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magazine of european medical oncology

Current lymphoma diagnostic standards: the pathologists' view

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Summary This short review aims at summarizing the current standards of lymphoma diagnostics and some novelties in the recent WHO classification. The importance of close collaboration between clinicians and pathologists to render the correct diagnosis and to find the most appropriate treatment for each individual patient is highlighted. In lymphomas, the diagnostic evaluation of histopathology, immune phenotype and genetics are puzzle pieces that have to be put into a broader context with the help of the information given by the clinical colleagues, such as patient's age and sex, location of the lesion, previous medical history and medication. An excision of the affected lymph node is always preferable to fine needle biopsies, as—in many instances—only the evaluation of the whole specimen allows for reliable diagnosis, grading and additional investigations.

The new WHO classification entailed many changes in the category of diffuse large B-cell lymphoma and high-grade B-cell lymphoma. The obligatory specification of the cell of origin in diffuse large B-cell lymphoma is obtained via additional immunohistochemical stainings. The identification of high-grade B-cell lymphomas with genetic double/triple hits, requiring a more aggressive management, can only be achieved by the detection of chromosomal translocations (*MYC, BCL2* and/or *BCL6*). Significant changes in the classification of T-cell lymphomas have occurred due to the recognition of the follicular T-helper cell origin in some instances, and sharpening diagnostic borders of intestinal T-cell- and Epstein-Barr-virus-associated proliferations. Finally, the discovery of disease-defining and/or prognostically relevant mutations makes the introduction of proper routine molecular testing mandatory.

Introduction

Lymphomas are the 5th to 7th most frequently occurring malignant diseases in both sexes. It is not completely understood why there is still an increasing incidence of mature B-cell lymphomas, yet a link to the broad use of immunomodulatory drugs, the increased prevalence of immunoderegulatory diseases and the exposure to environmental pesti-/herbicides is suspected [1, 2]. Fortunately, the progress in lymphoma therapy is noticeable: survival rates of patients continuously increase, at least when referring to the most common nodal lymphomas [1].

Here, we summarize the current standards in lymphoma diagnostics from the pathologist's point of view, with a special focus on a multidisciplinary approach.

Gain of material

Histopathology is the keystone in lymphoma diagnostics, since this is the procedure of choice to distinguish between benign and malignant lymph node (LN) changes [3]. Importantly, a substantial number of benign LN disorders may both clinically and morphologically mimic lymphomas. Furthermore, genetic aberrations detectable in lymphomas as well as clonal outgrowths may be observed in reactive lym-

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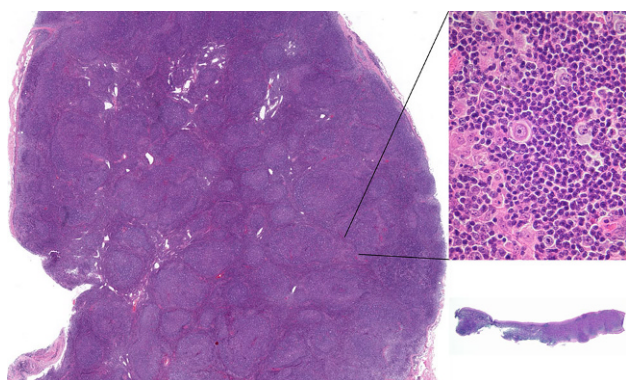M. M. Gerlach
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Fig. 1 Lymphadenectomy specimen of a patient suffering from nodular lymphocyte predominant Hodgkin lymphoma with hyperplastic follicles and progressively transformed germinal centers. Note that the so called lymphocytic and histiocytic (L&H) tumor cells are only focally present in the respective zoomed-in zone (*upper right* part of the figure). A previous core needle biopsy of the patient (shown in the *lower right* part of the figure) was of no diagnostic yield; H&E stain

phoid processes, emphasizing the role of specifically trained histopathologists with regard to this type of diagnostics.

