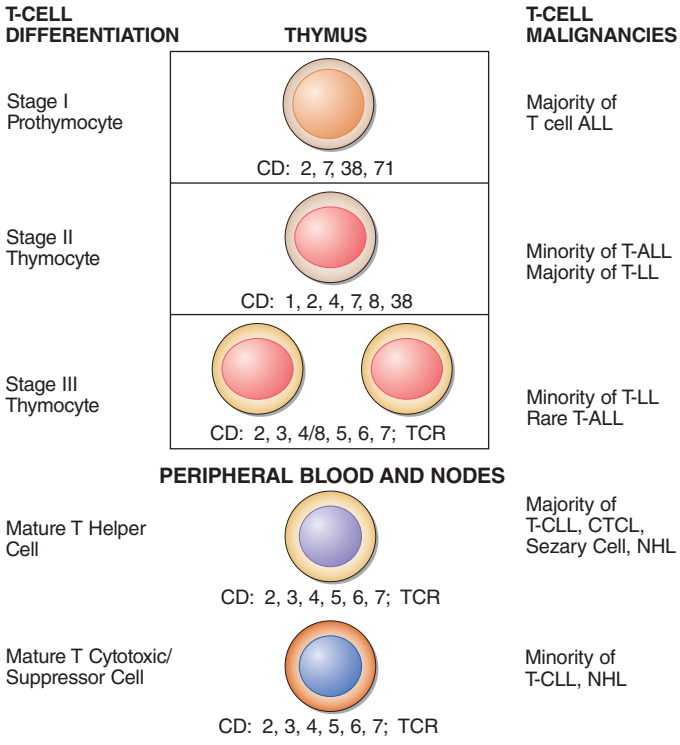

FIGURE 134-3 Pathway of normal T-cell differentiation and relationship to T-cell lymphomas. CD1, CD2, CD3, CD4, CD5, CD6, CD7, CD8, CD38, and CD71 are cell markers used to distinguish stages of development. T-cell antigen receptors (TCR) rearrange in the thymus, and mature T cells emigrate to nodes and peripheral blood. ALL, acute lymphoid leukemia; T-ALL, T-cell ALL; T-LL, T-cell lymphoblastic lymphoma; T-CLL, T-cell chronic lymphoid leukemia; CTCL, cutaneous T-cell lymphoma; NHL, non-Hodgkin's lymphoma.

bcl-2 gene found on chromosome 18. Some other patients without the translocation also overexpress the BCL-2 protein. This protein is involved in suppressing apoptosis—i.e., the mechanism of cell death most often induced by cytotoxic chemotherapeutic agents. A higher relapse rate has been observed in patients whose tumors overexpress the BCL-2 protein, but not in those patients whose lymphoma cells show only the translocation. Thus, particular genetic mechanisms have clinical ramifications.

Table 134-6 presents the most common translocations and associated oncogenes for various subtypes of lymphoid malignancies. In some cases, such as the association of the t(14;18) in follicular lymphoma, the t(2;5) in anaplastic large T/null cell lymphoma, the t(8;14) in Burkitt's lymphoma, and the t(11;14) in mantle cell lymphoma, the great majority of tumors in patients with these diagnoses display these abnormalities. In other types of lymphoma where a minority of the patients have tumors expressing specific genetic abnormalities, the defects may have prognostic significance. No specific genetic abnormalities have been identified in Hodgkin's lymphoma other than aneuploidy.

In typical B-cell CLL, trisomy 12 conveys a poorer prognosis. In ALL in both adults and children, genetic abnormalities have important prognostic significance. Patients whose tumor cells display the t(9;22) and translocations involving the *MLL* gene on chromosome 11q23 have a much poorer outlook than patients who do not have these translocations. Other genetic abnormalities that occur frequently in adults with ALL include the t(4;11) and the t(8;14). The t(4;11) is associated with younger age, female predominance, high white cell counts, and L1 morphology. The t(8;14) is associated with older age, male predominance, frequent CNS involvement, and L3 morphology. Both are associated with a poor prognosis. In childhood ALL, hyperdiploidy has been shown to have a favorable prognosis.

Gene profiling using array technology allows the simultaneous assessment of the expression of thousands of genes. This technology provides the possibility to identify new genes with pathologic importance in lymphomas, the identification of patterns of gene expression with diagnostic and/or prognostic significance, and the identification of new therapeutic targets. Recognition of patterns of gene expression is complicated and requires sophisticated mathematical techniques. Early successes using this technology in lymphoma include the identification of previously unrecognized subtypes of diffuse large B-cell lymphoma whose gene expression patterns resemble either those of follicular center B cells or activated peripheral blood B cells. Patients whose lymphomas have a germinal center B-cell pattern of gene expression have a considerably better prognosis than those whose lymphomas have a pattern resembling activated peripheral blood B cells. This improved prognosis is independent of other known prognostic factors. Similar information is being generated in follicular lymphoma and mantle cell lymphoma. The challenge remains to provide information from such techniques in a clinically useful time frame.

TABLE 134-6 CYTOGENETIC TRANSLOCATION AND ASSOCIATED ONCOGENES OFTEN SEEN IN LYMPHOID MALIGNANCIES

Disease	Cytogenetic Abnormality	Oncogene
CLL/small lymphocytic lymphoma	t(14;15)(q32;q13)	—
MALT lymphoma	t(11;18)(q21;q21)	*API2/MALT, BCL-10*
Precursor B-cell acute lymphoid leukemia	t(9;22)(q34;q11) or variant	*BCR/ABL*
	t(4;11)(q21;q23)	*AF4, MLLI*
	t(12;21)	*TEL, AML1*
Precursor acute lymphoid leukemia	t(9;22)	*BCR, ABL*
	t(1;19)	*E2A, PBX*
	t(17;19)	*HLF, E2A*
	t(5;14)	*HOX11L2, CTIP2*
Mantle cell lymphoma	t(11;14)(q13;q32)	*BCL-1, IgH*
Follicular lymphoma	t(14;18)(q32;q21)	*BCL-2, IgH*
Diffuse large cell lymphoma	t(3;-)(q27;-)[a]	*BCL-6*
	t(17;-)(p13;-)	*p53*
Burkitt's lymphoma, Burkitt's leukemia	t(8;-)(q24;-)[a]	*C-MYC*
CD30+ anaplastic large cell lymphoma	t(2;5)(p23;q35)	*ALK, NPM*
Lymphoplasmacytoid lymphoma	t(9;14)(p13;q32)	*PAX5, IgH*

[a]Numerous sites of translocation may be involved with these genes.

Abbreviations: CLL, chronic lymphoid leukemia; IgH, immunoglobulin heavy chain; MALT, mucosa-associated lymphoid tissue.

APPROACH TO THE PATIENT: Lymphoid Cell Malignancies

Regardless of the type of lymphoid malignancy, the initial evaluation of the patient should include performance of a careful history and physical examination. These will help confirm the diagnosis, identify those manifestations of the disease that might require prompt attention, and aid in the selection of further studies to optimally characterize the patient's status to allow the best choice of therapy. It is difficult to overemphasize the importance of a carefully done history and physical examination. They might provide observations that lead to reconsidering the diagnosis, provide hints at etiology, clarify the stage, and allow the physician to establish rapport with the patient that will make it possible to develop and carry out a therapeutic plan.

For patients with ALL, evaluation is usually completed after a complete blood count, chemistry studies reflecting major organ function, a bone marrow biopsy with genetic and immunologic studies, and a lumbar puncture. The latter is necessary to rule out occult CNS involvement. At this point, most patients would