New developments in the pathology of malignant lymphoma. A review of the literature published from January 2014–April 2014

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Introduction

The Journal of Hematopathology aims to increase the knowledge of pathologists who deal with lymphoma diagnosis. Since there are increasingly different treatment options, this becomes more and more important. In several previous literature reviews, I have reviewed articles that deal with the importance of panel or expert review of lymphomas, indicating the increased awareness of this issue. Bowen et al. [1] reviewed 1,010 biopsies from patients referred for lymphoma during 2009 to 2010. For each case, referral diagnosis and second review diagnosis were compared. Revised diagnoses were grouped into major and minor discrepancies, and hematologist analysed whether therapy changes were needed, based on changed diagnosis. There was no change in diagnosis in 861 (85 %) cases; in 149 (15 %) cases, there was a major change, of which 131 (13 %) would have resulted in a therapeutic change. The highest rates of revision were for follicular, high-grade B-cell, and T-cell lymphomas. There were more often major discrepancies in diagnoses from non-academic centers (16 %) compared to academic centers (9 %) and in excisional biopsies (18 %) compared to smaller biopsies (10 %). Herrera et al. [2] also published their experience, focusing on T-cell lymphomas. From 131 cases, the referral diagnosis was concordant in 57 (44 %). In about one third of the cases that were referred with a final diagnosis, there was a discordant read in the center. The rates of discordance among patients with peripheral T-cell lymphoma not otherwise spec-

ified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), ALK-negative anaplastic large cell lymphoma (ALCL), and ALK-positive ALCL were 19, 33, 34, and 6 %, respectively. In 14 patients (44 % of discordant results), pathologic reclassification could have resulted in a different therapeutic strategy. Forty-two patients (32 %) were referred for classification with a provisional diagnosis. These data confirm that referral of lymphoma biopsies, especially for the rarer types, is very important.

Biology of lymphoma

Hodgkin lymphoma

The importance of the tumor microenvironment has been recognized in HL already many years ago, and since the amount of neoplastic cells is much lower than that of the inflammatory cells, has received a lot of attention. Hansen et al. [3] wondered how communication between the neoplastic cells and the innate immune response takes place since there is a distance between the cells. They studied the crosstalk of the transmembrane proteins CD30 and CD30 ligand (CD30L) because these are selectively expressed on the neoplastic and innate immune cells, respectively. They showed that HRS cells released both the ectodomain as a soluble molecule (sCD30) and the entire receptor on the surface of 40–800 nm large extracellular vesicles. Other vesicle markers were tetraspanins, flotillins, heat shock proteins, and adhesion molecules. The vesicles caused a CD30-dependent release of interleukin-8 in CD30L-positive eosinophil-like cells and primary granulocytes from healthy donors. In extracellular matrix-embedded culture of cells, a network of actin and tubulin-based protrusions guided CD30-positive vesicles into

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the microenvironment and towards distant immune cells. This network may provide a target for the therapy of classical Hodgkin lymphoma (cHL) with antitubulin-based CD30 antibody constructs.

After the detection of Jak2 amplification and activation in cHL and mediastinal diffuse large B-cell lymphoma (m-DLBCL), Hao et al. [4] used cell lines and mouse models to investigate the effect of JAK2 inhibition. They found that JAK2 inhibition results in apoptosis of the tumor cells and that this effect is largest in cells with the highest level of JAK2 amplification. They also found that pSTAT3, a downstream molecule of the JAK2 pathway, is a good biomarker for JAK2 activation and effect of inhibition.

B-cell lymphomas

The role of the tumor microenvironment is increasingly recognized as a critical factor in cancer development. It is already well known that the inflammatory background in follicular lymphoma (FL) is the key to the maintenance of the tumor. Smeltzer et al. [5] investigated by immunohistochemistry the different immune cells that contribute to the inflammatory background and correlated their data to time to transformation of the lymphoma. Using 58 low grade cases and antibodies against CD68, CD11c, CD21, CXCL13, FOXP3, PD1, and CD14, they found that CD14-positive cells localized in the follicle and PD1-positive cells with diffuse staining were associated with a shorter time to progression. Multicolor IHC and flow cytometry identified CD14-positive cells as follicular dendritic cells (FDC), whereas PD1-positive cells represented two separate populations, follicular helper and exhausted T cells. Koch et al. [6] investigated how the communication between neoplastic cells and stromal cells takes place in DLBCL. They discovered that Wnt-signaling is important and that communication takes place through exosome transfer.

