REVIEW OF THE LITERATURE

New developments in the pathology of malignant lymphoma: a review of the literature published from January to August 2009

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Introduction

The previous issue of the Journal of Hematopathology lacked a review of the literature because there were five commentaries on the 2008 classification by members of the editorial team [1–5] and the first regular review on literature for bone marrow pathology by Jon VanderWalt [6]. Therefore, this issue contains a quite long review of the literature covering the first half of 2009, a longer period compared to the previous three reviews [7–9] and the selection was therefore, more strict.

The wealth of information that is coming available is more and more difficult to grasp, and reviews like this can only lift a tip of the veil. Huang et al. [10] have developed an intelligent database that enables to integrate many data that are available on lymphoma patients. Since the majority of patients are not the average patient, this type of approach may be helpful to reach a level of knowledge that will enable real personalized medicine, by comparing many data of an individual patients to those present in the database. In principle, the opposite approach to collecting large amounts of data and comparing that to individual patients is to try to unravel the pathogenesis of lymphomas by experimental work. Also in the last months, exiting new data have become available which will eventually lead to more biological approaches in the treatment of lymphoma patients.

Blocking the effect of gene activation by mRNA interference is a promising approach for various tumor types. It is therefore quite helpful that Anastasov et al. [11] were able to develop an efficient lentiviral vector-based system to study gene knockdown in lymphoid cell lines. The work will form the foundation of a series of studies on the effect of knocking out specific proteins in cell cultures.

Biology of lymphoma

Hodgkin lymphoma

Now that a large amount of biological features of Hodgkin lymphoma (HL) tumor cells has become available, amongst others, by studying cell lines, several new drugs are being tested preclinically. Hartlapp et al. [12] show that targeting multiple signaling pathways by inhibition of histone deacetylase using depsipeptide results in apoptosis induction and cell cycle inhibition. Especially the inhibition of apoptsis had been difficult to achieve so far, and thus, this might be a promising new treatment for HL patients.

It is now well-known that HL represents a B cell neoplasia with an aberrant B cell differentiation program. Jones et al. [13] pursue an already old observation that in the culture of HL cell lines small populations of phenotypic normal B cells occur that express immunoglobulin. They were able to demonstrate that this small population is the precursor and generator of the HL cells, and also that such cell can be found in the blood of HL patients, regardless of stage.

B cell lymphomas

As referred to in the previous review [9], the tumor microenvironment was the main topic at the European Association of Heamatopathology symposium in Bordeaux
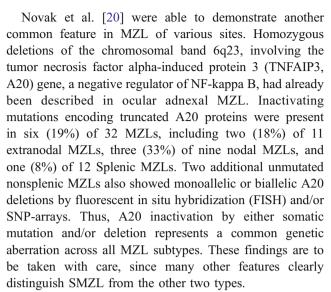
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in 2008. It became very clear that this is an important topic, but that our understanding is far from complete. Maby-El Haijami et al. [14] show that resting human mesenchymal stem cells (MSC) sustain activated normal B cell proliferation and survival, whereas IFN-gamma-conditioned MSCs mediate B cell growth arrest and apoptosis. IFN-gamma, TNF, and lymphotoxin-alpha1beta2 (LT) are significantly overexpressed by the microenvironment of follicular lymphoma (FL), but their relative expression patterns are highly heterogeneous between samples. In vitro, IFN-gamma abrogates the B cell supportive phenotype induced by TNF and LT on MSCs. Moreover, IFN-gamma overrules the growth promoting effect of MSCs on primary purified FL B cells. Altogether, these results underline the crucial role of the cytokine context in the local crosstalk between malignant cells and their microenvironment and provide new insights into our knowledge of the FL cell niche that emerges as a new promising target for innovative therapeutic strategies. But cytokines have not only an effect on MSCs. Especially in FL it is well-known that T cells are an important component of the microenvironment. Yang et al. [15] show that in B cell lymphoma samples the amount TH17 cells is decreased and by using cell cultures they showed that this is due to IL-2 production by malignant B cells, that activates regulatory T cells, which in turn downregulates the number of TH17 cells. In mantle cell lymphoma (MCL), Kurtova et al. [16] found high levels of CXCR4, CXCR5, and VLA-4. Since these chemokine receptors and adhesion molecule enable cell motility and migration, this finding may explain the often early high stage of disease patients present with.

The relation between B and T cells was even more intimate in observations by Krejsgaard et al. [17]. It was already known that B-lymphoid kinase (Blk), normally expressed in B cells and thymocytes only, transferred into mature T cells results in T cell lymphomas. They observed that Blk can be found in cutaneous T cell lymphomas, but not in benign T cell infiltrates, a finding when confirmed is quite relevant.

Anti CD20 antibodies are now a cornerstone in the therapy of B cell lymphomas. Rossi et al. [18] developed bispecific antibodies, anti CD20/CD22, and showed that in vitro these lead to apoptosis of B cells, and more efficiently in B cell lymphoma cells.

The relation between specific infections and extranodal marginal zone lymphomas (MZL) is well-known, with H. Pylori (HP) activating specific anti-HP T cells driving the lymphoma cells as prime example. The mechanism may be different in ocular marginal zone lymphomas since Bahler et al. [19] show that these lymphomas use specific immunoglobulin VH gene segments. Furthermore, the mutation spectrum suggests antigen-driven selection, and thus a potential antigen may have a more direct effect on the tumor cells in these cases.

