Oliver W. Press

Marshall A. Lichtman

John P. Leonard

# WILLIAMS HEMATOLOGY

# Malignant Lymphoid Diseases

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**Oliver W. Press, MD, PhD**
Giuliani/Press Endowed Chair in Cancer Research
Fred Hutchinson Cancer Research Center
Professor of Medicine and Bioengineering
University of Washington
Seattle, Washington

**Marshall A. Lichtman, MD**
Professor Emeritus of Medicine
   (Hematology-Oncology) and of Biochemistry
   and Biophysics
Dean, Emeritus School of Medicine and Dentistry
University of Rochester Medical Center
Rochester, New York

**John P. Leonard, MD**
Richard T. Silver Distinguished Professor of Hematology and
   Medical Oncology
Joan and Sanford I. Weill Department of Medicine
Weill Cornell Medical College
New York Presbyterian Hospital
New York, New York

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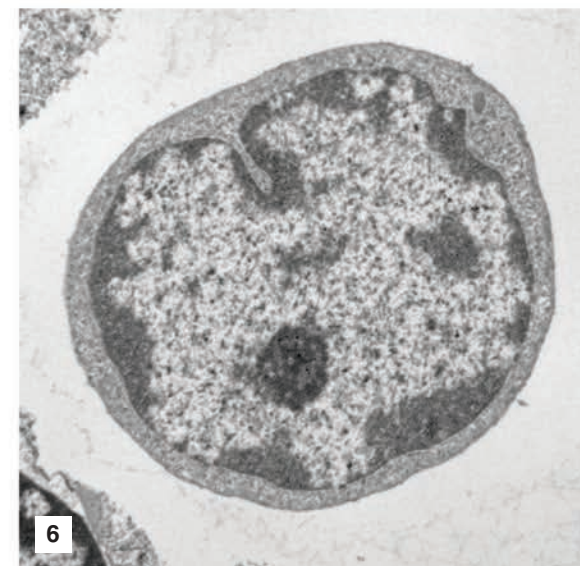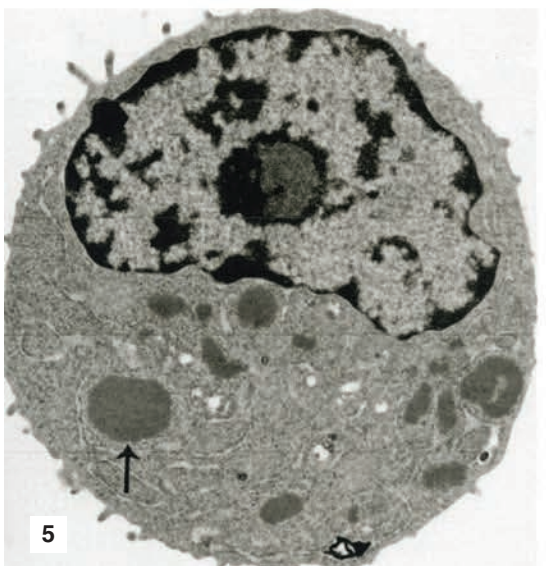
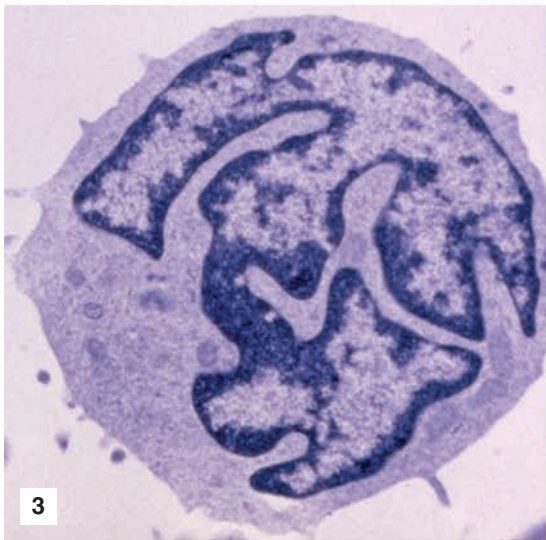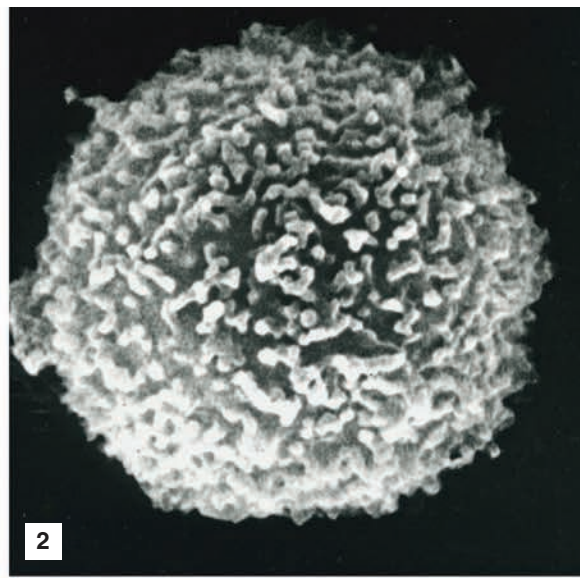**William J. Williams, MD**
**1926 – 2016**

