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REVIEW OF THE LITERATURE

New developments in the pathology of malignant lymphoma: a review of the literature published from January 2013 to April 2013

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Introduction

Writing literature reviews for the *Journal of Hematopathology* is an interesting experience. One sees topics gaining interest; others are losing it. Some lymphomas get a lot of attention, and others do not. New technologies are important drivers of research, especially in genetics. The hot topics are now the double hit lymphomas and Epstein–Barr virus (EBV). A continuous hot topic is mantle cell lymphoma. This review reflects not only these topics but also others that are equally interesting, but often published in less high impact journals.

Biology of lymphoma

The EBV is an important driver of oncogenesis and especially lymphomagenesis. Although much is known, there is still a lot to be learned. Tang et al. [1] investigated 98 lymphomas for the presence of EBV by PCR and confirmed that Epstein–Barr-encoded RNA (EBER) is a reliable test for the presence of EBV. They also found that four of the ten infected lymphomas had evidence of atypical viral genomes, including three of four infected T-cell lymphomas with aberrant loss of LMP2 amplicons and a single diffuse large B-cell lymphoma lacking the central part of the viral genome. The meaning of this finding remains uncertain.

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Hodgkin lymphoma

One of the special features of Hodgkin lymphoma (HL) is the contiguous spread, very different from most other lymphoma types. Kluk et al. [2] explored the role of the sphingosine-1-phosphate (S1P)–sphingosine-1-phosphate receptor 1 (S1PR1) axis in HL cell migration and the expression of S1PR1 in classical (c)HL cell lines and clinical cases. S1P, a bioactive sphingolipid present at high concentrations in the plasma and lymphatic fluid, is known to have a critical role in regulating lymphocyte trafficking mainly through S1PR1. S1PR1 is present in HL cell lines, and S1P stimulates migration in these cell lines. Immunohistochemical assessment of the tissue from cHL samples revealed that a subset of cases (7/57; 12 %) show strong, membranous staining for S1PR1 in Hodgkin/Reed–Sternberg (HRS) cells. They conclude that S1PR1 is a functional receptor on HRS cells, which governs tumor cell migration, and is expressed in a subset of cHL cases. This suggests that S1PR1 could be a future therapeutic target.

B-cell lymphomas

The great advances in methodology in genetics are rapidly changing our ideas on cancer. Cancer cells are more complex than previously thought, and tumors are more heterogeneous than expected. Green et al. [3] investigated follicular lymphoma (FL) cases and found indeed more genetic complexity than expected. Using elaborate bioinformatics, they conclude that IGH-B-cell lymphoma (BCL)2 translocations and CREBBP mutations are early events, whereas MLL2 and TNFRSF14 mutations probably represent late events during disease evolution, which fits with the biological hypotheses that were created for this disease already 25 years ago.

Garcia et al. [4] investigated the amount and type of T cells in gastric lymphomas and gastritis focusing on

forkhead box P3-positive ($FOXP3^+$) regulatory T cells. Samples of 35 patients with gastric extranodal marginal zone lymphoma (EMZL) at diagnosis and after treatment were included and compared to 19 cases of chronic gastritis and diffuse large B-cell lymphoma (DLBCL) of the stomach. The median number of $FOXP3^+$ infiltrating cells was higher in gastric EMZL than in DLBCL, but similar to chronic gastritis. No characteristic or specific distribution pattern of infiltrating $FOXP3^+$ cells was found. Gastric EMZL lymphoma patients responding to *Helicobacter pylori* eradication had higher number of $FOXP3^+$ cells at study entry which fits to the data on the importance of the T-cell infiltrate in gastric EMZL lymphoma, but not in DLBCL. Unfortunately, data on the difference between cases with and without t(11;18) are lacking.

Although the overexpression of cyclin D1 due to the t(11;14) is the hallmark of mantle cell lymphoma (MCL), there are other important genetic alterations as well. Molavi et al. [5] focused on the suppressor of cytokine signaling (SOCS)3 that is lost due to hypermethylation in more than 50 % of the MCLs and was related to poor outcome. Restoring SOCS3 function in cell lines of MCL resulted in increased apoptosis and thus may be a potential approach for treatment.

Another marker of MCL is the neural transcription factor SRY-box containing gene 11 (SOX11) that is overexpressed in most MCLs in contrast to other mature B-cell lymphomas or normal B lymphocytes. Vegliante et al. [6] show that SOX11 promotes tumor growth in a MCL-xenotransplant mouse model, resulting in the block of mature B cell differentiation, modulation of the cell cycle, apoptosis, and stem cell development. SOX11 silencing down regulates paired box (PAX)5, induces B lymphocyte-induced maturation protein 1 (BLIMP1) expression, and promotes the shift from a mature B cell into initial plasmacytic differentiation. A small subset of MCLs is, like normal lymphocytes, SOX11 negative. According to Wasik et al. [7], the SOX11 promoter region is hypomethylated in both MCL and normal B lymphocytes. Treatment with 5-azacytidine decreased SOX11 levels in SOX11-positive MCL cell lines. How these two findings relate to the role of SOX11 in MCL remains unclear.

