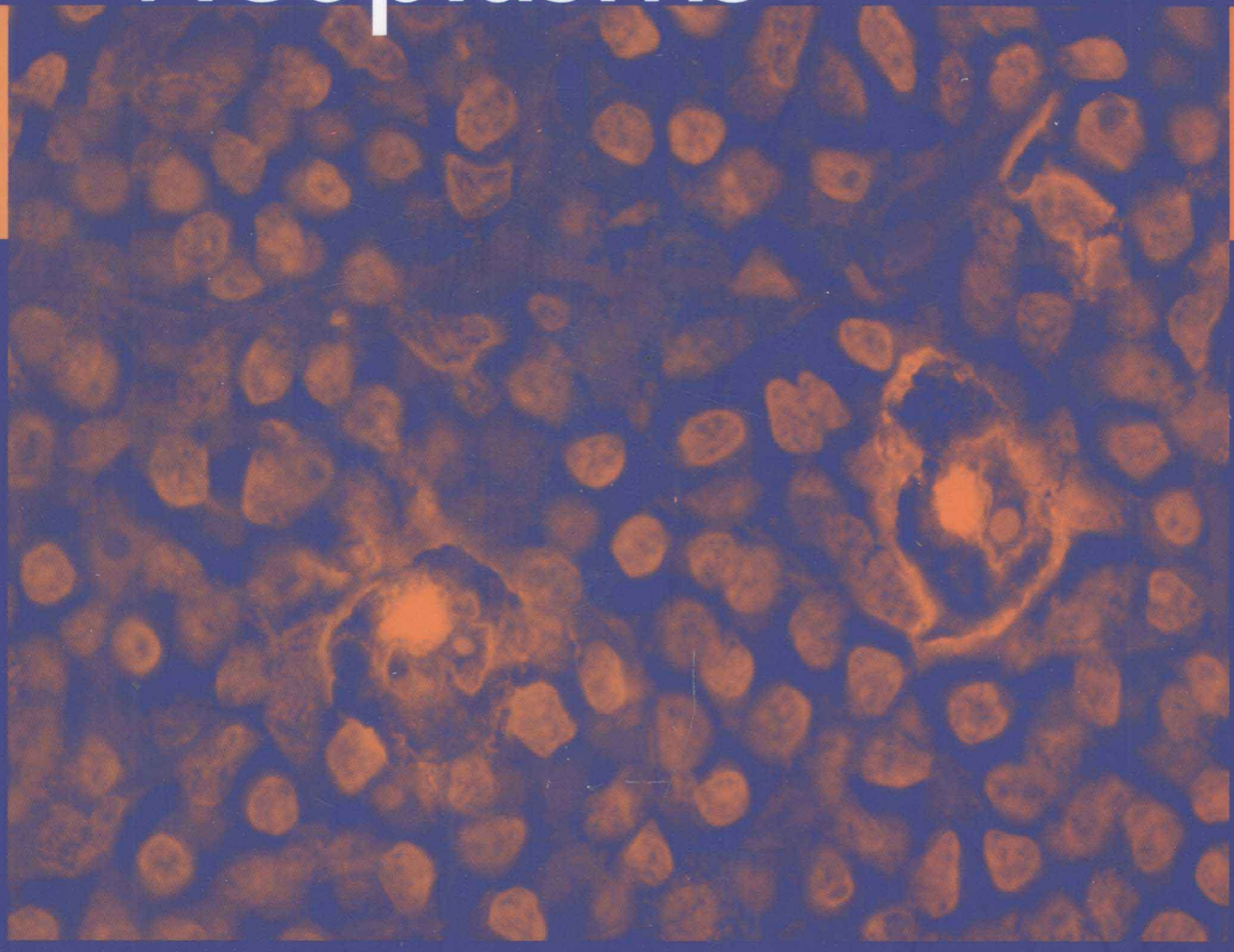
Tsieh Sun

Atlas of Hematologic Neoplasms



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Tsieh Sun, M.D.
Editor

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Editor
Tsieh Sun, M.D.
Director of Hematopathology and Flow Cytometry Pathology and Laboratory Medicine Service
Veterans Affairs Medical Center
Eastern Colorado Health Care System
Professor of Pathology Department of Pathology
University of Colorado School of Medicine
Denver, Colorado 80220
USA
tsieh.jack.sun@va.gov

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Preface

Due to its rapid development in recent years, hematopathology has become a very complex discipline. The current development is mainly in two aspects: the new classification of lymphomas and leukemias, and new techniques.