Medical educator, investigator, physician, mentor, academic leader, colleague, and the founding editor of *Williams Hematology*

1. Transmission electron micrograph (TEM) of a normal blood lymphocyte. 2. Scanning electron micrograph (SEM) of a normal blood lymphocyte. 3. TEM of Sézary cell in a patient with the erythrodermic type of cutaneous T-cell lymphoma. Note the cell's characteristic profoundly misshaped (cerebriform) nucleus. 4. TEM of a hairy cell. Arrow indicates a ribosome-lamella complex. This structure is not specific for hairy cell leukemia but is found in a variable proportion of hairy cells in about 50 percent of cases examined by TEM. Frequent cytoplasmic membrane, "hairy," projections. 5. TEM of plasmablast (undifferentiated myeloma cell). Arrow points to a Russell body. 6. A lymphoblast from the marrow of a patient with acute lymphoblastic leukemia. Very high nuclear-to-cytoplasmic ratio. Prominent nucleolus. The nucleus is virtually all euchromatin (likely transcriptionally active). (*Reproduced with permission from* Lichtman's Atlas of Hematology, *www.accessmedicine.com.*)

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# CONTRIBUTORS

**Kenneth Anderson, MD**
Dana-Farber Cancer Institute
Boston, Massachusetts

**Farrukh T. Awan, MD**
Associate Professor of Internal Medicine
Division of Hematology
Department of Internal Medicine
The Ohio State University Comprehensive Cancer Center
Columbus, Ohio

**Robert A. Baiocchi, MD, PhD**
Associate Professor of Medicine
Division of Hematology
Department of Internal Medicine
The Ohio State University
Columbus, Ohio

**Alessandro Broccoli, MD**
Institute of Hematology "L. e A. Seràgnoli"
University of Bologna
Bologna, Italy

**Francis K. Buadi, MD**
Division of Hematology
Mayo Clinic
Rochester, Minnesota

**John C. Byrd, MD**
D. Warren Brown Chair of Leukemia Research
Professor of Medicine, Medicinal Chemistry, and Veterinary
    Biosciences
Director, Division of Hematology
Department of Medicine
The Ohio State University
Columbus, Ohio

**Jorge J. Castillo, MD**
Assistant Professor of Medicine
Dana-Farber Cancer Institute
Harvard Medical School
Boston, Massachusetts

**Carla Casulo, MD**
Assistant Professor of Medicine
James P. Wilmot Cancer Institute
University of Rochester Medical Center
Rochester, New York