Novak et al. [20] were able to demonstrate another common feature in MZL of various sites. Homozygous deletions of the chromosomal band 6q23, involving the tumor necrosis factor alpha-induced protein 3 (TNFAIP3, A20) gene, a negative regulator of NF-kappa B, had already been described in ocular adnexal MZL. Inactivating mutations encoding truncated A20 proteins were present in six (19%) of 32 MZLs, including two (18%) of 11 extranodal MZLs, three (33%) of nine nodal MZLs, and one (8%) of 12 Splenic MZLs. Two additional unmutated nonsplenic MZLs also showed monoallelic or biallelic A20 deletions by fluorescent in situ hybridization (FISH) and/or SNP-arrays. Thus, A20 inactivation by either somatic mutation and/or deletion represents a common genetic aberration across all MZL subtypes. These findings are to be taken with care, since many other features clearly distinguish SMZL from the other two types.

Mantle cell lymphoma is a very widely studied tumor type, and may have a highly complex karyotype next to the characteristic t (11; 14). Wang et al. [21] show that MCL have high levels of Jun kinases (JNK) mitogen-activated protein kinase, and that this is needed for cell proliferation and maintaining diploidy. In a subset of MCL's, loss of JNK results in a hyperdiploid state.

Now that technology to study genome-wide methylation has become available, it is no surprise that also lymphomas are studied using this powerful method. Bennett et al. [22] analyzed FL and compared the results to benign lymph follicles. The results indicate that extensive hypermethylation in promoters of polycomb target genes is a characteristic of FL, and that loss of expression of certain SUZ12 target genes could be functionally relevant for lymphomagenesis. Using a more traditional approach, Kondo et al. [23] found that gastric lymphomas, both MZL and diffuse large B cell lymphomas (DLBL), have many hypermethylated CGP islands, and that in gastric specimens without lymphoma, only hypermethylation was seen in case of HP infection. This suggests that hypermethylation may be an early event in EMZL lymphomas under the influence of HP infection.

Interleukin (IL)-21 has been recently shown to modulate the growth of specific types of B cell neoplasm, and MCL expresses the IL21 receptor. Gelebart et al. [24] show that IL-21 can effectively induce apoptosis in MCL via a STAT1-dependent pathway, which may be useful in designing novel therapeutic approaches.

Although the frequent occurrence of bcl-6 abberations in DLBL is well-known, the functional consequences were enigmatic. In a series of elegant experiments, Saito et al. [25] show a link between bcl-6 and bcl-2 in DLBL explaining the mutual exclusive gene alteration of bcl-2 and bcl-6. In normal germinal center B cells, BCL6 binds to the BCL2 promoter region by interacting with the transcriptional activator Miz1 and suppresses Miz1-induced

activation of BCL2 expression. BCL6-mediated suppression of BCL2 is lost in FL and DLBCL, where the two proteins are pathologically coexpressed, because of BCL2 chromosomal translocations and other mechanisms, including Miz1 deregulation and somatic mutations in the BCL2 promoter region. These results identify an important function for BCL6 in facilitating apoptosis of germinal centre (GC) B cells via suppression of BCL2, and suggest that blocking this pathway is critical for lymphomagenesis.

Although the association between Burkitt lymphoma (BL) and Epstein–Barr virus (EBV) infection is well-known, the exact mechanism by with the virus results in lymphoma development is not clear: in BL-cells, EBV is not always present. It has been suggested that EBV-positive and EBV-negative BL have different cells of origin. In particular, according to immunoglobulin gene mutation analysis, EBV-negative BLs may originate from early centroblasts, whereas EBV-positive BLs appears to arise from postgerminal center B cells or memory B cells. Leucci et al. [26] found that hsa-miR-127 is differentially expressed between EBV-positive and EBV-negative BLs. In particular, it was strongly upregulated only in EBV-positive BL samples, whereas EBV-negative cases showed levels of expression similar to normal controls, including microdissected GC cells. In addition, they found evidence that hsa-miR-127 is involved in B cell differentiation process through post transcriptional regulation of BLIMP1 and XBP1. The overexpression of this mRNA may thus represent a key event in the lymphomagenesis of EBV positive BL, by blocking the B cell differentiation process.

The Janus kinase 2 (JAK2)-signal transducers and activators of transcription pathway plays an important role in hematological malignancies. Mutations and translocations of the JAK2 gene, mapped at 9p24, lead to constitutive activation of JAK2 and its downstream targets. The presence of JAK2 mutations in lymphomas has been addressed in larger cohorts, but there are little systemic data on numerical and structural JAK2 aberrations in lymphoid neoplasms. Using TMAs and FISH with split signal JAK 2 probes, Meier et al. [27] show that 9p24 gains were present in six of 17 (35%) primary mediastinal B cell lymphomas, 25 of 77 (33%) Hodgkin's lymphomas, three of 16 (19%) angioimmunoblastic T cell lymphomas, and one of five ALK1 (+) anaplastic large cell lymphomas; breaks were observed only in three cases. They stress that despite the rarity of activating JAK2 mutations in lymphomas, JAK2 is recurrently targeted by numerical, and rarely by structural, genetic aberrations in distinct lymphoma subtypes.