Vogt and Klapper [8] analyzed a cohort of 47 MCLs at primary diagnosis and relapse for cytology, growth pattern, and Ki67 index and correlated the findings with outcome. In the majority of cases, the mantle zone growth pattern was lost, but it had been reacquired in a small subset of MCLs at relapse. Twenty-two percent of MCLs with classical/small cell cytology acquired blastoid features during the course of the disease; 50 % of MCLs with blastoid cytology at primary diagnosis recurred as a classical variant. The Ki67 index increased over time and was associated with prognosis in the primary and relapse biopsy specimens. These results confirm that MCL is a relatively stable disease over time, with very rare transformation which is commonly seen in other small B-cell lymphomas.

Telomere shortening is of pathogenic and prognostic importance in many cancers. Jebaraj et al. [9] investigated the length of telomeres in 73 MCL, 55 chronic lymphocytic leukemia (CLL), and 20 normal B cell samples. Telomere length was found to be highly variable in MCL but had no association with any biologic or clinical feature. This was in contrast to CLL, in which a significant correlation of short telomeres with poor prognostic subgroups was confirmed. It would be very interesting to perform this analysis on the series of Vogt and Klapper [8] as mentioned above and to see whether telomere length does change over time.

Recently, hot-spot mutations of enhancer of zeste homolog 2 (Ezh2), the enzymatic component of the polycomb repressive complex 2, which represses gene expression, were identified in DLBCL and FL. EI1, a potent and selective small molecule inhibitor, inhibits the enzymatic activity of Ezh2 through direct binding to the enzyme, resulting in decreased proliferation, cell cycle arrest, and apoptosis in DLBCL cells carrying an Ezh2 mutation, and thus, this might be an interesting therapeutic approach [10].

T-cell lymphoma

Several lymphoma types are associated with EBV, but the precise mechanism that makes EBV-infected lymphocytes malignant is not completely clear. Lin et al. [11] investigated the early and late manifestations of nasal NK/T-cell lymphoma, which are invariably associated with EBV, and found that in aggressive cases, T-bet is blocked by the microRNA miR-BART20-5p. Based on a confirmation in cell lines and animal models, they suggest that targeting miR-BART20-5p might be an effective therapy.

Epidemiology of lymphoma

A surprising finding was reported by Saarinen et al. [12]. Although several malignancies have a familial background, this is rarely the case for lymphomas. Based on the national Finnish registry, they discovered that nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) has an unexpectedly high familial association. They collected the data of 692 patients with NLPHL, identified their 4,280 first-degree relatives, and calculated the registry-based standardized incidence ratios (SIRs) for different cancers in the first-degree relatives. A particular strength of the study is that they re-reviewed the diagnostic biopsies. The SIR for NLPHL was 19 in the first-degree relatives and most prominent in female relatives of young patients. The SIR for classical HL was 5.3, and for non-Hodgkin lymphoma, it

was 1.9. When confirmed, these data imply that a search for the genes involved is warranted.

Duarte et al. [13] analyzed clinical and pathological features of 200 patients with follicular lymphoma presenting before the age of 40. They did not find differences with those who present above that age.

By collecting case series, we learn on rare tumors. Levasseur et al. [14] share their 20-year experience on vitreoretinal lymphomas (VRL) based on data from vitrectomies. The review of 463 diagnostic vitrectomy specimens from 430 patients resulted in a total of 22 patients with VRL with a preoperative clinical diagnostic sensitivity of 77 %, specificity of 73 %, positive predictive value of 13 %, and negative predictive value of 98 %. The cytologic diagnostic sensitivity was 87 % (27 of 31 specimens). The incidence of VRL in British Columbia doubled from 1990 to 2010, with a final incidence of 0.047 cases per 100,000 people per year. The mean age at diagnosis was 66 years. The initial diagnosis of lymphoma was VRL in 19 patients (86 %), of whom 7 (37 %) had concurrent central nervous system lymphoma. Recurrent disease was found in 11 patients. DLBCL was diagnosed in 20 patients (91 %). The median progression-free survival was 11 months, and the median survival was 33 months from the initial diagnosis.