**Francesca Cottini, MD**
Dana-Farber Cancer Institute
Boston, Massachusetts

**Angela Dispenzieri, MD**
Division of Hematology
Mayo Clinic
Rochester, Minnesota

**Martin Dreyling, MD**
Department of Internal Medicine III
Medical Center of the University of Munich
Munich, Germany

**Andrew G. Evans, MD, PhD**
Assistant Professor
Department of Pathology and Laboratory Medicine
University of Rochester Medical Center
Rochester, New York

**Aharon G. Freud, MD, PhD**
Assistant Professor
Department of Pathology
The Ohio State University
Columbus, Ohio

**Jonathan W. Friedberg, MD**
Samuel Durand Professor of Medicine
Director, Wilmot Cancer Institute
University of Rochester Medical Center
Rochester, New York

**Randy D. Gascoyne, MD, FRCPC**
Clinical Professor of Pathology
Research Director, Centre for Lymphoid Cancers
Departments of Pathology and Advanced Therapeutics
British Columbia Cancer Agency, the BC Cancer Research Center, and
    University of British Columbia
Vancouver, British Columbia, Canada

**Morie A. Gertz, MD, MACP**
Division of Hematology
Mayo Clinic
Rochester, Minnesota

**Larisa J. Geskin, MD, FAAD**
Associate Professor of Dermatology and Medicine
Director, Division of Cutaneous Oncology and Comprehensive Skin
    Cancer Center
Department of Dermatology
Columbia University
New York, New York

**Michael G. Grever, MD**
Chair and Professor
Department of Internal Medicine
Bertha Bouroncle MD and Andrew Pereny Chair in Medicine
The Ohio State University
Columbus, Ohio

**Steven Horwitz, MD**
Department of Medicine
Memorial Sloan Kettering Cancer Center
New York, New York

**Zachary R. Hunter, PhD**
Bing Center for Waldenstrom's Macroglobulinemia
Dana-Farber Cancer Institute
Instructor of Medicine, Harvard Medical School
Boston, Massachusetts

**Siegfried Janz, MD, DSc**
Division of Hematology/Oncology and Blood and
    Marrow Transplantation
Department of Pathology, Carver College of Medicine
University of Iowa Health Care
Iowa City, Iowa

**Robert A. Kyle, MD**
Professor of Medicine
Laboratory Medicine and Pathology
Mayo Clinic
Rochester, Minnesota

**Richard A. Larson, MD**
Section of Hematology/Oncology
Department of Medicine and the Comprehensive Cancer Center
University of Chicago
Chicago, Illinois

**John P. Leonard, MD**
Richard T. Silver Distinguished Professor of Hematology and
    Medical Oncology
Joan and Sanford I. Weill Department of Medicine
Weill Cornell Medical College
New York Presbyterian Hospital
New York, New York

**Marshall A. Lichtman, MD**
Professor Emeritus of Medicine and of Biochemistry and Biophysics
Dean Emeritus, School of Medicine and Dentistry
University of Rochester Medical Center
Rochester, New York

**Gerard Lozanski, MD**
Director, Hematopathology
Medical Director
Flow Cytometry Laboratory
Associate Professor—Clinical
Department of Pathology
The Ohio State University
Columbus, Ohio

**Neha Mehta, MD**
Department of Medicine
Memorial Sloan Kettering Cancer Center
New York, New York

**Giampaolo Merlini, MD**
Director, Center for Research and Treatment of Systematic
    Amyloidosis
University Hospital Policlinico San Meteo
Professor, Department of Medicine
University of Pavia
Pavia, Italy

**Alison Moskowitz, MD**
Department of Medicine
Memorial Sloan Kettering Cancer Center
New York, New York

**Kalyan Nadiminti, MD**
Division of Hematology/Oncology and Blood and
    Marrow Transplantation
Department of Pathology, Carver College of Medicine
University of Iowa Health Care
Iowa City, Iowa