The trend towards less invasive procedures in the past years did not stop in front of hemato-oncology, leading to widespread use of fine needle biopsies (FNB) for diagnostic purposes. Though being informative in approximately 85% of cases (Fig. 1 and Table 1), there are several objective limitations and risks arising from the general use of FNB. For instance the distinction between angioimmunoblastic T-cell lymphoma (AITL) and (e.g. drug-induced) paracortical hyperplasia [3] can only be achieved by the assessment of the total LN architecture, including the capsule and the surrounding soft tissue. These features cannot be evaluated on FNB as they merely contain a small detail of the LN. For obvious reasons, partial LN involvements by any processes are hardly possible to be diagnosed on FNB. In follicular lymphoma (FL), a statement about the grading is required, since grade 3B and—probably—grade 3A require a more aggressive clinical management, but this is barely obtainable on FNB. Additionally, some entities, such as Hodgkin lymphoma (HL) and AITL, go along with a very small amount of diagnostic tumor cells, which can easily be missed in a thin core cylinder (Fig. 1). Last but not least, lymphoma diagnostics require in almost all cases additional work-up, which sometimes cannot be applied to FNB due to lack of material or a too small amount of tumor cells. This also implies that there will be usually no material available for scientific questions after a diagnostic FNB work-up.

For the reasons stated above, we strongly recommend—whenever possible—a total LN excision for lymphoma diagnostic purposes in order to avoid misinterpretations and unnecessary re-biopsies. If

a positron emission tomography (PET) is preformed prior to the excisional procedure, the LN with the highest PET activity should be extirpated [4]. FNB should remain a tool for exceptional situations, e.g. in difficult surgically accessible regions such as the mediastinum and retroperitoneum. To avoid material waist in such circumstances, careful histotechnical handling is advisable, particularly production of sufficient amounts (at least 15) of unstained sections on adhesive glass slides for subsequent *in situ* histopathologic (immunohistochemistry, *in situ* hybridization) and *in vitro* molecular (gene expression profiling, sequencing on material scrapped-off those slides) analyses. In addition and minimizing the risk of expiry, parafilm wrapped unstained sections can be stored for a long time for scientific questions.

Processing of the specimen

Optimally, the gained material should be fixed immediately. If specific queries such as frozen section examination arise—which must be regarded as an exception in that consideration—the fresh specimen should be immediately brought to the histopathology lab and the remaining LN tissue timely fixed. Usually, buffered formalin (final formaldehyde concentration 4%) is used and should be applied in a specimen:formalin ratio of at least 1:10. The fixed material is best stored at a temperature between 4 and 8 °C. Due to crystallization artefacts, storage below 0 °C should be avoided. Depending on the size, sufficient fixation is obtained after 4 to 12 h. If frozen section is considered inevitable and immediate delivery for histopathologic examination is not feasible but manageable within 3 h, the material should be sent in a dry container for respective examination by means of a courier transport, in our opinion—taxi. Contact of the tissue with any fluids, such as saline, would induce considerable freezing procedure artifacts, and is therefore not recommended. If transportation within 3 h is not possible, a fast-track formalin/paraffin technical processing (fixation/dehydration) should be preferred to frozen section examination. If submission of unfixed material is considered for other requests, such as flow cytometry or cytogenetics, one part of the obtained tissue can be put into Roswell Park Memorial Institute (RPMI) medium and used for these examinations, while the other should be submitted in formalin and utilized for morphological diagnostics.

Clinical information

The delivery of sufficient clinical information is crucial for lymphoma diagnostics. Indeed, as indicated in Table 2, several lymphoma entities cannot be diagnosed outside specific clinical settings. In the following, we list the minimum clinical key-facts for rendering a correct diagnosis.

Table 1 Diagnostic yield of lymphadenectomies compared to fine needle biopsies with respect to lymphomas

Indicator	Ectomy	Biopsy
Informative value	>99%	85%
If informative		
Differentiation between malignant and benign processes	>99%	99%
If determination possible		
Entity-specific diagnosis	>99%	90%[a]
Molecular analyses	>99%	90%
Archival material	Lots	Scarce
Scientific studies	Possible	Impeded

[a]e.g. Hodgkin lymphoma subtypization or follicular lymphoma grading impossible

Table 2 Lymphoma entities, establishing the diagnoses of which require integration of clinical, anamnestic, endoscopic, imaging or genetic data