The Revised European – American Classification of Lymphoid Neoplasms (REAL classification) and the World Health Organization (WHO) classification of hematologic neoplasms require not only morphologic criteria but also immunophenotyping and molecular genetics for the diagnosis of hematologic tumors. Immunophenotyping is performed by either flow cytometry or immunohistochemistry. There are many new monoclonal antibodies and new equipment in recent years that make immunophenotyping more and more accurate and helpful. There are even more new techniques invented in recent years in the field of molecular genetics. In cytogenetics, the conventional karyotype has been supplemented and partly replaced by the fluorescence in situ hybridization (FISH) technique. The current development of gene expression profiling is even more powerful in terms of subtyping the hematologic tumors, which may help to guide the treatment and predict the prognosis. In molecular biology, the tedious Southern blotting technique has been largely replaced by the polymerase chain reaction (PCR). The recent developments in reverse-transcriptase PCR and quantitative PCR make these techniques even more versatile.

Because of these new developments, hematopathology has become too complex to be handled by a general pathologist. Many hospitals have to hire a newly trained hematopathologist to oversee peripheral blood, bone marrow, and lymph node examinations. These young hematopathologists are geared to the new techniques, but most of them are still inexperienced in morphology. No matter how well-trained a hematopathologist is, they still need to see enough cases so that they can recognize the morphology and use the new techniques to substantiate the diagnosis. In other words, morphology is still the basis for the diagnosis of lymphomas and leukemias.

Therefore, a good color atlas is the most helpful tool for these young hematopathologists and for surgical pathologists who may encounter a few cases of hematologic tumors from time to time. In a busy daily practice, it is difficult to refer to a comprehensive hematologic textbook all the time. There are a few hematologic color atlases on the market to show the morphology of normal blood cells and hematologic tumor cells. These books are helpful but not enough, because tumor cell morphology is variable from case to case and different kinds of tumor cells may look alike and need to be differentiated by other parameters.

The best way to learn morphology is through the format of clinical case study. This format is also consistent with the daily practice of hematopathologists and with the pattern in all the specialty board examinations. Therefore, it is a good learning tool for pathology residents and hematology fellows as well as medical students.

This book presents 85 clinical cases with clinical history and morphology of the original specimens. This is followed by further studies with pictures to show the test results. The reader is expected to make a preliminary diagnosis on the basis of the material provided before turning to the answer. At the end, a concise discussion and a correct diagnosis are rendered. The list of references is not exhaustive, but it provides the most recent information, current up to 2008. In fact, the entire book is based on the 2008 WHO classification.

The major emphasis is the provision of more than 500 color photos of peripheral blood smears, bone marrow aspirates, core biopsies, lymph node biopsies, and biopsies of other solid organs that are involved with lymphomas and leukemias. Pictures of other diagnostic parameters, such as flow cytometric histograms, immunohistochemical stains, cytogenetic karyotypes, fluorescence in situ hybridization, and polymerase chain reaction, are also included.

A comprehensive approach with consideration of clinical, morphologic, immunophenotypic and molecular genetic aspects is the best way to achieve a correct diagnosis. After reading this book, the reader will learn to make a diagnosis not only based on the morphology alone but also in conjunction with other parameters.

Denver, Colorado, USA Tsieh Sun

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Contents

Part I

Introduction

Classification of Lymphoma and Leukemia

Hematologic neoplasms are tumors of blood cells. All the blood cells are derived from a pluripotent stem cell that can differentiate into various cell lineages, including erythrocyte, megakaryocyte, basophil, eosinophil, neutrophil, monocyte, and lymphocyte (Fig. 1). These cell lineages are grouped into lymphoid cells and nonlymphoid cells or myeloid cells. Therefore, leukemias can be divided into lymphoid leukemia and myeloid leukemia. Leukemic cells originate from the bone marrow and circulate in the peripheral blood, whereas lymphoma is lymphoid tumor confined to the lymphoid organs or extranodal tissues. However, with the advent of new technology, lymphoma cells can be detected in the blood and bone marrow even in a relatively early stage, and thus the demarcation between lymphoma and leukemia is sometimes blurred.