**Elizabeth O'Donnell, MD**
Massachusetts General Hospital
Boston, Massachusetts

**Christina C. Patrone, BA**
Columbia University College of Physicians and Surgeons
New York, New York

**Pierluigi Porcu, MD**
Professor of Internal Medicine
Division of Hematology and Comprehensive Cancer Center
The Ohio State University
Columbus, Ohio

**Oliver W. Press, MD, PhD**
Giuliani/Press Endowed Chair in Cancer Research
Fred Hutchinson Cancer Research Center
Professor of Medicine and Bioengineering
University of Washington
Seattle, Washington

**Noopur Raje, MD**
Massachusetts General Hospital
Boston, Massachusetts

**Taimur Sher, MD**
Division of Hematology/Oncology
Mayo Clinic
Jacksonville, Florida

**Brian F. Skinnider, MD**
Clinical Associate Professor
Department of Pathology
Vancouver General Hospital, British Columbia Cancer Agency, and
  University of British Columbia
Vancouver, British Columbia, Canada

**Stephen D. Smith, MD**
Seattle Cancer Care Alliance
Seattle, Washington

**Steven P. Treon**
Director, Bing Center for Waldenstrom's Macroglobulinemia
Dana-Farber Cancer Institute
Associate Professor, Harvard Medical School
Boston, Massachusetts

**Guido Tricot, MD, PhD**
Division of Hematology/Oncology and Blood and
  Marrow Transplantation
Department of Pathology, Carver College of Medicine
University of Iowa Health Care
Iowa City, Iowa

**Dietlind L. Wahner-Roedler, MD**
Professor of Medicine
Mayo Clinic
Rochester, Minnesota

**Erik Wendlandt, PhD**
Division of Hematology/Oncology and Blood and
  Marrow Transplantation
Department of Pathology, Carver College of Medicine
University of Iowa Health Care
Iowa City, Iowa

**Fenghuang Zhan, MD, PhD**
Division of Hematology/Oncology and Blood and
  Marrow Transplantation
Department of Pathology, Carver College of Medicine
University of Iowa Health Care
Iowa City, Iowa

**Pier Luigi Zinzani, MD, PhD**
Professor
Institute of Hematology "L. e A. Seràgnoli"
University of Bologna
Bologna, Italy

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# PREFACE

Bifurcation is an essential feature of biology. It underlies differentiation as one cell, through a process of mitosis accompanied by altered gene expression, forms two distinct cell lineages. The hematopoietic system is a dramatic example of this phenomenon. A single lymphohematopoietic stem cell, can over the course of several bifurcations, differentiate and then mature into at least 11 unique functional cells. In some cases, these cells can mature further into different phenotypes influenced by the environment in which they reside. Consider, for example, the monocytes, Kupffer cells, osteoclasts, microglia, and alveolar macrophages.

One of the critical points of hematopoietic bifurcation is the differentiation of the lymphohematopoietic stem cell into the common myeloid and common lymphoid progenitor. It is at this point that differentiation into these distinct lineages separates hematology into two specialized areas of research and clinical practice: the myeloid and lymphoid neoplasms. Unlike most of the maturing myeloid cells, the lymphoid cells do not lose their mitotic capability. This requirement for continued replication and repair of DNA, along with the rearrangements required of immunoglobulin and T-cell receptor genes during maturation, provides the risk of neoplastic gene mutations; these requirements result in a panoply of lymphocytic neoplasms, grossly divided into B-lymphocyte, T-lymphocyte, and natural killer cell tumors. The complexity of this array is extensive, with over 70 specific lymphocytic tumors in the 2016 World Health Organization classification of lymphocytic malignancies.

