binucleated lymphocytes)[37,38]. This is characterized by a persistent (> 6 months) presence

of peripheral blood lymphocytosis that is polyclonal with a normal kappa:lambda ratio. The B cell population includes a variable number of cells with characteristic bi-lobed nuclei. The condition occurs predominantly in young or middle aged females who are usually smokers [39]. There may be mild splenomegaly, but hepatomegaly and lymphadenopathy are not seen. There is a polyclonal increase in serum IgM. In up to 90% of cases human leukocyte antigen (HLA)-DR7 is found. Familial clustering has been described [40].

Morphologically the cells are mostly small mature lymphoid cells with a sub-population with bi-lobed nuclei. A variant resembling hairy cell leukaemia has been described in a Japanese population [41]. The cells have a non-specific B cell immunophenotype without expression of CD5, CD23, CD43 or cyclin D1 but with expression of CD27. The cells are thought to be CD27+, IgD+, IgM+ memory cells with some evidence to suggest that there is a defect in the CD40-induced B-cell activation pathway, which may have a role in the pathogenesis [42,43]. There may be a pathogenetic role for EBV in some cases [44].

Although not clonal by immunophenotyping, cytogenetic abnormalities are frequently found. An additional iso-chromosome 3q10 is found in up to 77% of patients, premature chromosome condensation is described in 50% and both can occur together in up to 41% of cases [45]. Trisomy of chromosome 3 has also been described [46]. There are frequently multiple variants of t(14;18) involving both MBR and mcr regions found in individual cases [47]. Older patients have greater numbers of variants, and following initial presentation, additional translocations can be detected intermittently over time.

It is uncertain whether this condition is premalignant but occasional cases have shown subsequent development of diffuse large B cell lymphoma, gastric lymphoma or splenic marginal zone lymphoma. In a large study following 111 patients with PPBL with median follow-up of 4.4 years (range 0.5–29 years) Cornet et al [48] described a stable course in 89% of patients. Development of non-Hodgkin lymphoma occurred in 3 patients, with 2 diffuse large B cell lymphomas (3 and 9 years after presentation) and 1 splenic marginal zone lymphoma after 3 years. In some patients the lymphocytosis may decrease with cessation of smoking or following splenectomy, but the genetic abnormalities persist [48].

Workshop cases

Dr. Piris submitted a case of PPBL with massive splenomegaly (case 5). The patient was a 41-year-old female smoker with a peripheral blood lymphocytosis including 3% binucleated cells. The cells expressed CD19, CD20, CD22, CD27, FMC7, IgM, and IgD with polyclonal light chains. HLA-DR7 was positive. After 34 months, massive splenomegaly developed with anaemia and splenectomy (weight 3,900gms) was performed. There was macroscopic prominence of white pulp. Histologically the spleen showed white pulp with widened marginal zones and infiltration of the red pulp by small B cells with an immunophenotype similar to that seen in the peripheral blood (CD20+, IgM+, IgD+, CD5–, CD23–, cyclinD1–, CD10–, bcl-6– with no light chain restriction)(Figure 4B–F). There was polyclonal IGH gene rearrangement and +i(3q). While the spleen size in this patient is unusually large, the case illustrates the pattern of infiltration in the spleen previously described by Del Giudice et al. [49] with increased white pulp associated with marginal zone hyperplasia and extensive infiltration of red pulp sinuses. Following the splenectomy, the white cell count normalized and the patient was well 12 months later. A further case submitted (case 7) illustrated the morphology in the peripheral blood (Figure 4A) and the pattern of bone marrow infiltration in PPBL (Figure 4G)[50]. There was an interstitial pattern with an intrasinusoidal component and occasional small lymphoid aggregates. Five years after initial presentation and following a gradual increase in white cell counts, the patient presented with splenomegaly and a circulating clonal B cell proliferation with features typical of splenic marginal zone lymphoma.

Monoclonal B-cell lymphocytosis (session 2.2)

Monoclonal B-cell lymphocytosis (MBL) is defined as the presence of a circulating clonal B cell population with a persistent absolute lymphocyte count that is below the level required for a diagnosis of chronic lymphocytic leukaemia ($5 \times 10^9/l$). The clonal population may be documented by the presence of light chain restriction (kappa:lambda ratio $>3:1$ or $<0.3:1$), a low level or lack of surface immunoglobulin, the presence of monoclonal IGH gene rearrangements or the presence of a disease-specific immunophenotype. In addition there should be no features of autoimmune disease and no symptoms (e.g. drenching night sweats, fatigue, weight loss, unexplained fever) or signs (lymphadenopathy, splenomegaly) to suggest a lymphoproliferative disorder/lymphoma [51]. MBL's are subdivided on the basis of their immunophenotype into those with a CLL-type phenotype (CD5+; CD19+; CD20(dim); CD23+ with dim surface immunoglobulin), an atypical-CLL phenotype (CD5+; CD19+ but CD20(bright) or CD23-) and non-CLL phenotype (CD5-; CD20+) [51]. Detailed investigation of CLL-type MBL has shown that not all cases are truly clonal with some showing biclonal, oligoclonal or polyclonal CD5+/CD23+ populations [52,53]. The presence of non-CLL MBL is an indication for further clinical study as in a proportion this will be associated with overt non-Hodgkin lymphoma [51]. In cases with an atypical CLL phenotype, studies for t(11;14) should be undertaken to exclude the indolent form of mantle cell lymphoma.

The prevalence of CLL-type MBL depends on the method of detection used, varying from about 0.14% (2 colour flow cytometry) to 12% (8 colour flow) [51]. The prevalence increases with age and the highest prevalence is detected in first degree relatives of CLL patients (13.5–18%). Non-CLL MBL is detected in 1–2% of the general population [51].

MBL can be further sub-typed depending on the method of presentation into clinical MBL (c-MBL), in which the lymphocytosis is often detected following clinical investigation for a modestly elevated lymphocyte count, and population-screened MBL (ps-MBL) in which the abnormal population is detected as part of a screening process [51]. These two groups appear to differ, with c-MBL showing features similar to CLL such as similar IGHV gene usage and the presence of chromosomal abnormalities, while ps-MBL have different IGHV usage [54]. While almost all cases of CLL will have a preceding MBL [55] the rate of progression from MBL to CLL is low with a rate of about 1–2% per year. The majority of patients, around 75%, will have stable lymphocyte counts over many years [54]. Progression from MBL to overt CLL with the eventual requirement for treatment is dependent on the level of lymphocytosis with $>90\%$ of patients with a clonal B-cell count $< 2,000$ per μl having a stable lymphocyte count while if the clonal B-cell count exceeds 2,000 per μl , up to 1% per year will require treatment [56].

Workshop cases

Dr. Harris presented case 93.1 of a 43-year-old female who underwent lymph node dissection with total thyroidectomy for FNA-detected papillary carcinoma (Figure 5A–D). A 10 mm lymph node was thought to show mild lymphoid hyperplasia and was sent for flow cytometry that revealed a clonal B cell population with CD19+; CD20(dim); CD5+; CD23+ FMC7- immunophenotype associated with lambda light chain restriction. Tissue immunohistochemistry showed small infiltrates of CD5+/CD23+ cells in primary follicles and the interfollicular areas. Examination of the peripheral blood showed a clonal B lymphocytosis ($2.3 \times 10^9/l$) with identical phenotype. Retrospective investigation suggested that the MBL had been present with a stable mild absolute lymphocytosis for up to 10 years prior to this presentation. As the involved lymph node was not enlarged, the infiltration would not have been detected, had the lymph node not been excised, and the diagnosis would have remained typical MBL.

Similar cases were presented by Drs. Swerdlow (case 2)(Figure 5E–H) and Gibson (case 52). In case 2, there was disseminated, but minor lymphadenopathy detected by FDG/PET, whereas the case presented by Dr. Gibson was being investigated for persistent anaemia. Both cases showed sparse infiltration with perifollicular clusters of small lymphocytes with a CLL-like phenotype associated with small proliferation centres/pseudofollicles.

The workshop discussion highlighted the difficulties in the nomenclature reflecting the overlap between MBL, small lymphocytic lymphoma (SLL) with circulating cells and low count CLL. While the case presented by Dr. Harris would have been considered as MBL without the analysis of lymph nodes sampled for a separate clinical indication, the cases from Drs. Swerdlow and Gibson were detected following investigation for a potential haematological disorder. It was concluded that this pattern of nodal infiltration would at present best be considered clinically equivalent to MBL, with a suggested diagnosis of partial involvement by clonal CLL-like B cells, as will be discussed below.

Indolent mantle cell lymphoma (Session 2.3)

Mantle cell lymphoma is typically an aggressive neoplasm characterized by rapid clinical evolution, short responses to therapy and median survivals of 3 to 4 years. However, in a subset of patients, mantle cell lymphoma displays an indolent behavior; patients may not require chemotherapy for long periods and survive more than 7 to 10 years.