Toda et al. [15] collected 39 patients with localized nasal/paranasal DLBCL. Immunohistochemistry-based subclassification revealed that 11 patients (28 %) were of the germinal center B cell (GCB) type according to Hans' algorithm, and also, but not the same, 11 (28 %) were of the GCB type according to Choi's algorithm. Overall survival did not differ significantly between the GCB and non-GCB subgroups, but the prognosis of localized nasal/paranasal DLBCL was better than that of other localized extranodal DLBCLs.

Posttransplantation lymphoproliferative diseases (PTLD) are mainly EBV-associated disorders of B cell origin, but some are of T cell derivation. Tiede at al. [16] collected their own cases and combined this information with that in the literature resulting in a series of 163 cases. Hematopoietic stem cell transplantation was associated with early-onset T-cell PTLD (T-PTLD), whereas late onset occurred after immunosuppression with steroids and azathioprine without administration of calcineurin inhibitors. The major independent favorable prognostic factors were T-PTLD of the large granular lymphocytic leukemia subtype, young age, and a combination of radiotherapy/radiochemotherapy and reduced immunosuppression, whereas the hepatosplenic T-cell lymphoma subtype and cases with involvement of bone marrow, the central nervous system, or graft had an adverse prognosis, which is not very different compared to B cell cases.

Defining entities

Hodgkin lymphoma

Kim et al. [17] performed immunohistochemistry on 85 cases of HL and 52 cases of anaplastic large cell lymphoma (ALCL) using antibodies against glioma-associated homologue (GLI)3, class III β-tubulin (TUBB3), fascin, clusterin, γ-synuclein, podoplanin, syntenin, CD21, CD35, and epidermal growth factor receptor (EGFR). HRS cells were diffusely positive for GLI3, fascin, and TUBB3; the mean positivity rates per case were 94 % for GLI3, 82 % for fascin, 69 % for TUBB3, 17 % for clusterin, 17 % for γ-synuclein, and 14 % for syntenin. Podoplanin, CD21, CD35, and EGFR were almost negative. The frequency of marker expression was not associated with the histologic subtype or the presence of EBV. ALCL showed a similar pattern to HL, but the overall frequency of positivity was lower than that observed in HL. The mean positivity rates were 56 % for GLI3, 62 % for fascin, 58 % for TUBB3, and 21 % for clusterin. The other markers were nearly negative. Anaplastic large cell lymphoma kinase positivity did not affect the expression rates.

B-cell lymphomas

Patients with immune suppression are at risk to develop EBV-associated lymphoproliferations. EBV-positive lymphoproliferations are a spectrum from relatively well treatable cases to aggressive forms. A negative regulator of the nuclear factor kappa (κ)B pathway, A20 (TNFAIP3), has been observed in EBV-related lymphomas, but it precise role is unclear. Ando et al. [18], using fluorescent in situ hybridization analysis, identified A20 deletions in 4 of 13 samples (31 %) from patients with pyothorax-associated lymphoma (PAL), 3 of 20 samples (15 %) from nasal-type NK/T-cell lymphomas (NKTLs), and 1 of 8 samples (13 %) of EBV-positive DLBCL of the elderly (DLBCL-e), but not in any of the 11 samples (0 %) from individuals with methotrexate-related lymphoproliferative disorder (MTX-LPD). Immunohistologically, the A20 protein was absent in 2 of the 13 (15 %) PAL samples, 1 of the 11 (9 %) MTX-LPD samples, and none of the 20 (0 %) NKTL or 8 (0 %) DLBCL-e samples. They conclude that A20 deletion and/or dysfunctional expression is frequently associated with PALs, and A20 abnormalities may be related to the pathogenesis of PAL.

Zhao et al. [19] had previously shown that amplified RPS6KB1 and CDC2 are commonly detected in the EBV^+ DLBCL in HIV patients. They further evaluated the amplified RPS6KB1 and CDC2 genes in 12 HIV-related aggressive B-cell lymphomas and 10 non-HIV-related DLBCL using real-time quantitative PCR. They confirmed that

amplified RPS6KB1 and CDC2 are markers for DLBCL in HIV^+/EBV^+ patients. This study also suggests that HIV^+/EBV^+ aggressive DLBCL could be potentially treated by targeting RPS6KB1 and CDC2 genes.

In inflammatory bowel disease (IBD), one can commonly encounter EBV-positive cells in variable amounts, but real EBV-positive lymphomas are rare. Magro et al. [20] showed that more than one third of the IBD patients have detectable EBV in their blood, and the amount is associated with the severity of the immune suppression (especially infliximab) and high age.