The lymphoid neoplasms are the subject of this text. Neoplasms originating in the lymphoid progenitor cell hierarchy constitute the lymphomas and lymphocytic leukemias. These tumors afflicted over 105,000 Americans and resulted in over 23,000 deaths in 2017. Their effects worldwide are dramatically larger. It is these compelling numbers that prompted the editors to prepare a "breakaway" text on the malignant lymphocytic neoplasms, based on the chapters that discussed these diseases in the ninth edition of *Williams Hematology.* Approximately 3 years have passed since those chapters were written. The editors asked the authors of these 21 chapters to revise and update them in the light of three recent developments: an expanded classification of the lymphocytic neoplasms by the World Health Organization, advances in the understanding of biology and genetics of these tumors, and advances in therapeutic approaches to the lymphomas and lymphocytic leukemias. The authors have graciously and expeditiously done so. With their help and expertise, we can now provide a timely text that covers the lymphomas and lymphocytic leukemias.

It is hoped the reader, from the accessibility of these new versions of the chapters, will derive benefit in their research, clinical practice, and learning.

Marshall A. Lichtman
Oliver W. Press
John P. Leonard

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# CHAPTER 1
# CLASSIFICATION OF MALIGNANT LYMPHOID DISORDERS

Robert A. Baiocchi

## SUMMARY

This chapter outlines the category of preneoplastic and neoplastic lymphocyte and plasma cell disorders. It introduces a framework for evaluating neoplastic lymphocyte and plasma cell disorders, outlines clinical syndromes associated with such disorders, and guides the reader to the chapters in the text that discuss each of these disorders in greater detail.

## CLASSIFICATION

Lymphocyte and plasma cell malignancies present a broad spectrum of different morphologic features and clinical syndromes (Table 1–1). Lymphocyte neoplasms can originate from cells that are at a stage prior to T- and B-lymphocyte differentiation from a primitive stem cell or from cells at stages of maturation after stem cell differentiation. For example, acute lymphoblastic leukemias arise from an early lymphoid progenitor cell that may give rise to cells with either B- or T-cell phenotypes (Chap. 2), whereas chronic lymphocytic leukemia arises from a more mature B-lymphocyte progenitor (Chap. 3) and myeloma from progenitors at even later stages of B-lymphocyte maturation (Chap. 18). Disorders of lymphoid progenitors may result in a broad spectrum of lymphocytic diseases, such as B- or T-cell lymphomas (Chaps. 9 and 15), hairy cell leukemia (Chap. 4), prolymphocytic leukemia (Chap. 3), natural

**Acronyms and Abbreviations:** $a/\beta$ TCR, T-cell-receptor genes encoding the $a$ and $\beta$ chains of the T-cell receptor; *ALK*, gene encoding anaplastic lymphoma kinase; *BCL2*, gene encoding B-cell chronic lymphocytic leukemia (CLL)/lymphoma 2; *BCL6*, gene encoding B-cell chronic lymphocytic leukemia (CLL)/lymphoma 6; cIg, cytoplasmic immunoglobulin; EBER, Epstein-Barr-virus-encoded RNA; EBV, Epstein-Barr virus; $\gamma/\delta$ TCR, T-cell-receptor genes encoding the $\gamma$ and $\delta$ chains of the T-cell receptor; HL, Hodgkin lymphoma; HLA, human leukocyte antigen; HTLV-1, human T-cell leukemia virus type 1; HHV8, human herpes virus 8; Ig, immunoglobulin; IgR, immunoglobulin gene rearrangement; IL, interleukin; MALT, mucosa-associated lymphoid tissue; *MUM1*, gene encoding multiple myeloma oncogene 1; neg., negative; NK cell, natural killer cell; NOS, not otherwise specified; *NPM*, gene encoding nucleophosmin; *PAX5*, paired box gene 5; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes; REAL, revised European-American lymphoma; R-S, Reed-Sternberg; sIg, surface immunoglobulin; sIgD, surface immunoglobulin D; sIgM, surface immunoglobulin M; *TAL1*, gene encoding T-cell acute leukemia-1; TCR, T-cell receptor; TdT, terminal deoxynucleotidyl transferase; Th2, T-helper type 2; WHO, World Health Organization.

killer cell large granular lymphocytic leukemia (Chap. 5),[1] myeloma, and plasmacytoma (Chap. 18). Hodgkin lymphoma also is derived from a neoplastic B cell that has highly mutated immunoglobulin genes that are no longer expressed as protein (Chap. 8).