Workshop Cases

Two cases of indolent mantle cell lymphoma were submitted and confirmed by the panel. Case 78.1, presented by Dr. Campo, was a 66-year-old man who presented with a clonal B lymphocytosis positive for IgM/IgD, lambda (bright), CD19, CD79b, CD20 (bright), FMC7, and CD22 and negative for CD5, CD23, CD43 and CD10. No adenopathy was identified. The patient was not treated because of stable disease and good performance status. Three years later he underwent a splenectomy that was confirmed to be involved by mantle cell lymphoma (Figure 6A–C). This was followed by decrease and stabilization of the number of circulating lymphocytes and the patient is alive 9 years after diagnosis with stable leukemic disease. Case 31 was an example of a nodal mantle lymphoma that also exhibited indolent behaviour; the patient had been followed for 10 years without therapy.

Although it is not always possible to predict clinical course in an individual patient at presentation, it has been shown that patients with indolent mantle cell lymphoma often have non-nodal, leukemic disease, similar to the case presented (Case 78.1). They exhibit predominantly hypermutated *IGHV* genes and non-complex karyotypes. Differences in gene expression profile have also been described [57,58]. Reports of nuclear expression of SOX11 as identified by immunohistochemistry and correlation with survival have, to date, been contradictory [58,59]. Of note, Case 78.1 was SOX11 negative and Case 31 was positive.

Early/indolent plasma cell proliferations (Session 2.4)

The last part of session 2 addressed early or indolent plasma cell proliferations. The first entity discussed was monoclonal gammopathy of undetermined significance (MGUS), a disorder that could be the prototype for early lymphoid/plasma cell lesions. In 1952, Waldenström described patients with small, monoclonal proteins, but with no evidence for plasma cell myeloma or lymphoma [60]. Many synonyms have been used for this condition including “benign monoclonal gammopathy” a term that emphasizes the constancy of the abnormal protein spike. However, in 1978, Kyle et al, suggested the term MGUS since follow up revealed that a subset patients with small monoclonal proteins went on to develop plasma cell myeloma, Waldenström macroglobulinemia, or related disorders [61]. MGUS is

common, occurring in about 3% of adults older than 50 years of age and 5% over the age of 70 years. Long-term follow-up studies show that the risk of progression from MGUS to myeloma or related disorder is about 1% per year [62]. Recent studies have shown that MGUS precedes manifest plasma cell myeloma in most patients [63].

Workshop Cases

Dr. Peterson presented the one case (case 89) of MGUS submitted to the workshop and it is an example of MGUS in which the plasma cells exhibit an immunophenotypic profile and chromosomal abnormalities similar to plasma cell myeloma. The patient had a small (1.1 g/dL) monoclonal IgA kappa serum protein with no evidence for myeloma or lymphoma. The plasma cells in the bone marrow were mildly increased (8%) and were CD19⁻, CD38⁺, CD56⁺ and cyclin D1⁺ (Figure 6D–F). Although conventional cytogenetic studies were normal, FISH analysis of the plasma cells showed monosomy 13 and t(11;14)(IGH;CCND1). It has been reported that the genetic changes observed in patients with myeloma such as aneuploidy, chromosome 13q deletions, and translocations involving 14q32 are similarly frequent in MGUS. Currently, there is no evidence that detection of these genetic abnormalities can predict which patients with MGUS will go on to develop myeloma [62]. The plasma cells in MGUS also have an immunophenotypic profile similar to myeloma plasma cells, however, the proportion of phenotypically normal plasma cells is higher in patients with MGUS than in patients with plasma cell myeloma [55].

Two cases of indolent extramedullary plasma cell proliferations were also discussed. One case (case 22.3) presented by Dr. Bhagat was an example of a nodal plasmacytoma of IgA type occurring in a 23-year-old male with an elevated serum monoclonal IgA. The patient exhibited cervical, axillary and inguinal lymphadenopathy and had a prior history of immune thrombocytopenic purpura. Biopsy of a cervical lymph node showed sheets of IgA kappa positive plasma cells in the interfollicular regions (Figure 6G–I). A group of similar cases of IgA plasmacytomas have been recently described [64]. This report suggests that extramedullary IgA plasmacytomas may be a distinct form of plasma cell neoplasm characterized by younger age at presentation, frequent lymph node involvement, and low risk of progression to myeloma. Case 39 was a focal indolent proliferation of monoclonal plasma cells identified in a routine circumcision specimen. By immunohistochemistry, the plasma cells were CD138⁺ (weak), CD20⁻, Cyclin D1⁻, PAX5⁻, CD56⁻ and C-KIT⁻ and monotypic (IgG kappa). PCR showed a clonal rearrangement of *IGH@* and kappa light chains. No serum monoclonal protein and no evidence for myeloma or lymphoma were identified. The patient was followed for 1 year without recurrence of disease. This case appears to be an example of what has been referred to as plasma cell balanitis or Zoon's disorder. It typically affects middle and older age uncircumcised males and is characterized clinically by red or red-brown patches affecting the glans penis and/or prepuce [65]. Plasma cells predominate in later lesions and it is felt that it represents a reactive, chronic mucositis. Little information is known about the immunophenotype of the plasma cells in these lesions, although they have been reported to express primarily IgG [65].

Conclusions drawn from the plasma cell session are (1) MGUS is a precursor lesion and can exhibit cytogenetic/FISH abnormalities and an abnormal immunophenotype similar to plasma cell myeloma; (2) extramedullary IgA plasmacytoma may be a distinct form of plasmacytoma characterized by younger age at presentation, frequent lymph node involvement, and low risk of progression to myeloma; and (3) Correlation with clinical and laboratory information is essential in interpreting plasma cell proliferations.

Session 3

Follicular lymphoma in situ (Session 3.1)

The first part of session 3 dealt with follicular lymphoma in situ (FLIS), alternatively termed intrafollicular neoplasia in the 2008 WHO classification. FLIS was first recognized in tissue sections by Cong et al. in 2002 [55] when they described a series of 25 cases in which cells with the immunophenotypic and genotypic features of follicular lymphoma (FL) were seen localized to selective germinal centers in lymph nodes that otherwise had features of reactive follicular hyperplasia. In the cases studied the FLIS lesions were monoclonal and carried the BCL2/IGH@ translocation. When those patients were evaluated, some were found to have evidence of FL at other sites, but in a substantial proportion, no other clinical evidence of FL was found at diagnosis, or during follow-up, although the period of follow-up was limited. Previously, studies of peripheral blood and tonsils from healthy individuals had been found using sensitive nested PCR techniques to harbor cells with the BCL2/IGH@ translocation in a proportion of individuals [66,67]. These cells exist at very low frequency, approximately 1 in 10⁵. Further studies of this phenomenon showed that these FL-like B-cells, as they were termed, increased in numbers with age, with smoking and with exposure to pesticides [68,69]. Some patients were found to have several independent clones with the t(14;18), although one clone usually predominated. The level of the FL-like B-cells may fluctuate in the peripheral blood, and notably, in patients with Hepatitis C infection treated with anti-viral therapy, the number of FL-like B-cells decreased following therapy [68]. An increased risk of clinical FL in patients with FL-like B-cells in the blood has not been identified. Evidence connecting FLIS to FL-like B-cells in the blood was provided by a single case report in which a patient with FLIS was found to have a clonally related population in the blood, but without clinical evidence of FL during the period of follow-up [70]. The incidence of FLIS is unknown, but a subsequently published study of more than 1,200 reactive lymph nodes from 132 patients removed for a variety of causes demonstrated the presence of FLIS in 2.5% of individuals, at a much lower rate than circulating t(14;18)+ B-cells [71]. A goal of the panel in reviewing the cases from the workshop was to apply rigorous histological criteria to distinguish lymph nodes and other histological specimens involved by FLIS from those showing partial involvement by FL (Table 1) [72]. Also submitted and reviewed in this session were unusual variants of FL, including intestinal FL and cases that were clinically early with localized diseases. Cases of the pediatric type of FL were also included.

Workshop cases

Nine cases classified as FLIS by the submitters and the panel were examined at the workshop (Figure 7). Case 33.2, presented by Dr. Adam was a prototypic case of FLIS, in which subsequent follow up and re-biopsy of another lymph node from the same location at two years, showed evidence of FLIS (Figure 7D–G). However, the patient never developed clinical evidence of FL beyond the FLIS lesions. Most of the other FLIS cases were discovered incidentally, when the biopsy was performed for totally unrelated reasons, or in lymph nodes removed for staging of carcinoma. Case 38.1 contained the FLIS lesion in reactive lymphoid infiltrates within lung parenchyma. Notably, progression to clinical FL was not observed in any presented case, although some patients had received therapy, such as rituximab or chemotherapy. Case 49, presented by Dr. Farinha, showed FLIS involving mesenteric lymph nodes and reactive lymphoid follicles in mucosa of the small bowel; the latter site was also involved by diffuse large B-cell lymphoma. Molecular examination of both tumor compartments performed by the panel indicated a clonal relationship of the two lesions, but it was unknown if the diffuse large B-cell lymphoma carried the t(14;18).

