Chapter 9
Waldenstrom’s Macroglobulinemia/
Lymphoplasmacytic Lymphoma

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9.1 Introduction

Waldenström’s macroglobulinemia (WM) is a distinct clinicopathological entity resulting from the accumulation, predominantly in the bone marrow, of clonally related lymphocytes, lymphoplasmacytic cells, and plasma cells that secrete a monoclonal IgM protein (Figure 9.1) (1). This condition is considered to correspond to the lymphoplasmacytic lymphoma (LPL) as defined by the Revised European American Lymphoma (REAL) and World Health Organization (WHO) classification systems (2, 3). Most cases of LPL are WM, with less than 5% of cases made up of IgA, IgG, and nonsecreting LPL.

9.2 Epidemiology and Etiology

Waldenström’s macroglobulinemia is an uncommon disease, with a reported age-adjusted incidence rate of 3.4 per million among males and 1.7 per million among females in the United States and a geometrical increase with age (4, 5). The incidence rate for WM is higher among Caucasians, with African descendants representing only 5% of all patients. Genetic factors appear to be important in the pathogenesis of WM. Approximately 20% of WM patients have an Ashkenazi (Eastern European) Jewish ethnic background, and there have been numerous reports of familiar disease, including multigenerational clustering of WM and other B-cell lymphoproliferative diseases (6–10). In a recent study, approximately 20% of 257 serial WM patients presenting to a tertiary referral had a first-degree relative with either WM or another B-cell disorder (7). Frequent familiar association with other immunological disorders in healthy relatives, including hypogammaglobulinemia and hypergammaglobulinemia (particularly polyclonal IgM), autoantibody (particularly to thyroid) production, and manifestation of hyperactive B-cells have also been reported (9, 10). Increased expression of the bcl-2 gene with enhanced B-cell survival might underlie the increased immunoglobulin synthesis in familial WM (9). The role of environmental factors in WM remains to be clarified,
but chronic antigenic stimulation from infections, certain drug, and Agent Orange exposures remain suspect. An etiological role for hepatitis C virus (HCV) infection has been suggested though in a recent study examining 100 consecutive WM patients; no association could be established using both serological and molecular diagnostic studies for HCV infection (11–13).

9.3 Biology

9.3.1 Cytogenetic Findings

Several studies, usually performed on limited series of patients, have been published on cytogenetic findings in WM demonstrating a great variety of numerical and structural chromosome abnormalities. Numerical losses involving chromosomes 17, 18, 19, 20, 21, 22, X, and Y have been commonly observed, although gains in chromosomes 3, 4, and 12 have also been reported (7, 14–19). Chromosome 6q deletions encompassing 6q21–22 have been observed in up to half of WM patients and at a comparable frequency among patients with and without a familial history (7, 19). Several candidate tumor suppressor genes in this region are under study, including BLIMP-1, a master regulatory gene implicated in lymphoplasmacytic differentiation. Notable, however, is the absence of IgH switch region rearrangements in WM, a finding that might be used to discern cases of IgM myeloma where IgH switch region rearrangements are a predominant feature (20).