Chapter 6

ADVANCES IN THE DIAGNOSIS AND CLASSIFICATION OF CHRONIC LYMPHOPROLIFERATIVE DISORDERS

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1. INTRODUCTION

The diagnosis and classification of the chronic lymphoproliferative disorders (mature B, T, and NK-cell leukemias/lymphomas, CLPDs) is constantly undergoing revision and refinement as more is learned about the pathology and clinical behavior of these diseases. Research in immunology and molecular genetics has also driven laboratory medicine and transformed our practice of hematopathology as technological advances make their way into the clinical laboratory. Although many of the disease entities that are recognized in the World Health Organization (WHO) classification have long been known, our ability to recognize important subgroups based on immunophenotypic and/or molecular genetic features has grown.

Many of the CLPDs present or commonly involve the blood and appear as mature lymphoid leukemias. It is from this viewpoint that we approach this review. Rather than providing a compendium of all the known lymphoid leukemias, we focus on those disorders in which there have been recent advances in our understanding of either their pathogenesis or diagnosis. Specifically we address new developments in chronic lymphocytic leukemia (CLL), prolymphocytic leukemia (PLL) and its relationship to mantle cell lymphoma (MCL), splenic marginal zone lymphoma (SMZL)/splenic lymphoma with villous lymphocytes, T-
prolymphocytic leukemia (T-PLL), Sezary syndrome (SS), and T-cell large granular lymphocytic leukemias (T-LGL).

2. **CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)**

From a pathologist’s standpoint, the diagnosis of CLL can be relatively straightforward from examination of the blood smear and immunophenotyping. Most cases demonstrate the typical morphology of mature lymphocytes with condensed, clumped nuclear chromatin, round nuclear contours, and scanty cytoplasm. Routine use of multiparameter flow cytometry confirms the morphologic impression when the typical phenotype of CD5+, CD19+, CD20+ (usually low level expression), CD23+, CD79b dim/negative, FMC7 dim/negative, and surface immunoglobulin light chain restricted (often low level expression). While most cases fit this description well, there is heterogeneity in the pathologic features of CLL. Some cases show increased numbers of prolymphocytes or morphologic deviation with clefted lymphocytes or lymphocytes with more abundant cytoplasm. Such cases have been termed “atypical CLL” by some investigators. Although definitions have differed, atypical CLL has been shown to also deviate from the typical immunophenotype (brighter FMC7, surface immunoglobulin, and CD23 expression) and is associated with trisomy 12. Atypical features also appear to correlate with worse outcome for these patients. This heterogeneity from the pathologist’s perspective confirms what clinicians have long known - that CLL is a heterogeneous disorder. Although clinical staging systems have proven useful in stratifying patients, there are still patients in intermediate stages that rapidly progress while others have stable disease for years.

In the post-genomic era we have the ability to add molecular-genetic information to refine our diagnosis. It may no longer be sufficient to only correctly diagnose CLL. Important genetic prognostic information or assessment for the presence of certain molecules that are the targets of specific therapies may be required. Although not yet standard of care, we need to be aware of developments that might advance our understanding of CLL as a disease entity and lead to diagnostic tests that will add clinical value to the diagnosis of CLL. We will focus on three areas that could impact pathologists – chromosomal abnormalities and the prognosis of CLL, immunoglobulin heavy chain gene (IGH) mutational analysis and CD38 expression, and cDNA microarray data.

Standard karyotyping and application of fluorescence in situ hybridization (FISH) has given us the ability to begin to dissect the