Hairy cell leukemia is often a straightforward diagnosis based on morphology and phenotype, but some cases are more difficult. CD103 is a well-known marker for hairy cell leukemia (HCL), but this was not well applicable on formalin-fixed paraffin-embedded tissue sections. Morgan et al. [21] describe their results using a new antibody on 68 cases, all positive, and more than 100 different other B-cell lymphomas/leukemias that may mimic HCL, all negative HCL and hairy cell leukemia variant (HCL-v) are rare diseases with overlapping clinicopathological features. Shao et al. [22] performed flow cytometric analysis (FCM) of 213 cases (169 HCL, 35 HCL-v, and 9 splenic marginal zone lymphoma (SMZL) cases). FCM distinguished HCL-v from HCL and SMZL based solely upon expression of four antigens (CD11c, CD25, CD103, and CD123) combined with B cell markers (CD19, CD20, and CD22). HCL-v uniformly lacked CD25 (100 %); HCL expressed bright CD25 in all cases. SMZL cases were CD103 negative. Because this analysis is biased by a circular argument (the same panel of antibodies was used for the original diagnosis), BRAFV600E and annexin A1 mutation were determined in a subset of cases. HCL-v was negative for both annexin A1 and BRAFV600E mutations. In contrast, HCL was positive for annexin A1 in 74 % and positive for BRAFV600E mutation in 76 % of the cases.

Salaverria et al. [23] collected a series of 40 of the rare cyclin D1-negative MCLs. The patients with these tumors presented with generalized lymphadenopathy, advanced stage, and poor outcome, similar to cyclin D1-positive MCL. Markedly, chromosomal rearrangements of the CCND2 locus were detected in 55 % of the cases, with an IG gene as partner in 18 of 22, in particular with light chains (ten IGK@ and five IGL@). No mutations in the phosphorylation motifs of CCND1, CCND2, or CCND3 were detected. The global genomic profile and the high complexity of the 32 cyclin D1(−) SOX11(+) MCL patients analyzed by using copy number arrays were similar to the conventional cyclin D1(+)/SOX11(+) MCL; 17p deletions and high Ki67 expression conferred a significantly worse outcome for the patients. This comprehensive characterization of a large series of cyclin D1(−) MCL patients indicates that these tumors are clinically and biologically similar to the conventional cyclin D1(+) MCL and provide a basis for the proper identification and clinical management of these patients.

Waldenström's macroglobulinemia (WM) is characterized by monoclonal gammopathy, usually IgM, in association with lymphoplasmacytic lymphoma (LPL). Roberts et al. [24] investigated 29 cases for expression of PAX5/BSAP, multiple myeloma oncogene 1 (MUM1)/interferon regulatory factor (IRF)4, and PRDM1/BLIMP1 by double immunohistochemical staining with CD138 and CD22. The percentage of plasma cells coexpressing CD138 and PAX5 was significantly higher in LPL/WM compared with benign tissues, MZL, and plasma cell myeloma, whereas the percentage of plasma cells coexpressing CD138 and MUM1 was lower. These findings show that a subset of plasma cells in LPL/WM demonstrates a nuclear protein expression pattern characteristic of the B cell developmental program, which may be helpful in difficult cases.

Marafioti et al. [25] analyzed 205 follicular lymphomas with fluorescence in situ hybridization (FISH) for BCL2 breaks and immunohistochemistry. They divided the cases into four groups: (a) CD10 positive/BCL2 break positive, (b) CD10 positive/BCL2 break negative, (c) CD10 negative/BCL2 break positive, and (d) CD10 negative/BCL2 break negative. All cases were BCL6 protein positive. Stathmin (STMN1) was shown to be helpful in diagnosing BCL2 break-negative and/or CD10-negative follicular lymphomas and in their distinction from MZL. However, STMN1 has the same problem as other germinal center cell markers; it does not discriminate between reactive and malignant cells, and thus, extensive follicular colonization remains an issue.

Campuzano-Zuluaga et al. [26] analyzed 167 cases of DLBCLs and show that 21 % of these cases expressed CD30, and in 52 % of them, CD30 was positive in >80 % of tumor cells. CD30 expression was more frequent in DLBCLs with non-germinal center origin phenotype, in BCL2(+) DLBCLs, and in patients of ≤47 years old. They suggest that such cases might benefit from anti-CD30 therapy.

Perry et al. [27] describe a retrospectively selected series of 39 B-cell lymphomas, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma (BL). This category was described in the WHO classification and represents likely a variety of cases. Perry et al. performed FISH for MYC, BCL2, and BCL6 and immunohistochemistry, but surprisingly conclude that this is a lymphoma that can be recognized by morphology alone. This is in contrast with the WHO criteria, and therefore, it is difficult to evaluate the value of their data.

The MYC oncogene is an important factor in some B-cell lymphomas. Especially, the connection to an immunoglobulin gene by translocation is a feature of BL and a part of the

DLBCL. Valentino et al. [28] observed also abnormally large spots using CISH and found that this is related to increased expression of the mRNA, so likely indicates amplification, which is easier to see using FISH.

