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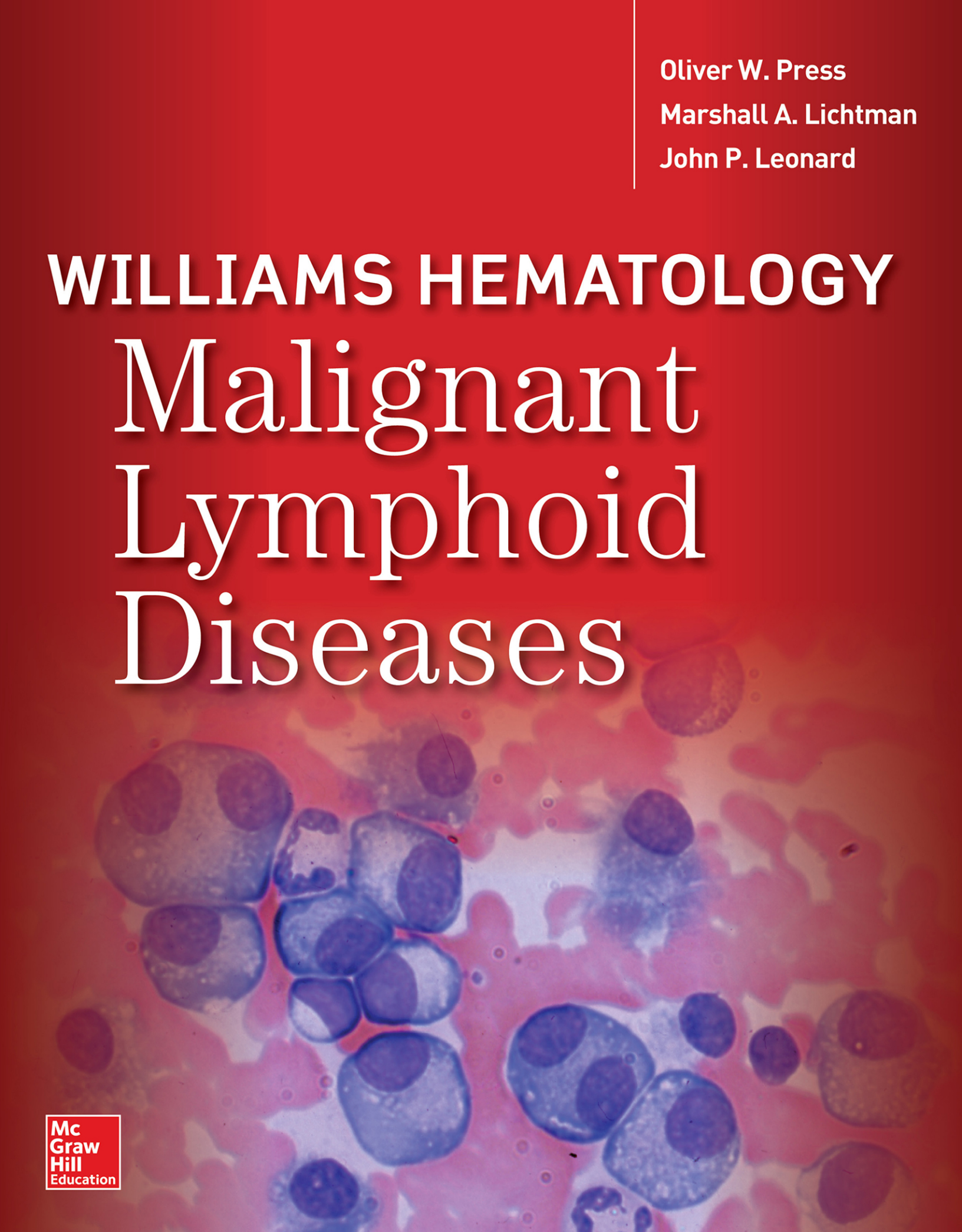
WILLIAMS HEMATOLOGY

Malignant Lymphoid Diseases



Mc Graw Hill Education

Williams Hematology

Malignant Lymphoid Diseases

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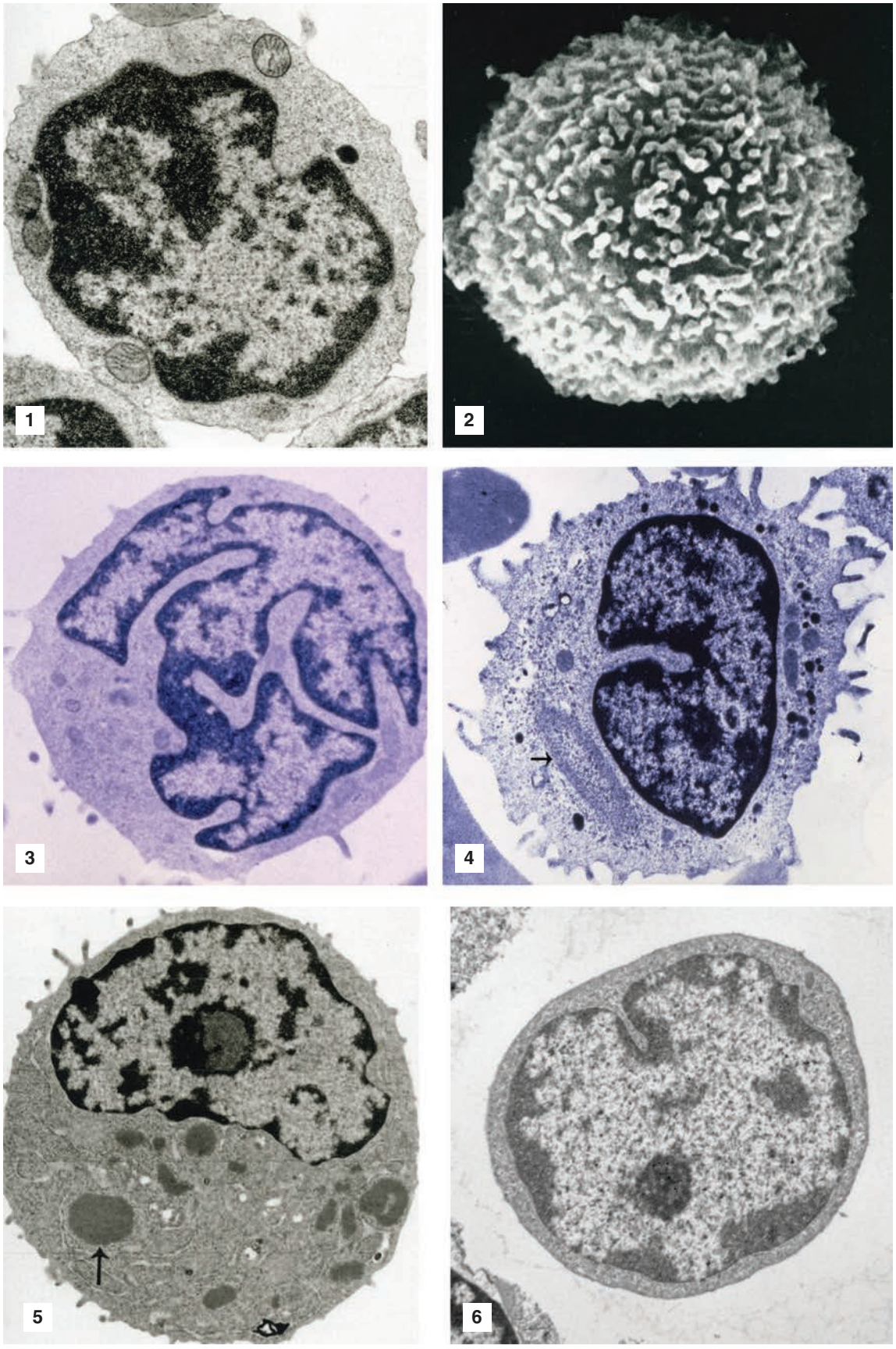
William J. Williams, MD
1926 – 2016

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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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
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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 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

Acronyms and Abbreviations: *α/β* TCR, T-cell-receptor genes encoding the *α* and *β* 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; *γ/δ* TCR, T-cell-receptor genes encoding the *γ* and *δ* 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.

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*)

TABLE 1–1. Classification of Lymphoma and Lymphoid Leukemia by the World Health Organization (Continued)