Setting	Specific (sub-)entities defined by the WHO 2017	Comment
Entities that can be diagnosed only in a *specific clinical setting*	Immunodeficiency-associated and post-transplant lymphoproliferative diseases (LPD)	Diagnosis cannot be established without knowledge of the clinical history or the local findings at the site of involvement
	Diffuse large B-cell lymphoma (DLBCL) associated with chronic inflammation	
	Breast implant-associated anaplastic large cell lymphoma (ALCL)	
Entity diagnoses depending to a certain extent on *integration of clinical information*	EBV-positive T- and NK-cell LPD of childhood	Age, ethnicity, clinical symptoms, serology
	Adult T-cell lymphoma/leukemia	Ethnicity, clinical symptoms, serology
	Pediatric nodal marginal zone and follicular lymphoma	Age
	All intestinal T-cell lymphomas and LPD	Ethnicity, history of celiac disease, endoscopic aspect
	Angioimmunoblastic T-cell lymphoma	Presence of typical clinical symptoms
Entity diagnoses largely depending on integration of *topographic information, clinical, endoscopic or imaging findings*	Follicular lymphoma, duodenal type	Endoscopic aspect, imaging staging results
	All extranodal marginal zone B-cell lymphomas	Site of primary involvement, imaging staging results
	Primary DLBCL of the CNS	Site of primary involvement, imaging staging results
	Primary cutaneous DLBCL, leg type	Site of primary involvement, imaging staging results
	Primary effusion lymphoma	Site of primary involvement, imaging staging results
	Primary cutaneous follicle center lymphoma	Site of primary involvement, imaging staging results
	EBV-associated mucocutaneous ulcer	Local findings at the site of involvement & clinical history
	All primary cutaneous T-cell lymphomas and LPD	Local findings at the site of involvement
Entities (co-)defined by the presence of specific *genetic alterations*	Mantle cell lymphoma (*CCND1* rearrangement)	In all these entities the presence of a respective genetic abnormality either defines the disease, or is very highly recommended to be assessed while establishing the initial diagnosis, or is present in >90% of cases
	Large B-cell lymphoma with *IRF4* rearrangement	
	ALK-positive large B-cell lymphoma	
	High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangement	
	Burkitt lymphoma (*MYC-IG* translocation as a sole structural genetic aberration)	
	Burkitt-like lymphoma with 11q aberration	
	T-cell prolymphocytic leukemia (chromosome 14q11;q32 aberration)	
	ALCL, ALK-positive	
	ALCL, ALK-negative, *DUSP22* rearranged	
	ALCL, ALK-negative, *TP63* rearranged	

ALCL anaplastic large cell lymphoma, *CNS* central nervous system, *DLBCL* diffuse large B-cell lymphoma, *EBV* Epstein-Barr virus, *LPD* lymphoproliferative disorder
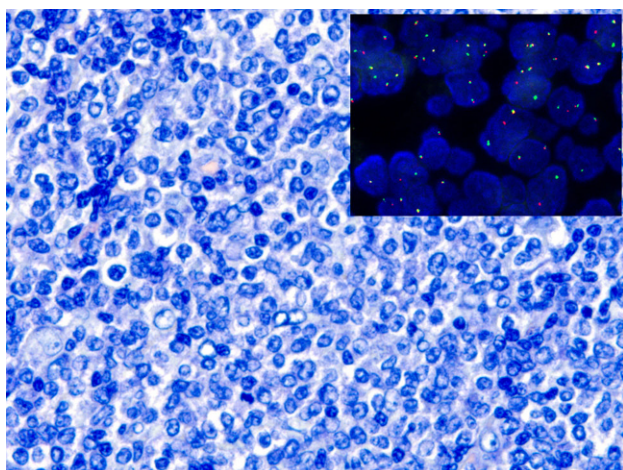
Fig. 2 Large B-cell lymphoma (Giemsa stain) with *IRF4* rearrangement (*insert*). Without application of fluorescent *in situ* hybridization (FISH) this consultational case has elsewhere been diagnosed as diffuse large B-cell lymphoma, illustrating that the sole possibility establishing this integrative genetico-pathologic diagnosis is specific testing for the respective recurrent aberration. The insert shows the typical appearance of a translocation/chromosomal break with a break-apart FISH probe with fused *yellow-orange IRF4* locus signals corresponding to the non-rearranged allele at 6p25 and free *red* and *green* signals corresponding to the rearranged allele

1. Age: Several lymphoma entities are defined by the patient's age as they almost exclusively occur in young individuals and are thought to be associated with the immaturity of the immune system: e.g. pediatric type follicular lymphoma (PTFL), pediatric nodal marginal zone lymphoma and EBV-positive T-cell and NK-cell lymphoproliferative diseases of childhood [5]. PTFL is an impressive example how the correct pathological classification influences the following treatment: in contrast to patients with conventional FL, who are often treated with multimodal chemotherapy, surgical excision alone seems to be sufficient for most PTFL patients [6, 7]. Information on sex and especially on ethnicity may be of upmost diagnostic importance in some virally driven lymphomas such as adult T-cell lymphoma/leukemia [5].