T cell lymphoma

The mechanism causing chromosomal translocations involving antigen receptors are quite well understood, but

much more limited ideas exist on other translocations. Mathas et al. [28] investigated anaplastic large cell lymphoma (ALCL) cases with and without a t (2; 5) translocation and found that that several genes near both breakpoints are dysregulated regardless of whether the translocation is present. The authors speculate that the activity of these genes may be related to the occurrence of the translocation itself, thereby assuming the both types of ALCL represent the same entity.

Also, Lim et al. [29] show that many more genes than those involved in the translocation are aberrantly expressed in ALCL. Using mass spectrometry, they identified protein expression signatures related to, amongst others, cell survival and angiogenesis. They also found that a subset of proteins distinguished ALK-positive from ALK-negative cases.

Singh et al. [30] focused on the sonic hedgehog signaling (SHH) pathway, and demonstrate that this pathway is activated in ALK-positive ALCL due to SHH gene amplification and is further mediated by NPM-ALK through activation of PI3K/AKT and stabilization of GLI1 protein. Dien Bard et al. [31] look into the JAK3/STA3 activation which is known to be present in ALK-positive ALCL using cell lines and tumor samples, and shows that next to other factors, IL-21 contributes to that activation. Finally, although overexpressed at the RNA level, Bobos et al. [32] could not detect overexpression of cyclinD1 at the protein level in ALCL. All this work indicates the complexity of tumorigenesis in lymphomas, even in a type that has such a characteristic translocation as Alk-positive ALCL.

Epidemiology of lymphoma

Etiological studies into lymphomas are difficult, due to the rarity of the different types of lymphoma. The role of the Epstein–Barr virus is well-established, especially in individuals with a reduced T cell function. The polyomavirus SV40 has been detected with various incidences and its role is not so clear. Toracchio et al. [33] investigated lymphoma tissue for the presence of these two viruses. They show that in Houston, there exist a difference in frequency of the polyomavirus and EBV, with 23% and 39% in one hospital and 3% and 18% in another, whereas the lymphoma type distribution was similar. The polyomavirus occurred more often in younger patients and in T cell lymphomas. These results show that marked differences in involvement of viruses occur even in areas from the same city. Another virus that is involved in the pathogenesis of some lymphomas is the Human herpesvirus 8 (HHV8), especially in patients with HIV. According to a study by Chen et al., [34] on 52 posttransplant lymphoproliferative disorders, HHV8 does not play a role in this entity.

Given the fact the lymphomas arise in immune compromised patients and that germline polymorphisms are well-known for solid cancers, it does not come as a surprise that such polymorphisms are relevant in lymphoma development too. Morton et al. [35] studied almost 2000 patients and controls for the presence of single nucleotide polymorphisms (SNP's) in 203 genes and found significant differences between patients with specific lymphoma types and controls. They indicate that the results support the role of genetic variation in cell cycle, apoptosis, and lymphocyte development regulatory genes in lymphomagenesis, and suggest that effects may vary by nonhodgkin lymphoma (NHL) subtype.

Geographical variation in incidence of lymphoma types is well-known. In most cases, the cause of this variation is not clear. An important point to understand this variation lies in case definition and molecular findings. A Chinese series of chronic lymphocytic leukemia (CLL) was molecularly characterized revealing some remarkable differences. In China, CLL is rare and the most frequent cytogenic findings were the occurrence of 14q breaks in 24% of the cases (Irons et al. [36]). The mutation status was prognostically significant, like in Western series, but in contrast, trisomy 12 was not.

Defining entities

Hodgkin lymphoma

The diagnosis of lymphocyte rich classical HL (cHL) can be difficult. Nam-Cha et al. [37] compared this type of HL with the other types of cHL and with nodular lymphocyte predominant (NLP)-HL. Lymphocyte-rich cHL displayed features intermediate between those of cHL and NLP-HL. The expression of B cell transcription factors such as Oct.1, Oct.2, Bob.1, and BCL6 was more frequent in lymphocyte-rich cHL than in cHL. A follicular T cell microenvironment was also identified in 50% of lymphocyte-rich classical Hodgkin's lymphoma cases. NF-kB markers were expressed at frequencies comparable with those observed in cHL. Lymphocyte-rich cHL was characterized by a stronger expression of the B cell transcription program by the neoplastic cells and by a follicular T cell background, occupying an intermediate position between cHL and NLP-HL. According to a study of Bharqava et al. [38] on 35 archival cases of NLP-HL (n=24) and LRcHL (n=11) from adults and children, fascin and junB expressions can be used as markers to separate these subtypes: Whereas, occasional L and H cells were weakly positive for fascin in three out of 24 (12.5%) cases of NLP-HL, RS cells in LRCHL were positive for fascin in 11 out of 11 (100%) cases with a strong cytoplasmic staining pattern. JunB was

positive in ten out of 24 (41.7%) of NLP-HL cases, and 11 out of 11 (100%) of LRCHL cases, showing a stippled and/or diffuse nuclear staining pattern. The L and H cells of NLP-HL cases were negative for concomitant staining in 24 out of 24 (100%) cases. Concomitant positive staining of classic RS cells for fascin and JunB was found in 11 out of 11 (100%) of LRCHL cases.