Neoplasm	Morphology	Phenotype*	Genotype†
Mantle cell lymphoma: unmutated IgHV and SOX11+ (Chap. 11)	Small-to-medium cells	sIgM+, sIgD+, CD5+, CD10–, CD19+, CD20+, CD23–, cyclin D1+, FMC-7+, SOX11+	Unmutated IgHV, SOX11+ MCL type. IgR, t(11;14)(q13;q32) (~100% by FISH), involving *CCND1* and IgH. Highly proliferative variants often show TP53 mutation, deletion of *INK4a/ART* and *p18INK4c. CCND1– MCL show CCND2 rearrangement in 50% of cases*
Mantle cell lymphoma: mutated IgHV and SOX11–	See above	See above, SOX11–	See above
Follicular lymphoma (follicle center lymphoma; FL, Chap. 10)	Small, medium, or large cells with cleaved nuclei	sIg, CD5–, CD10+, CD19+, CD20+(bright), CD23–/+, CD38+, CD45+	IgR, t(14;18)(q32;q21) (~85%) involving *BCL2* and IgH. Mutated 3q27 (5–15%, *BCL6*)
Predominantly diffuse FL with 1p36 deletion	See above	See above	1p36 deletion. Lacks *BCL2* rearrangement
Duodenal-type FL	See above	See above	See above
Pediatric-type FL	See above	See above	See above
Nodal marginal zone B-cell lymphoma (Chap. 12)	Small or large monocytoid cells	sIgM+, sIgD–, cIg+ (~50%), CD5–, CD10–, CD11c+/–, CD19+, CD20+, CD23–, CD43+/–	IgR, commonly with trisomies 3, 7, and 18
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) type (Chap. 12)	See above	See above	t(11;18)(q21;q21) involving *API2, MLT1*, or t(1;14)(p22;q32) involving *BCL10*
Splenic B-cell marginal zone lymphoma	Small round lymphocytes replace reactive germinal centers and/or villous lymphocytes in blood	sIgM+, sIgD–, CD5+/–, CD19+, CD20+, CD23–, CD103–	IgR, allelic loss of chromosome 7q31–32 (40%)
Splenic B-Cell Lymphoma, Unclassifiable			
Splenic diffuse red pulp small B-cell lymphoma	Blood: villous lymphocytes similar to SMZL. Marrow: intrasinusoidal infiltration. Spleen: monomorphous small-to-medium lymphocytes with round nuclei, vesicular chromatin, occasional small nucleoli	CD20+, DBA.44+, IgG+/IgD–, CD25–, CD5–, CD103–, CD123–	T(9;14)(p13;q32) involving *PAX5* and *IGH*
Hairy cell leukemia variant	Hybrid features of prolymphocytic leukemia and classic hairy cell leukemia	sIg+(bright), CD5–, CD10–, CD11c+(bright), CD19+, CD20+, CD25–, CD45+, CD103+, FMC7+, CD123–, annexin A1–, TRAP–	BRAF mutation negative
Diffuse Large B-Cell Lymphoma (DLBCL; Chap. 9)			
DLBCL NOS			
Common Morphologic Variants:			
Centroblastic	Medium-to-large lymphoid cells with vesicular nuclei containing fine chromatin. Multiple nucleoli	sIgM+, sIgD+/–, CD5-, CD10–/+, CD19+, CD20+, CD22+, CD79a+, CD45+, PAX5+	IgR, 3q27 abnormalities and/or t(3;14)(q27;q32) involving *BCL6* (~30%) or t(14;18)(q32;q21) (~25%) involving *BCL2*
Immunoblastic	>90% of cells are immunoblasts with central nucleolus	See above. May express CD30+	See above

(*Continued*)

TABLE 1–1. Classification of Lymphoma and Lymphoid Leukemia by the World Health Organization (Continued)

Neoplasm	Morphology	Phenotype*	Genotype†
Anaplastic	Very large round, oval, or polygonal cells with bizarre pleomorphic nuclei resembling R-S cells	See above. Often CD30+	See above
Molecular Subgroups			
Germinal center B-cell–like (GCB)	See above	See above	See above; MYC and BCL2 co-expression considered new prognostic marker
Activated B-cell–like (ABC)	See above. Often with more immunoblastic morphology	See above	t(14;18) (35%), 12q12 (20%), IG mutation, BCL2 rearrangement (20–25%), Rel amplification (15%). Amplification of microRNA-17-92 cluster
Immunohistochemical subgroups			Gain of 3q (26%), 9p (6%), 12q12 (5%), NF-κB activation
CD5-positive DLBCL	See above	See above. CD5+	t(11;14) and t(14;18) negative. +3 and gain on chromosome 16/16p and 18/18q common. Deletion p16/INK4a
Nongerminal center B-cell–like (non-GCB)	See above	See above	See above. Uniform FOXP1 expression with IRF4/MUM1 and BCL6 expression
T-cell/histiocyte-rich large B-cell lymphoma	See above; large cells dispersed among nonepitheloid histiocytes. Background lymphocytes are predominantly T cells	See above; negative for CD15, CD30, CD138. Background has CD68+ histiocytes and CD3+/CD5+ T cells	See above
Primary DLBCL of the CNS	See above	See above; positive for CD20, CD22, CD79a. CD10 expression present in 10–20% of cases. See above; BCL6 expression in 60–80% and IRF4/MUM1 in 90% of cases	High burden of somatic hypermutations. + Mutations in *BCL6, PIM1, MYC, Rho/TTFn*, and *PAX5*
Primary cutaneous DLBCL, leg type	See above	See above; high percentage of tumor cells express BCL2, BCL6, IRF4/MUM1, FOXP1	See above; deletion of 9p21.3 containing CDKN2a, CDKN2b, and MTAP in >60% cases
EBV+ DLBCL, NOS	See above; R-S–like cells present	See above; EBV+ with expression of LMP1, EBNA2 in 90% of cases. Malignant cells often CD30+ and CD15–	See above, uniformly EBV+
Primary mediastinal (thymic) large B-cell lymphoma (Chap. 9)	Variable from case to case. Medium-to-large cells often with pleomorphic nuclei (R-S–like cells)	sIg–, CD5–, CD10–/+, CD15–, CD19+, CD20+, CD22+, CD23+, CD30+ (80%), CD45+, CD79a+, IRF4/MUM1 (75%). Variable BCL2 (50–80%) and BCL6 (45–100%) expression	IgR+, gain of 9q24 (75%), gain 2p15 (50%) Amplification of *REL, BCL11A, JAK2, PDL1, PDL2*. Transcriptome similar to CHL
Intravascular large B-cell lymphoma	Neoplastic cells infiltrated within small-to-intermediate vessels of all organs	CD19+, CD20+, CD5 (38%), CD10 (13%). Lack of CD29 (β1 integrin) and CD54 (ICAM1) may account for intravascular growth pattern	IgR+, otherwise poorly characterized
Large B-cell lymphoma with *IRF4* rearrangement	See above	See above	*IRF4* rearrangement
ALK-positive large B-cell lymphoma	Sinusoidal growth pattern, monomorphic large immunoblast-like cells	Strongly positive for ALK, CD138+, VS38+, cytoplasmic IgA or IgG	IgR+, t(2;17) *ALK/CLTC*
Plasmablastic lymphoma	Diffuse proliferation of immunoblasts with plasmacytic differentiation, frequent mitotic figures, monomorphic morphology common in HIV+ patients. Frequently extranodal, EBV+	CD138+, CD38+, VS38C, IRF4/MUM1+, high Ki67, CD79a+ CD30+ in most cases. Negative for CD45, CD20, PAX5. Cytoplasmic Ig (50–70%). CD56 negative (if positive, suspect plasma cell myeloma)	IgR+, frequently Epstein-Barr virus-encoded RNA (EBER)+ (60–70%) but most cases negative for LMP1. HHV8+ status consistent with large B-cell lymphoma from MCD (below)

(*Continued*)

TABLE 1–1. Classification of Lymphoma and Lymphoid Leukemia by the World Health Organization (Continued)

Neoplasm	Morphology	Phenotype*	Genotype†
Large B-cell lymphoma arising from multicentric, HHV8+ Castleman disease (MCD)	HHV8 MCD: B-cell follicles with involution and hyalinization of germinal centers with prominent mantle zones. Large plasmablastic cells within mantle zone HHV8 plasmablastic lymphoma. Confluent sheets of HHV8+ LANA1+ cells effacing lymph node architecture. Extranodal involvement common	HHV8+, LANA1+, viral IL6+, cytoplasmic IgM, CD20+/–. Negative for CD79a, CD138, and EBV (EBER)	Polyclonal IgM. IgHV unmutated. IL6R pathway activation. Cytogenetics poorly characterized
Primary effusion lymphoma	Range of infiltrating cells with highly abnormal morphology, including immunoblastic, plasmablastic, anaplastic. Large nuclei with prominent nucleoli	CD45+; lack expression of CD19, CD20, CD79a, sIg	IgR+ and hypermutated. No recurrent chromosomal anomalies
Burkitt lymphoma (Chap. 9)	Medium cells arranged in diffuse, monotonous pattern. Basophilic cytoplasm, high proliferative index with frequent mitotic figures. "Starry sky" pattern present	Positive for CD19, CD20, CD10, BCL6, CD38, CD77, and CD43. Negative for BCL2 and TdT. Ki67+ in nearly 100% of tumor cells	t(8;14)(q24;q32), t(2;8)(q11;q24), or t(8;22)(q24;q11), involving Ig loci and *C-MYC* at 8q24. *TCF3* or *ID3* mutations in up to 70% of cases
Burkitt lymphoma with 11q aberration	See above	See above	See above; *TCF3* or *ID3* mutations
High-grade B-cell lymphoma NOS with *MYC* and *BCL2* and/or *BCL6* translocations	Medium, round cells with abundant cytoplasm. More variation in nuclear size and contour compared to BL. Commonly >90% Ki67+. Unlike BL, can show strong BCL2 expression	Same as above except sIg–, cIg+/–, and CD10–	Same as above except more typically expresses high levels of *BCL2* and ~30% have *BCL2* rearrangements (double-hit type)
B-cell lymphoma unclassifiable, features intermediate between DLBCL and classical Hodgkin lymphoma (HL)	Confluent, diffuse, sheet-like growth of pleomorphic cells within a fibrotic stroma. Pleomorphic cells resembling HL R-S–like cells and lacunar cells. Necrosis frequent	In contrast to HL, CD45+. Positive for CD30 and CD15	Poorly characterized
Plasma Cell Neoplasms			
Monoclonal gammopathy of undetermined significance (MGUS)	Marrow infiltrate with mature plasma cells comprising 1–9% of cellularity	M-protein <30 g/L, marrow <10% plasma cells, no end-organ damage. CD138+. Often difficult to demonstrate LC restriction because of small number of plasma cells	Abnormal cytogenetics rarely encountered in MGUS. FISH studies involving *IgH* occur in ~50% of cases: t(11;14), t(4;14). Del13q. Hyperdiploidy 40%
Plasma cell myeloma	Myeloma plasma cells seen in marrow arranged in interstitial clusters	sIg+, CD5–, CD10–, CD19–, CD20–, CD38+(bright), CD45+/–, CD56+, CD117+(bright), CD138+(bright)	IgR, commonly with complex karyotypes and/or t(6;14)(p25;q32) involving *MUM1*. t(11;14) seen in 15–25% of cases
Extraosseous plasmacytoma	Plasma cells in extraosseous organs must be distinguished from other lymphoproliferative disorders (i.e., MALT type)	Same as plasma cell myeloma	Same as above
Solitary plasmacytoma of bone	Plasma cells	Same as plasma cell myeloma	Same as above