2. Location: Some lymphomas manifest at characteristic locations and information about the site can be an important diagnostic component. For example, primary cutaneous follicle center lymphomas occur most often at the head or trunk, have an excellent prognosis and mostly require only localized therapy; without the knowledge of the clinical appearance, the differential diagnosis to cutaneous involvement by conventional FL might be difficult if not impossible [5]. The same applies to CD30+ cutaneous lymphoproliferations with respect to the differential diagnosis of cutaneous involvement by systemic anaplastic T-cell lymphoma (ALCL) [5]. The rare entity of large B-cell lymphoma with *IRF4* rearrangement (Fig. 2) is almost exclusively found in the Waldeyer ring or head and neck region of younger individuals. It has to be distinguished from PTFL, on the one hand, as it probably needs a more aggressive treatment, and from DLBCL or FL grade 3B, on the other, as the latter two will need much more aggressive treatment [8].

Special characteristics of the site of involvement can play an important diagnostic role. The presence of chronic inflammatory conditions such as chronic pyothorax, vascular and joint prosthesis, chronic skin ulcers or chronic osteomyelitis will render the correct diagnosis of a DLBCL associated with chronic inflammation [9, 10]. These cases should be recognized since they benefit from adjuvant surgical treatment of the underlying inflammatory condition and, despite being associated with Epstein–Barr virus (EBV) infection and displaying *MYC* amplifications and *TP53* mutations, seem not to run a very aggressive course. Unquestionably, almost all patients with breast implant-associated ALCL, which is also a nice example of an integrative diagnostic entity, will be in need of excision alone [11].

3. Previous illnesses: Detailed anamnestic information about pre-existing illnesses are indispensable. For example, the diagnosis of post-transplant lymphoproliferative disorders cannot be set without appropriate background. The same applies for lymphoproliferative diseases associated with (primary) immunodeficiencies, such as e.g. Wiskott-Aldrich syndrome or ataxia-teleangiectasia [5]. Furthermore, the correct classification of DLBCL arising in/transforming from chronic lymphocytic leukemias (CLL), marginal zone lymphomas and FL can only be made with the clinical note of a previously existing small B-cell lymphoma (SBCL), in case the low grade compound is not found in the diagnostic LN. This is of importance since DLBCL, high-grade B-cell lymphoma (HGBCL) or HL transformed from SBCL show a more aggressive behavior than their *de novo* counterparts [12].

4. Medication: Considering the above-mentioned examples, it becomes also obvious that information about the patient's previous medication is essential for the correct diagnosis of iatrogenic immunodeficiency-associated lymphoproliferative disorders, which not only virologically and genetically differ from their immunoproficient equivalents, but also often require a different management [5, 13, 14]. A number of applied drugs (e.g. carbamazepine, allopurinol, sulfonamides, methimazol, lamotrigine, gabapentin, nevirapine) and vaccinations against hepatitis B virus and smallpox can induce profound morphologic LN changes mimicking AITL, DLBCL or HL [3], the misdiagnosis of which will be most likely avoided in the setting of proper medication history knowledge.

Morphology and phenotype

After paraffin embedding of the LN specimen, conventional histotechniques will mostly allow the correct differentiation between benign and malignant lesions or at least establishing a few differential diagnoses. The proper lymphoma classification concerning B- versus T-cell origin, developmental stage of the lymphoma cells and specific entity assignment is mostly done via immunohistochemical stainings. The current WHO classification brought important changes in this regard, two of which will be exemplified here. Inevitably, now the "cell of origin" specification has to be given in all DLBCL, not otherwise specified: distinguishing these deriving from germinal center B-cells from those displaying a program of activated B-cells [15]. There are several techniques and algorithms to tackle the cell of origin in DLBCL, such as gene expression profiling and immunohistochemistry, each with different costs, prerequisites, feasibility and validity. No special technique has currently been recommended by the WHO [5], yet data suggest that stratification based on immunohistochemical algorithms for guiding therapy should be viewed very cautiously [16]. Nonetheless, it appears that stratification according to the so-called "Tally" algorithm, based on the evaluation of CD10, GCET1, FOXP1, MUM1p and LMO2, avoiding BCL6, may give the best results [17].