Lymphocyte depleted (LD) HL had been a bit neglected the last years, but regained interest lately (see previous review; 9). Slack et al. [39] studied eight cases that fulfilled diagnostic criteria of LDHL according to the 2008 World Health Organization classification. The cases involved lymph nodes (seven cases) and pleura (one case) from four males and four females (age 30–71 years; median 62 years). All tumors contained numerous Hodgkin–Reed Sternberg (HRS) cells, fibroblasts and histiocytes, and scattered lymphocytes. In three cases, the tumors had a more diffuse fibrotic appearance, while in five cases they appeared reticular and anaplastic. Neoplastic cells in all cases expressed CD30, CD15, fascin, weak PAX5, and MUM-1 and lacked CD45, Alk-1, EMA, CD3, CD68, Mart-1, and cytokeratin. Oct.2 and/or Bob-1 were expressed in all cases. Two cases variably expressed CD20 but were CD79a negative. Four cases were positive for EBV. All the four cases with adequate DNA had clonally rearranged IGH genes. The combined morphologic, immunophenotypic and molecular genetics features of this group of cases distinguish LDHL from other disease entities, including gray-zone lymphomas.

B cell lymphomas

Precursor B-lymphoblastic leukemia/lymphoma is according to the WHO-classification one entity, although the clinical presentation of the lymphoma cases differs markedly from the leukemic ones. Schaders et al. [40] used genomic profiling and found that there are subtle but significant differences between the two types of presentation, whereas that was not the case for T-lymphoblastic lymphoma/leukemia. Whether or not this indicates that this points to a different pathogenesis remains unclear.

After it became clear in the late eighties of the previous century, mainly through work of Peter Isaacson, that nodal and extranodal lymphomas are different, many studies into lymphomas of specific sites have been published. Schniederjan et al. [41] describe 40 lymphomas from the urinary tract and genital organs (but not testis and ovary). This study confirms the predominance of diffuse large B cell lymphoma in extranodal sites, the findings also highlight the variety of lymphomas that may occur in the genitourinary tract; only four cases of marginal zone lymphoma were seen, all in the kidney, none in the bladder. This diversity of subtypes affirms the importance of fully

characterizing lymphomas by immunohistochemistry and other modalities. Validire et al. [42] describe 45 lymphomas with breast incolvement, 38 of which were DLBL. Most cases had lymph node involvement and thus were not primary breast lymphomas. The survival data confirm that nodal lymphomas that present with extranodal involvement have a poorer outcome. Mozos et al. [43] describe a series of ten cases of the rare primary adrenal lymphoma. Histologically, eight cases were DLBL, all of which carried a nongerminal center B cell phenotype. Fluorescence in situ hybridization revealed BCL6 gene rearrangement in five (83%) of six DLBL investigated. The prognosis of these patients was poor as compared with those with nodal DLBL. The remaining cases were one case each of plasmablastic lymphoma and extranodal NK/T cell lymphoma, nasal type, the first and third case of primary adrenal lymphoma of these particular lymphoma subtypes in the English literature, respectively.

Yin et al. [44] describe six new cases of CLL with t (2; 14), involving the Bcl11A gene. This series differs from other cases of CLL since they have irregular nuclei and plasmacytoid differentiation and all were unmutated.

CD103 is a good marker for hairy cell leukemia (HCL), but other lymphoproliferations with CD103 expression exist. Dong et al. [45] describe 215(!) CD103-positive lymphoproliferations. Almost 80% coexpressed CD25 indicative of HCL, all of which were annexin-A1 positive. All cases negative for annexin-A1 lacked CD25 also. The remaining 20% of cases had a variable morphology and phenotype representing HCL variant, splenic marginal zone lymphoma, prolymphocytic leukemia, and DLBL and did not respond to stand HCL therapy. It is actually curious that such treatment had been given to those patients.

Ongoing studies of the Kluin-group in Groningen into testicular and central nervous lymphomas (so called immune-privileged sites) have shown several specific features of this group of DLBL. In a study on the expression of 15 microRNAs (miRNAs) of 50 DLBL (19 localized nodal, 11 testicular, nine CNS, and 11 other extranodal ones) they show that MiR-17-5p has higher expression level in the CNS cases compared to testicular and nodal DLBL. MiR-127 levels were higher in testicular than in central nervous system and in nodal DLBL. They conclude that the site of presentation of DLBL is an important factor in determining the differential expression of miRNAs (Robertus et al. [46]).

For CLL, the mutation status of the immunoglobulin gene is an important prognostic factor, but for MCL this is not so clear. Schraders et al. [47] show, using many clinical and pathological features, including CGH and expression array, that mutation status in this disease does not indicate a clinical and biological subentity.

Translocation t (11; 18; q21; q21) is the most frequent chromosomal aberration reported in gastric mucosa-associated lymphoid tissue lymphomas. Intriguingly, this translocation has been reported only rarely in diffuse large B cell lymphomas; it has been proposed that t (11; 18)-positive tumors rarely progress to diffuse large B cell lymphomas. Torrachio et al. [48] investigated the occurrence of this translocation in primary gastric lymphomas, both MZL and DLBL. Remarkably, the frequency was similar in both groups, about 20–25%. It is an intriguing question whether this might also indicate response to HP eradication in the BLBL cases.

Nodal marginal zone lymphoma (NMZL) is difficult to diagnose, since there is not a specific phenotype. Especially the differentiation from FL is sometimes difficult. Kanellis et al. [49] selected from expression array data myeloid cell nuclear differentiation antigen (MNDA), a nuclear protein expressed by myeloid cells and a subset of B cells. MNDA was expressed in subgroups of CLL, MCL, and DLBL, but MNDA was especially expressed by lymphomas derived from the marginal zone, such as mucosa-associated lymphoid-tissue lymphoma, splenic MZL, and NMZL. MNDA expression was rarely observed in FL, a characteristic that is of potential value in distinguishing NMZL from FL.