(*Continued*)

TABLE 1–1. Classification of Lymphoma and Lymphoid Leukemia by the World Health Organization (Continued)

Neoplasm	Morphology	Phenotype*	Genotype†
Monoclonal immunoglobulin deposition disease	Prominent organ (kidney most common; occasionally liver, heart, nerve, blood vessels involved) deposits of nonamyloid, nonfibrillary, amorphous eosinophilic material that does not stain with Congo red. Heavy chain (HCDD) and light chain (LCDD)	LCDD is κ light chain predominant. HCDD shows λ chain predominance. Marrow may show abnormal κ/λ ratio	HCDD with VλVI overrepresentation. LCDD with VκIV variable region
Hodgkin Lymphoma (HL)			
Nodular lymphocyte predominant HL (Chap. 8)	"Popcorn cells" with nuclei resembling those of centroblasts	BCL6+, CD19+, CD20+, CD22+, CD45+, CD79a+, CD15–, and rarely CD30+/–, Bob1+, Oct2+, PAX5+	IgR, with high-level expression of *BCL6*
Classic HL (Chap. 8)			
Nodular sclerosis HL	R-S cells and lacunar cells dispersed in reactive lymphoid nodules	R-S cells typically are CD15+, CD20–/+, CD30+, CD45–, CD79a–, PAX5+(dim)	R-S cells generally express *PAX5* and *MUM1*, variable expression of *BCL6*, and have IgR without functional Ig
Lymphocyte-rich HL	Few R-S cells with occasional "popcorn" appearance dispersed in lymphoid nodules	Same as above	Same as above
Mixed-cellularity HL	R-S cells dispersed among plasma cells, epithelioid histiocytes, eosinophils, and T cells	R-S cells typically are CD15+, CD20–/+, CD30+, CD45–, CD79a–	R-S cells generally express *PAX5* and *MUM1*, variable expression of *BCL6*, and have IgR without functional Ig
Lymphocyte-depleted HL	Prominent numbers of R-S cells with effacement of the nodal structure	Same as above	Same as above
T-CELL NEOPLASMS			
Immature T-Cell Neoplasms			
Lymphoblastic leukemia (Chap. 2)	Medium-to-large cells with finely stippled chromatin and scant cytoplasm	TdT+, CD2+/–, cytoplasmic CD3+, CD1a+/–, CD5+/–, CD7+, CD10–/+, CD4+/CD8+ or CD4–/CD8–, CD34+/–	Abnormalities in *TCR* loci at 14q11 (TCR-α), 7q34 (TCR-β), or 7p15 (TCR-γ), and/or t(1;14)(p32-34; q11) involving *TAL1*
Lymphoblastic lymphoma (Chap. 2)	Same as above	Same as above	Same as above
Mature T- and NK-Cell Neoplasms			
Leukemias			
T-cell prolymphocytic leukemia (Chap. 15)	Small-to-medium cells with cytoplasmic protrusions or blebs	TdT–, CD2+, CD3+, CD5+, CD7+, CD4+ and CD8– is more common than CD4– and CD8+, but can be CD4+ and CD8+	α/β TCR rearrangement, inv14(q11;q32)(~75%). Inv14 in ~80% of cases. Translocations frequently involve *TCL1A* and *TCL1B* genes. +8q seen in ~75% of cases. del 11q23 and abnormalities with chromosome 6 (33%) and 17P (26%) seen
T-cell large granular lymphocytic leukemia (Chap. 5)	Abundant cytoplasm and sparse azurophilic granules	CD2+, CD3+, CD4 –/+, CD5+, CD7+, CD8+/–, CD16+/–, CD56–, CD57+/–	α/β TCR rearrangement, γ/δ rearrangement can be seen. Subtypes with *STAT3* and *STAT5B* mutations. *STAT5B* mutations associated with aggressive disease
Lymphomas/Lymphoproliferative Disorders			
Extranodal T/NK-cell lymphoma, nasal type ("angiocentric lymphoma"; Chaps. 5 and 15)	Angiocentric and angiodestructive growth	CD2+, cytoplasmic CD3+, CD4–, CD5–/+, CD7+, CD8–, CD56+, EBV+	TCR rearrangements usually neg., EBV present by *in situ* hybridization

(*Continued*)

TABLE 1–1. Classification of Lymphoma and Lymphoid Leukemia by the World Health Organization (Continued)

Neoplasm	Morphology	Phenotype*	Genotype†
Cutaneous T-cell lymphoma (mycosis fungoides; Chap. 14)	Small-to-large cells with cerebriform nuclei	CD2+, CD3+, CD4+, CD5+, CD7+/–, CD8–, CD25–, CD26+	*α/β* TCR rearrangements, complex karyotype common. STAT3 activation
Sézary syndrome (Chap. 14)	Same as above	Same as above	Same as above
Angioimmunoblastic T-cell lymphoma[34]	Small-to-medium immunoblasts with clear-to-pale cytoplasm around follicles and high endothelial venules	CD3+/–, CD4+, CD10+, CXCL13+, PD-1+ (60–100%), EBV+	*α/β* TCR rearrangement (75–90%), IgR (25–30%), trisomy 3 or 5 noted
Peripheral T-cell lymphoma (not otherwise unspecified; Chap. 15)	Highly variable	CD2+, CD3+, CD5+, CD7–, CD4+/CD8– more often than CD4–/CD8+, which is more often than CD4+/CD8+	*α/β* TCR rearrangement
Subcutaneous panniculitis-like T-cell lymphoma[35]	Variable size atypical cells with hyperchromasia infiltrating fat lobule	CD2+, CD3+, CD4–, CD5+, CD7–, CD8+, and cytoxic molecules (perforin, granzyme B, and TIA1)	*α/β* TCR rearrangement
Enteropathy-associated T-cell lymphoma (EATL) type 1	Medium-to-large cells with prominent nucleoli, abundant pale cytoplasm invading mucosal membranes of the small intestine	CD3+, CD5–, CD7+, CD8+/–, CD4–, CD103+, TCR*β*+/–. CD30+ (most cases)	*TRB, TRG* clonally rearranged. >90% *HLADQA1*0501, DQB1*0201;* type 1: associated with celiac disease
Monomorphic epitheliotropic intestinal T-cell lymphoma	See above	See above	Not associated with celiac disease
Indolent T-cell lymphoproliferative disorder of the GI tract	See above; superficial monoclonal intestinal T-cell infiltrate	See above	See above
Hepatosplenic T-cell lymphoma[37–39]	Small-to-medium cells with condensed chromatin and round nuclei	CD2+, CD3+, CD4–, CD5+, CD7+/–, CD8+/–	*γ/δ* TCR rearrangement, rarely *α/β* TCR rearrangement, isochromosome 7q
Adult T-cell leukemia/lymphoma (Chap. 2)	Highly pleomorphic with multilobe nuclei	CD2+, CD3+, CD5+, CD7–, CD25+, CD4+/CD8– more often than CD4–/CD8+	*α/β* TCR rearrangement, integrated HTLV-1
Anaplastic large cell lymphoma ALK-positive	Large pleomorphic cells with "horseshoe"-shaped nuclei, prominent nucleoli, and abundant cytoplasm	TdT–, ALK1+, CD2+/–, CD3–/+, CD4–/+, CD5–/+, CD7+/–, CD8–/+, CD13–/+, CD25+/–, CD30+, CD33–/+, CD45+, HLA-DR+, TIA+/–	TCR rearrangement, t(2;5)(p23;q35) resulting in nucleophosmin—anaplastic lymphoma kinase fusion protein (*NPM/ALK*); other translocations involving 2p23 are also seen
Anaplastic large cell lymphoma ALK-negative	Similar morphologic spectrum to that seen in ALK+ ALCL. No small cell variant seen in ALK–	TdT–, ALK1–, CD2+/–, CD3–/+, CD4–/+, CD5–/+, CD7+/–, CD8–/+, CD13–/+, CD25+/–, CD30+, CD33–/+, CD45+, HLA-DR+, TIA+/–	TCR rearrangement, cytogenetic subsets with 6p25 rearrangements at *IRF4/DUSP22* locus
Primary cutaneous CD30+ anaplastic large cell lymphoma[43,44]	Anaplastic large cells as above in cutaneous nodules	TdT–, CD2–/+, CD3+/–, CD4+, CD5–/+, CD7+/–, CD25+/–, CD30+, CD45+	TCR rearrangement but without t(2;5)(p23;q35)
Breast implant–associated anaplastic large cell lymphoma	Noninvasive disease associated with excellent outcome. Neoplastic cells confined to seroma fluid proximal to implant	See above	See above
Primary cutaneous acral CD8+ T-cell lymphoma	Indolent disease originating in the ear	See above; CD8+	See above

(*Continued*)

TABLE 1–1. Classification of Lymphoma and Lymphoid Leukemia by the World Health Organization (Continued)