Dr. Chott presented a case of FL involving the small intestine (Case 85), and compared the features of duodenal FL, which is usually localized with a low risk of nodal dissemination, to FLIS and to usual FL (Figure 7H–K)[73]. Duodenal FL is positive for the *BCL2/IGH* translocation, and shows strong expression of BCL2 and CD10, similar to FLIS. In four cases studied the *BCL2/IGH* translocation was the sole abnormality detected by classical cytogenetics. In contrast to FLIS, residual reactive germinal centers were not identified in any case of duodenal FL, suggesting that this process may not occur by colonization of reactive follicles.

The panel recognized a number of cases as not meeting the strict criteria for FLIS, and instead, representing partial involvement by FL. Case 67.1, falling into this category, was presented by Dr. Ashton-Key. The patient presented with inguinal lymphadenopathy. One groin lymph node showed a cluster of abnormal follicles, while an adjacent lymph node was largely replaced by FL. Interestingly, upon further clinical evaluation no other sites of disease were identified (Stage I). Two similar cases, although occurring in small nodes, were felt by the panel to meet criteria for partial involvement, when atypical follicles clustered together and were expanded, with more blurred edges than the true FLIS lesion, which is confined to the germinal center compartment. Of interest, both cases had clinical and/or imaging evidence of more widespread disease.

Further cases included in this group were four unusual examples of Stage I FL. Two of them, cases 22.1 and 44, were felt to represent the pediatric type of FL. They had large, expansile follicles with a monotonous cytological composition of medium-sized cells. While clonal by IGH PCR, they were negative for the t(14;18) (see also Session 1.2).

In conclusion, histological criteria can distinguish FLIS from partial involvement by FL, which is often associated with other clinical evidence of disease, although partial nodal involvement by FL at presentation is more often found in patients with limited disease [74]. (Table 1) As strictly defined, FLIS appears to be associated with a very low rate of clinical progression, even if more than one site is involved [72]. Notably, repeat biopsy of subsequent lymph nodes may show persistence of the FLIS lesion. However, FLIS may be seen sometimes in association with other manifest lymphomas, as well as other *in situ* lesions, as will be discussed below. In contrast, cases classified as partial involvement by FL were more likely to show evidence of FL at distant sites.

Mantle cell lymphoma in situ (Session 3.2)

The second part of session 3 was devoted to “early” manifestations of mantle cell lymphoma, including so-called “*in situ*” MCL (MCLIS) and cases in which the MCLIS formed part of a composite lymphoma. A total of 16 cases were discussed in this session, which provided a broad basis for defining the boundaries of MCLIS in both nodal and extranodal locations. Conventional mantle cell lymphoma is an aggressive B-cell lymphoma characterized by the hallmark translocation t(11;14)(q13;q32) which leads to overexpression of the cell cycle protein cyclin D1 [75]. Since cyclin D1 is absent from normal lymphoid cells and most NHL, detection of nuclear staining by immunohistochemistry is a sensitive and specific marker for MCL in the appropriate setting and is a prerequisite for the diagnosis, if one disregards the rare cases of true cyclin D1-negative MCL [55]. Most commonly, MCL presents with widespread nodal disease, but primary gastrointestinal involvement in the form of lymphomatous polyposis and a leukemic picture with or without splenomegaly are well-recognized clinical forms of presentation. In recent years, rare cases of otherwise reactive-looking lymph nodes showing cyclin D1 expression in a minor cell population usually residing within the inner mantle zones of reactive follicles have been described [55] [76]. By FISH, these cells carry the t(11;14) and thus contain the hallmark genetic lesion of MCL cells. This pattern has received a variety of terms, including, “early”, “*in situ*-like” or “*in situ*” MCL. Of note, the clinical behaviour of the few reported cases

varied significantly. Whereas the two patients reported by Espinet et al. [77] and Nodit et al. [78] showed a very prolonged, indolent course without specific therapy and discrete PB and BM involvement, reminiscent of the indolent variant of MCL discussed in more detail above, the two patients studied by Richard et al. [79] had clinical evidence of more widespread disease, with early relapse and subsequent widespread dissemination in one of them. Of note, the two cases published by Richard et al. had a more pronounced population of cyclin D1+ cells, better classified as early or partial involvement by MCL. These examples indicate clearly, however, that a MCLIS or early pattern can be taken neither as evidence for limited disease nor as indication for indolent behavior. Morphologically, MCLIS shows a monotonous population of small cells difficult or impossible to identify on routine sections, even with the knowledge of the cyclin D1 stain (Table 2). Phenotypically, in addition to cyclin D1, MCLIS shows expression of pan B-cell markers, IgD and BCL2, but seems to be more commonly negative for CD5 and CD43 compared to conventional MCL [77,78,80,81]. Similar to FLIS, there are no data on the frequency of this lesion. One could speculate that MCLIS is rarer than FLIS, given that the frequency of B-cells carrying the t(11;14) in the blood of healthy individuals is significantly lower than for t(14;18)+ cells [82,83]. Since MCLIS is an incidental finding in most instances, neither the risk nor the timeline for progression of this lesion currently is known, as well as whether MCLIS is a common precursor lesion of MCL.

Workshop Cases

The data presented by Racke et al. at the workshop provided evidence that minimal, clinically occult infiltrates of clonally related t(11;14)+ cells may precede manifest MCL for several years. They reported 3 cases of MCL in whom retrospective examination of morphologically reactive lymphoid tissues obtained 3 to 15 years prior to lymphoma diagnosis revealed the presence of minor cyclin D1+ B-cell populations, as well as a case of MCL arising simultaneously in donor and recipient 12 years after allogeneic bone marrow transplantation (Case 90).

Three cases submitted to the workshop were considered to be good examples of nodal MCLIS (43.1, 43.2 and 79)(Figure 8). They exhibited reactive-looking, architecturally well-preserved nodes with cyclin D1+ cells located primarily as narrow rims in the inner mantle zone, directly adjacent to and sometimes encroaching on preserved germinal centers, and occasionally colonizing primary follicles. One case (36.1) showed MCLIS both in mesenteric nodes and in lymphoid follicles in the colonic mucosa. The case presented by Dr. Quintanilla-Martinez (33.1) was a small normal-appearing node from a patient with a history of MCL, which showed cyclin D1+ cells exclusively located within the germinal centers of secondary follicles, indicating that different “in situ” patterns of MCL may be observed and that an “in situ” pattern can also be observed at relapse.

Case 85.2 by Dr. Copie-Bergman provided a good example for the difficult borderline between MCLIS and partial nodal involvement by MCL. The panel felt that the expansion of the mantle zone in this case which already was suspicious on routine H&E sections justified a diagnosis of early partial LN involvement by MCL (Table 2).

Four cases submitted to the workshop exhibited early or minimal MCL infiltrates identified exclusively in extranodal locations, including urinary bladder, gall bladder, lung and Waldeyer's ring. With the exception of case 24 detected in the urinary bladder, in which the cyclin D1+ cells were present as small nodules without clear relationship to follicular structures, the distribution of the cells was the same as in the lymph node, surrounding reactive germinal centers. Similar to case 85.2 mentioned above, based on the extent of cyclin D1+ cells in the expanded mantle zones, case 100 was felt to represent an early case of lymphomatous polyposis presenting in the gall bladder rather than a true “in situ” lesion

(Figure 8 F,G). Of interest, case 61 submitted by T. Molina, which showed minimal, only retrospectively detected “in situ” involvement of reactive follicles within a chronic inflammatory pulmonary infiltrate developed a leukemic blastoid MCL two years later, again highlighting the unpredictable behavior of these lesions.

A recurrent topic at the workshop was the question, whether some cases of MCLIS may represent an early tissue manifestation of the indolent form of MCL described above, which commonly shows leukemic, non-nodal disease with splenic involvement and more often contains hypermutated immunoglobulin genes [55]. For this reason, the panel stained all MCLIS cases for the transcription factor Sox11, which has recently been described as a reliable marker of MCL, but was found lacking in certain CLL-like cases, but also in some blastoid variants [58,84-86]. Of interest, all evaluable cases of MCLIS from the workshop were Sox11 positive, which is in contrast to a recent study reporting that more than half of MCLIS were negative for Sox11 [76]. The significance of Sox11 positivity in the setting of MCLIS will require further study of prospectively collected cases to resolve.