Another important component of the microenvironment is the vasculature. Cao et al. [7] looked for the factors that determine the role of the endothelial cells. They show that FGF4 produced by B-cell lymphoma cells through activating FGFR1 upregulates the Notch ligand Jagged1 on neighboring endothelial cells. This reciprocally induces Notch2-Hey1 in the lymphoma cells. This crosstalk enforces extranodal invasion and chemoresistance. Deletion of *Fgfr1* or *Jag1* in a lymphoma models diminished lymphoma aggressiveness and prolonged mouse survival. Thus, targeting the angiocrine loop might be an attractive target for therapy.

Kuo et al. [8] investigated the role of Sox11, since it is a relatively specific marker for MCL. They used high-resolution chromatin immunoprecipitation sequencing to identify the direct target genes of SOX11. Pathway analysis identified WNT, PKA, and TGF-beta signaling pathways as significantly enriched by SOX11-target genes. Quantitative chromatin

immunoprecipitation sequencing and promoter reporter assays confirmed that SOX11 directly binds to individual genes and modulates their transcription activities in these pathways in MCL. Functional studies using RNA interference demonstrate that SOX11 directly regulates WNT in MCL.

Ambrosio et al. [9] compared microRNA profiles (miRNA) from EBV-positive and negative Burkitt lymphomas (BL), and detected a couple of EBV encoded miRNAs in the EBV-positive cases. One of these, BART6-9p results in a down-regulation of the IL-6 receptor and PTEN, but there was no effect on WT1. These results imply a direct effect of viral miRNAs on the cell growth of and the immune response to BL.

The distinction between GBC and non-GBC DLBCL is increasingly seen a relevant for therapy choices. Since expression profiling is cumbersome and not readily available for the individual patient, several immunohistological algorithms have been developed. Hwang et al. [10] compared these algorithms in 147 R-CHOP- and 138 CHOP-treated patients, and used gene expression profiling as gold standard. High concordance was observed among the Hans, Choi, and Visco-Young algorithms (total concordance, 87.1 %; κ score, 0.726 to 0.889), whereas the Tally algorithm exhibited slightly lower concordance (total concordance 77.4 %; κ score, 0.502 to 0.643). On multivariate analysis, Hans algorithm retained its prognostic significance in CHOP-treated patients, but neither of the algorithms nor individual antigens predicted survival in R-CHOP treatment. This is especially remarkable for the Visco-Young algorithm, which was developed in R-CHOP-treated patients. The authors suggest that this may be due to the larger fraction of non-GBC patients in Asia, but to me this explanation is not very strong. Given the large variety of results of studies using immunohistochemistry for determination of the DLBCL subtype, my explanation would be that the perfect algorithm is not found yet.

Epidemiology of lymphoma

There are differences in incidences of lymphomas in different regions in the world. It is less known whether the same incidence of gene alteration can be found in lymphomas in different regions. Gain-of-function mutations of enhancer of Zeste homolog 2 (EZH2) occur frequently in DLBCL and FL. Guo et al. [11] determined EZH2 codon 641 mutations in Chinese FL ($n=124$) and compared them with Western follicular lymphomas ($n=70$). They found similar frequencies of EZH2 codon 641 mutations (16–18 %) including all five reported mutation variants. There was a much lower frequency of EZH2 mutation in cases without BCL2 translocation which suggests a different pattern of evolution of this subtype of FL. GEP studies showed a set of differentially expressed

genes and suggested that EZH2 mutation may help to lock the tumor cells at the germinal center stage of differentiation.

Defining entities

We classify lymphomas based on morphology, immunophenotype, genetics, and clinical features. Because protein expression is the end result of gene regulation, detailed analysis of proteins might become more important especially when phosphorylation can be detected in addition. Rolland et al. [12] performed mass spectrometry-based, semiquantitative phosphoproteomic profiling of 11 cell lines derived from three B-NHL categories: Burkitt lymphoma (BL), FL, and MCL. Hierarchical clustering highlighted distinct phosphoproteomic signatures associated with each lymphoma subtype. Interestingly, germinal center-derived B-NHL cell lines were characterized by phosphorylation of proteins involved in the B-cell receptor signaling. Of these proteins, phosphoprotein associated with glycosphingolipid-enriched microdomains 1 (PAG1) was identified with the most phosphorylated tyrosine peptides in BL and FL. PAG1 knockdown resulted in perturbation of the tyrosine phosphosignature of B-cell receptor signaling components. This study revealed the utility of unbiased phosphoproteome interrogation in characterizing signaling networks that may provide insights into pathogenesis mechanisms in B-cell lymphomas, which might ultimately be used for classification.