Leukemia can be further divided into acute and chronic types. In acute leukemia, the clinical course is rapidly progressive and the leukemic cells are immature blasts. Chronic leukemia, on the other hand, has a slow and indolent clinical course and the tumor cells are mature-looking in lymphoid leukemia and intermediate forms (promyelocytes, myelocytes, and metamyelocytes) in myeloid leukemia.

Lymphoma does not have acute or chronic types, but its clinical course is essentially determined by the maturity of the tumor cells. The mature tumor cells behave like those in chronic leukemia, whereas the immature form is similar to acute leukemia. The homogeneity of lymphoma cells in terms of their maturation stage prompted the theory of maturation arrest as the mechanism of tumorigenesis [1].

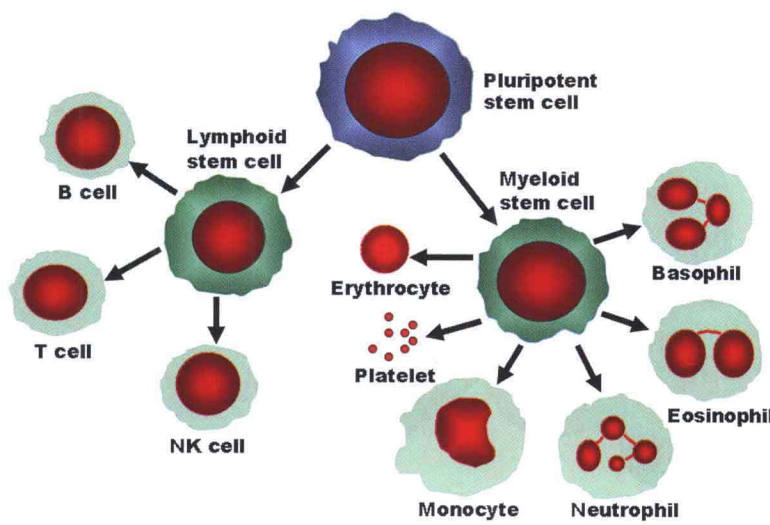

Fig. 1 Development of hematopoietic cells (hematopoietic tree)

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Development of B and T Lymphocytes

The development of B cells is confined to the bone marrow. There are several schemes to define the developmental stages of B cells, but the current scheme divides B cells into pro-B, pre-B, immature B, mature B, germinal center B, memory (marginal zone) B, and plasma cell stages [2].

The development of T lymphocytes starts when the T cells migrate from the bone marrow to the thymus. The stage I thymocyte is called prothymocyte, stage II, cortical thymocyte, and stage III, medullary thymocyte [2]. When the mature thymocyte enters the peripheral circulation, it becomes a postthymic or peripheral T cell.

The third lineage of lymphocyte is natural killer (NK) cell. NK cells share a common progenitor cell with T cells and they attain maturity in the thymus preceding αβ T-cell differentiation [3]. However, their exact developmental stages are still unclear.

Intranodal B-Cell Differentiation

Both T cells and B cells recirculate in the blood and home to various lymphoid organs, including lymph nodes, spleen, and mucosa-associated lymphoid tissue (MALT), due to the attraction of their surface homing receptors to the high endothelial venules at the hilum of the lymph nodes and spleen. In the lymph node, lymphocytes travel from one compartment to another, undergoing further morphologic changes (Fig. 2) [4]. The recirculating B cells first come to the mantle zone, where small lymphocytes develop into intermediate lymphocytes (*mantle cells*). The mantle cells then move into the germinal center and evolve through the stages of centroblasts and centrocytes. These cells are collectively called *follicular center cells*.