The t (14; 18) is the hallmark of FL, but various frequencies of negative cases are described, depending on the technique used to detect the translocation. A series of 17 t (14; 18) negative FL was studied by Leich et al. [50], and they found that in contrast to positive cases, no numerical aberrations in the bcl2 region and in addition a different gene expression profile. Remarkably, the cases were weak or negative for CD10, which opens the question whether cases might represent nodal marginal zone lymphomas with completely colonized germinal centers. A remarkably large series of t (14;1 8) negative FL (63 out of 142 cases of FL) was investigated by Gu et al. [51] using FISH and show that there is a similar frequency of bcl6 breaks compared to t (14; 18) positive cases, but that the breakpoint differs.

Two studies on FL of the spleen were done. Howard et al. [52] describe 16 cases, all with bcl2 or bcl6 breaks, positive for bcl2 and CD10, but often pure intrafollicular growth, which makes the differential diagnosis with reactive lesions difficult. Spleen weight remains an important issue! A series of 32 cases by Mollejo et al. [53] had different results: 20 had weak or absent bcl2 staining and many of these were CD10 negative and lacked a break in bcl2. This latter group had a higher proliferation rate and was more often restricted to the spleen. It is likely that such cases have been given another diagnosis, i.e., marginal zone lymphoma, by Howard et al. [52]

Chromosomal breaks in the MYC gene are characteristic for Burkitt lymphoma but occur also in progressed

lymphomas and DLBL. Such cases have an aggressive clinical course and it is debated whether morphological features point towards cases with potential MYC break. Obermann et al. [54] studied 333 DLBL with FISH for MYC, and had a reliable result in 220 of these. Only nine (4%) had a MYC break but these could not be predicted using conventional methods, including proliferative index. The authors suggest that routine screening of DLBL for MYC break is needed, but with such a low percentage, a cost-effectiveness study is called for. In BL, MYC breaks are not the only genomic change and Molina-Privado et al. [55] provided evidence based on studies in cell lines and tumor samples that E2F1 is also overexpressed in almost all sporadic BL.

Korac et al. [56] investigated the expression of FoxP1 in multiple myeloma and monoclonal gammopathy of undetermined significance and show that there is expression in contrast to normal plasma cells, and also that there is an increased gene copy number.

T cell lymphomas

In celiac disease patients, abnormal T-lymphocytes may occur intraepithelial in the small bowel. Using flow cytometry Verbeek et al. [57] analyzed the T-lymphocytes in celiac disease patients with aberrant T cells in the lamina propria and in skin lesions, and found that also in these compartments, aberrant cells can be found.

Cho et al. [58] reiterate the difficulties that may occur in evaluating staging bone marrow biopsies from patients with angioimmunoblastic T cell lymphoma (AILDT). In a series of 33 patients, about 70% had a positive marrow, but about one-third had been missed initially. Especially when clinical data are lacking cases with a mixed infiltrate were not recognized.

Rarely, T cell lymphomas have a follicular growth pattern, and such cases are suggested to be associated with t (5; 9). Huang et al. [59] studies 30 such cases and that these are often CD4, CD10, Bcl6, PD-1, CXCL13, and ICOS positive, a pattern that is similar to that of follicular helper T cells; four of 22 had the translocation. Three patients had in-follow biopsies AILDT.

Falchook et al. [60] describe their experience with 15 patients who had gamma-delta T cell lymphoma and confirmed the poor outlook in this disease: Median overall survival was 11 months (range 2 to 36+ months)

Most cases of T cell large granular lymphocytosis carry the alpha beta T cell receptor, but occasional cases have gamma delta receptors. Shaw et al. [61] describe two such cases which appeared in most clinical and pathological features very similar to the common type.

Although it is well known that CD99 is not specific for a certain disease, it is remarkable that 103 out of 160 ALCL stain for this antibody. In contrast to the suggestion of Buxton et al. [62], this antibody was not initially described as a marker for Ewings sarcoma, but for precursor T cells. The tumor cells in ALCL are, however, mature T cells.

A very large series of 136 cases of primary CD4 positive cutaneous T cell lymphoma was described by Beltraminelli et al. [63]. Patients with skin nodules characterized by the infiltrate of pleomorphic small/medium T lymphocytes are currently classified as "primary cutaneous CD4+ small-/medium-sized pleomorphic T cell lymphoma" or as T cell pseudolymphoma. The distinction is often arbitrary, and patients with similar clinicopathologic features have been included in both groups. All but three patients presented with solitary nodules located mostly on the head and neck area (75%). Histopathologic features were characterized by nonepidermotropic, nodular, or diffuse infiltrates of small- to medium-sized pleomorphic T lymphocytes. A monoclonal rearrangement of the T cell receptor-gamma gene was found in 60% of tested cases. Follow-up data available for 45 patients revealed that 41 of them were alive without lymphoma after a median time of 63 months (range: 1–357 months), whereas, four were alive with cutaneous disease (range: 2–16 months). The incongruity between the indolent clinical course and the worrying histopathologic and molecular features poses difficulties in classifying these cases unambiguously as benign or malignant, and it may be better to refer to them with a descriptive term such as "cutaneous nodular proliferation of pleomorphic T lymphocytes of undetermined significance," rather than forcing them into one or the other category.