Valera et al. [29] investigated MYC rearrangement and the expression of MYC, phosphorylated STAT3, BLIMP1, PAX5, and XBP1 in 12 activin receptor-like kinase (ALK)-positive large B-cell lymphomas. PAX5 was negative in all cases, whereas BLIMP1 and pSTAT3 were expressed in all tumors, and XBP1, in 11 of 12. MYC rearrangements were not identified, but MYC gains and amplification were detected in six cases and one case, respectively. MYC protein was expressed in all tumors independent of MYC gene alterations. These results indicate that ALK-positive large B-cell lymphomas express a complete plasmablastic differentiation program, but not as in plasmablastic lymphoma due to a MYC translocation.

T-cell lymphomas

Aurora-A is a mitotic kinase implicated in oncogenesis and is known to be overexpressed in B-cell lymphomas and plasma cell myeloma. Kanagal-Shamanna et al. [30] looked at expression of Aurora-A kinase in 100 T-cell lymphomas. Aurora-A expression was highest in ALCL and variably expressed in other types of T-cell lymphomas. In addition, the pattern of Aurora-A expression was predominantly cytoplasmic in ALK-positive ALCL and was nuclear in ALK-negative ALCL and other T-cell lymphomas. Using a cell line derived from ALK-positive ALCL, they showed that Aurora-A expression is decreased after treatment with either MYC or MEK inhibitors. These findings suggest that Aurora-A inhibition could be a potential therapeutic approach for patients with ALCL.

Cutaneous lymphomas

Rodríguez-Pinilla et al. [31] made use of a new antibody for T cell receptor gamma (TCR-γ) that can be used on formalin-fixed paraffin-embedded material. They stained 146 cutaneous lymphomas of various types and found 12 positive cases: five primary cutaneous gamma-delta T-cell lymphomas (PCGD-TCL), two mycosis fungoides (MF), and five lymphomatoid papulosis (LyP). All five PCGD-TCL patients and one MF patient died of the disease, whereas the other MF patients and all those with LyP were alive. All cases expressed cytotoxic markers were frequently CD3(+)/CD8(+) and tended to have lost CD5 and CD7. Eight of 12 and 5 of 11 cases were CD30(+) and CD56(+), respectively. Interestingly, 5/12 TCR-γ-positive cases also expressed TCR-BF1. All cases analyzed were negative for Epstein–Barr virus-encoded RNA. In conclusion, TCR-γ expression seems to be rare and is confined to cytotoxic primary cutaneous TCLs. Nevertheless, its expression is not exclusive to PCGD-TCLs, as TCR-γ protein can be found in other cutaneous T-cell lymphomas. Moreover, its expression does not seem to be associated with bad prognosis by itself, as it can be found in cases with good and bad outcomes.

Kiran et al. [32] analyzed 53 cases of CD30-positive cutaneous T cell lymphoproliferative disorders including LyP, primary cutaneous CD30(+) ALCL (PCALCL), transformed MF, and systemic ALK(−) ALCL with skin involvement. The presence of IRF4 translocation had a specificity and positive predictive value for PCALCL of 100 %. In contrast, MUM1/IRF4 protein expression was distributed widely without any predictive value.

The diagnosis of subcutaneous panniculitis-like T-cell lymphoma (SPTCL) can be very challenging. For the differential diagnosis with lupus panniculitis (LP), Liau et al. [33] compared the histological features of these diagnostic categories ($n=11$ and 21, respectively). The results indicate that the presence of lymphoid follicles, dermal mucin deposition, distinct patterns of fat necrosis, and lack of moderate to marked nuclear atypia or adipocyte rimming were more suggestive of LP. Since these features had likely been used in the original classification, this is a circular argument. New is that clusters of plasmacytoid dendritic cells were characteristically seen in LP lesions (17/21, 81 %), but not in SPTCL lesions (2/11, 18 %). It remains to be seen whether indeed this is really a helpful criterion.

Hydroa vacciniforme-like lymphoma (HVL) is a rare and aggressive cutaneous T-cell lymphoma occurring mainly in children in Latin America and Asia. Chronic latent Epstein–Barr virus infection has been associated with HVL. Sangueza and Plaza [34] describe the clinicopathological data of 12 cases from Bolivia. All patients had skin lesions in both sun-exposed and non-sun-exposed areas, with a slowly progressive relapsing course; they all presented with systemic symptoms and showed a characteristic swelling of the nose and lips and periorbital edema. Eight patients died an average of 5.3 months after initial diagnosis. Four patients remained alive with persistent disease. Histopathologic examination showed an atypical lymphocytic infiltrate with angiotropism and angiocentricity. The immunophenotype showed a cytotoxic T cell (CD8(+)) profile. All cases were associated with Epstein–Barr virus infection.