Also by immunophenotyping, a more precise classification of mature T-cell lymphomas is now possible. Next to AITL, further entities of follicular T-helper cell (TFH) origin have been identified (nodal peripheral T-cell lymphoma with TFH phenotype (mostly T-zone lymphoma), and follicular T-cell lymphoma) and can be diagnosed using proper markers: PD1, BCL6, ICOS, CXCL13 and CD10 [18]. The detection of EBV by *in situ* hybridization has become extremely sensitive [19] and should be broadly applied to identify EBV-associated lymphomas and related lymphoproliferations [5, 19].

Genotype

Several lymphomas bear characteristic, to a part entity-specific, chromosomal aberrations (Table 2). This is also reflected in the recent WHO classification with the introduction of several genetically defined entities such as HGBCL with *MYC* and *BCL2* and/or *BCL2* rearrangements, large B-cell lymphoma with *IRF4* rearrangement, Burkitt-like lymphoma with 11q aberration, and ALK-positive lymphomas. Importantly, the (over)emphasis of genetics over other diagnostic parameters is particularly noticeable in HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements, which are defined only by the presence of the respective rearrangements [20, 21]. Put into practice, this means that all mature blastic B-cell lymphomas have to be tested for those translocations, e.g. by FISH, irrespective of their double-expressor score, since protein

recognition by antibodies for MYC and, occasionally, of BCL2 may be abrogated due to somatic (hyper-)mutation of the respective genes [22]. Since interphase FISH with histopathological material is performed on sliced cells, cut-off scores to judge cases positive for rearrangements are needed. These scores depend on the probes utilized, the exact slide thickness and the size of the (tumor) cells studied, and are—in the case of commonly used break-apart FISH probes for *MYC, BCL2* and *BCL6* applied to 4 μm slides of DLBCL—4, 3 and 1.5% cells with break-apart signals, respectively [23].

Besides structural chromosomal anomalies, point mutations play an important role in the development of lymphomas and can be used for diagnostic or—yet to be broadly proven—theranostic purposes. For instance, diagnosing a lymphoplasmacytic lymphoma (LPL) used to be difficult and not always doubtlessly possible. Since the characteristic *MYD88* L265P mutation (especially in combination with *CXCR4* mutation) has been detected, the correct diagnosis can easily be set in many cases [24]. Importantly, in the setting of LPL and DLBCL (particularly of the ABC subtype) this *MYD88* mutation seems to predict sensitivity towards ibrutinib [25]. The same applies for the *BRAF* V600E-mutation in hairy cell leukemia: although the mutation is not specific for this entity, its detection in the context of mature leukemic B-cell lymphomas provides not only an important diagnostic tool, but also predicts sensitivity towards vemurafenib [26, 27]. Furthermore, quantification of both described mutations is valuable for monitoring disease progression or detection of minimal residual disease. Alterations in the *TP53* gene are found in many malignant diseases, including different lymphomas. Identifying such mutations allows in small lymphocytic B-cell lymphoma (B-CLL) very precise risk stratification, prediction of lack of response to fludarabine-containing therapy and sensitivity towards ibrutinib [28, 29]. In B-CLL, the landscape of predictive mutations steadily grows (e.g. *NOTCH1,* ibrutinib-resistant *BTK* mutations), and we expect that similar data will soon emerge for other lymphomas [30, 31].

Finally, genetic testing is helpful in the diagnostics of recurrent disease: e.g. the differentiation between true late relapsing DLBCL or HL and metachronous *de novo* lymphoma can only be answered by proving a clonal relationship between both; same applies for the distinction of true SBCL transformation into e.g. DLBCL versus independent metachronous DLBCL [32–34].

Conclusion

The close collaboration between clinical oncologists and pathologists is indispensable for high standard lymphoma diagnostics. Equally, the pathologists depend on the information given by the clinical colleagues, as the clinician is dependent on a correct di-

agnosis provided by the pathologist. In the last few years, an enormous increase of knowledge considering tumorigenesis in general and lymphomagenesis in particular, has been recorded. This progress will make individualized, patient- and disease-tailored and, thus, more efficient and effective treatment possible.

Take-home message For rendering a correct lymphoma diagnosis, a minimum of information provided by the clinician is needed: patient's age (sex, ethnicity), tumor location, medical history and medication.

Besides accurate diagnostics, progress in molecular pathology makes statements on prognosis and theranostics in lymphomas possible.

Conflict of interest M.M. Gerlach and A. Tzankov declare that they have no competing interests.

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