New entities/subtypes

The data on IgG4 disease are accumulating fast. Sato et al. [64] compare IgG4-related lymphadenopathy (nine cases) with multicentric Castleman's disease. Histologically, systemic IgG4-related lymphadenopathy was classified into two types by the infiltration pattern of IgG4-positive cells: interfollicular plasmacytosis type and intragerminal center plasmacytosis type. The interfollicular plasmacytosis type showed either Castleman's disease-like features or atypical lymphoplasmacytic and immunoblastic proliferation-like features. By contrast, the intragerminal center plasmacytosis type showed marked follicular hyperplasia, and infiltration of IgG4-positive cells mainly into the germinal centers, and some cases exhibited features of progressively transformed germinal centers. Since eight of the nine cases had eosinophil infiltration in the affected tissue and elevation of serum IgE, the authors suggest an allergic mechanism in the pathogenesis of systemic IgG4-related lymphadenopathy.

Chen et al. [65] describe five B cell neoplasias with CDK6 translocation. Common clinical characteristics

included marked neoplastic lymphocytosis, systemic lymphadenopathy, splenomegaly, and bone marrow involvement. Three patients were diagnosed with low-grade B cell lymphoma and had an indolent clinical course, and two patients (one who transformed to large B cell lymphoma, and the other who was initially diagnosed with a high-grade B cell lymphoma) had an aggressive clinical course. Immunophenotypically, the neoplastic B cells expressed CD5, CDK6, and cytoplasmic retinoblastoma 1 protein in all cases, expressed phospho-RB, p27kip1, and cyclin D2 in most cases, and uniformly lacked expression of all other cyclins. In four cases, the CDK6 translocation partner was kappa immunoglobulin light-chain gene; and in the fifth case, the CDK6 translocation partner was unknown. These distinct clinicopathologic and cytogenetic features distinguish the CDK6 translocation-associated BLPDs from other mature B cell lymphomas.

EBV-positive lymphomas of the elderly have received quite some attention recently. Gibson et al. [66] collected six such cases in the US, where this disease seems rare. They also screened 60 cases of DLBL, in which no case was EBER positive. The six cases were similar as described by the Japanese, and also as posttransplant cases.

Maeshima et al. [67] screened 529 cases of DLBL and found 38 (7.2%) cases positive for CD5. Five cases gained CD5 expression during the clinical course of DLBCL. Three cases showed transformation from CD5- low-grade B cell lymphoma to CD5+ DLBCL. The remaining case showed coexistence of CD5+ DLBCL and CD5+ follicular lymphoma. The clonal relationships of CD5- and CD5+ tumors were confirmed in all four available cases. These results indicate that cases in the east differ from those in the west, since no MCL were in this group, and CD5 is seldom seen in Western cases.

Although methotrexate-associated lymphoproliferations receive less attention in the last WHO classification, it remains an important topic. Such cases need withdrawal of the drug rather than chemotherapy, but can only be recognized when the information on the fact that the patient uses methotrexate is available to the pathologist. Cases look very much like regular DLBL or HL or AILT according Hatanaka et al. [68], based on three cases.

Prognostic factors in lymphoma

Again, the largest number of articles referred this time deal with prognostic factors. As I discussed in the previous review [9], the issue now is to have predictive factors. In this period, an important paper was published that comes up with a predictive factor. It is widely accepted that at least two groups of DLBL exists, the activated and germinal centre type, and that these are prognostically different.

Dunleavy et al. [69] show that bortezomib enhances the effect of chemotherapy in patients with activated B cell like DLBL and not in the germinal center type. This makes the subclassification, for which still no reliable immunohisto-chemical approach exists, quite relevant. A next step will be a clinical trial that takes this information into account. Another study that preludes on a predictive approach investigates the expression of CD52 in T cell lymphomas, since ant-CD52 antibodies become available. Jiang et al. [70] determined by flow cytometry in 78 T cell neoplasias the level of CD52 expression. All AITL, hepatosplenic-TCL and T-PLL cases were CD52-positive but CD52 expression was low in ALCL (50%) and ENT/NKCL (25%). Although the authors suggest that this finding may be important for treatment selection, clinical data are needed to determine the minimum level of expression that warrants treatment with the anti CD52 antibody.

Troncone et al. [71] had shown that high UbcH10 expression indicates aggressive behavior in solid tumors and now studied this enzyme in lymphomas, both on cell lines and tissue samples of a variety of types. They show that UbcH10 expression is related to proliferation and that high expression is found in aggressive lymphomas, the highest in BL.

Marquard et al. [72] studied the expression levels of a series of proteins of histone deacetylase system, which is targeted by several new drugs. The shows that HDAC1, HDAC2, HDAC6, and acetylated H4 are overexpressed in DLBCL and PTCL relative to normal lymphoid tissue. Furthermore, HDAC6 indicated favorable outcome in DLBCL and a more aggressive course in PTCL.

Diepstra et al. [73] studied a large series of 412 patients with classical HL for the clinical relevance of EBV-infection. About one-third was positive and these had a better 5 years survival, but only in the age group from 50–74 years. In this age, group EBV negative cases had a 5 years survival of only 60% versus 85%.

Retuximab is now a cornerstone in the treatment of B cell lymphomas. Johnson et al. [74] show that mutation in this gene are rare and not prognostically relevant in B cell lymphomas at diagnosis and relapse, so mutation analysis of the CD20 gene has no role in routine practice.