Composite lymphomas with MCLIS component

The last group of six cases comprised composite B-cell lymphomas with a MCL component, of which five resembled MCLIS in the amount and distribution of cyclin D1-positive cells. Composite B-NHL, which is defined as a combination of two morphologically and phenotypically distinct clonal B-cell populations involving the same site, but usually with distinct distribution patterns, has been recognized for some time. For most cases studied by microdissection or similar approaches, a distinct clonal origin of the two components has been demonstrated [87].

In four of the six cases submitted to the workshop, the main tumor component was follicular lymphoma, with the cyclin D1-positive MCL cells forming narrow rims at the periphery of the neoplastic follicles, recapitulating the pattern observed in MCLIS in reactive lymph nodes. The unique case presented by Drs. Rouillet and Bagg (case 4) showed, in addition to fully developed follicular lymphoma, both FLIS and MCLIS components in a splenectomy specimen [88]. Undoubtedly, the routine use of cyclin D1 immunostaining in the diagnostic work-up of B-NHL facilitates the detection of such composite cases with a minor MCL-like population. Nevertheless, the repeated observation of such cases, as well as of more conventional composite lymphomas with two fully developed, usually unrelated malignant populations such as workshop case 86 presented by Dr. Novero [55] raises the question as to whether there is an underlying susceptibility for the development of B-NHL that results in the occasional outgrowth of more than one unrelated clone. Due to the rarity of these cases, it is unknown whether the clinical behaviour is solely determined by the predominant lymphoma clone or whether the minor MCL population can develop into a full-blown MCL.

In conclusion, “early” manifestations of MCL may be encountered in a range of clinical settings and at both nodal and extranodal locations, and currently do not allow any predictions concerning extent of disease or clinical behavior. The panel felt that any infiltrate of cells with a MCL pheno- and genotype resulting in altered lymph node architecture already discernible on routinely stained sections should be classified as partial involvement by MCL, whereas the above cases termed MCLIS are only detectable by immunohistochemistry and lack histologically evident infiltrates. Given the fact that at least some cases of MCLIS may show no clinical evidence of lymphoma and will remain free of disease for several years, the term “MCL-like cells of undetermined significance” was found to better reflect the clinical ambiguity of this finding and probably represents a preferable terminology. Nevertheless, it needs to be stressed that an “in situ” pattern of MCL can also be associated with more widespread disease.

Session 4

Early lesions in T-cell and NK-cell lymphomas are not well known compared to B-cell lymphomas, therefore limiting the potential clinical impact of their diagnosis. Only a few situations with some notion of early lesions evolving into full-blown lymphomas are recognized, such as enteropathy-associated T-cell lymphoma (EATL) - the best example -, extranodal NK/T-cell lymphoma, nasal-type, which can be preceded by chronic manifestations of enteropathy and chronic active EBV infections (CAEV), respectively, and chronic/smoldering adult T-cell leukemia/lymphoma (ATLL, HTLV1-related). This session also comprised some T-cell lymphoproliferations with « indolent » behaviour, including recently described entities such as seroma-associated ALK-negative anaplastic large-cell lymphoma adjacent to breast implants [89,90] and NK cell enteropathy [91,92]. On the other hand, some cases of angioimmunoblastic T-cell lymphoma presented in the workshop, which showed very subtle histological changes despite the presence of the full-blown clinical syndrome, may be considered “early” lesions at least from the morphological point of view. Twenty-two cases were submitted mostly from Europe and North America, meaning that no case of HTLV1-positive ATLL was discussed.

Angioimmunoblastic T-cell lymphoma (Session 4.1)

Session 4.1 was devoted to the spectrum of angioimmunoblastic T-cell lymphoma (AITL), aiming to answer the following questions: 1) Can we recognize « early » morphological lesions in AITL? 2) Do these “early” lesions in AITL have any clinical impact? 3) Is the group of so-called « follicular peripheral T-cell lymphoma (PTCL) » - sometimes with an indolent course – an “early” PTCL derived from follicular helper T cells (T_{FH}), possibly related to AITL?

Described in the seventies as a non-neoplastic abnormal immune condition, AITL has later been recognized as a subtype of PTCL, given the demonstration of cytogenetic alterations and clonal T-cell receptor (TCR) gene rearrangements in most instances and the identification of clearly malignant morphologic features in some cases [93]. Recently, the T_{FH} cell, normally located in the light zone of reactive germinal centres, has been recognized as the cell of origin of the disease [55]. AITL is reported as the second most common PTCL worldwide, but appears more prevalent in Europe than in North America or Asia [94]. Clinically, AITL often manifests with systemic symptoms (fever, weight loss, skin rash and arthralgias). The concomitant generalized lymphadenopathy in an elderly individual and often immunologic derangements such as polyclonal hypergammaglobulinemia and Coombs-positive hemolytic anemia, are hints to the diagnosis which relies on a lymph node biopsy. However, these clinical and biological features are inconstant as some patients have asymptomatic lymphadenopathy [55]. In lymph nodes, AITL is characterized by a polymorphous infiltrate including variable proportions of atypical neoplastic T cells with small to medium-sized nuclei and abundant clear cytoplasm, admixed with small lymphocytes, histiocytes or epithelioid cells, immunoblasts, eosinophils and plasma cells, usually spreading out in the capsule and perinodal tissue with sparing of the peripheral cortical sinus, with a prominent proliferation of arborizing high endothelial venules and follicular dendritic cells (FDCs). The lymphoma cells tend to form clusters around high endothelial venules and usually represent a minor component of the infiltrate. They are CD4+ with frequent aberrant expression of CD10 in at least a subset of the neoplastic cells and expression of several T_{FH} markers, such as PD1(CD279), CXCL13, BCL-6, and ICOS that can be detected in routine specimens. In fact, AITL shows a morphological spectrum that may be categorized according to cell content (including variants rich in epithelioid cells and in clear cells), but also according to architecture. Three overlapping architectural patterns, as described by Attygalle et al. [95] have been recognized. Up to 17% of AITL [96] can present with pattern I with hyperplastic follicles,

the pattern which remains the most difficult to diagnose. Pattern II is characterized by more profound architectural disturbance and the presence of depleted follicles with concentrically arranged FDCs responsible for Castleman's-like features, whereas the most frequent pattern III shows complete effacement of architecture [55]. Mixed patterns are common.

Pattern I is characterized by hyperplastic germinal centers with ill-defined borders and poorly developed mantle zones and a polymorphous infiltrate extending into the paracortex comprising more or less inconspicuous neoplastic cells and hyperplastic venules [55]. The peculiar distribution of the neoplastic lymphocytes at the outer rim of the germinal centers with variable expansion into the paracortex is highlighted by staining for CD10 (usually stronger than CD10+ germinal center B-cells) and T_{FH} markers which help to accurately separate AITL pattern 1 from reactive follicular hyperplasia. Cases with pattern I may show histological progression to typical AITL in sequential biopsies. Notably, despite "early" histological involvement likely reflecting the prevalent *in situ* expansion of neoplastic T_{FH} cells in the outer zone of the germinal centers, the majority of patients in all series presented with advanced clinical stages suggesting that progression from pattern I to III represents a histological evolution rather than a truly clinical progression of the disease [55]. It is still open whether these different architectural aspects may reflect a variable degree of involvement in different lymph nodes.

A goal of the panel in reviewing the cases from the workshop was to apply rigorous histological and immunohistochemical criteria including investigation for CD10 and T_{FH} markers to highlight the distribution of the neoplastic cells in early lesions and distinguish lymph nodes involved by AITL from other reactive or neoplastic conditions and to compare the histopathological pattern with the clinical and biological features. An unusual variant of "follicular" PTCL was also submitted and discussed in this session as well as an intriguing case of persistent clonal expansion of CD10+ T_{FH} cells in multiple sites, of unknown significance.

Workshop cases

Eight cases classified as AITL by the submitters and by the panel were submitted to the workshop. Case 62.2 (Figure 9 A–F) presented by Drs. Rosati and Kluin, was a prototypic case of early lesion of AITL, occurring in a 45-year-old woman presenting with the full-blown clinical and biological pictures of the disease, i.e. fatigue, fever, lymphadenopathy, splenomegaly and Coombs-positive hemolytic anemia. Lymph node biopsy showed a massive follicular growth pattern with numerous follicles lacking distinctive mantle zones. These features together with an expansion of CD10+ lymphocytes spreading outside the follicles and small B-cell clones were initially mistaken for follicular lymphoma. However, there was no FDC expansion outside the follicles, BCL-2 was negative within the follicles and the stronger reactivity for CD10 and PD1 of lymphocytes with a perifollicular pattern fit well with pattern I AITL. The diagnosis was supported by the demonstration of large B blasts in the interfollicular areas with numerous EBV-infected cells, the presence of small clusters of CD5+, CD4+ clear cells surrounding venules and a clonal T-cell population. Finally, subsequent follow-up and re-biopsy five months later, showed evidence of histologically typical AITL pattern III with marked proliferation of EBV-infected B-cells (Figure 9 E–G). Other cases similarly highlighted the discrepancy between the full-blown clinical syndrome and morphologically characteristic features of "early-stage" AITL (pattern I-II, case 33.3, Dr. Fend), or demonstrated morphological progression in subsequent biopsies (case 87, Dr. Thorns) or a more mixed architectural pattern I to III depending on investigated areas. Of note, the expression of the different T_{FH} cell markers varied from case to case.