New entities/subtypes

Guinee et al. [35] investigated six cases of pulmonary nodular lymphoid hyperplasia (PNLH) for the presence of IgG4-positive plasma cells. Compared to reactive lesions, low-grade pulmonary B-cell lymphoma, and lymphocytic

interstitial pneumonia, the number of IgG4-positive cells and the IgG4/IgG ratio were significantly increased. This suggests that PNLH is a distinct form of a reactive lymphoid proliferation that belongs to the family of IgG4-related sclerosing diseases.

Merkel cell carcinomas (MCCs) express ALK, but this is dependent of the antibody used. According to Filtenborg-Barnkob [36], there was expression in 93.8 % (30/32) with clone D5F3, 87.5 % (28/32) with clone 5A4, and 12.5 % (4/32) with clone anaplastic lymphoma kinase 1. One small cell lung carcinoma (1/12; 8.3 %) showed low anaplastic lymphoma kinase expression with clone D5F3 and none with the other two clones. They could not find genetic alterations with FISH. Why is this article discussed in this review? According to Zur Hausen et al. [37], MCC may be a B cell-derived neoplasm. Based on immunohistochemistry for terminal deoxynucleotidyl transferase (TdT) and PAX5 (in all MCCs, either of the two is positive), light chain restriction (present in most PAX5-positive cases), and clonality testing, they believe that a precursor B cell is the cell of origin. However, the clonality testing is very puzzling since only few targets were positive even in cases with light chain restriction, and incomplete targets (to be expected in TdT-positive cases) were not done. Confirmation of these findings is needed.

Kolhe et al. [38] looked at MCC as well using antibodies against PAX5 and TdT and compared it to pulmonary small cell carcinoma. PAX5 was expressed in 24/27 (89 %) MCCs and in 0/10 (0 %) pulmonary small cell carcinomas. TdT was expressed in 21/27 (78 %) MCCs and in 9/10 (90 %) pulmonary small cell carcinomas. These data confirm that PAX5 and TdT are expressed in a high percentage of MCC and are not diagnostic of lymphoblastic leukemia/lymphoma when positive. PAX5 negativity would favor a diagnosis of pulmonary small cell carcinoma over Merkel cell carcinoma. They did not perform clonality testing.

Pillai et al. [39] looked into double-hit lymphomas and compared double-hit lymphomas with MYC and BCL6 with those with MYC and BCL2. Based on their own 6 cases and 17 cases from the Mitelman database, they conclude that the MYC/BCL6 cases are present in older persons (median age 83) and are more often of extranodal origin. Five out of six cases were BCL2 negative and germinal center B cell type, and the median Ki-67 score was 98 % (35 to 100 %). Double-hit (DH)-BCL6/MYC lymphomas are aggressive, frequently involve extranodal sites, and are often DLBCL/BL with a germinal center phenotype. However, unlike DH-BCL2/MYC lymphomas, they are more likely to be CD10(−) but IRF4/MUM1(+) and, more like BL, only infrequently express BCL2. These results indicate that we need to refer to BCL2/MYC lymphomas rather than double-hit lymphomas.

Pitfalls in lymphoma diagnosis

Ha et al. [40] reviewed 1,176 cases of surgically resected nasal lesions signed out as benign (often polyps) to find missed nasal NK/T-cell lymphoma. Based on morphology they selected 40 cases for further evaluation including EBER in situ hybridization. In three children, they found EBER positivity, but this was in B cells. Therefore, the data indicate that this tumor type is rarely overlooked.

Monoclonal B-cell lymphocytosis (MBL) is a relatively common disorder of the elderly with a benign course in most individuals. Randen et al. [41] looked at bone marrow biopsies of 26 persons with MBL and found in 20/26 three infiltration patterns: focal interstitial lymphoid infiltration, focal rounded and non-paratrabecular lymphoid aggregates, and discrete diffuse lymphocytosis. Using flow cytometry, all 26 patients had abnormal B-cell lymphocytosis. These results confirm that one needs to be careful in diagnosing malignant lymphoma in bone marrow biopsies with limited infiltration clonal B cells.

Peripheral T-cell lymphomas may contain (HRS-like cells). Nicolae [42] collected 57 of these cases, 52 of which had EBV in such cells. They were most commonly present in angioimmunoblastic T-cell lymphoma (AITL), but in other types too. Only 6/38 had a clonal B cell population detected. The five EBV-negative cases had CD4, PD1-positive T cells resetting around the HRS-like cells, which were positive for CD20, PAX5, CD30, and CD15. This is a real pitfall since it may lead to the diagnosis of HL.