It is quite clear that the future of array studies leis in the use of formalin-fixed and paraffin-embedded tissues. Sanchez-Espiridion et al. [75] studied such tissues from 52 cases of HL with a low-density array and were able to successfully use more than 80% of the samples and develop a predictor for relapse free survival. A more standard approach was taken by Canioni et al. [76] who studied 59 cases with immunohistochemistry: expression of bcl2 and CD20 in Hodgkin and Reed Sternberg cells, and expression of TiA1 in microenvironmental lymphocytes, and c-kit positive mast cells in microenvironment, were independent prognostic markers.

Bhagavathi et al. [77] used an even more classical approach in FL where they analyzed the growth pattern in 457 patients in relation to survival. Since they found no independent value of this factor, reporting the amount of follicular growth is not necessary. In contrast, according Carreras et al. [78] the amount of PD-1 positive T cells is; a high content is in a multivariate analysis does predict a favorable outcome. It is a pity that in this series now known prognostic factors like intrafollicular growth fraction and vessel density (Koster et al. [79, 80], 2x) were not taken along.

FoxP1 expression was studied in gastric extranodal MZL by Han et al. [81]. About half the cases had nuclear expression, which was correlated with shorter survival. It is remarkable that in these patients surgery was often the primary treatment, and the t (11; 18) status and HP eradication data were not given. Sumida et al. [82] looked into that specifically by analyzing HP-eradication success in t (11; 18) positive cases; as expected, none of these responded, nor did any f the HP negative cases. In HP-positive, t (11; 18) positive responders' serum titers of antibodies against HP and the CagA protein were higher than in nonresponders.

Several studies reported on prognostic factors in DLBL, most of them took the activated-B and germinal center type into account, although most study use the poor correlating immunohistochemical profile for that. The 92 patients of Ilic et al. [83] with immunohistochemically determined GCB-type DLBCL did not have an improved prognosis, irrespective of whether they had received rituximab or not. According to Morito et al. [84], low serum soluble interleukin-2 receptor levels and germinal center B cell-like cases in 80 patients treated with rituximab were predicting favorable outcome, but the results correlate strongly with the IPI. Although these two markers may substitute the IPI according to the authors, it seems to me that the IPI is so well-established and easy to use, that this will not happen.

Johnson et al. [85] report on 54 lymphomas with bcl2 and MYC translocations. These cases were classified as B cell lymphoma unclassifiable with features intermediate between Burkitt lymphoma and diffuse large B cell lymphoma (DLBCL) [36], DLBCL [17] or follicular lymphoma [1]. Non-immunoglobulin gene/MYC (non-IG/MYC) translocations occurred in 24 of 54(44%) and were highly associated with DLBCL morphology ($p<0.0001$). A non-IG/MYC translocation partner, absent BCL2 protein expression and treatment with rituximab-based chemotherapy were associated with a more favorable outcome but a low IPI score and DLBCL morphology were independent predictors of OS.

An interesting study was reported by Balague et al. [86], who analyzed the expression of activated X box-binding protein 1 (Xbp-1) in reactive lymphoid tissues, 411 lymphomas and plasma-cell neoplasms, and 24 B cell lines. Xbp-1 is a transcription factor that is required for the terminal differentiation of B lymphocytes into plasma cells. The Xbp-1 gene is activated in response to endoplasmic reticulum stress signals, which generate a 50-kDa nuclear protein that acts as a potent transactivator and regulates the expression of genes related to the unfolded protein response. Activated Xbp-1 is essential for cell survival in plasma-cell tumors. None of the low-grade lymphomas showed evidence of Xbp-1 activation; however, Xbp-1 activation was found in 28% of diffuse large B cell lymphomas, independent of germinal or postgerminal center phenotype, as well as in 48% of plasmablastic lymphomas and 69% of plasma-cell neoplasms. Diffuse large B cell lymphomas with nuclear Xbp-1 expression had a significantly worse response to therapy and shorter overall survival compared with negative tumors.

In 20 primary cutaneous follicle center cell lymphomas, Soltani-Arabshahi et al. [87] found that high RNA expression levels of bcl-xL were related to low numbers of apoptotic cells and indicated poor survival, whereas bcl-2 levels were not.

In 44 patients with nodal DLBL, Lee at al describe that out of a series of eight genes studies, MGMT and p57 methylation correlated with better prognosis, dependent on risk status. According to Curry et al. [88], based on 68 cases, c-Rel expression (65%) indicates better survival, but only in the germinal center B subgroup. Kim et al. [89] found the sonic hedgehog signaling proteins are more prevalent in DLBL and patients with high expression of ABCG2 have short survival (67 cases).

In a series of 30 PTCL, Briones et al. [90] investigated the role of bcl10 and show that Bcl-10 is expressed in two-thirds of the PTCLs, correlates with the expression of upstream proteins PKC theta and Pp65(Ser536) and is associated with better survival.

The amount of information on regulatory T cells (Treg) is increasing fast, even though debate on their precise phenotype in humans is ongoing. Using only FOXP3 as marker for these cells, Kim et al. [91] show that in 64 cases of extranodal NK/TCL high numbers of Treg are associated with better survival, and that this is an independent prognostic marker.