Presence of large B-cell blasts, usually but not always infected by EBV, scattered throughout the tissues is an almost constant and characteristic feature of AITL. Clonal expansions of B-cells are found in up to one third of AITL patients [97–99]. A subset of AITL patients go on to develop a clonal B-cell lymphoproliferation, in most instances an EBV-positive diffuse large B-cell lymphoma, less commonly an EBV-negative B-cell or plasma cell neoplasm [100–102]. Case 32.2 (Dr. Dirnhofer) nicely illustrated an AITL case with an EBV+ B-cell expansion with numerous large CD30+ B-cells, sometimes multilobated with “Reed-Sternberg-like” features, present either scattered or focally as large aggregates or small sheets in a background of AITL. Molecular analysis disclosed the presence of a clonal B-cell population in addition to the T-cell clone. This case raised the question of an associated EBV+ diffuse large B-cell lymphoma (DLBCL). Although there are no strict criteria established in this setting, the panel felt that areas of destructive cohesive sheets of large B-cells are needed for a diagnosis of DLBCL and classified the case as AITL with EBV+ clonal large B-cell expansion. The common presence of a large B-cell component and the risk for development of a B-cell LPD has been the basis for testing the combination of Rituximab with chemotherapy in AITL patients.

Two complex and intriguing cases, including case 26 (Dr. Vornanen) and case 22.4 (Dr. Alobeid), raised the question of whether premalignant clonal T_{FH} cell proliferations exist and can be identified. Case 26 was diagnosed as AITL pattern II with regressive Castleman-like follicles based on the presence of a clonal T-cell population and the full clinical and biological manifestations of AITL, initially regarded as Castleman’s disease. Interestingly, the patient had been treated with steroids for a highly similar episode six years before. At that time, the lymph node biopsy had shown only non-specific hyperplastic changes with, however, the presence of small foci of CD10+, PD1+ cells in the interfollicular areas. Of note, long term remission after steroids is common in AITL [93]. Another peculiar feature of this case was the occurrence of PTCL, NOS in the intestine one year after the AITL diagnosis, since this is a rather rare event in the course of AITL [103]. Case 22.4 was from a 20-year-old woman presenting with skin urticaria with mild improvement with topical steroids, who subsequently developed diffuse lymphadenopathy without B symptoms. Infectious etiologies were ruled out. Two sequential lymph node biopsies showed morphologically reactive changes with well-defined hyperplastic follicles without atypia in the paracortex. However, flow cytometry and PCR analysis of the lymph nodes, as well as multiple peripheral blood samples and skin showed a CD3 dim, CD10+ minor T-cell population with a similar T-cell clone in all samples. By immunohistochemistry, a striking expansion of small lymphocytes expressing CD5, PD1 and strongly CD10 was found at the periphery of some germinal centers and as small aggregates in interfollicular areas of the lymph node (Figure 9 H,I). In the absence of changes at the histological level in a young patient, the panel diagnosed a “clonal expansion of CD10+ T_{FH} cells in multiple sites, of unknown significance”.

Case 78.4 submitted by Dr. Martinez was a good example for the difficulties at the border between AITL and some PTCL, NOS with T_{FH} markers. Histologically, the lymphoma showed a perifollicular pattern with slightly atypical CD10+, CXCL13+ T-cells and a few EBV-positive cells. In view of these findings and the presence of some FDC expansion, a diagnosis of AITL with a perifollicular pattern was preferred by the panel over that of PTCL, NOS with T_{FH} phenotype (Figure 9 J–N).

A related topic in this session was follicular PTCL, recognized as a variant of PTCL/NOS in the updated WHO classification. Its possible relationship to AITL has been brought up in view of the T_{FH} phenotype, the interaction with B-cells and FDC, and overlapping clinicopathologic features with AITL reported in some cases [104,105]. It comprises cases with a truly follicular pattern, mimicking follicular lymphoma [106], and T-cell lymphomas

involving follicles with expanded mantle zones, therefore mimicking progressive transformation of germinal centres or NLPHL. Neoplastic cells are CD4+ BCL6+ CD10 +/- CD57-, with expression of T_{FH} molecules [104]. A recurrent chromosomal translocation t(5;9)(q33;q22) involving ITK and SYK tyrosine kinase, has been described in at least some follicular PTCLs [55]. Case 85.3 presented by Dr. Huang, occurred in a 60-year-old woman with generalized lymphadenopathy but no constitutional symptoms. Two sequential lymph node biopsies showed the same histological picture with large CD20+, IgD+ B-cell nodules reminiscent of PTGC or NLPHL, containing aggregates of small/medium sized T cells with a CD3+, CD7-, CD4+, CD10+/-, CXCL13+ phenotype, admixed with scattered EBV + cells. The demonstration of a T-cell clone by PCR and of clonal aberrations by conventional cytogenetics supported the diagnosis of PTCL. Of note, the patient showed spontaneous regression of adenopathies and was alive without treatment with a 14-month follow-up.

Conclusion

The cases presented illustrated well that the histological patterns in AITL reflect a morphological continuum, but have little relationship with the clinical picture. However, the recognition of these “early” morphological features is important for the pathologist and its recognition should prompt further immunohistological and molecular investigations. The need for strict minimal diagnostic criteria for AITL and the criteria for recognizing follicular PTCL were discussed.

Enteropathy-associated T-cell lymphoma (EATL) (Session 4.2)

EATL is an intestinal neoplasm derived from intestinal intraepithelial lymphocytes (IELs). EATL *usually* arises in the small intestine, presenting as ulcerated jejunal lesions that may cause intestinal perforation. The prognosis is usually poor [107,108]. Two types of disease are recognized: type I EATL, associated with celiac disease, and type II EATL, unrelated to celiac disease. EATL is not associated with EBV.

EATL type I

EATL type I usually occurs as a complication of gluten-sensitive enteropathy (celiac disease), thus being more common in regions with a high prevalence of celiac disease, such as Northern Europe. The lymphoma may arise in patients with longstanding celiac disease, but may also be diagnosed after a short period of symptoms or even in patients with asymptomatic villous atrophy. Most patients with type I EATL have celiac disease human leukocyte antigen (HLA) haplotypes (HLA-DQ2)[109]. Morphologically, type I EATL shows a non-monomorphic proliferation of variably sized lymphoid cells, ranging from small to large immunoblasts or even anaplastic cells, often accompanied by inflammation and necrosis. In typical cases the adjacent non-tumoural mucosa shows an increase of IELs with or without villous atrophy (enteropathic features), but these features may be absent, if the patient is on a gluten-free diet. The lymphoma cells express CD103 which is the mucosal homing receptor, characteristic of intraepithelial lymphocytes. They usually are CD3+ / CD5- / CD4- / CD8- T-cells with an activated cytotoxic profile. Variable CD30 expression is common.

Of interest to this session is the closely related pathogenesis of celiac disease and EATL type I, with both sharing increased numbers of activated IELs [110]. The development of lymphoma in patients with symptomatic celiac disease may be preceded by refractory celiac disease. In fact, an identical T-cell clone has been demonstrated in paired samples of refractory celiac disease and the subsequent lymphomas. Thus being, refractory celiac disease with these features may be considered as an ‘in situ’ or ‘intraepithelial’ EATL [111,112]. Chronic ulcerative jejunitis is another known complication of celiac disease, closely related to refractory celiac disease and EATL [111,113]. Upregulation of IL-15 in

the epithelium of patients with celiac disease is believed to play a major role in the promotion of the transformation of IELs, by triggering an antiapoptotic pathway in these cells [114,115].

EATL type II

A fraction of EATLs seems unrelated to celiac disease and may represent the majority in countries where celiac disease is uncommon. Histologically, type II EATL consists of a monomorphic proliferation of medium-sized cells, with few admixed inflammatory cells and usually little or no necrosis. The neoplastic cells have a CD8+ / CD56+ activated cytotoxic profile. Increased numbers of IELs with a similar immunophenotype can be found in the adjacent mucosa [116]. Genetically EATL type II is similar to type I, sharing common 9q gains and 16q deletions, but additionally may show gains at 8q24, harbouring the MYC oncogene [117].

