The General Pathology

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1.1 Introduction

1.1.1 What Are Indolent Lymphomas?

The current WHO classification of lymphomas basically contains the overruling categories of Hodgkin lymphoma, B-cell lymphoma, and T-cell lymphoma, the latter two separated in precursor cell and mature neoplasms [1]. A categorization into indolent and aggressive lymphomas is not an integral part of the classification. Historically, classifications of Non-Hodgkin Lymphoma (NHL) grouped entities according to the cytologic appearance of the lymphoma cells and correlated them to the stages of differentiation of normal lymphocytes. This ultimately led to the pathologic/morphologic concept of "low" (small mature cells) and "high" (blastic cells) grades of malignancy, which actually proved to correlate, to a certain degree, with the clinical behavior of each given subtype: "low" grade with indolent and "high" grade with aggressive clinical behavior. The absence of such categories like indolent/aggressive and "low"/"high" grade in the current classification of WHO is based on several observations and biologic considerations. Indolent behavior implies a clinical course that is characterized by low growth dynamics, frequent relapses, and lack of curability despite chemosensitivity. These clinical features correlate only imperfectly with pathologic features, for example, small-cell morphology and low amounts of blasts. Examples are follicular lymphoma, which may show considerable number of blasts in cases of follicular lymphoma grade 3A but an indolent clinical course (low growth dynamics, frequent relapses). In contrast, mantle cell lymphoma may show aggressive clinical behavior with fast progression despite non-blastic (small cell) morphology. Moreover, the clinical course is heavily influenced by clinical management, which is not reflected by the classification of diseases. Finally, the identification of molecular and clinico-pathological subgroubs within lymphoma entities explains to some extent the variability in clinical behavior but prevents the assignment of an entity to the category of indolent lymphomas with certainty. Nevertheless, the distinction of lymphomas with an indolent course from those with an aggressive course is still a frequent although arbitrary process in daily practice.

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The diagnostic workup of indolent NHL as it is considered in this book roughly deals with two basic clinical–biologic scenarios. The first one, and vastly most common, is that of a lymphoid proliferation composed of cells that resemble one of the mature stages of lymphocyte differentiation, typically as small- to medium-sized cells and, in fact, mostly show features of an indolent clinical course (Table 1.1). This group of lymphomas contains very frequent diseases, such as chronic lymphocytic leukemia/small lymphocyte lymphoma and follicular lymphoma (FL). NHL with marginal zone and lymphoplasmacytoid differentiation follows next in the list, plus mycosis fungoides as a T-cell neoplasia. In clinical practice, mantle cell lymphoma (MCL) is usually still considered part of this arbitrary group despite the fact that the disease may present with an aggressive clinical behavior. In fact, the recognition of the distinct, indolent "leukemic/non-nodal" subset of MCL, on the one hand, and aggressive variants, on the other hand, exemplifies the heterogeneity in respect to indolent and aggressive clinical courses that may be observed within a biologically well defined entity.

Table 1.1 List of non-Hodgkin lymphoma subtypes with indolent course

B-cell phenotype
"Low grade" histology, B-cell
• Follicular lymphoma
• Chronic lymphocytic leukemia/small lymphocyte lymphoma
• Mantle cell lymphoma (leukemic/non-nodal variant)
• Extranodal marginal zone lymphoma
• Nodal marginal zone lymphoma
• Splenic marginal zone lymphoma
• Lymphoplasmacytic lymphoma
• Hairy cell leukemia
• Splenic B-cell leukemia/lymphoma, unclassifiable (splenic diffuse red pulp small-B-cell lymphoma, hairy cell leukemia variant)
"High grade" histology
• Lymphomatoid granulomatosis (grade 1–2 histology)
• Epstein-Barr-Virus-positive mucocutaneous ulcer
• Fibrin-associated diffuse large-B-cell lymphoma
T/NK-cell phenotype
"Low grade" histology
• Mycosis fungoides
• Primary cutaneous peripheral T-cell lymphomas, rare subtypes (primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder, primary cutaneous acral CD8+ T-cell lymphoma)
• T-Cell large granular lymphocytic leukemia
• Chronic lymphoproliferative disorder of NK cells
"High grade" histology
• Primary cutaneous CD30-positive T-cell lymphoproliferative disorders (lymphomatoid papulosis, primary cutaneous anaplastic large-cell lymphoma)
• Breast implant-associated anaplastic large-cell lymphoma
• Subcutaneous panniculitis-like T-cell lymphoma

The second, less-common scenario is that of NHL that presents as localized and often curable diseases. NHL may resemble either a subgroup of otherwise indolent lymphomas (e.g., FL of pediatric type) or independent entities, such as primary cutaneous CD30-positive T-cell lymphoproliferative disorders. The latter may also be considered as rather benign variants of aggressive lymphomas since they frequently present with a "high grade" histology (Table 1.1).

1.1.2 General Considerations on Indolent NHL Diagnostics

1.1.2.1 Technical Issues

As the label of "indolent" for a given case is based on proper clinical evaluation and follow-up, the importance of the dialogue between pathologists and hematologists to achieve a fruitful clinic-pathologic correlation cannot be overstressed. Indolent NHL is mostly seen in adult patients; thus, great caution should be taken in the pediatric setting, in which atypical reactive processes may mimic neoplastic processes.

In the precision medicine era, cytology of lymphoma cells still acts as the prime discriminator, particularly with regard to the aggressive subtypes. Thus, morphologic assessment of smears and histologic slides (May–Grünwald–Giemsa, hematoxylin-eosin, and Giemsa stains), coupled with immunohistochemistry, constitutes the gold standard for guiding the diagnosis of indolent NHL and allows the prognostic stratification and the detection of therapeutic targets.

This task requires the availability of representative specimens of good quality and proper size,

to render the cytologic detail and the architecture of the lesion. Molecular-genetic analysis may help the diagnosis in challenging cases but, most promisingly, can add valuable information both to predict the clinical behavior and to guide the therapeutic approach.

1.1.2.2 Anatomic Issues

There is no anatomic compartment specifically associated with indolent NHL; however, it should be underscored that non-nodal modality of presentation is predominant in certain subtypes and is of prognostic significance in others. A consequence of the diagnostic ground is that pathologists are often required to deal with specimens from peripheral blood and bone marrow, which allow to collect and integrate a wide array of morphologic, phenotypic (either by flow or by immunohistochemistry), histologic, and molecular parameters.

Reference

1. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, editors. WHO classification of tumours of haematopoietic and lymphoid tissues (revised). 4th ed. IARC: Lyon; 2017.