A few studies deal with prognostic markers for cutaneous TCL. In the erythrodermic group (124 cases, Vidulich et al. [92]), serum LDH and age were the strongest predictive factors for overall survival. ALCL (48 cases; Woo et al. [93]) run an aggressive course in patients presenting with extensive limb disease. In MF (70 cases; Chandra et al. [94]), clusterin expression was in about half of the patients, and especially in those with many large atypical cells and high stage.

Staging

Although it is well-known that bone marrow involvement is rare in cutaneous lymphomas, and according to the WHO classification in fact excludes the diagnosis of primary cB-NHL, it is not clear whether all patients with cB-NHL need to undergo a bone marrow biopsy. Based on a series of 57 patients, with only three positive marrows, Quereux et al. [95] conclude that this investigation is not indispensible.

Most pathologists now perform routine immunohisto-chemistry to detect limited involvement of the bone marrow in staging biopsies. According to Baiyee et al. [96]., based on 113 cases of DLBL, CD20 staining does not enhance sensitivity, even not in histologically discordant cases, which were about 40% of their 10% positive cases.

Ilgenfritz et al. [97] investigated the value of molecular analysis for staging of the bone marrow in comparison with routine methods. They conclude on data from 60 patients that IGH PCR alone is not good enough for bone marrow assessment, especially in FL. On the other hand, the PCR study for BCL2 is more sensitive than morphology, without any false negative results in this series, suggesting that BCL2-MBR PCR can be used as an alternative and more sensitive examination for disease evaluation, providing that there is careful analysis of data, adequate knowledge of PCR pitfalls and absence of other hematological disorders. These latter remarks are quite important and preclude the use in routine practice.

Ancillary techniques

Detection of leptomeningeal disease may influence treatment of patients with aggressive B-NHL. Quijano et al. [98] used advanced flow cytometrical (FCM) approaches and found that 27 (22%) of 123 patients showed infiltration by FCM, while conventional cytology (CC) was positive in only seven patients (6%), with three other cases being suspicious (2%). CC+/FCM+ samples typically had more than 20% neoplastic B cells and/or>or=one neoplastic B cell/microL, while FCM+/CC- samples showed lower levels of infiltration. Interestingly, in Burkitt lymphoma, presence of CNS disease by FCM could be predicted with a high specificity when increased serum beta2-microglobulin and neurological symptoms coexisted, while peripheral blood involvement was the only independent parameter associated with CNS disease in diffuse large B cell lymphoma, with low predictive value. A similar study, but on a variety of lymphoma types and in only 32 cases by Wu et al. [99] came to the same conclusion.

Fine needle aspirations are more and more done, also to diagnose and classify lymphomas. Although HL is regarded as a disease that can be reliably diagnosed on cytological specimens, Das et al. [100] show that in about 25% of HL diagnosis on cytology, the histological diagnosis was different. When flow cytometry is added (252 cases of NHL, Demurtas et al. [101]) diagnostic sensitivity and specificity of the combination cytomorphology/FC were 97% and 94%, respectively. This therefore, might reduce the number of invasive lymph node resections, especially from difficult to reach sites.

Fromm et al. [102] looked into the reliability of flow cytometry for the diagnosis of HL in lymph nodes. Of the 53 morphologically defined CHL cases identified, the FC assay diagnostic sensitivity and specificity were 88.7% and 100%, respectively. With the current availability of eight (or more) color clinical flow cytometers, this assay can now be applied to routinely immunophenotype and confirm a diagnosis of CHL or as an adjunct to immunohistochemical analysis. However, this study does also show that there is no added value above standard practice.

Intraocular lymphoma is very difficult to diagnose due to the limited amount of cells that can be obtained. Sugita et al. [103] show that using clonality testing and cytokine profiling (IL6 and IL10) is very usefull to come to a reliable diagnosis (22 patients). A completely different and new approach was taken by Pantanelli et al. [104], who used autofluorescence of cells in preclinical models and were able to separate B- from T cells. Since the main differential diagnosis from a B cell lymphoma in the uvea is uveitis, and thus a T cell infiltrate, this approach is promising.

Clonality testing has become routine practice in most laboratories for hematopathology. There are several well-known pitfalls. Fan et al. [105] studied liver biopsies from 40 hepatitis C virus infected patients and 800 controls. In the hepatitis group, light chain restriction was present in four (10%) and three (0.4%) in the controls. In five of these seven, a clonal IgH rearrangement was found, and two of these five patients proved to have a B cell lymphoma. So clonality does not always indicate malignancy and light chain restriction not always clonality. It is well-known that HL is a B cell lymphoma, and with the new Biomed approach for clonality testing, that includes detection of incomplete rearrangements, it could be expected that HL samples will give clonal results. Hebeda et al. [106] show that out of 24 cHL samples, 19 (79%) proved to be clonal using standard clonality testing with the Biomed primers, i.e., without enrichment by dissection of the tumor cells.

Several proteomic approaches are being tried for classification of lymphomas, as discussed in an earlier review. Now, Miquet et al. [107] did a mass spectrometry of plasma membrane microparticles on 158 patients with chronic B cell proliferation and 30 controls. This resulted in the confirmation of CD 148 as a good marker for MCL, specificity of 91%, but sensitivity of 78%.

Romesser et al. [108] build further on their gene expression array work in a mouse model, where they were able to translate the results in protein patterns and conclude that results support the central hypothesis that clusters of proteins of known function represent a panel of expression markers uniquely associated with malignancy and not normal proliferation. A fact that conclusion was already supported by the work of Jansen et al. [109], although their approach made identification of individual proteins not possible.

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