Prognostic factors in lymphoma

Even though the cure rate of Hodgkin lymphoma is high, there are still almost 20 % of treatment failures. It is, at present, not possible to identify patients who may not respond well to treatment. Wha et al. [43] examined the prognostic significance of methionine (c-Met) and macrophage-stimulating protein receptor (MST1R) expression in 100 patients with cHL. Thirty-eight patients (38 %) expressed MET protein in HRS cells, and 26 patients (26 %) expressed MST1R, and both were associated with better overall survival.

Several recent studies showed that high numbers of macrophages in HL indicate worse outcome. Panico et al. [44] found in 121 HLs an association between high numbers of macrophages and high vascularity, but the latter was not related to the outcome.

Although few people believe that T-cell HL exists, most agree that HL is a B-cell neoplasia with sometimes aberrant T cell expression. This is difficult to evaluate since HRS cells often have a roset of T cells so that it is difficult to see whether a T cell antigen is really on the membrane of the

HRS cells. Venkataraman et al. [45] collected 50 HLs expressing a T cell-associated antigen (TCA) on the HRS cells (TCA-cHL) from two cohorts (National Cancer Institute, $n=38$; Basel, $n=12$). The median age in the TCA-cHL group was 40 years (range, 10–85 years). Seventy percent presented in low stage (stage I/II) at presentation with nodular sclerosis histology predominating in 80 % of cases. Among the TCAs, CD4 and CD2 were most commonly expressed and seen in 80.4 and 77.4 % of cases, respectively. TRG@ PCR was negative for clonal rearrangements in 29 of 31 cases. During a median follow-up of 113 months, TCA expression predicted shorter overall survival and event-free survival compared to TCA-negative cases.

Iwaya et al. [46] determined the number of FOXP3-positive cells in the stomach of 63 patients with extranodal MZL and 55 with gastritis. Both the FOXP3(+)/CD4(+) cell ratio and the absolute number of FOXP3(+) cells per high-power field in the lymphoma patients were significantly greater in *H. pylori* eradication responders compared with nonresponders. Unfortunately, those data on the t(11;18), which indicates poor response to eradication, were not given.

Horn et al. [47] investigated the prognostic relevance of MYC, BCL2, and BCL6 rearrangements and protein expression in a prospective randomized trial. This approach is obviously superior to smaller studies with patients with different treatments. Paraffin-embedded tumor samples from 442 de novo DLBCL treated within the German RICOVER study were investigated using immunohistochemistry and FISH to detect protein expression and breaks of MYC, BCL2, and BCL6. Rearrangements of MYC, BCL2, and BCL6 were detected in 8.8, 13.5, and 28.7 %, respectively. Protein overexpression of MYC (>40 %) was encountered in 31.8 % of tumors. BCL2 and BCL6 were expressed in 79.6 and 82.8 % of the tumors, respectively. MYC translocations, MYChigh, BCL2high, and BCL6low protein expressions were associated with inferior survival. In multivariate Cox regression modeling, protein expression patterns of MYC, BCL2, and BCL6 and the MYC rearrangements were predictive of outcome and provided prognostic information independent of the International Prognostic Index (IPI) for overall survival and event-free survival. A combined immunohistochemical or FISH/immunohistochemical score predicts outcome in DLBCL patients independent of the IPI and identifies a subset of 15 % of patients with dismal prognosis in the high-risk IPI group following treatment with R-CHOP.

Huang et al. [48] looked at the prognostic relevance of high MET gene copy numbers in 28 DLBCLs because this had not been studied yet. Copy number (CN) gain was observed in 11 cases, including 5 with CN greater than 3, and patients with gain or diploid CN showed significantly worse prognosis than those with CN loss. Intestinal perforation at presentation was the sole clinicopathological factor associated with a poor prognosis, and perforation was correlated with CN greater than 3. Such small numbers make conclusions difficult, and the biological rationale remains unclear. The authors conclude that MET CN gain is a poor prognostic factor in DLBCL patients and might serve as the rationale for targeting MET signaling pathway in the treatment of these patients. Actually, even without being a prognostic factor, that might be the case.

Activated B cell-like subtype of DLBCL is characterized by chronic active B cell receptor signaling and a constitutive activation of the nuclear factor κB pathway. As a driving force of nuclear factor κB overactivity, myeloid differentiation primary response gene 88 (MYD88) L265P mutation occurs in activated B cell-like DLBCL. Choi et al. [49] determined the MYD88 L265P mutation in conjunction with MYD88 protein expression in 124 DLBCL cases. Cytoplasmic MYD88 was present in 38.7 % (48/124) of DLBCL cases and associated with older age, tumor recurrence, and reduced disease-free survival. MYD88 L265P mutation was found in 6.5 % (8/124) of DLBCL cases but was not associated with MYD88 expression and clinicopathological parameters of DLBCL. Thus, MYD88 may be crucial for lymphoma progression, independent of MYD88 L265P mutation.