Hodgkin lymphoma

Xing et al. [13] compared matched samples (1:2) of nodular lymphocyte-predominant HL (NLPHL) with cHL and found that NLPHL patients have more often progression to DLBCL, although the overall survival did not differ. The matching included treatment and the authors conclude that NLPHL patients may need different therapy, including rituximab. Although this conclusion is likely to be correct, the proper approach of this question is not to compare the patients with those that have a different disease. In fact, most institutions already use a different treatment approach for patients with NLPHL.

Bhakirev et al. [14] looked for alterations in the BCL6 gene and its expression in NLPHL and found BCL6 rearrangement in 5 of 11 cases (46 %). In addition, BCL6 gene amplification, with large clusters of BCL6 signals in the absence of chromosome 3 aneuploidy, was detected in 3 of 11 cases of NLPHL (27 %). One NLPHL showed extra copies of BCL6 present in conjunction with multiple copies of chromosome 3. Altogether, BCL6 abnormalities were present in 9 of 11 cases of NLPHL (82 %). None of the progressive transformation of germinal centers or follicular hyperplasia cases showed BCL6

abnormalities. When confirmed, this might be a valuable diagnostic marker.

Doring et al. [15] addressed the question whether more data can be found to distinguish cHL from ALCL using gene expression arraying from microdissected cells. They developed a classifier, comprising four genes strongly expressed in Hodgkin and Reed-Sternberg cells of cHL (MDC/CCL22, CD83, STAT3, and TUBB2B). Applying this classifier to a test cohort, HL was successfully distinguished from ALCL with an accuracy of 97 % (43/44). I doubt, however, whether will be introduced rapidly in routine practice.

B-cell lymphomas

Monoclonal gammopathy of undetermined significance (MGUS) may precede a diagnosis of plasma cell myeloma and on histology the distinction is sometimes not possible. Xiao et al. [16] demonstrated nuclear MYC expression in CD138-positive plasma cells in 22 of 26 (84 %) plasma cell myeloma samples and in none of the 29 bone marrow samples from patients with MGUS. They also demonstrated that plasma cells gained MYC expression in five of eight patients who progressed from MGUS to plasma cell myeloma. There was no expression of MYC in other lymphoma types with plasmacytic differentiation, including lymphoplasmacytic lymphoma, marginal zone lymphoma (MZL), and plasmablastic lymphoma, and the authors conclude therefore that MYC detection can be a useful tool in the diagnosis of plasma cell myeloma.

Takata et al. [17] investigated by gene expression the characteristics of duodenal follicular lymphoma (dFL; $n=32$) and compared the results with those of gastric extranodal MZL (ENMZL; $n=19$) and nodal FL (nFL; $n=27$). The results indicate the dFL is closer to ENMZL than to nFL.

Cook et al. [18] looked for MYC expression and morphology in 260 DLBCL from a clinical trial and found 31 with morphological features intermediate with BL and 27 with MYC expression, with a significant overlap of these two groups. Morphology did not indicate poor outcome, whereas MYC expression did. The conclusion from the authors that the intermediate category, as introduced in the 2008 WHO classification, does not represent a separate entity can in my opinion not be drawn from these data, since no FISH for MYC breaks was performed. This is important: Lynnhntun et al. [19] compared FISH and immunohistochemistry for MYC detection using 30 cases of DLBCL with 80 % or more Ki-67 index, one case of DLBCL transformed from follicular lymphoma, three cases of B-cell lymphoma intermediate between DLBCL and BL, six cases of BL, and one case of reactive lymph node. MYC protein expression detected by IHC was more common than MYC translocation detected by FISH analysis. The indices of specificity and positive predictive value were low and varied widely with different

thresholds of IHC positivity in percentage; good sensitivity and negative predictive value were maintained at all different thresholds. Therefore, at best, MYC immunohistochemistry can be used as a pre-screening for MYC rearrangement.

T-cell lymphomas

Kikuma et al. [20] described their expertise with 26 cases of type II enteropathy associated T-cell lymphoma (EATL-II), including some unusual results. Their results on the clinical features, morphological, and standard lymphoma markers were as expected, but they also performed studies on MET and MYC. Surprisingly, the lymphoma cells expressed tyrosine kinase receptor c-Met, c-MYC, and BCL2 in 18 (78 %), 11 (42 %), and 19 (73 %) of the total cases, respectively. By fluorescence in situ hybridization, chromosomal loci 7q31 (c-Met) and 8q24 (c-Myc) were amplified in 11 (65 %) and 12 (71 %) of the 17 cases analysed. Especially, these latter figures are very high and need to be confirmed.