Workshop cases

Case 101, presented by Dr. Marafioti encompassed the full spectrum of the disease in the same specimen, with areas of celiac disease, refractory celiac disease and areas of overt enteropathy-associated T-cell lymphoma, type I (Figure 10 A–F). Of interest is the change of phenotype with loss of CD3 by the large cells in the lymphoma lesions, and the fact that clinically this was the first manifestation of the disease. Further examples at the workshop comprised a case of EATL type I preceded four years earlier by clonal lymphocytic gastritis, and a case of type II EATL with expansion of clonal intraepithelial lymphocytes in the adjacent intestinal mucosa.

Case 66.2, presented by Dr. Jaffe, represented the newly recognized entity of NK cell enteropathy [92,118]. The case was included in this group due to the possible clinical and morphological confusion with a T-cell lymphoma (Figure 10 G,H). This asymptomatic patient was found to have superficial hemorrhagic lesions in the colon and terminal ileum during an elective colonoscopy. He also had high titers of anti gliadin IgA and IgG antibodies. Follow up for 7 years revealed similar lesion in the stomach, small bowel and colon, without progression. The atypical cells were CD56+, CD7+, cytoplasmic CD3+, TIA-1+, Granzyme B+, and CD94+ (by flow cytometry). Other T- and B-cell markers were negative. This case was diagnosed as NK cell enteropathy and originally published by Vega et al. [118]. Recently, a very similar series of cases arising in the stomach was reported [91].

Conclusion

The cases presented illustrated well the spectrum of EATL types I and II, and support the hypothesis that clonal intraepithelial T-cell proliferations are early or “in situ” lymphomas with a definite risk for transformation. The newly defined entity of NK cell enteropathy is a good example how an indolent disorder can mimic an aggressive disease and requires integration of clinical features as well as, detailed pathological work-up.

Cutaneous T-cell proliferations(Session 4.3)

The cases sent in this category belong to the group of primary cutaneous CD30 positive T-cell lymphoproliferative disorders (LPD). They include primary cutaneous anaplastic large cell lymphoma (C-ALCL) and lymphomatoid papulosis. This group of diseases forms a continuum rather than constituting discrete entities, and the clinical appearance and evolution are critical in the final diagnosis. The relapsing nature in a part of the cases raises the question on the meaning of “early lesion” in this context.

Only two cases were received in this category, including case 78.2 of a young girl who presented with cutaneous lesions, but soon afterwards developed an enlarged lymph node

with features of anaplastic large cell lymphoma, similar to the one observed in the skin. The tumor was CD30+, ALK-1 negative, and no *ALK* rearrangements were found by FISH. In view of the cutaneous presentation and relapse, the panel diagnosed this case as primary cutaneous ALCL with local lymph node involvement, which can occur in 5–10% of patients with cutaneous ALCL.

Other indolent T-cell lymphoproliferative disorders (Session 4.4)

An association between anaplastic large cell-lymphoma (ALCL) and breast implants has been recently recognized [89,90,119]. According to a systematic literature review, among 36 cases of lymphomas in patients with implants, 29 (81%) were ALCLs. These lymphomas – also referred as “seroma-associated primary ALCL adjacent to breast implant” – often involves the capsule and/or presents as unexplained seroma or mass adjacent to silicone or saline breast implants without evidence of systemic disease. Despite the morphology and phenotype of ALK-negative ALCL, they constitute a usually clinically indolent disease with a favourable outcome that is distinct from systemic ALK-negative ALCL.

Case 59 presented by Dr. Dogan was a prototypic case occurring as a seroma six years after saline breast implants for breast carcinoma. A first diagnosis of large cell lymphoma by FNA was followed by several relapses 2, 4 and 7 years after first diagnosis that were only treated by aspiration and finally capsule removal. Large cells with pleomorphic sometimes lobated nuclei had a CD30+, EMA+, CD3+, CD2+, CD4–/CD8– phenotype with expression of cytotoxic molecules (Figure 10 I–L) and were clonal by PCR. They lacked ALK expression. A second case with very similar clinical presentation was unusual in that the neoplastic cells had a CD4 phenotype and did not express cytotoxic molecules.

Since the workshop was held, the association between ALCL and breast implants has been recognized by the FDA and guidelines have been produced: a recurrent seroma occurring > 6 months after breast implantation should be aspirated and sent for cytological analysis; management should consist of removal of the involved implant and the newly generated capsule. Adjuvant radiation or chemotherapy appears not required when the disease is confined to the capsule [120,121].

Another example of clonal T-cell lymphoproliferative disorder (indolent?) was case 34 presented by Dr Pinilla-Rodriguez occurring in a 66-year-old woman with splenomegaly and without B symptoms. She had mild relative lymphocytosis (37.8%) with normal lymphocyte counts and phenotype by FCM. At splenectomy, the spleen was homogeneously enlarged with a moderate infiltration of the red pulp by mature T cells with a F1+, CD2+, CD3+, CD5+, CD7+, CD4–, CD8–, TCR –, TIA1+, perforin+, Granzyme B+ phenotype (Figure 10 M–O). Identical monoclonal rearrangements of TCRG genes were found in the spleen and the peripheral blood. Bone marrow findings were recorded as normal. The patient was followed without additional treatment and was doing well without symptoms but with persistent T-cell clone in the PB one year after splenectomy. In view of the indolent presentation with splenomegaly, a diagnosis of T-LGL leukemia was first considered. However, in the absence of CD8+, CD57+ LGL and of bone marrow infiltration, the panel felt more appropriate to propose a diagnosis of “clonal T-cell population of uncertain significance”. This indicates that there is a spectrum of indolent, transient or persistent clonal cytotoxic T-cell proliferations, which need to be differentiated from classical T-LGL and variants, which themselves often show a very indolent clinical evolution.

General conclusion for the session

As mentioned in the introduction, in T-cell lymphomas, the concept of “early “or precursor lesion is hard to define. Therefore, from the analysis of the workshop cases it is not possible

to draw definitive conclusions regarding the morphological phenotypic or molecular features that may suggest an incipient neoplasm. On the contrary, the AITL cases presented in the workshop seem to support the previously recognized lack of correlation between the morphological features and the clinical behavior. Although these “early” morphological patterns in AITL are important to recognize, we support the concept that the architectural grading is not relevant for the clinical management in this type of lymphoma.

Session 5

Session 5 focused mainly on lymphoid proliferations associated with the lymphotropic gamma Herpes viruses, Epstein Barr virus (EBV) and HHV-8. 14 cases were submitted from North America and 11 from Europe. The spectrum of the cases examined at the workshop was clearly impacted by the lack of cases submitted from Asia, as there are clear epidemiological differences in the nature of EBV-related disease in different parts of the world, and among different ethnic groups.

EBV+ proliferations related to acute EBV infection (Session 5.1)

Session 5.1 included examples of acute EBV-infection, and chronic active EBV infection of both B-cell and T-cell types. The cases illustrated the spectrum in clinical manifestations ranging from acute, self-limited disease, in the instance of infectious mononucleosis, to persistent and sometimes progressive disease-associated chronic active EBV infection (CAEBV). CAEBV was originally defined as a severe illness of greater than six months duration that followed acute infection, and was associated with markedly elevated viral titers, increased EBV in tissues, and histological evidence of organ damage [122]. An elevated viral load can be detected in peripheral blood by PCR. While the term CAEBV has been used most often in association with EBV proliferations of T-cells or NK-cells [123], the B-cell equivalent, sometimes also seen in Western countries, is now well recognized [124]. Classification of CAEBV should include the lineage of the EBV-infected cell, and the clonality of the proliferation, if it can be determined. However, all clonal and monomorphic proliferations of atypical EBV-infected T-cells are considered neoplastic, and in the 2008 WHO classification are diagnosed as systemic EBV-positive T-cell lymphoproliferative disease (of childhood), usually presenting in the pediatric age group [125].

Workshop cases

Dr. Jaffe presented a case (case 66.3) of CAEBV of T-cell type, in which the EBV-positive proliferation appeared to be polyclonal, and although the patient had persistence of symptoms over several years, the disease did not progress. The patient had disease mainly referable to hepatic involvement, with cholestasis, and EBV-positive T-cells distributed in hepatic sinusoids. Dr. Pittaluga submitted a case (case 66.1) of CAEBV of B-cell type, that was associated with recurrent involvement of tonsils and lymph nodes, but without histological progression or evidence of monoclonality. As in many cases of CAEBV of B-cell type, the patient developed hypogammaglobulinemia [126].

EBV-associated lymphoproliferations (Session 5.2–5.5)

Session 5.2 included EBV-associated lymphoproliferations following immunosuppression for solid organ or bone marrow transplantation or for autoimmune disease. The cases presented by Dr. Smith (case 21.2) and Dr. McGinn (case 92.3) demonstrated the difficulties in the differential diagnosis of primary EBV infection with plasma cell expansion and early infectious mononucleosis-like PTL. Serological studies are essential in this setting. At the other end of the spectrum Dr. Arcila submitted a case (case 69) of EBV positive large B-cell lymphoma following allogeneic bone marrow transplantation. Multiple sites were involved, all showing the same clone by PCR analysis of *IGH@* genes. Interestingly, the lesion was

shown to be of host origin, differing from most PTLDs following allogeneic bone marrow transplantation.

