Molecular Pathology
Predictive, Prognostic, and Diagnostic Markers in Lymphoid Neoplasms

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• Lymphoma • Mutation • Molecular marker • Genetics • B cell • T cell • Targeted therapy

ABSTRACT

Lymphoid neoplasms show great diversity in morphology, immunophenotypic profile, and postulated cells of origin, which also reflects the variety of genetic alterations within this group of tumors. This review discusses many of the currently known genetic alterations in selected mature B-cell and T-cell lymphoid neoplasms, and their significance as diagnostic, prognostic, and therapeutic markers. Given the rapidly increasing number of genetic alterations that have been described in this group of tumors, and that the clinical significance of many is still being studied, this is not an entirely exhaustive review of all of the genetic alterations that have been reported.

OVERVIEW

Lymphoid neoplasms can be broadly divided into those derived from B lymphocytes, T lymphocytes, and natural killer (NK) cells, with the latter 2 sharing some immunophenotypic and functional properties.[1] Besides differences in morphology, immunophenotypic profile, and postulated cells of origin, the lymphoid neoplasm subtypes also differ tremendously in their underlying genetic alterations. The genetic alterations can be at the chromosomal level or at the level of individual genes, through mutations in the gene's coding region, promoter region, intronic changes that affect splicing sites, as well as epigenetic modifications. Understanding the genetic changes associated with the different subtypes of lymphoid neoplasms can shed light on the pathogenesis of the tumors, and ultimately leads to better prognostication and therapy development. The availability of next-generation sequencing (NGS) platforms has allowed investigators to conduct whole-genome/exome sequencing (WGS/WES) more effectively than before, leading to breakthrough discoveries of genetic mutations associated with different lymphoid neoplasms. These in turn have set the foundation for precision medicine and personalized care in this area. Due to the scope of the topic, this review highlights selected B-cell and T-cell lymphoid neoplasms, with an emphasis on findings from more recent studies, particularly those made possible through the NGS platforms.

MATURE B-CELL LYMPHOID NEOPLASMS

CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

Clinical Features

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is one of the most common mature B-cell neoplasms in the Western countries.[1] The incidence increases with age, with the mean age of diagnosis at approximately 65, and it frequently involves the peripheral blood, bone marrow, lymph node, spleen, and liver.

Histologic Features and Immunophenotypic Profile

The neoplastic lymphoid cells are usually small, monomorphic, and round, with variable amount of larger admixed prolymphocytes[1] (**Fig. 1**).

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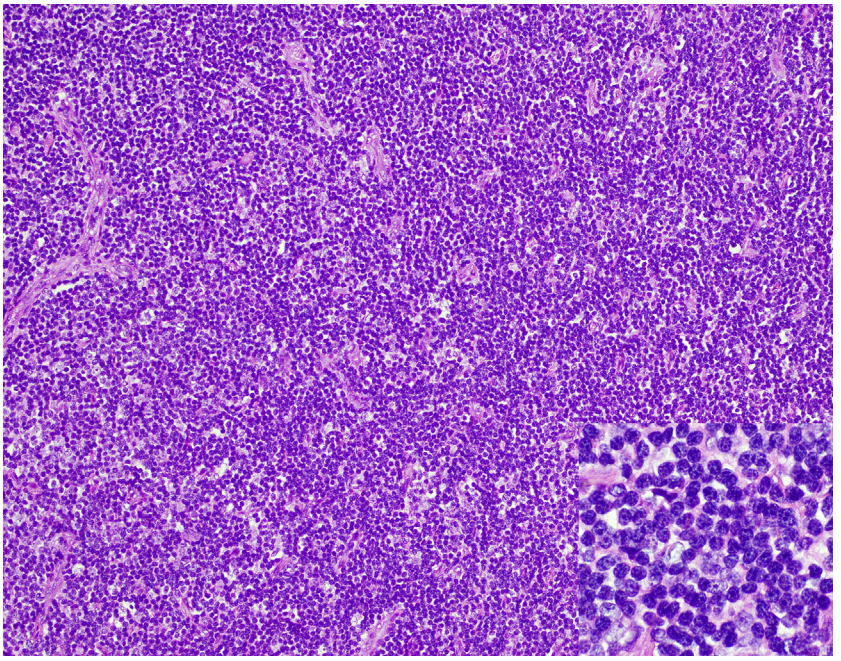

Fig. 1. Hematoxylin-eosin (H&E) image of small lymphocytic lymphoma (SLL) involving a lymph node at ×20 and ×60 (*inset*). Most neoplastic cells are small, monomorphic lymphoid cells with indistinct nucleoli and clumped chromatin pattern. There are scattered larger prolymphocytes.

Classically, CLL/SLL has a very distinctive immunophenotypic profile that allows its separation from other mature B-cell neoplasms: CD19+ CD20dim+ CD5+ CD10− CD23+ CD43+ CD11c weak+ FMC7− cyclin D1− surface heavy chains immunoglobulin (Ig)M/IgD and surface light chain dim+.[1]

Molecular Diagnostic and Prognostic Markers

Cytogenetic abnormalities are found in up to 80% of CLL/SLL cases, although none is unique to this disease.[1] Isolated deletion of 13q14.3, the most common cytogenetic alteration, is associated with a favorable prognosis, whereas other abnormalities, such as trisomy 12, deletion 11q22 to 23 (ataxia telangiectasia mutated [*ATM*] locus), deletion 17p13 (*TP53* locus), and deletion 6q21, have been associated with an intermediate and/or adverse prognosis.[1] CLL/SLL is thought to arise from antigen-stimulated, post–germinal center B cells, and more than half of the cases have undergone somatic hypermutation (SHM) in the variable regions of the immunoglobulin heavy chain (*IGVH*) and light chain (*IGVL*) genes.[2,3] CLL/SLL cases with unmutated/germline *IGVH*, as well as cases with high ZAP-70 or CD38 expression, are associated with worse prognoses and higher chance of chemotherapy requirements.[1–6] A subsequent study showed that loss of methylation at a specific single CpG dinucleotide in the 5′ regulatory region of *ZAP-70* transcription start site 1 (TSS1) predicted variably increased ZAP-70 mRNA and protein expression and poor prognosis.[7]

In addition to cytogenetic abnormalities, somatic mutations are also common in CLL/SLL (**Table 1**). The most frequent recurrent mutations occur in *NOTCH1, SF3B1, TP53, ATM*, and *MYD88*.[8–12] Among these, *NOTCH1, SF3B1*, and *TP53* have been associated with adverse prognostic implications among untreated patients in retrospective studies,[13–15] as well as among patients with relapsed/refractory CLL in whom mutations in multiple genes (*TP53, ATM, SF3B1*) were frequent and associated with poor outcome.[16] A proposed model integrating cytogenetic abnormalities and gene mutations has been shown to improve prognostic accuracy compared with using karyotype alone.[15]

NOTCH1 is one of the most frequently mutated genes in CLL/SLL. It encodes for a ligand-activated transmembrane heterodimer that plays a key role in cell differentiation and lineage determination.[10,17–19] After ligand binding, a series of proteolytic cleavages leads to the liberation of the functionally active Notch intracellular domain (NICD), allowing its translocation to the nucleus and transcriptional activation of target genes, including *MYC* and *NF-κB*.[10,19–21] *NOTCH1* mutations were described earlier in up to 50% to 60% of T-lymphoblastic leukemia/lymphoma (T-ALL)