Some activated B cells transform into memory B cells and migrate to the marginal zone to become *marginal zone cells*. Under certain conditions, the marginal zone cells move to the parafollicular perisinusoidal area and become parafollicular B cells. These cells have ovoid nuclei and relatively abundant clear cytoplasm resembling monocytes and are thus called *monocytoid B cells*, which are now called *marginal zone B cells*. Some B cells transform into effector cells, which are *plasma cells*. The plasma cell is the terminal stage of the B cell, which moves to the medullary cord and finally migrates

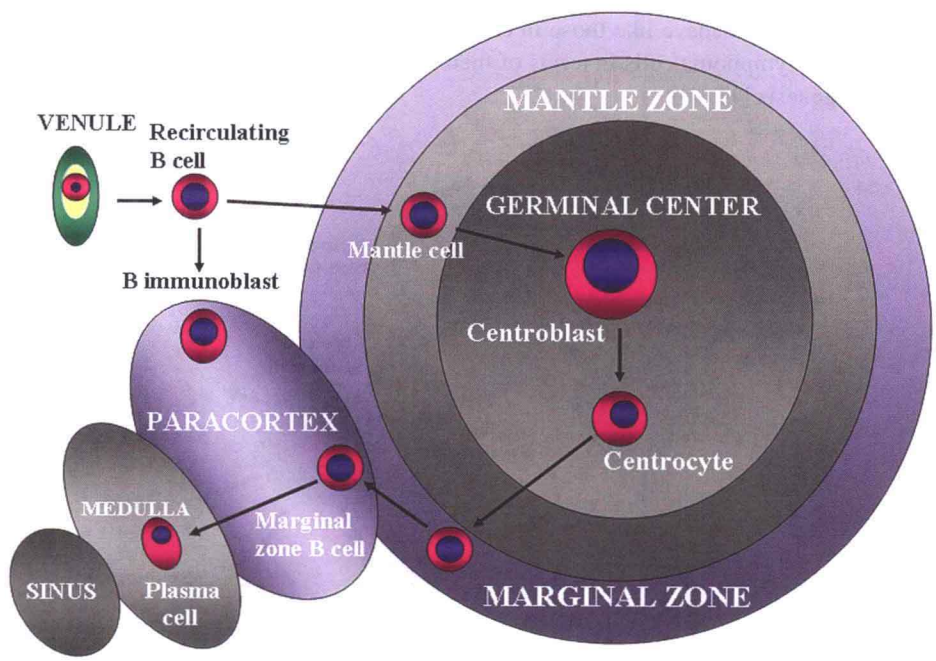

Fig. 2 Intranodal B-cell differentiation (maturation). Recirculating B cells migrate through the high endothelial venule in the hilum of lymph node to mantle zone, germinal center, marginal zone, paracortex, and finally the sinus

back to the bone marrow. The recirculating B cells also migrate directly without passing through the germinal center and the mantle and marginal zones to the paracortex and become *B immunoblasts*.

Pre-germinal Center, Germinal Center and Post-germinal Center Lymphomas

Lymphoma may develop at each stage of intranodal differentiation [2]. The origin of these lymphomas can be determined by the status of the variable region of heavy chain gene (V_H) mutation. Lymphomas that show no V_H gene mutation represent a tumor from the pre-germinal center. Lymphomas that express V_H gene mutation and intraclonal diversity are derived from the germinal center; whereas those that have V_H gene mutation but not intraclonal diversity originate from post-germinal center B cells.

Pre-germinal center lymphoma is represented by mantle cell lymphoma. Germinal center lymphoma includes follicular lymphoma, Burkitt lymphoma, a subset of diffuse large B-cell lymphoma, and Hodgkin lymphoma. Post-germinal center lymphoma includes nodal marginal zone-B-cell lymphoma, extranodal marginal zone B-cell lymphoma, splenic marginal zone lymphoma, plasma cell myeloma, lymphoplasmacytic lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, and a subset of diffuse large B-cell lymphoma [2].