Neoplasm	Morphology	Phenotype*	Genotype†
Lymphomatoid papulosis	Three histologic subtypes (A, B, C). Type A: scattered clusters of large R-S–like cells admixed with histiocyte-rich infiltrate. Type B: rarely seen, epidermotropic infiltrate of small atypical cells with cerebriform nuclei (MF-like). Type C: monotonous large CD30+ T cells with few inflammatory cells	Type A and C have similar phenotype to C-ALCL. Type B phenotype CD3+, CD4+, CD8–, CD30–	TCR rearrangement in 60% of cases. No t(2;5)(p23;135)
Primary Cutaneous Peripheral T-Cell Lymphomas, Rare Subtypes:			
Primary cutaneous γ/δ T-cell lymphoma	Epidermotropic, dermal, and subcutaneous histologic patterns. Neoplastic cells medium to large with coarse chromatin, frequent apoptosis/necrosis	CD3+, CD2+, CD5–, CD7+/–, CD56+. Most cases CD4–, CD8–	*TCRG, TCRD* clonal rearrangement. EBV negative
Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma	Variable histology ranging from lichenoid epidermotropism to deeper nodular infiltrates. Tumor cells small to medium with pleomorphic or blastic nuclei	CD3+, CD8+, granzyme B+, perforin+, TIA1+, CD45RA+/–, CD45RO–, CD2+/–, CD4–, CD5–, CD7+/–	Clonal *TCR* rearrangement. EBV negative
Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder	Dense, diffuse, dermal infiltrates. Predominance of small/medium pleomorphic cells	CD3+, CD4+, CD8–, CD30–. No cytotoxic proteins expressed	Clonal *TCR* rearrangement. EBV negative
Systemic EBV+ T-cell lymphoma of childhood	Infiltrating T cells are EBV+ but lack cytologic atypia. Erythrophagocytosis and histiocytosis seen frequently	CD2+, CD3+, CD56–, CD8+, EBER+	Clonal TCR rearrangement. EBV+ with LMP1 expression
Hydroa vacciniforme-like lymphoproliferative disorder	Cutaneous presentation, small-to-medium cells without clear cytology atypical	CD3+, CD8+, CD56+	Clonal TCR rearrangement. EBV+ without LMP1
NATURAL KILLER (NK) CELL NEOPLASMS			
Large granular lymphocytic leukemia (Chap. 5)	Abundant cytoplasm and sparse azurophilic granules	TdT–, CD2+, CD3–, CD4–, CD5–/+, CD7+, CD8–/+, CD11b+, CD16+, CD56+, CD57+/–	No TCR rearrangement
Aggressive NK-cell leukemia[1]	Same as above	Same as above	No TCR rearrangement, EBV present
Extranodal NK-cell lymphoma, nasal-type ("angiocentric lymphoma")[1,45,46]	Angiocentric and angiodestructive growth	CD2+, cytoplasmic CD3ε +, CD4–, CD5–/+, CD7+, CD8–, CD56+	No TCR rearrangement, EBV present
Immunodeficiency-Associated Lymphoproliferative Disorders			
Lymphoproliferative disorders associated with primary immune disorders	Range of morphology from reactive hyperplasia, polymorphous lymphoid infiltrate, to high-grade lymphomas. Lymphoma and HL morphology is similar to that seen in immune-competent patients	Immunophenotype similar to that seen in immune-competent patients with corresponding malignancy	FAS mutation seen in *ALPS*. Mutations in *SAP/SLAM* in XLP. *ATM* mutations in AT

(*Continued*)

TABLE 1–1. Classification of Lymphoma and Lymphoid Leukemia by the World Health Organization (Continued)

Neoplasm	Morphology	Phenotype*	Genotype†
Lymphomas associated with HIV infection	Similar to above. Typical histologic features seen in Burkitt lymphoma, HL, DLBCL. Lymphomas seen more frequently in HIV setting include primary effusion, plasmablastic, lymphomas, multicentric Castleman disease	Similar to above	*MYC* and *BCL2* translocations seen in DLBCL
Posttransplant Lymphoproliferative Disorders (PTLDs)			
Early lesions: plasmacytic hyperplasia (PH) and infectious mononucleosis (IM)–like	PH: numerous plasma cells, lymphocytes, and immunoblasts. IM: numerous immunoblasts on a background of T cells	Similar to above	EBV+ in both IM and PH. Oligoclonal polyclonal IgH rearrangement. EBV+
Polymorphic PTLD	Effacement of tissue architecture with infiltrate showing full range of B-cell maturation	Similar to above with exception that R-S cells in HLs often express CD30+, CD20+ but frequently are CD15–	Clonal *IG* rearrangement. EBV+ by EBER ISH. Mutated IgH in 75% of cases
Monomorphic PTLD	Similar to DLBCL, Burkitt lymphoma, or plasmacytoma morphology	Similar to above	EBV+/–. Clonal B cell or T cells. Cytogenetics frequently with *TP53, RAS* mutations, *BCL6* translocations
Other iatrogenic immunodeficiency-associated lymphoproliferative disorders	Increased frequency of HL and lymphoproliferation with Hodgkin-like features. Histologic features can otherwise resemble the range of features seen in other immune deficiency–related LPDs	HL-like show CD20+, CD30+, CD15– or CD20–, CD30+, CD15+ staining. EBV is variably positive	Same as above

FISH, fluorescence *in situ* hybridization; IgR, immunoglobulin gene rearrangement; IgHV, immunoglobulin heavy chain variable region; MCD, multicentric Castleman disease; neg., negative; NF-κB, nuclear factor-κB; NK, natural killer; R-S, Reed-Sternberg; SMZL, splenic marginal zone lymphoma; STAT, signal transducer and activator of transcription; TCR, T-cell receptor. Also see "Acronyms and Abbreviations" at the beginning of this chapter.

*The immunophenotype revealed by immunohistochemistry and/or flow cytometry of surface antigens that typically are found for neoplastic cells of a given disorder are listed. If a CD antigen is indicated, then most of the neoplastic cells express that particular surface protein that is expressed by most tumor cells. CD antigens that have a minus (–) sign suffix are characteristically not expressed by the neoplastic cells of that disease entity. CD antigens that have a +/– sign suffix are not expressed by the neoplastic cells of all patients with that entity or are expressed at low or variable levels on the tumor cells. Antigens that have a –/+ sign suffix are expressed at very low levels or by the tumor cells of a minority of patients.

†The common genetic features associated with a given type of neoplasm are indicated. The numbers in parentheses provide the approximate proportion of cases that have the defined phenotype or genetic abnormality.

disease progression, survival, and/or response rates to standard therapies (Chap. 7).[19–25] An example of how gene-expression profiling has had a major impact on refining lymphoma diagnoses can be found with two newly defined working categories as "gray zone" lymphomas between Hodgkin lymphoma and primary mediastinal large B-cell lymphoma[12,26] and between Burkitt and DLBCL.[13,14] These new intermediate groups make clear distinctions between biologic and clinical features of conventional DLBCL and HL.

ASSOCIATED CLINICAL SYNDROMES

EARLY PRECURSOR LESIONS IN LYMPHOID NEOPLASMS

The 2008 WHO classification highlights several clinical, histologic, and immunophenotypic observations supporting the notion that lymphoid neoplasms arise from clonal expansion and, ultimately, malignant transformation of precursor lesions. Monoclonal B-cell lymphocytosis (MBL) can be found in first-degree relatives of patients with CLL and in 5 to 15 percent of adults older than 60 years of age who present with lymphocytosis.[27,28] The documented rate of progression to CLL of 1 to 2 percent/year and immunophenotypic evidence of evolving CLL-like clones with cytogenetic anomalies suggest that mantle cell lymphoma may represent a potential precursor to CLL.[29] Other potential precursor lesions for follicular lymphoma and mantle cell lymphoma are currently under investigation.[4]

ABNORMAL PRODUCTION OF IMMUNOGLOBULIN

When B lymphocytes undergo neoplastic transformation and clonal proliferation, they can secrete monoclonal proteins inappropriately

TABLE 1–2. Indolent Lymphomas

Disseminated lymphomas/leukemias
Chronic lymphocytic leukemia
Hairy cell leukemia
Lymphoplasmacytic lymphoma
Splenic marginal zone B-cell lymphoma (with or without villous lymphocytes)
Plasma cell myeloma/plasmacytoma
Nodal lymphomas
Follicular lymphoma
Nodal marginal zone B-cell lymphoma (with or without monocytoid B cells)
Small lymphocytic lymphoma
Extranodal lymphomas
Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type

(Chaps. 16 and 17). If the monoclonal protein is immunoglobulin (Ig) M, IgA, or a member of certain subclasses of IgG (e.g., IgG_3), its presence may increase the viscosity of the blood, impairing blood flow through the microcirculation (Chaps. 18 and 20). This process may be impeded further by the associated homotypic erythrocyte aggregation (pathologic rouleaux) that often occurs in blood with a high concentration of immunoglobulin protein. Collectively, this situation may result in the hyperviscosity syndrome, manifested clinically by headache, dizziness, diplopia, stupor, retinal venous engorgement, or frank coma (Chap. 20).[30,31]

Monoclonal immunoglobulin proteins also can interact with cell surfaces and impair granulocyte or platelet function or they can interact with coagulation proteins to impair their function in hemostasis. Excessive excretion of immunoglobulin light chains can lead to several types of renal tubular dysfunction and renal insufficiency (Chaps. 17 and 18). IgM deposited in glomerular tufts also can lead to renal disease (Chap. 20). Cryoglobulins (immunoglobulins that precipitate at temperatures below 37°C) can result in Raynaud syndrome, skin ulcerations, purpura, digital infarction, and gangrene. These manifestations result from immune complex formation, complement activation, and precipitation of cryoglobulins in cutaneous blood vessels. Excessive production of monoclonal immunoglobulin or immunoglobulin fragments in myeloma (Chap. 18) or in heavy-chain disease (Chap. 21) may lead to formation of amyloid, resulting in primary amyloidosis (Chap. 19).