To provide a unified international basis for clinical and investigative work in this field, the International Lymphoma Study Group proposed a classification termed the *revised European-American Lymphoma* (REAL) classification (Chap. 6),[2] which was modified in 2001 and again in 2008 by the World Health Organization (WHO).[3,4] The REAL/WHO classification scheme makes use of the pathologic, immunophenotypic, genetic, and clinical features of given lymphocyte tumors to delineate them into separate disease entities (Table 1–1 and Chap. 7).[5] For some of these entities, the neoplastic lymphocytes have distinctive cytogenetic abnormalities, which can be identified using molecular techniques that are increasingly being used in clinical pathology laboratories.[6,7]

The REAL/WHO classification recognizes a basic distinction between nodular lymphocyte-predominant Hodgkin lymphoma and classic Hodgkin lymphoma, reflecting the differences in clinical presentation and behavior, morphology, phenotype, and molecular features (Chap. 8).[3] Studies have identified features that can be used to distinguish classical Hodgkin lymphoma from anaplastic large cell lymphoma and, to a lesser extent, between nodular lymphocyte-predominant Hodgkin lymphoma and T-cell/histiocyte-rich large B-cell lymphoma.

The updated WHO classification (summarized in Ref. 4) provided several revised guidelines for defining diseases such as chronic lymphocytic leukemia (CLL),[8] Waldenström macroglobulinemia,[9] plasma cell neoplasms,[10] and diffuse large B-cell lymphoma (DLBCL).[11–14] The classifications of several T-cell lymphomas were also refined, including enteropathy-associated T-cell lymphoma, anaplastic large cell lymphoma (*ALK* positive and *ALK* negative), and subcutaneous panniculitis-like T-cell lymphoma.[4] In 2014, a Clinical Advisory Committee meeting was held to review literature and provide an update prior to the preparation of the next WHO tumor monograph series. The update reviews major areas from the WHO 2018 edition that changed significantly[14a] and are summarized in Table 1–1.

## CLINICAL BEHAVIOR

Lymphomas of similar histology can have widely different spectra of associated clinical symptoms and clinical aggressiveness, making the categorization of lymphoid tumors impossible using a generic grading system based on morphology alone. For example, the neoplastic cells in mantle cell lymphoma appear smaller and more differentiated than those of anaplastic large cell lymphomas. However, the validation studies for the REAL classification revealed that patients with mantle cell lymphoma and anaplastic large cell lymphomas have 5-year survival rates of approximately 30 percent and approximately 80 percent, respectively.[15,16] Generally, T-cell lymphomas/leukemias have a more aggressive clinical behavior than B-cell lymphomas of comparable histology. The tendency for more aggressive disease also applies to lymphoid tumors derived from natural killer cells. A helpful distinction is to divide the lymphoid tumors into one of two categories, namely, indolent lymphomas versus aggressive lymphomas, based upon on the characteristics of the disease at the time of presentation and patients' life expectancy if the disease is left untreated.[17,18] Clinical studies have verified that the different disease categories defined in the REAL/WHO classification each can be segregated into one or the other of these two major categories (Tables 1–2 and 1–3, respectively).[15] Analyses of gene-expression patterns using microarray technology have enabled identification of subcategories within some of the disease categories defined by the REAL/WHO classification that have different tendencies for