Other EBV-driven proliferations presented in Sessions 5.3 and 5.4 occur in settings in which the nature of the immunosuppression is less well defined. These include lymphomatoid granulomatosis and EBV related lymphoid proliferations in the elderly. In case 13, submitted by Dr. Montes-Moreno, an early lesion was felt to be reactive, with EBV restricted to germinal centers. However, an *IGH* clone was detected, and the patient relapsed with EBV-positive large B-cell lymphoma in an inguinal lymph node. Also included in this group was an example of EBV-positive plasmablastic lymphoma presenting on the penis of a 81-year-old male (case 81). Thus, the cases ranged from early EBV-associated lymphoproliferations to fully developed lymphomas.

In summary, diagnosis of EBV-related lymphoproliferations requires integration of clinical features, namely a history of antecedent EBV-related symptoms, serological findings and presence or absence of immunosuppression, morphological features, immunohistochemical findings including the lineage of EBV-infected cells (B-cell vs T-cell) and EBV latency type, as well as work-up for clonality.

HHV-8 associated lymphoproliferations (Session 5.6)

Session 5.6 was devoted to lymphoid proliferations associated with HHV-8 (Figure 11). These also represent a clinical and biological spectrum, ranging from the polyclonal B-cell proliferations of multicentric Castleman's disease (MCD), to the high grade and monoclonal proliferations of primary effusion lymphoma (PEL) and the solid variants of PEL. Co-infection by EBV further complicates the picture in PEL. Three cases of MCD were presented (Cases 53, 75 and 82). Clustering of HHV-8 infected cells as present in cases 47 and 58 has been termed "microlymphoma" [127], but true progression in such cases is rare, and the term "microlymphoma" is not currently favored. Patients with MCD may have increased numbers of EBV-infected cells in the lymph nodes, but they usually do not colocalize with the HHV-8-positive cells, as evidenced by case 47 (Dr Canioni) (Figure 11 H). If co-infection is observed, this finding favors histological progression. As evidence of clonality is not observed in MCD, identification of a B-cell clone also favors histological progression.

The differential diagnosis of HHV-8+ positive plasmablastic lesions requires analysis of IG heavy and light chains, evaluation of clonality by PCR, pan B and plasma cell antigens and the presence of EBV co-infection. Neoplastic cells with plasmablastic morphology in both primary effusion lymphoma (PEL) and germinotropic lymphoproliferative disease carry EBV and HHV-8 coinfection. Whereas the neoplastic cells in PEL lack B-cell markers and IgH or light chain expression and are positive for plasma cell antigens, plasmablastic cells in germinotropic LPD show either kappa or lambda light chain restriction but at the molecular level are negative for clonal *IG* rearrangements [128].

Case 58 submitted by Dr Peker was an interesting example of MCD with expansion of plasmablastic cells involving the germinal centers. These cells were coinfecting by EBV and HHV-8, but lacked immunoglobulin expression, favoring PEL over germinotropic LPD (Figure 11 A–G). This session demonstrated that the spectrum of HHV-8 lymphoid proliferations is greater than originally appreciated, and now includes MCD, PEL, and germinotropic lymphoma, as well as other unusual proliferations difficult to classify [129].

General conclusions and recommendations for terminology

The lymphoma workshop of the XV. EAHP/SH meeting in Uppsala provided a forum to discuss the clinical, morphological, immunophenotypic and molecular features of early or subclinical manifestations of lymphoproliferative disorders and their precursor lesions. An important part of the discussions at the workshop revolved around terminology of early lesions, especially the well recognized small B-cell proliferations with defined phenotypic and genotypic alterations. The panel and participants felt that the commonly used terms “follicular lymphoma in situ (FLIS)” and “mantle cell lymphoma in situ (MCLIS)” might inappropriately indicate a diagnosis of - albeit early stage - lymphoma. Although the risk for progression of these lesions, which are usually detected by chance is currently unknown, it seems reasonable to assume from currently available data that at least a proportion of individuals will remain free from clinically manifest lymphoma for their lifetime. Therefore, the panel proposed the alternative terms “FL-like B-cells of undetermined significance” (FLBUS) and “MCL-like B-cells of undetermined significance” (MCLBUS) in order to indicate the unknown clinical outcome of these lesions. Furthermore, this designation reflects the terminology used for the prototypic premalignant clonal B-cell proliferation, monoclonal gammopathy of undetermined significance (MGUS). Whether and to what extent individuals receiving such a diagnosis in the absence of any other evidence for malignant lymphoma should undergo clinical staging still needs to be determined [130].

The identification of CLL-like B-cells in morphologically unsuspicious lymph nodes poses a similar problem. Some of these patients may receive a diagnosis of CLL in the peripheral blood, others may present with monoclonal B-cell lymphocytosis (MBL) of CLL type. Although the term „tissue equivalent of MBL” or “nodal MBL” was proposed by some participants and recently in the literature [131], the panel thought that the usage of a term defined for the peripheral blood might be misleading, especially considering the fact that some of these patients will fulfill the diagnostic criteria for CLL in the PB or bone marrow. Also considering the advantages of consistent terminology, the panel suggested the term „CLL-like B-cells of undetermined significance” (CLLBUS) for cases with minimal lymph node involvement in which the status of PB or BM is unknown. A recent publication after the workshop has investigated a series of cases with mostly nodal involvement by cells with an SLL/CLL phenotype in patients lacking the diagnostic features of CLL in the peripheral blood and may help to refine criteria for differentiating between SLL and nodal involvement by CLL-like B-cells of undetermined significance or nodal MBL [132].

Given the lack of clinical consequences, the panel felt that an active search for these lesions by performing immunohistochemical stains is not indicated for lymph nodes lacking architectural or cytological changes potentially indicating malignancy in patients without clinical suspicion of lymphoproliferative disease.

Compared to the B-cell proliferations discussed above, other early lymphoproliferations are even less well defined. This applies to B-cell lesions such as clonal marginal zone or follicular expansions lacking clear-cut criteria of malignancy, such as gross architectural disturbances or clonal genetic aberrations. Even less is currently known about early clonal T-cell proliferations. With the exception of extranodal lesions such as refractory celiac disease, well-defined premalignant T-cell proliferations currently are not recognized.

Some clonal T-cell proliferations such as CD4+ cutaneous small to medium size T-cell lymphoma and seroma-associated ALK- ALCL usually show a very benign clinical course, questioning whether the term lymphoma is indeed justified, whereas morphologically “early” AITL often shows discordance with a usually fully developed clinical picture.

In summary, at the 2010 EAHP/SH lymphoma workshop, a range of “early” lymphoid lesions were presented most of which have only been recognized in recent years and for which universally accepted diagnostic criteria and guidelines for clinical handling are still lacking. Although much still needs to be learned about these lymphoid proliferations, the workshop and the resulting report may provide a common ground for future investigations and discussions.

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Figure 1.

Session 1.2 and 1.3. Case 19. Pediatric follicular lymphoma. (A) The lymph node contains two types of ‘follicles’ – ordinary, reactive GCs (right) and neoplastic follicles (left) lacking polarization and expressing CD10 and BCL6 but not BCL2. Immunostaining for (B) and (C) light chains confirmed the light chain restriction detected by flow. PCR for immunoglobulin heavy chain and kappa light chain gene rearrangements, however, were equivocal. Case 76.2. Lymphadenopathy with progressively transformed germinal centers and concomitant marginal zone hyperplasia. (D) The lymph node shows a complex nodular pattern reminiscent of nodal marginal zone lymphoma. Immunostains for BCL-6 (E) and CD23 (F) document the disrupted follicular structures. However, neither immunohistochemical nor molecular studies showed evidence for malignancy.

Figure 2.

Session 1.4. Marginal zone lesions. Case 30. Cervical lymph node of a 62-year-old female with rheumatoid arthritis with clonal expansion of CD5+ marginal zone B-cells. A reactive germinal center is surrounded by an expanded marginal zone with monotonous small cells (A), which show light chain restriction (B, C) and co-expression of CD5 (insert).

Figure 3. Session 1.4. Case 78.3. Extranodal monotypic marginal zone hyperplasia in a 4-year-old child. (A,B) The appendix shows both marked follicular and marginal zone hyperplasia which showed monotypic light chain expression but was polyclonal by PCR.

Figure 4.

Session 2.1. Persistent polyclonal B-cell lymphocytosis. (A) Case 7: Peripheral blood smear showing lymphocyte with bilobed nucleus. (B) Case 5: Section of spleen showing hyperplastic white pulp with cellular infiltration and nodules with reactive germinal centres (C) and expanded marginal zone (D). CD20 immunostaining (E) highlights the increased number of B cell in the red pulp. Kappa (F, left) and lambda (F, right) stains show polytypic light chain expression. (G) Case 7: CD20 immunostain of the bone marrow shows interstitial infiltration with a focal intra-sinusoidal component.