SOCS1 is frequently mutated in primary mediastinal and DLBCL. Schif et al. [50] performed SOCS1 sequencing in tumors of 154 comprehensively characterized DLBCL patients and identified 90 SOCS1 mutations in 16 % of the lymphomas. There were two distinct subtypes: those with truncating and those with non-truncating mutations. These SOCS1-mutated subgroups cannot be predicted on clinical grounds, but there were significant associations of SOCS1-truncated cases with germinal center and specific pathway activation pattern signatures; also, these patients have an excellent overall survival, even better than the GCB-like subgroup. SOCS1-non-truncated mutations had a dismal survival, even worse than the activated B-cell gene signature group.

He et al. [51] investigated 62 primary central nervous system B-cell lymphomas and found that perivascular tumor cells expression for CD44 and XBP1 are negative prognostic markers, although also the group with so-called good prognosis still had a poor survival.

Rodríguez-Pinilla et al. [52] investigated 89 AITLs and 104 peripheral T-cell lymphomas not otherwise specified (PTCL-NOS) for the prognostic relevance of a series molecules in the TCR and CD30 pathway and some others. They found in AITL only Ki67 of prognostic relevance. In the PTCL-NOS group, a score was made using expression of TCR-beta F1 and EZRIN, based on which they could separate the cases in two groups with 5- and 35-month survival.

According to Komohara et al. [53], tumor-associated macrophages, especially with the CD163(+) alternatively

activated phenotype (M2), were closely involved with progression of adult T-cell leukemia/lymphoma, based on staining 58 cases and correlating the number of positive cells with clinical outcome.

Staging

To evaluate the prognostic utility of the American Joint Committee on Cancer (AJCC) staging system for ocular adnexal lymphoma, Graue et al. [54] analyzed data from a multicenter, consecutive case series of patients with biopsy-proven conjunctival, orbit, eyelid, or lacrimal gland/sac lymphoma. Extranodal MZL of mucosa-associated lymphoid tissue was the most common (n=60/83, 72 %). Ann Arbor clinical stages were IE (76 %), followed by IIE (17 %) and IIIE (7 %). AJCC clinical stages were cT1NOMO (21.7 %), cT2NOMO (44.6 %), cT3N0M0 (5 %), and cT4NOMO (2.4 %). Local control was achieved in 75 % of treated patients. There were 19 local recurrences from which 14 (74 %) belonged to the non-radiation treatment groups. Lower-risk groups (T1 and T2 without lymph node involvement or metastatic disease of AJCC and IE of Ann Arbor) had longer disease-free survival than the higher-risk groups (AJCC T1, T2 with nodal involvement or metastatic disease, T3, and T4 as well as Ann Arbor II, III, and IV). Regardless of stage, recurrence and disease-free survival were more closely related to treatment and histopathology rather than tumor size or site-specific location.

Ancillary techniques

The detection of chromosomal alterations in lymphomas is increasingly important, and fluorescent in situ hybridization is the preferred technique. Interpretation of the results is not always straightforward and requires good equipment and expertise. According to Laurent et al. [55], the use of whole slide digital imaging results in better images and easier evaluation.

Demurtas et al. [56] collected their data on 1,792 tissue samples from which they had also flow cytometry results. A strong correlation between morphology and flow cytometry (FC) data was observed among hematological malignancies (1,268/1,304; 97.2 %) with the exception of HL. Among B-NHL, FC detection of clonally restricted B cell allowed the identification of lymphomas that were not histologically clear and the differential diagnosis between follicular lymphoma and reactive hyperplasia. Among T-NHL, FC detection of an aberrant phenotype directs histologic diagnosis in cases having less than 20 % of neoplastic cells. In nine cases, FC suggested the need to evaluate a neoplastic population, not morphologically evident. These data show that FC can provide valuable extra information in some cases suspected for lymphoma. Maybe even more important, it provides an extra, independent check on lymphoma diagnosis.

Double-hit lymphomas (DHLs) are, by definition, defined by genetic alterations, and a specific immunophenotype would be very helpful. Platt et al. [57] looked with flow cytometry to the expression of CD19, CD20, CD45, and surface light chain. Relatively few DHL cases showed dim expression of CD19 or CD20, and statistically significant differences were found only in the frequency of dim CD19 expression between DHL and BL or DLBCL. Although concomitant dim CD19 and CD20 expression was exclusive to DHL, it was present in only a minority of cases. Genetic analysis remains therefore needed.

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