**TABLE 1–1.** Classification of Lymphoma and Lymphoid Leukemia by the World Health Organization

| Neoplasm | Morphology | Phenotype* | Genotype† |
|---|---|---|---|
| **B-CELL NEOPLASMS** | | | |
| Immature B-Cell Neoplasms | | | |
| Lymphoblastic leukemia/lymphoma not otherwise specified (NOS) (Chap. 2) | Medium-to-large cells with finely stippled chromatin and scant cytoplasm | TdT+, sIg–, CD10+, CD13+/–, CD19+, CD20–, CD22+, CD24+, CD34+/–, CD33+/–, CD45+/–, CD79a+, PAX5+ | Clonal DJ rearrangement of *IGH* gene T(17;19), *E2A-HLF*, *AML1* iAMP21 associated with poor prognosis |
| Lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities (Chap. 2) | See above | See above. B-ALL with t(9;22) with CD25 and more frequent myeloid antigens CD13, CD33 | See individual genetic features in B-ALL subtypes below |
| B-ALL with t(v;11q23); *MLL* rearranged | See above | CD19+, CD10–, CD24–, CD15+ | Multiple MLL (11q23) fusion partners, including *AF4* (4q21), *AF9* (9p22), and *ENL* (19p13). B-ALL with MLL translocations overexpress *FLT-3*. Poor prognosis |
| B-ALL with t(12;21) (p13;q22); *TEL-AML1* (*ETV6-RUNX1*) | See above | CD19+, CD10+, CD34+. Characteristically negative for CD9, CD20, and CD66c | t(12;21)(p13;q22) *ETV6-RUNX* translocation |
| B-ALL with hyperdiploidy | See above | CD19+, CD10+, CD45–, CD34+ | Numerical increase in chromosomes without structural abnormalities. Most frequent chromosomes +21, X, 14, and 4. +1, 2, 3 rarely seen. Favorable prognosis |
| B-ALL with hypodiploidy | See above | See above | Loss of at least one or more chromosomes (range from 45 chromosomes to near haploid). Rare chromosome abnormalities. Poor prognosis |
| B-ALL with t(5;14) (q31;q32); *IL3-IGH* | See above with increase in reactive eosinophilia | See above. Even rare blasts with B-ALL immunophenotype with eosinophilia strongly suggestive of this subtype of B-ALL | t(5;14)(q31;q32); *IL3-IGH* leading to overexpression of IL3. Unclear prognosis |
| B-ALL with t(1;19) (q23;p13.3); *E2A-PBX1* | See above | CD10+, CD19+, cytoplasmic μ heavy chain. CD9+, CD34– | t(1;19)(q23;p13.3); leads to overexpression of *E2A-PBX1* fusion gene product interfering with normal transcription factor activity of E2A and PBX1 |
| Mature B-Cell Neoplasms | | | |
| Leukemias | | | |
| Chronic lymphocytic leukemia/small lymphocytic lymphoma (Chap. 3) | Small cells with round, dense nuclei | sIg+(dim), CD5+, CD10–, CD19+, CD20+(dim), CD22+(dim), CD23+, CD38+/–, CD45+, FMC-7– | IgR+, trisomy 12 (~30%), del at 13q14 (~50%), 11q22–23, 17p13, and *IGHV* mutated status associated with poor prognosis. Mutations in *TP53*, *NOTCH1*, *SF3B1*, *ATM*, and *BIRC3* |
| Prolymphocytic leukemia (Chap. 3) | ≥55% prolymphocytes | sIg+(bright), CD5+/–, CD10–, CD19+, CD22+, CD23+/–, CD45+, CD79a+, FMC7+ | del13q.14(~30%); del17p (50%), IgR+ |
| Hairy cell leukemia (Chap. 4) | Small cells with cytoplasmic projections | sIg+(bright), CD5–, CD10–, CD11c+(bright), CD19+, CD20+, CD25+, CD45+, CD103+, Annexin A+ | BRAF mutations (~100%), IgR+ *MAP2K* mutations in *BRAF* wt |
| Lymphomas | | | |
| Lymphoplasmacytic lymphoma (Chap. 20) | Small cells with plasmacytoid differentiation | cIg+, CD5–, CD10–, CD19+, CD20+/– Plasma cell population: CD38+, CD138+, cIgM+ | IgR, 6q- in 50% of marrow-based cases [the t(9;14) was proved to be wrong], +4 (20%) |

(*Continued*)