Figure 5.

Session 2.2. Monoclonal B-cell lymphocytosis. Case 93.1 (A–D) Low power shows a small lymph node with preservation of the architecture (A), and high power (B) reveals a small follicle showing clustered cells in the mantle with appearances of prolymphocytes. CD5 (C) and CD3 (D) stained sections highlight a CD5+/CD3– cell population in the follicle mantle. Case 2 (E–H) Low power shows preservation of the nodal architecture (E), and high power (F) reveals a proliferation centre within the mantle of a follicle. CD5 (G) and CD3 (H) stained sections show a population of CD5+/CD3– cells in the upper part of the follicle mantle.

Fig 6.

Sessions 2.3 and 2.4 Mantle cell lymphoma, small cell variant. Case 78.1. (A–C) (A) Sections of spleen show expansion of the white pulp. At high power (B), the lymphocytes appear small. (C) Immunostaining shows the lymphocytes to be cyclin D1 positive. Monoclonal gammopathy of undetermined significance. Case 89. (D–F) (D) Bone marrow aspirate exhibits a mild plasmacytosis. (E) Bone marrow core biopsy shows scattered plasma cells, some with Dutcher bodies (arrow). (F) Immunostain shows that the plasma cells are cyclin D1 positive and FISH (inset) demonstrates a t(11;14). Nodal plasmacytoma of IgA type. Case 22.3. (G–I) (G) Low power of lymph node shows an expansion of the interfollicular area. (H) At high power the interfollicular regions show sheets of plasma cells. (I) By immunostaining the plasma cells exhibit monoclonal IgA kappa.

Figure 7.

Session 3.1. Follicular lymphoma „in situ“. Case 68 (S. Owens). (A) Scanning magnification shows a small node with preserved architecture, activated parafollicular areas and small, inconspicuous follicles. (B) Some of the follicles show intense BCL-2 staining restricted to some germinal centers (arrowheads). (C) Case 17 (K. Kelemen). CD10 shows abnormally strong expression in the germinal centers. The insert shows the presence of a t(14;18) translocation within the abnormal germinal centers. Case 33.2 (D–G) (D) HE staining shows two morphologically indiscernible follicles. (E) BCL-2 staining reveals intense positivity in one of the two germinal centers. (F) The proliferation rate is reduced in the area of the follicle containing BCL-2+ FL-like cells. (G) CD23 highlights an intact follicular dendritic cell meshwork. (H–K) Intestinal follicular lymphoma. Case 83. (H) Scanning magnification reveals numerous nodular lymphoid aggregates in the mucosa. (I) Higher magnification reveals a nodular proliferation of small lymphoid cells without discernible follicle mantle or germinal center. (J) The proliferation rate, assessed by MIB1 staining, is very low. (K) The cells show strong BCL-6 expression.

Figure 8.

Session 3.2. Mantle cell lymphoma „in situ“. Case 43.1 (P. Browne). (A) At low power, the lymph node shows a normal architecture with hyperplastic germinal centers. (B) The narrow follicle mantle does not reveal an abnormal cell population in routine histology. (C) Immunostaining demonstrates rims of cyclin D1 positive cells around the reactive germinal centers. Case 43.2 (V.Nelson). (D) CD5 highlights rims of weakly CD5+ MCL-like cells surrounding reactive germinal centers. Insert: FISH demonstrates the presence of CCND1/IgH fusion. (E) The MCL-like cells show strong nuclear SOX11 staining. Case 100 (F) Minimal involvement of the gall bladder by lymphomatoid polyposis-like lesions. (G) Cyclin D1+ cells surround and invade the germinal center.

Figure 9.

Session 4.1. Angioimmunoblastic T-cell lymphoma and related lesions. Case 62.2 (A–G) AITL with morphological progression. (A) Low power of the first lymph node shows a pattern of atypical follicular hyperplasia with lack of distinct mantle zones. (B) High power reveals focal proliferation of atypical clear cells along high endothelial venules. (C) CD20 immunostain confirms a follicular B-cell proliferation. (D) CD10 staining highlights a proliferation of strongly CD10+ neoplastic cells outside the germinal centre, whereas the germinal center B-cells (asterisk) stain only weakly. (E) A second biopsy 5 months later shows diffuse effacement of the architecture with extensive proliferation of high endothelial venules and (F) CD21+ follicular dendritic cells. Case 22.4 (H,I) Clonal expansion of T_{FH} cells AITL with perifollicular growth pattern. (H) The lymph node shows follicular hyperplasia without evidence of an atypical perifollicular population. (I) CD10 immunostain demonstrates a striking proliferation of strongly CD10 T_{FH} cells in the periphery of a weakly stained germinal center (asterisk). Case 78.4 (J–N) AITL with features of PTCL NOS. (J) Low power shows a lymph node with a predominantly perifollicular proliferation. (K) At high power, a proliferation of mildly atypical cells lacking the typical polymorphous appearance of AITL is visible. (L) CD10 highlights the accumulation of CD10+ neoplastic cells around the reactive germinal center (asterisk). (M) CD3, (N) CD20.

Figure 10.

Session 4. Case 101 (A–F). Progression of celiac disease to enteropathy-associated T-cell lymphoma. (A) Intestinal mucosa with celiac disease with blunted villi with increase in intraepithelial lymphocytes. (B) Refractory celiac disease with intraepithelial accumulation of (C) CD3+ and (D) CD8 negative lymphocytes. (E) Manifest EATL with large, pleomorphic tumor cells with (F) co-expression of CD30. Case 66.2 (G,H). NK cell enteropathy. (G) Accumulation of atypical cells in the lamina propria of the colon with strong (H) CD56 expression. Case 59 (I–L) Seroma-associated primary anaplastic large cell lymphoma adjacent to breast implant. (I) The aspirate cytology shows large, pleomorphic cells with sometimes lobated nuclei. (J) Cell block preparation. The tumor cells show strong expression of CD30 (K) and TIA-1 (L). Case 34 (M–O) Indolent clonal splenic T-cell proliferation. (M) The red pulp contains a moderate infiltrate of mature small T-cells double negative for CD4 and CD8 and expression of cytotoxic markers. (N) CD2 immunostain. (O) TIA-1 immunostain.

Figure 11.

Session 5.6. Case 58 Early PEL (A–G) (A) Early PEL with few neoplastic follicles (circle) within a background of follicular hyperplasia (arrow). (B) The neoplastic follicles are composed of large cells with immunoblastic features. (C) neoplastic large cells are positive with CD138 and (D) negative with CD20 (double staining : brown CD20, red CD3). (E–G) The atypical intrafollicular cells were coinfectd by both HHV8 and EBV (double staining EBER and HHV8). Case 47. Multicentric Castleman's disease (H). Scattered EBV-positive cells were present, but did not co-localize with the HHV-8-positive population. EBER positive cells are largely interfollicular, whereas HHV-8-positive cells are intrafollicular. (double staining EBER and HHV8).

Table 1

Differential diagnosis of follicular lymphoma with partial lymph node involvement versus FL-like B-cells of undetermined significance (FLBUS)

	FL partial involvement	FLBUS (FLIS)
Histopathology		
architectural alteration	focal	no
germinal centers (GC)	occasionally enlarged, ill-defined borders	normal size, well defined, sharply demarcated
follicle mantles	focally attenuated and ill defined	well defined, normal configuration
cytology of GC	monotonous, mostly centrocytes but centroblasts may be present	monotonous, mostly centrocytes
perifollicular spread	occasionally	absent
Distribution within LN	Affected follicles often clustered	Affected follicles widely scattered, often not contiguous
Immunohistochemistry		
BCL2	positive, variable intensity, whole GC	strongly positive, sometimes only partial GC involvement
CD10	positive, occasional interfollicular tumor cells	strongly positive, restricted to involved GC
MIB1	low proliferation	low proliferation, except for partially involved GC
Clinical		
manifest FL at other site	possible	absent by definition, but FLBUS may involve more than one node

Table 2

Differential diagnosis of MCL with partial involvement vs. MCL-like B-cells of undetermined significance (MCLBUS)

	MCL partial involvement (mantle zone pattern)	MCLBUS (MCL IS)
architectural alteration	focal	no
germinal centers	may be partially overrun	normal
follicle mantles	Often expanded, monotonous	well defined, normal configuration
cytology of follicle mantle	may be abnormal	normal
intra- or perifollicular spread	occasionally	absent
Immunohistochemistry		
cyclin D1	positive in whole follicle mantle	positivity usually restricted to border between GC and inner follicle mantle
CD5	usually positive	variably positive
manifest MCL at other site	possible	absent by definition but MCLBUS in theory may involve more than one site