Classification of Acute Leukemias

The French – American – British (FAB) classification has been used as the basis for the classification of acute leukemia for many years [5]. However, the 2008 World Health Organization (WHO) classification has made many changes to the FAB classification [6]. The FAB divides acute lymphoblastic leukemia (ALL) into L1, L2, and L3, but the WHO classification considers that the division of L1 and L2 does not serve any clinical purpose and merges them into B-cell and T-cell ALLs. L3 is morphologically associated with Burkitt leukemia, but the 2008 WHO classification discourages the inclusion of Burkitt leukemia in the category of acute lymphoblastic leukemia. In the new WHO classification, all acute lymphoblastic leukemias and precursor B- and T-cell lymphomas are classified under precursor lymphoid neoplasms (Table 1).

In acute myelogenous leukemia (AML), the original FAB categories, M0, M1, M2, M3, M4, M5, M6, and M7, are now classified in the category of AML not otherwise categorized (Table 2). Also included in the AML classification are acute basophilic leukemia, acute panmyelosis with myelofibrosis, myeloid sarcoma, myeloid proliferations related to Down syndrome, and blastic plasmacytoid dendritic cell neoplasm. However, the major addition is the acute myeloid leukemia with recurrent cytogenetic abnormalities, which includes nine well-defined entities.

Classification of Lymphoma

Modern classification of non-Hodgkin lymphoma started with Rappaport, whose classification was based on the histologic pattern (nodular or diffuse), cytology (lymphocyte or histiocyte), and cell differentiation (well differentiated or poorly differ-

Table 1 WHO classification for precursor lymphoid neoplasms

B-lymphoblastic leukemia/lymphoma, not otherwise specified
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
B-lymphoblastic leukemia/lymphoma with t(9;22)(q34;q11.2); BCR-ABL1
B-lymphoblastic leukemia/lymphoma with t(v;11q23); MLL rearranged
B-lymphoblastic leukemia/lymphoma with t(12;21)(p13;q22); TEL-AML 1 (ETV6-RUNX1)
B-lymphoblastic leukemia/lymphoma with hyperdiploidy
B-lymphoblastic leukemia/lymphoma with hypodiploidy (hypodiploid ALL)
B-lymphoblastic leukemia/lymphoma with t(5;14)(q31;q32); IL3-IGH
B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); E2A-PBX1 (TCF3-PBX1)
T-lymphoblastic leukemia/lymphoma

Table 2 WHO classification of acute myeloid leukemia

Acute myeloid leukemia with recurrent cytogenetic abnormalities
AML with t(8;21)(q22;q22), RUNX1-RUNX1T1
AML with inv(16)(p13q22) or t(16;16)(p13.1;q22), (CBFβ/MYH11)
Acute promyelocytic leukemia with t(15;17)(q22;q12), (PML/RARα) (AML-M3)
AML with t(9;11)(p22;q23); MLLT3-MLL
AMLwith t(6;9)(p23;q34); DEK-NUP214
AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EV11
AML (megakaryoblastic) with t(1;22)(p13;q13); RBM15-MKL1
AML with mutated NPM1
AML with mutated CEBPA
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
Acute myeloid leukemia not otherwise categorized
AML, minimally differentiated (AML-M0)
AML without maturation (AML-M1)
AML with maturation (AML-M2)
Acute myelomonocytic leukemia (AML-M4)
Acute monoblastic and monocytic leukemia (AML-M5)
Acute erythroid leukemia (AML-M6)
Acute megakaryoblastic leukemia (AML-M7)
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Blastic plasmacytoid dendritic cell neoplasm
Acute leukemia of ambiguous lineage
Acute undifferentiated leukemia
Mixed phenotype acute leukemia with t(9;22)(q34;q11.2); BCR-ABL1
Mixed phenotpe acute leukemia with t(v;11q23), MLL rearranged
Mixed phenotype actue leukemia, B/lymphoid, NOS
Mixed phenotype acute leukemia, T/myeloid, NOS
Natural killer (NK)-cell lymphoblastic leukemia/lymphoma

FAB classification in parenthesis, provisional entity in italic type

entiated). In the 1970s, there were many classifications; the better known ones included Lukes and Collins, Kiel, Dorfman, British National Lymphoma Investigation, and the U.N. World Health Organization classifications. These different schemes inevitably caused some confusion among pathologists; thus the National Cancer Institute in the United States organized a team of experts to evaluate the available classifications and establish a "compromise" new scheme. As a result, a working formulation of non-Hodgkin lymphomas for clinical use was proposed [7]. The Working Formulation is relatively simple and yet incorporates all the major components from other schemes. Its major advantage is dividing the lymphomas into three prognostic groups that make the Working Formulation clinically relevant. It was promptly accepted and has been widely used, especially in North America. However, in Europe the Kiel classification is more popular than the Working Formulation [8].