Production of autoreactive antibodies spontaneously or in relationship to a B-lymphocyte neoplasm may lead to autoimmune hemolytic anemia, autoimmune thrombocytopenia, or, rarely, autoimmune neutropenia. Autoantibodies directed against tissues are implicated in the pathogenesis of diseases such as autoimmune thyroiditis, adrenalitis, encephalitis, and conditions with other organ involvement. Peripheral neuropathies as a result of demyelinization can occur in patients with monoclonal immunoglobulin (Chaps. 17, 18, and 19). The neural injury often is related to antibody activity against myelin-associated glycoproteins or absorption by nerve tissue.[31] Rarely, the polyneuropathy is part of the polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes (POEMS) syndrome (Chap. 18).[32]

TABLE 1–3. Aggressive Lymphomas

Immature B-cell neoplasms
B-cell lymphoblastic leukemia/lymphoma
Mature B-cell neoplasms
Burkitt lymphoma/Burkitt cell leukemia
Diffuse large B-cell lymphoma
Follicular lymphoma grade III
Mantle cell lymphoma
Immature T-cell neoplasms
T-cell lymphoblastic lymphoma/leukemia
Peripheral T- and natural killer (NK) cell neoplasms
T-cell prolymphocytic leukemia/lymphoma
Aggressive NK-cell leukemia/lymphoma
Adult T-cell lymphoma/leukemia (associated with HTLV-1 [human T-cell leukemia virus type 1])
Extranodal NK/T-cell lymphoma
Enteropathy-associated T-cell lymphoma
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Peripheral T-cell lymphomas, not otherwise specified
Angioimmunoblastic T-cell lymphoma
Anaplastic large cell lymphoma, primary, systemic
Immune deficiency-associated lymphoproliferative disorders

MARROW AND OTHER TISSUE INFILTRATION

Well-differentiated malignant B lymphocytes, such as those found in the early stages of CLL or Waldrenstrom macroglobulinemia, may infiltrate the marrow extensively, causing impairment of hemopoiesis. Eventually, however, massive infiltration of marrow by malignant B lymphocytes can suppress normal hemopoiesis, resulting in varying combinations of anemia, neutropenia, and/or thrombocytopenia (Chap. 3). Malignant B-lymphocyte proliferation or infiltration may result in any combination of splenomegaly and lymphadenopathy of either superficial or deep lymph nodes. DLBCLs tend to involve isolated lymph node groups (Chaps. 8 and 9), whereas low-grade lymphomas (follicular lymphoma) and lymphoproliferative disorders (CLL) tend to present with more diffuse lymphadenopathy and splenic involvement (Chaps. 3 to 5). Prolymphocytic leukemia and hairy cell leukemia, two uncommon B-lymphocyte malignancies, are prone to infiltrate the marrow and spleen, sometimes causing bone marrow fibrosis and massive splenomegaly (Chaps. 3 and 4).

LYMPHOKINE-INDUCED DISORDERS

In addition to the consequences of monoclonal immunoglobulin and tumor proliferation, some lymphoid malignancies may produce cytokines that contribute to the disease morbidity. Recent work has identified several immune activation syndromes, mediated in large part as a result of unchecked inflammatory cytokines (interleukin [IL] 1, IL-6) and defects in perforin/granzyme pathways, are associated with lymphomas and infection with oncogenic herpes viruses. Hemophagocytic lymphohistiocytosis and macrophage-activating syndrome are two distinct complications arising from dysregulated effector lymphocyte-tumor interaction at the immunologic synapse and can lead to life-threatening complications if not rapidly diagnosed and treated with

immunochemotherapy.[33] Patients with cutaneous T-cell lymphomas have elevated plasma levels of T-helper type 2 (Th2)-associated cytokines, which may account for the relatively high incidence of eosinophilia (Chap. 14) and eosinophilic pneumonia observed in patients with this disease.[34] In addition, the neoplastic plasma cells in myeloma may secrete various cytokines and osteoclast-activating factors that stimulate osteoclast proliferation and activity, leading to extensive osteolysis, severe bone pain, and pathologic fractures (Chap. 18).[35] Dysregulated extrarenal production of calcitriol, the active metabolite of vitamin D, appears to underlie the hypercalcemia associated with Hodgkin lymphoma and other lymphomas (Chaps. 6 and 8).[36]

SYSTEMIC SYMPTOMS

Large cell lymphoma, poorly differentiated lymphoma, and Hodgkin lymphoma frequently are associated with fever, night sweats, weight loss, and anorexia-cachexia (Chaps. 6, 8, and 9). Patients with lymphomas or Hodgkin lymphoma have an increased incidence of localized or disseminated herpes zoster,[37] and 10 percent or more of these patients may be affected at some time during the course of their illness. Pruritus is common in Hodgkin lymphoma,[38] and its severity parallels disease activity (Chap. 8). Systemic symptoms may be present in Hodgkin lymphoma in the absence of obvious, bulky lymph node or splenic tumors, whereas in well-differentiated small cell lymphomas, such as CLL or Waldenström macroglobulinemia, fever, night sweats, and significant weight loss are uncommon despite generalized lymphadenopathy and splenomegaly. Rather, fever in patients with CLL or macroglobulinemia usually is secondary to infectious disease (Chaps. 3 and 20).

METABOLIC SIGNS

Lymphoid malignancies are associated with several dramatic metabolic disturbances associated with cancers (Chap. 6). Some lymphomas and lymphocytic leukemias may have a high proliferative rate, a high death fraction of cells, and, therefore, an enormous turnover of nucleoproteins, sometimes causing hyperuricemia and extreme hyperuricosuria. Highly proliferative neoplasms like Burkitt lymphoma or lymphoblastic lymphoma are particularly likely to cause an extreme degree of hyperuricemia, sometimes leading to renal failure complicating initiation of cytotoxic therapy (Chaps. 2 and 13). Also, because these and other lymphocytic malignancies are sensitive to cytotoxic drugs and glucocorticoids, cytotoxic therapy may cause a *tumor lysis syndrome*, characterized by extreme hyperuricemia, hyperuricosuria, hyperkalemia, and/or hyperphosphatemia.[39,40] Precipitation of uric acid in the renal tubules and collecting system can lead to acute obstructive nephropathy and renal failure unless precautions are taken, such as pretreatment with allopurinol, hydration, and alkalization of the urine.[41] For extreme cases, or in cases in which allopurinol cannot be administered (e.g., drug allergy), the drug rasburicase may be required for treatment of hyperuricemia (Chap. 13).[42]

Hypercalcemia and calciuria are common complications of myeloma because of osteolysis. Hypercalcemia also may occur during the course of lymphomas (Chap. 5)or myeloma (Chap. 18). This situation may be caused by several mechanisms, including tumor cell production of IL-1, ectopic parathyroid hormone elaboration, excessive bone resorption, and impaired bone formation.[43]

EXTRANODAL INVOLVEMENT

T-cell leukemias and lymphomas, in addition to causing lymph node and spleen enlargement, may involve the skin, mediastinum, or CNS. As the name implies, cutaneous T-cell lymphomas have malignant cells that home to the skin,[44] sometimes producing a severe desquamating erythroderma, as in Sézary syndrome, or small (<2-cm) subcutaneous nodules, as in primary cutaneous CD30-positive T-cell lymphoproliferative disease or anaplastic large cell lymphoma,[45] or a variety of nodular infiltrative lesions, as in mycosis fungoides or adult T-cell leukemia/lymphoma associated with human T-cell leukemia virus type 1 (HTLV-1; Chap. 14).[46] T-cell acute lymphoblastic leukemia and lymphoblastic lymphoma frequently cause mediastinal enlargement (Chap. 2). These diseases frequently involve testicles and the leptomeninges and other structures that are transverse to the subarachnoid space, such as the cranial and peripheral nerves.

B-cell lymphomas frequently may involve the salivary glands, endocrine glands, joints, heart, lung, kidney, bowel, bone, or, less frequently, other extranodal sites, such as the CNS and testes (Chap. 6). These diseases may begin as an extranodal tumor, or the tumor may develop during the course of the disease. Aggressive lymphomas, such as Burkitt lymphoma,[47] primary testicular lymphoma,[47,48] and double-hit DLBCLs (Chap. 9),[49] frequently involve the CNS and require upfront assessment during diagnosis and treatment with either intrathecal chemotherapy or regimens capable of crossing the blood–brain barrier that contain high-dose methotrexate. Marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT) type frequently involves the stomach and salivary glands, although the disease may be encountered in any extranodal site distinguished by the presence of a columnar or cuboidal epithelium.

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CHAPTER 2
ACUTE LYMPHOBLASTIC LEUKEMIA

Richard A. Larson

SUMMARY

Acute lymphoblastic leukemia (ALL) is a malignant disorder that originates in a single B- or T-lymphocyte progenitor. Proliferation and accumulation of clonal blast cells in the marrow result in suppression of hematopoiesis and, thereafter, anemia, thrombocytopenia, and neutropenia. Lymphoblasts can accumulate in various extramedullary sites, especially the meninges, gonads, thymus, liver, spleen, and lymph nodes. The disease is most common in children but can be seen in individuals of any age. ALL has many subtypes and can be classified by immunologic, cytogenetic, and molecular genetic methods. These methods can identify clinically important, biologic subtypes, requiring treatment approaches that differ in their use of specific drugs or drug combinations, dosages of drug, or duration of treatment required to achieve optimal results. For example, cases of childhood ALL having a hyperdiploid karyotype respond well to extended treatment with methotrexate and mercaptopurine, whereas adults whose leukemic cells contain the Philadelphia chromosome and *BCR-ABL1* fusion benefit from intensive treatment that includes a tyrosine kinase inhibitor and transplantation of allogeneic hematopoietic stem cells. The relative lack of therapeutic success in adult ALL is partly related to a high frequency of cases having unfavorable genetic abnormalities and partly related to poor tolerance for intensive treatment. Nearly 90 percent of children and 40 percent of adults can expect long-term, leukemia-free survival—and probable cure—with contemporary treatment. Novel immunotherapeutic approaches are under development. Currently, emphasis is placed not only on improving the cure rate but also on improving quality of life by preventing acute and late treatment-related complications, such as second malignancies, cardiotoxicity, and endocrinopathy.