Cutaneous lymphomas

Although primary cutaneous follicle center cell lymphoma (PCFCL) is considered to be lacking BCL2 translocation, Abdul-Wahab et al. [21] decided to investigate a series of 57 cases and also looked for IgH-MALT1 translocations. Surprisingly, they found four BCL2 IgH-MALT-1 translocations and found that these were not related to any clinicopathologic factor, including stage and survival. The results are in contrast with other studies and need confirmation, since a BCL2 break in PCFCL is often considered to be indicative of nodal origin of the lymphoma.

It is well known that large B-cell lymphomas may be progressed low-grade B-cell lymphomas. Plaza et al. [22] wondered whether DLBCL of the skin might be derived from low-grade lymphomas and looked for the presence of (remnants) follicular dendritic cell network using immunohistochemistry. They found such networks in 12/85 cases and conclude that those may be transformed lymphomas. Although this may indeed be the case, follicular dendritic cell networks occur of course also in reactive follicles and the strength of the argument is therefore quite low. Nevertheless, the skin is a good organ system to study this question: one can see the development. If a DLBCL of the skin would be a progressed lymphoma, I would expect it to have also a precursor that had been noted by the patient. Although history taking is not completely reliable, one would expect to obtain at least an indication for this hypothesis from a larger group of patients, which to my knowledge was never reported.

Lee et al. [23] divided 45 patients with cutaneous ENKTL in two groups: (1) primary cutaneous ENKTL or (2) nasal ENKTL with cutaneous involvement. Clinical manifestations of both groups ENKTL included solitary or multiple

subcutaneous nodules and cellulitis or abscess-like lesions. Primary cutaneous ENKTL demonstrated a less aggressive clinical course with better survival. The extent of cutaneous lesions demonstrated a significant effect on the prognosis of primary cutaneous ENKTL, but not on nasal ENKTL with cutaneous involvement. The presence of nasal lesions in primary cutaneous ENKTL was associated with poor prognosis. Determination of the primary site of involvement is therefore important.

New entities/subtypes

Is IgG4-related disease still a new entity? There has been so much literature on the topic, often referred in this series of literature reviews, that it is at least quite well known, although it remains a rare disease. Takeuchi et al. [24] investigated the presence of EBV in this disease by looking into the number of EBER-positive cells in nodal [31] and extranodal [24] cases, as well as AILT [10] and reactive conditions [22]. EBER cells were present in 18 of nodal IgG4 cases (58 %) and in only 4 (18.1 %) non-IgG4-related reactive lymphoid hyperplasia and 5 (21 %) extranodal IgG4-related biopsies. The number of IgG4 cells in AILT was significantly less than that in IgG4-related lymphadenopathy. Although these data may be somewhat helpful in routine practice, in my opinion the number of EBER-positive cells, which of course reflects the extent of the immune deregulation, is not a very reliable criterion in this setting, morphology and phenotype together with clinical data remaining the gold standard.

About 5 % of DLBCL has cyclinD1 with amplification of the gene but no t(11;14). Juskevicius et al. [25] described two cases they refer to as grey zone between DLBCL and MCL, because these were t(11;14) positive DLBCL (one had a complex translocation) and had intermediate features in arrayCGH and morphology. This immediately brings the discussion on to what defines a disease entity (see editorial in this issue).

Subik et al. [26] encountered two patients with a very similar manifestation of lymphoma, which prompted them to search hospital database and that of a few others, the SEER database as well as the literature for similar cases. They found 20 patients with tibial presentation of lymphoma with a median age of 22.5 years (versus 42 for all bone lymphomas). Eighteen out of 20 patients had diffuse large B-cell lymphoma, and all patients aged ≤40 years achieved remission and apparent cure. Distinctive and unusual features were a tendency for bilateral involvement of the tibia and sclerotic changes on X-ray. SEER data included 808 cases of bone lymphoma; the fraction of cases presenting in the lower extremity versus other bone sites is higher at aged ≤40 years (38 vs. 19 %). Presentation in the lower extremity, as compared with other

bone sites, confers 97 % overall survival in patients aged ≤ 40 years (versus 82 %). In contrast, no significant difference in overall survival was identified for lower extremity versus non-lower extremity site for age >40 years. These data show a previously not described lymphoma subtype: lower extremity (especially the tibia) bone lymphoma in young patients, may be to named leg-type primary bone lymphoma of the young.

IgM-secreting DLBCL has been described as having a poorer outcome than those without secretion of IgM. Cox et al. [27] found among their 151 patients with DLBCL 19 with elevated IgM in the serum and 17 of those expressed IgM. Although these 17 patients had many negative prognostic features, only IPI and the IgM secretion remained prognostic in a multivariate analysis. Their data suggests that IgM-secreting cases are a distinct subset of DLBCL, originating from activated-B-cells with terminally differentiated features, prevalent extra nodal dissemination, and at high risk of CNS involvement.