The Working Formulation, nevertheless, does not identify individual disease entities and does not include many new entities, especially in the T-cell lymphoma category, that have appeared in recent years. In addition, the new treatments used currently have changed the outlook of many diseases; thus the prognostic grouping may no longer be valid for some of the lymphomas. Therefore, some American hematologists and oncologists believed that the Working Formulation has outlived its usefulness. Because of this situation, a Revised European – American Classification of Lymphoid Neoplasms (REAL classification) was proposed [9]. This new scheme encompasses many new entities, covers both Hodgkin lymphoma and non-Hodgkin lymphomas, and incorporates immunophenotypes and cytogenetics as an integral part of the diagnosis.

The REAL classification, however, contains a number of provisional entities that required additional studies for confirmation or elimination in future schemes. The WHO classification fulfills this function by verifying these provisional entities and has been accepted universally as the standard classification [5]. In 2008, a revised WHO scheme with many new changes was proposed (Table 3).

Table 3 WHO classification of lymphoid neoplasms

B-cell neoplasms
- Precursor B-cell neoplasms
  - B-lymphoblastic leukemia/lymphoma, NOS
  - B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities*
- Mature (peripheral) B-cell neoplasms
  - B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma
  - B-cell prolymphocytic leukemia
  - Splenic B-cell marginal zone lymphoma (± villous lymphocytes)
  - Hairy cell leukemia
  - *Splenic B-cell lymphoma/leukemia, unclassifiable*
    - *Splenic diffuse red pulp small B-cell lymphoma*
    - *Hairy cell leukemia variant*
  - Lymphoplasmacytic lymphoma
    - Waldenström macroglobulinemia
  - Heavy chain diseases
    - Alpha heavy chain disease
    - Gamma heavy chain disease
    - Mu heavy chain disease
  - Plasma cell myeloma
  - Solitary plasmacytoma of bone
  - Extraosseous plasmacytoma
  - Extranodal marginal zone lymphoma of MALT type
  - Nodal marginal zone lymphoma
    - *Pediatric nodal marginal zone lymphoma*
  - Follicular lymphoma
    - *Pediatric follicular lymphoma*
  - Primary cutaneous follicle center lymphoma
  - Mantle cell lymphoma
  - Diffuse large B-cell lymphoma (DLBCL), NOS
    - T-cell/histiocyte-rich large B-cell lymphoma
    - Primary DLBCL of the CNS
    - Primary cutaneous DLBCL, leg type
    - *EBV positive DLBCL of the elderly*
  - DLBCL associated with chronic inflammation
  - Lymphomatoid granulomatosis
  - Primary mediastinal (thymic) large B-cell lymphoma
  - Intravascular large B-cell lymphoma
  - ALK-positive large B-cell lymphoma
  - Plasmablastic lymphoma
  - Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
  - Primary effusion lymphpoma
  - Burkitt lymphoma
  - B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma
  - B-cell lymphoma unclassifiable, with feature intermediate between DLBCL and classical Hodgkin lymphoma

T- and NK-cell neoplasms
- Precursor T-cell neoplasms
  - T-lymphoblastic leukemia/lymphoma
- Mature T-cell and NK-cell neoplasms
  - T-cell prolymphocytic leukemia
  - T-cell large granular lymphocytic leukemia
  - *Chronic lymphoproliferative disorder of NK cells*
  - Aggressive NK-cell leukemia
  - Systemic EBV positive T-cell lymphoproliferative disease of childhood
  - Hydroa vacciniforme-like lymphoma
  - Adult T-cell leukemia/lymphoma
  - Extranodal NK/T-cell lymphoma, nasal type
  - Enteropathy-associated T-cell lymphoma