DEFINITION AND HISTORY

Acute lymphoblastic leukemia (ALL) is a neoplastic disease that results from multistep somatic mutations in a single lymphoid progenitor cell at one of several discrete stages of development. The immunophenotype of leukemic cells at diagnosis reflects the level of differentiation achieved by the dominant clone. The clonal origin of ALL has been established by cytogenetic analysis, by analysis of restriction fragments in female patients who are heterozygous for polymorphic X chromosome-linked genes, and by analysis of rearrangements of T-cell receptor or immunoglobulin genes. Leukemic cells divide more slowly and require more time to synthesize DNA than do normal hematopoietic counterparts. However, leukemic cells accumulate relentlessly because of their altered response to growth and death signals.[1,2] They compete successfully with normal hematopoietic cells, resulting in anemia, thrombocytopenia, and neutropenia. At diagnosis, leukemic cells not only have replaced normal marrow cells but also have disseminated to various extramedullary sites.

Velpeau[3] is generally credited with the earliest report, in 1827, of leukemia. Virchow,[4] Bennett,[5] and Craigie[6] recognized the condition as a distinct entity by 1845. In 1847, Virchow coined the terms *weisses blut* and, later, *leucaemie*, applying them to two distinct types of the disease—splenic and lymphatic—that could be distinguished from each other based on splenomegaly and enlarged lymph nodes and on the morphologic similarities of the leukemic cells to those normally found in these organs.[7] Ehrlich's introduction of staining methods in 1891 allowed further distinction of leukemia subtypes.[8] By 1913, leukemia could be classified as acute or chronic and as lymphatic or myelogenous.[9] The greater prevalence of ALL in children, especially those ages 1 to 5 years, was recognized in 1917.[10]

Shortly after leukemia was recognized as a discrete disease entity, physicians began using chemicals as palliative therapy. The first advance was the use of a four-amino analogue of folic acid (aminopterin), prompted by Farber's observation that folic acid appeared to accelerate the proliferation of leukemic cells. Strikingly, for the first time, complete clinical and hematologic remissions that lasted for several months were seen in children.[11] A year after the report of aminopterin-induced clinical remissions, a newly isolated adrenocorticotrophic hormone was reported to induce prompt, though brief, remissions in patients with leukemia.[12] Almost concurrently, Elion and colleagues synthesized antimetabolites that interfere with synthesis of purines and pyrimidines.[13] Their findings led to the introduction of mercaptopurine, 6-thioguanine, and allopurinol into clinical use. From 1950 to 1960, many new antileukemic agents were introduced, and occasional cures were seen. Pinkel and colleagues at St. Jude Children's Research Hospital, in 1962, devised a "total therapy" approach, consisting of four treatment phases: remission induction; intensification or consolidation; therapy for subclinical CNS leukemia (or preventive meningeal treatment); and prolonged continuation therapy.[14] By the early 1970s, as many as 50 percent of children achieved long-term event-free survival (EFS) using this innovative strategy. During the same period, a better understanding of the genetics of human histocompatibility and wider use of human leukocyte antigen (HLA) typing culminated in the successful use of hematopoietic stem cell transplantation for treatment of patients in whom leukemia relapsed. In the early 1980s, Riehm and coworkers introduced a so-called reinduction or delayed intensification treatment during early continuation therapy, consisting mainly of repetition of the initial remission induction and early intensification phases, and further improved the EFS to approximately 70 percent.[15] Parallel to advances in treatment has been the improved understanding of the biology of ALL. The recognition of ALL as a heterogeneous group of diseases—clinically, immunologically, and genetically[16]—set the stage for risk-directed therapy.[16a]

Treatment of ALL has progressed incrementally, beginning with the development of effective therapy for CNS disease, followed by intensification of early treatment, especially for patients at high risk of relapse. The current cure rates of nearly 90 percent for children (Fig. 2–1) and 40 percent for adults attest to the steady progress made in treating this disease.[17,18] Rapid evolution and convergence of multiple genome-wide platforms to identify the total complement of genetic and epigenetic alterations almost certainly will lead to the identification of

Acronyms and Abbreviations: ALL, acute lymphoblastic leukemia; ARID5B, AT-rich interactive domain 5b; *ATM*, ataxia-telangiectasia mutated gene; CD, cluster of differentiation; CNAs, copy number abnormalities; CSF, cerebrospinal fluid; EFS, event-free survival; FISH, fluorescence *in situ* hybridization; HLA, human leukocyte antigen; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; RT-PCR, reverse transcriptase polymerase chain reaction; SEER, Surveillance, Epidemiology, and End Results; SNP, single nucleotide polymorphism.

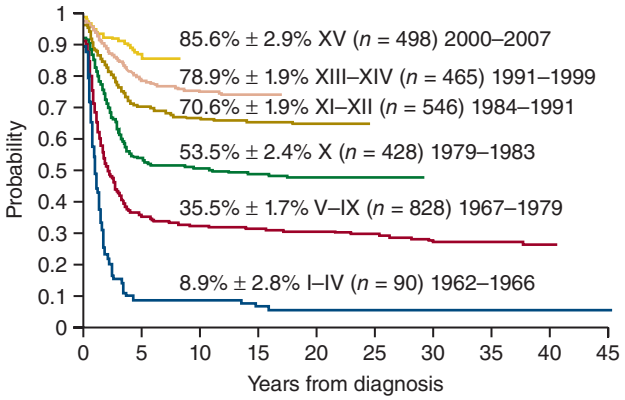

Figure 2–1. Kaplan-Meier analysis of event-free survival for 2855 children with ALL treated in 15 consecutive total-therapy studies at St. Jude Children's Research Hospital. Early intensification of systemic and intrathecal chemotherapy with a risk assignment based on sequential measurements of minimal residual disease in the 2000s has boosted the event-free survival estimate to 85.6 percent ± 2.9 percent (SE). *(Data from CH Pui and are unpublished.)*

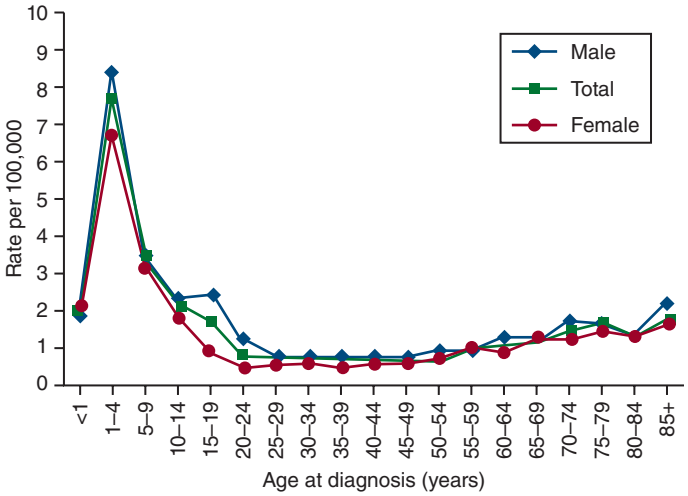

Figure 2–2. Age-specific incidence rates for acute lymphoblastic leukemia by sex. *(Data from SEER Cancer Statistics Review, 1975–2010, National Cancer Institute, Bethesda, MD. http://seer.cancer.gov/csr/1975_2010. Accessed July 4, 2014.)*

new targets for specific treatment.[19,20] A clear advance was the development of imatinib mesylate and dasatinib, which target leukemias with the *BCR-ABL1* fusion.[21]

ETIOLOGY AND PATHOGENESIS

Initiation and progression of ALL are driven by successive mutations that alter cellular functions, including an enhanced ability of self-renewal, a subversion of control of normal proliferation, a block in differentiation, and an increased resistance to death signals (apoptosis).[1,2] Familial disorders of DNA repair may play a role. Environmental agents, such as ionizing radiation and chemical mutagens, have been implicated in the induction of ALL in some patients. However, in most cases, no etiologic factors are discernible. In the favored theory, leukemogenesis reflects the interaction between host pharmacogenetics (susceptibility) and environmental factors, a model that requires confirmation in well-designed population and molecular epidemiologic studies.

INCIDENCE

The American Cancer Society estimated that in the United States there would be approximately 6020 new cases of ALL in 2014 (3140 in males and 2880 in females) and approximately 1440 deaths from ALL (810 in males and 630 in females).[22] Most cases of ALL occur in children, but most deaths from ALL (approximately four of five) occur in adults.

The age-adjusted incidence rate of ALL was 1.6 per 100,000 males and 1.2 for females per year in the United States, based on cases diagnosed in 1975 to 2010 from 17 Surveillance, Epidemiology, and End Results (SEER) geographic areas.[23] The risk for developing ALL is highest in children younger than 5 years of age. The risk then declines slowly until the mid-20s and begins to rise again slowly after age 50. The incidence is 7.9 per 100,000 children 1 to 4 years old and 1.2 for those older than age 60 years. Only 20 percent of adult acute leukemias are ALL, but about one-third of ALL cases are in adults. The average person's lifetime risk of developing ALL is less than one in 750. The risk is slightly higher in males than in females and higher in whites than in African Americans (Fig. 2–2).[23] The median age at diagnosis for ALL is 13 years, and approximately 61 percent of individuals are diagnosed before the age of 20 years; however, because of the bimodal peak in incidence, the age of 13 years is mathematically correct but medically nearly useless. ALL is the most common malignancy diagnosed in patients younger than age 15 years, accounting for 23 percent of all cancers and 76 percent of all leukemias in this age group.

The sharp incidence peak of ALL during early childhood has been observed only since the 1930s in the United Kingdom and the United States.[24] In the United States, the peak first appeared in children of European descent and subsequently was seen in children of African descent in the 1960s. The age peak is absent in many developing or underdeveloped countries, suggesting a leukemogenic contribution from factors associated with industrialization. Except for a slight predominance for females in infancy, ALL affects males of European descent more often than females in all age groups (Fig. 2–2). The frequency distribution is similar among those of African descent. In most age groups, the incidence of ALL is higher in those of European descent than in those of African descent, especially among children ages 2 to 3 years.