It is already long known that lymphomas that have both a BCL2 break and a MYC break are different from those with a BCL6 break and a MYC break. Nevertheless, in recent years, the term double hit lymphoma has come in vogue for both lesions. Gebauer et al. [28] confirmed that it is not a good idea to lump these since they find that BCL2-MYC cases often have p53 mutations, whereas these are not present in BCL6-MYC cases. They described that p53 immunohistochemistry is not sensitive for mutations in the gene.

Pitfalls in lymphoma diagnosis

Although the number of frozen tissue intraoperative diagnoses has substantially decreased, there remain indications, and these are increasingly difficult. One such area is brain tumors while the correct diagnosis intraoperatively guides the further surgery. Brain lymphomas are a known pitfall that may go unrecognized in a frozen section. Sugita et al. [29] presented 27 cases of brain lymphoma that had an intraoperative frozen tissue section as first approach. In 15 of these, touch preparations were made as well. In 18 cases, the lymphoma was correctly identified at the intraoperative frozen tissue section, others had diagnosis like gliosis ($n=4$), demyelination ($n=2$), glioma, ($n=1$), astrocytoma ($n=1$), and metastasis ($n=1$). They had also three cases that were diagnosed intraoperatively as glial tumor, but appeared to be a lymphoma. In all cases, in which a touch imprint was available, the diagnosis of lymphoma was made. Therefore, the authors advocate the combination of a frozen tissue section with a touch imprint for the intraoperative diagnosis of brain tumors. Another issue, which was not discussed by the authors, is the availability of the neuropathological and hematopathological expertise in case of intraoperative diagnosis at night or during weekends, which is not so rare in my institution. We have successfully

implemented live imaging which possibility to scan the slide (using the Visiontec) by which we can consult a colleague through Internet.

Prognostic factors in lymphoma

Pederson et al. [30] investigated 52 cases of ALCL and confirmed that ALK-expression is related to age and that a high content of CD68- or CD163-positive macrophages is correlated with adverse outcome both in ALK-positive and ALK-negative cases.

Staging

The evaluation of a bone marrow biopsy remains a cornerstone in staging lymphomas. The separation of reactive infiltrates from lymphoma localization remains difficult, but according to a study on 166 cases Zhao et al. [31] concluded that CD137L staining is helpful, since it does stain stromal cells of lymphoma deposits from most B-cell lymphomas (hairy cell leukemia, MCL, FL, B-lymphoblastic leukemia, and chronic lymphocytic leukemia and a small subset of MZL and most of lymphoplasmacytic lymphoma) and not of reactive infiltrates. Although the mechanism is not quite clear, this may indeed prove to be useful.

Nelson et al. [32] used flow cytometry to characterize small monotypic infiltrates of B-cells (5 %), present in a little more than 1 % of their series of more than 3,000 cases. Most were CD5– and from the CD5+ cases most had no other features of lymphoma or CLL. They conclude such infiltrates rarely ($<1/1,000$) represent a malignant B-cell population.

Ancillary techniques

The increasing importance of FISH for the detection of chromosomal aberrations that directly guide treatment decisions prompted Horn et al. [33] to analyze the reliability of this method. They assembled 46 cases with known karyotype and also 62 FL on TMAs a looked for the correctness of FISH testing. The overall hybridization efficiency was 94 %, which is a very good for TMA cases. FISH results regarding translocations matched karyotyping data in 93 %. For chromosomal deletions, they suggest that the proportion of cells showing deletions should exceed 25 % to be reliably detectable. They conclude that their method was robust and superior to quantitative PCR approaches. It must be noted though, that for deletions it is likely that NGS approaches will rapidly take over FISH approaches, for translocation probably not in the near future.

The other molecular test for lymphoma diagnosis is clonality testing. Jia et al. [34] investigated the value of clonality testing with the Biomed-2 primer set for the immunoglobulin heavy chain gene. The results of IgH testing in 65 lymphomas were compared with 27 reactive lesions; they found a clonal result in 86 % of the lymphomas and 12 % of the cases with gastritis. Although the authors conclude that IgH testing is a valuable tool, there are a few problems with their study. In fact, most reliable results can be expected when the complete immunoglobulin gene set is used, and especially the Kdel is a very good paraffin-based sample (which was what the authors used). It is also important to realize that clonality testing is potentially only useful in morphologically difficult cases, which was not what the authors selected. Finally, I am surprised by the relatively high percentage of clonality in reactive lesion. Our experience is that it is lower provided that careful interaction of morphological, immunohistochemical, and molecular findings used before a clonal result is determined.

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