The incidence of ALL differs substantially in different geographic areas. Rates are higher among populations in northern and western Europe, North America, and Oceania, with lower rates in Asian and African populations.[25] In Europe, the highest rates of ALL among males are found in Spain and the highest rates among females in Denmark. In the United States, the highest rates for both sexes are among Latinos in Los Angeles.

RISK FACTORS

Genetic Syndromes

The precise pathogenetic events leading to the development of ALL are unknown. Only a minority (5 percent) of cases are associated with inherited, predisposing genetic syndromes. Children with Down syndrome have a 10 to 30 times greater risk of leukemia; acute megakaryoblastic leukemia predominates in those patients younger than age 3 years, and ALL is predominant in older age groups. ALL in patients with Down syndrome is a heterogeneous disorder, comprising subtypes with the same well-recognized genetic abnormalities found in the general population, such as hyperdiploidy greater than 50 and t(12;21)[*ETV6-RUNX1*], plus those more commonly associated with Down syndrome, such as +X, del(9), and *CEBPD* rearrangement.[26,27] Studies show that *P2RY8-CRLF2* fusion and activating *JAK* mutations together contribute

to leukemogenesis in approximately half of the cases of Down syndrome patients with ALL.[28,29] Almost all ALL patients with Down syndrome have a deletion of IKZF1.[30] Autosomal recessive genetic diseases associated with increased chromosomal fragility and a predisposition to ALL include ataxia-telangiectasia, Nijmegen breakage syndrome, and Bloom syndrome.[31] Patients with ataxia-telangiectasia have a 70 times greater risk of leukemia and a 250 times greater risk of lymphoma, particularly of the T-cell phenotype.[32] The causative gene, termed *ATM* (ataxia-telangiectasia mutated), encodes a protein involved in DNA repair, regulation of cell proliferation, and apoptosis. Laboratory studies supporting the diagnosis of ataxia-telangiectasia include an elevated serum concentration of α-fetoprotein, presence of characteristic chromosomal aberrations, absent or reduced intranuclear serine protein kinase ATM, and increased *in vitro* radiosensitivity. A high prevalence of germline truncating and missense *ATM* gene alterations in children with sporadic T-cell ALL suggests a pathogenetic role of *ATM* in lymphoid malignancies. Although impaired immune surveillance contributes to the increased risk of Epstein-Barr-virus-related malignancies in patients with acquired immunodeficiencies, no compelling evidence indicates defective immunity contributes to the predisposition to ALL in patients with ataxia-telangiectasia or other congenital immunodeficiency syndromes. Genome-wide association studies have identified common allelic variants in four genes (*IKZF1*, *ARID5B*, *CEBPE*, and *CDKN2a*) that are consistently associated with childhood ALL.[33–35] These genes are key regulators of blood cell development, and acquired mutations of each are also detected in ALL cases. Thus, the risk of childhood ALL may be influenced by coinheritance of multiple low-risk variants. Inherited allelic variation may also affect response to treatment.[36]

Environmental Factors

In utero (but not postnatal) exposure to diagnostic x-rays confers a slightly increased risk of ALL, which correlates positively with the number of exposures.[37] The evidence is weak for an association between the development of ALL and nuclear fallout; exposure to occupational, natural terrestrial, or cosmic ionizing radiation; or paternal radiation exposure prior to conception. There has been concern that exposure to low-energy electromagnetic fields produced by a residential power supply may be associated with the development of childhood ALL. Case-control studies suggested a slightly increased risk of leukemia at very high levels of exposure; assuming the association is real, only approximately 1 percent of leukemias could be attributed to the exposure.[38,39] Pesticide exposure (occupational or home use) and parental cigarette smoking before or during pregnancy, administration of vitamin K to neonates, maternal alcohol consumption during pregnancy, and increased consumption of dietary nitrites have each been suggested causes. However, each of these associations is controversial, and most have been refuted after careful, controlled investigation. High birth weight is associated with an increased risk of leukemia before the age of 5 years with fair consistency,[40] and the birth weight is likely a marker for an endogenous factor, such as insulin-like growth factor.

Host Pharmacogenetics

Subtle genetic polymorphisms of xenobiotic-metabolizing enzymes, DNA repair pathways, and cell-cycle checkpoint functions might interact with environmental, dietary, maternal, and other external factors to affect the development of ALL.[2,41] Although the number of investigations and sample sizes are limited, data exist to support a causal role for polymorphisms in genes encoding detoxifying enzymes (e.g., glutathione *S*-transferase, nicotinamide adenine dinucleotide phosphate [NAD(P)H]: quinone oxidoreductase), folate-metabolizing enzymes (serine hydroxymethyltransferase and thymidylate synthase), cytochrome P450, methylenetetrahydrofolate reductase, and cell-cycle inhibitors in the development of adult and childhood ALL.[42,43] However, all these associations must be confirmed by larger studies with careful attention to ethnic and geographic diversity in the frequency of polymorphisms. Using genome-wide analysis, germline single nucleotide polymorphisms (SNPs) of AT-rich interactive domain 5b *(ARID5B)* gene have been associated with childhood hyperdiploid B-cell precursor ALL,[44] a clear example of host genetic variations affecting the susceptibility to the development of childhood ALL.

Development of Acute Lymphoblastic Leukemia In Utero

Retrospective identification of leukemia-specific fusion genes (e.g., *KMT2A/AFF1* [also known as *MLL-AF4*] and *ETV6-RUNX1* [also known as *TEL-AML1*]), hyperdiploidy, or clonotypic rearrangements of immunoglobulin or T-cell receptor loci in archived neonatal blood spots (Guthrie cards) and development of concordant leukemia in identical twins clearly indicate some leukemias have a prenatal origin.[45,46] In identical twins with the t(4;11)/*KMT2A/AFF1*, the concordance rate is nearly 100 percent, and the latency in the time of occurrence in the two twins is short (a few weeks to a few months). These findings suggest this fusion gene alone either is leukemogenic or requires only a small number of cooperative mutations to cause leukemia. By contrast, the lower concordance rate in twins with the *ETV6-RUNX1* fusion or T-cell phenotype and the longer postnatal latency period suggest additional postnatal events are required for leukemic transformation in these subtypes.[45] This theory is supported by the identification of rare cells expressing *ETV6-RUNX1* fusion transcripts in approximately 1 percent of cord blood samples from newborns, a frequency 100 times higher than the incidence of ALL defined by this fusion transcript.[45] The presence of a preleukemic clone with the *ETV6-RUNX1* has been established.[47] Hyperdiploid ALL, another common subtype of childhood ALL, also appears to arise before birth but requires postnatal events for full malignant transformation.[46] The observations of a peak age of development of childhood ALL of 2 to 5 years, an association of industrialization and modern or affluent societies with increased prevalence of ALL, and the occasional clustering of childhood leukemia cases have fueled two parallel infection-based hypotheses to account for postnatal events. The "delayed infection" hypothesis suggests that some susceptible individuals with a prenatally acquired preleukemic clone had low or no exposure to common infections early in life because they lived in an affluent hygienic environments.[45] Such infectious insulation predisposes the immune system of these individuals to aberrant or pathologic responses after subsequent or delayed exposure to common infections at an age commensurate with increased lymphoid cell proliferation. The "population-mixing" hypothesis predicts that clusters of childhood ALL result from exposure of susceptible (nonimmune) individuals to common but fairly nonpathologic infections after population mixing with carriers.[48] However, clearly not all childhood cases develop *in utero*. For example, t(1;19)/*TCF3-PBX1* (also known as *E2A-PBX1*) ALL appears to have a postnatal origin in most cases.[49] Cases of adult ALL most certainly arise over a protracted time.

ACQUIRED GENETIC CHANGES

Acquired genetic abnormalities are a hallmark of ALL; 80 percent of all cases have recurring cytogenetic or molecular lesions with prognostic and therapeutic relevance (Table 2–1).[2,19,41] Chromosomal changes include abnormalities in the number (ploidy) and structure of chromosomes.[50–52] The latter comprise translocations (the most frequent abnormality), inversions, deletions, point mutations, and amplifications. Although the frequency of particular genetic subtypes differs between childhood and adult cases, the general mechanisms underlying the induction are similar. Mechanisms include aberrant expression of oncoproteins, loss of

TABLE 2–1. Frequencies of Common Genetic Aberrations in Childhood and Adult Acute Lymphoblastic Leukemia

Abnormality	Children (%)	Adults (%)
Hyperdiploidy (>50 chromosomes)	23–29	6–7
Hypodiploidy (<45 chromosomes)	1	2
t(1;19)(q23;p13.3) *[TCF3-PBX1]*	4 in white, 12 in black	2–3
t(9;22)(q34;q11.2) *[BCR-ABL1]*	2–3	25–30
t(4;11)(q21;q23) *[MLL-AF4]*	2	3–7
t(8;14)(q23;q32.3)	2	4
t(12;21)(p13;q22) *[ETV6-RUNX1]*	20–25	0–3
NOTCH1 mutations*	7	15
HOX11L2 overexpression*	20	13
LYL1 overexpression*	9	15
TAL1 overexpression*	15	3
HOX11 overexpression*	7	30
MLL-ENL fusion	2	3
Abnormal 9p	7–11	6–30
Abnormal 12p	7–9	4–6
del(7p)/del(7q)/ monosomy 7	4	6–11
+8	2	10–12
Intrachromosomal amplification of chromosome 21 (iAMP21)	2	?
Ph-like genotype	10	27

*Abnormalities found in T-cell acute lymphoblastic leukemia (ALL).

tumor-suppressor genes, and chromosomal translocations that generate fusion genes encoding transcription factors or active kinases.

Primary genetic rearrangement by itself is insufficient to induce overt leukemia. Cooperative mutations are necessary for leukemic transformation and include genetic and epigenetic changes in key growth regulatory pathways.[19,20] The candidate gene approach has identified deletion of the *CDKN2A/CDKN2B* tumor-suppressor locus[53] and mutations of *NOTCH1* in T-cell ALL.[54] Current searches applying genome-wide microarray and high-throughput sequencing methodologies have identified a high frequency of common genetic alterations in both B-cell precursor ALL and T-cell ALL. Using SNP microarray, a mean of 6.46 DNA copy number abnormalities (CNAs) per case was identified, suggesting that gross genomic instability is not a feature for most ALL cases.[55] There was a wide variation in the number of CNAs across leukemic subtypes. Interestingly, infant ALL cases with *MLL* rearrangement had less than one CNA per case, suggesting that few additional genetic lesions are required for leukemogenesis in these cases. By contrast, *ETV6-RUNX1* and *BCR-ABL1* cases had more than six CNAs per case, with some having more than 20 lesions, a finding consistent with the concept that, although the initiating events may occur early in childhood, additional lesions are required for subsequent development of ALL. More than 40 percent of B-cell precursor ALL cases had mutations in genes encoding regulators of normal lymphoid development.[55] The most frequent target was the lymphoid transcription factor *PAX5* (mutated in approximately 32 percent of cases), which encodes a paired-domain protein required for the pro–B-cell to pre–B-cell transition and B-lineage fidelity. The second most frequently involved gene was *IKZF1* (mutated in almost 28 percent of the cases), encoding the IKAROS zinc finger DNA-binding protein that is required for the earliest lymphoid differentiation. *IKZF1* was deleted in the vast majority of cases of *BCR-ABL1* ALL cases as well as chronic myeloid leukemia in lymphoid blast crisis (but not chronic phase).[56] Approximately half of *BCR-ABL1* ALL cases also had deletions of *CDKN2A/B* and *PAX5*. This finding further supports the concept that multiple signaling pathways need to be disrupted to induce leukemia. A subgroup of ALL with very poor outcome was strongly associated with the presence of *IKZF1* deletions.[57,58] Together, these findings suggest that *IKZF1* directly contributes to treatment resistance in ALL.

BCR-ABL1–like B-cell ALL lacks the *BCR-ABL1* fusion or t(9;22) by cytogenetic, fluorescence *in situ* hybridization (FISH), or molecular analyses, but it shares the same gene-expression profile with typical *BCR-ABL1*–positive ALL.[59,59a–59c] In half of these cases, the *CRLF2* gene is involved in a cryptic translocation with the *IGH* gene or is fused to the *P2RY8* gene; both rearrangements lead to overexpression of CRLF2.[29,60] Mutations in *JAK2* or *JAK1* are detected in 30 to 40 percent of these cases, and many of the remaining have activating mutations in cytokine receptor and kinase signaling pathways.[30] Microarrays and genomic DNA sequencing identified monoallelic deletion of the *PAX5* gene at chromosome band 9p13.2 in 28 percent of ALL patients with cryptic or larger deletions on 9p.[55]

Gene-expression profiling with DNA microarrays allows nearly all T-cell cases to be grouped according to multistep oncogenic pathways.[61] Gene-expression studies also show that overexpression of FLT3, a receptor tyrosine kinase important for development of hematopoietic stem cells, is a secondary event in almost all cases with either *MLL* rearrangements or hyperdiploidy.[62] The finding has provided an impetus for clinical testing of FLT3 inhibitors in ALL. Other genome-wide interrogations of both leukemia cells and germline tissues have identified other genetic variations with prognostic or therapeutic relevance and may lead to the development of specific treatment.[17,36]

Epigenetic changes, including hypermethylation and silencing of tumor-suppressor genes and hypomethylation of oncogenes and abnormalities in posttranscriptional control mechanisms, such as those involving microRNA, are common findings in cancer. These changes are reversible and do not alter the DNA sequence, yet they can alter gene expression in subtle ways that encourage malignant transformation and progression. The analysis of epigenetic alterations has begun to apply to the development of new biomarkers for risk assignment or disease monitoring and to the design of alternative treatment in ALL.[63] Evidence indicates that the methylation of multiple genes in ALL is associated with a worse outcome. Surprisingly, methylation of genes was as prominent in childhood as in adult ALL. The differences in the response of children and adults appear not to be related to quantitative methylation but to the specific genes and the specific pathways deactivated. Preliminary studies of hypomethylating agents (e.g., azacitidine and decitabine) are being tested in patients refractory or resistant to current drug programs.[64]

CLINICAL FEATURES

SIGNS AND SYMPTOMS

The clinical presentation of ALL is highly variable. Symptoms may appear insidiously or acutely. The presenting features generally reflect the degree of marrow failure and the extent of extramedullary spread (Table 2–2).[18,65–67] Approximately half of patients present with fever, which can be caused by either neutropenia-induced infection or leukemia-released cytokines (e.g., interleukin-1, interleukin-6, and tumor necrosis factor) released from leukemia cells. In these patients, fever resolves within 72 hours after the start of antileukemia therapy.

Fatigue and lethargy are common manifestations of anemia in patients with ALL. In older patients, anemia-related dyspnea and lightheadedness may be the dominant presenting features. More than 25 percent of patients, especially young children, may have a limp from bone pain or arthralgia; an unwillingness to walk because of leukemic infiltration of the periosteum, bone, or joint; or because of expansion of the marrow cavity by leukemia cells. Children with prominent bone pain often have nearly normal blood counts, which can contribute to delayed diagnosis. In a small proportion of patients, marrow necrosis can result in severe bone pain and tenderness, fever, and a very high level of serum lactate dehydrogenase.[68,69] Arthralgia and bone pain are less severe in adults. Less common signs and symptoms include headache, vomiting, altered mental function, oliguria, and anuria. Occasionally, patients present with a life-threatening infection or bleeding (e.g., intracranial hematoma). Intracranial hemorrhage occurs mainly in patients with an initial leukocyte count greater than 400×10^9/L.[70] Very rarely, ALL produces no signs or symptoms and is detected during routine examination.

TABLE 2–2. Presenting Clinical Features in Children and Adults with Acute Lymphoblastic Leukemia

Feature	Children (%)	Adult (%)
Age (years)		
<1	2	—
1–9	72–78	—
10–19	20–26	—
20–39	—	40
40–59	—	40
≥60	—	20
Male	56–57	62
Symptoms		
Fever	57	33–56
Fatigue	50	Common
Bleeding	43	33
Bone or joint pain	25	25
Lymphadenopathy		
None	30	51
Marked (>3 cm)	15	11
Hepatomegaly		
None	34	65
Marked (below umbilicus)	17	Rare
Splenomegaly		
None	41	56
Marked (below umbilicus)	17	Uncommon
Mediastinal mass	8–10	15
CNS leukemia	3	8
Testicular leukemia	1	0.3

Data from Pui CH: *Acute lymphoblastic leukemia*, in *Childhood Leukemias*, 2nd ed, edited by CH Pui, p 439. Cambridge University Press, New York, 2006; and Larson RA, Dodge RK, Burns CP, et al: A five-drug remission induction regimen with intensive consolidation for adults with acute lymphoblastic leukemia: Cancer and Leukemia Group B study 8811. *Blood* 85:2025, 1995.

PHYSICAL FINDINGS

Among frequent findings are pallor, petechiae, and ecchymosis in the skin and mucous membranes and bone tenderness as a result of leukemic infiltration or hemorrhage that stretches the periosteum. Liver, spleen, and lymph nodes are the most common sites of extramedullary involvement, and the degree of organomegaly is more pronounced in children than in adults. An anterior mediastinal (thymic) mass is present in 8 to 10 percent of childhood cases and in 15 percent of adult cases (Fig. 2–3). A bulky, anterior mediastinal mass can compress the great vessels and trachea and possibly lead to superior vena cava syndrome. Patients with this syndrome present with cough, dyspnea, orthopnea, stridor, cyanosis, dysphagia, facial edema, increased intracranial pressure, and sometimes syncope. Painless enlargement of the scrotum can be a sign of testicular leukemia cell infiltration or hydrocele, the latter resulting from lymphatic obstruction. Both conditions can be readily diagnosed by ultrasonography. Overt testicular disease is relatively rare, is generally seen in infants or adolescents with T-cell leukemia and/or hyperleukocytosis, and does not require radiation therapy.[71] Other uncommon presenting features include ocular involvement (leukemic infiltration of the orbit, optic nerve, retina, iris, cornea, or conjunctiva), subcutaneous nodules (leukemia cutis), enlarged salivary

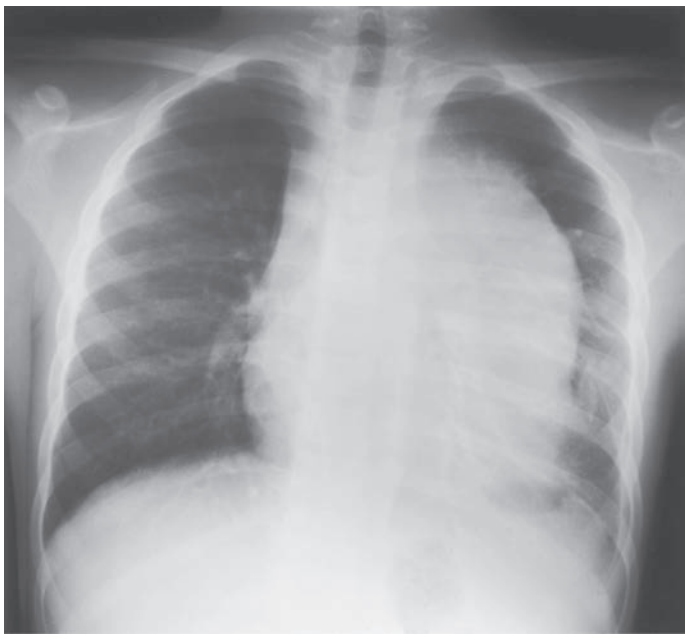

Figure 2–3. Chest radiograph of a 12-year-old black male with T-cell acute lymphoblastic leukemia (ALL) and an anterior mediastinal mass.