Lymphoma, a type of malignancy that affects B-lymphocytes or T-lymphocytes, is categorized as Hodgkin lymphoma (HL) or non-Hodgkin lymphoma (NHL). The key differences in the two groups comprise age, disease manifestation, and the presence of Reed-Sternberg cells in the lymph nodes. One of the more infrequent subtypes of non-Hodgkin lymphoma that affects about 3.8 per million people per year is Waldenstrom macroglobulinemia.1 Waldenstrom macroglobulinemia is a rare, slow-growing B-cell lymphoproliferative disorder that is characterized by bone marrow infiltration with malignant white blood cells.2 It is defined by the World Health Organization as lymphoplasmacytic lymphoma associated with IgM monoclonal gammopathy, and was first discovered by Dr. Jan Gosta Waldenstrom in 1944. Lymphoplasmacytic cells are in transition from B-cells to plasma cells. Approximately 1500 new cases of Waldenstrom macroglobulinemia present each year in America.3 The incidence is twice as high in males, higher in Caucasians than in African Americans, increases with age,3 and accounts for approximately 1 to 2% of all hematological cancers.4

Signs and Symptoms

Patients with WM can experience a broad spectrum of signs and symptoms affecting many organs in the body, or they can be completely asymptomatic without the need for any medical treatment for many years. The most common clinical presentation of Waldenstrom is fatigue due to normochromic, normocytic anemia and cytopenias. As a result of the overproduction of IgM by malignant B-cells in the bone marrow, the high concentration of proteins causes serum hyperviscosity. Patients whose IgM levels exceed 4 g/dL with a serum viscosity measurement greater than 4 are more likely to develop hyperviscosity syndrome, which generally includes oronasal bleeding, gingival bleeding, and blurred vision due to retinal hemorrhages.1 Other constitutional signs associated with hyperviscosity syndrome can include light-headedness, dizziness, and other central nervous system abnormalities. Hyperviscosity syndrome is less frequently seen today as more patients are diagnosed and treated earlier. Hepatosplenomegaly and lymphadenopathy are found in 20% to 30% of patients with WM, accompanied by occasional fever, night sweats, and weight loss.1 Patients may also develop Schnitzler’s syndrome, a term to describe skin lesions, fever, and arthralgia due to IgM monoclonal gammopathy.1 Such clinical presentations are consequences of abnormally
high concentrations of IgM antibodies circulating the blood and depositing in the organs. Patients with WM may also exhibit other nonspecific IgM-related manifestations such as cold agglutinin hemolytic anemia, cryoglobulin, and amyloid deposition in tissues. Previous studies have demonstrated the implication of anti-myelin–associated glycoprotein (MAG) in demyelinating neuropathy found in WM as well.

Patients with serum viscosity of less than 3 may not experience any symptoms due to the disease’s indolent behavior. In this case, patients with WM can be misdiagnosed with asymptomatic monoclonal gammopathy of undetermined significance (MGUS). In MGUS, the serum IgM monoclonal protein level is less than 3g/dL, bone marrow lymphoplasmacytic infiltration is less than 10%, and no constitutional symptoms or end-organ damage are seen in symptomatic WM. Asymptomatic WM is also referred to as indolent or smoldering Waldenstrom macroglobulinemia (SMW), in which the serum IgM monoclonal protein level does not exceed 3g/dL and there is no evidence of end-organ damage. Patients diagnosed with WM may remain asymptomatic for years and only require minimal observation and monitoring until the disease progresses with age.

**Diagnosis**

The clinical presentation of WM is almost indistinguishable from other IgM monoclonal gammopathies, so it is vital for clinicians to conduct a thorough investigation and meet all diagnostic criteria to prevent misdiagnosis. The median age of diagnosis ranges from 63 to 68 years old, with males over age 65 being in the high-risk category. Initial findings from complete blood count may show normochromic, normocytic anemia and thrombocytopenia; marked rouleaux may be present on peripheral blood smear. Total protein level in patient serum is usually higher than normal range (>8.5 g/dL). Monoclonal gammopathy can be detected by the M-spike, or monoclonal spike, on serum protein electrophoresis, and serum immunofixation is used to identify the immunoglobulin M (IgM) heavy chain and the type of light chain involved. M-spicies restricted to the kappa-light chain were more frequently reported in patients diagnosed with WM. To help further differentiate WM from other lymphoplasmacytic lymphomas, a bone marrow biopsy, immunophenotyping by flow cytometry, and cytogenetic analysis are necessary. Intrabecular monoclonal lymphoplasmacytic infiltrate of greater than 10% by small lymphocytes shows plasmacytoid cell differentiation. WM cells typically express pan B-cell markers such as CD19, CD20, CD22, and surface IgM, but do not express CD10, CD23, CD38, and cytoplasmic Ig. Expression of CD5 occurs in only about 5% to 20% of cases. The exact cause of WM is yet to be explained, but it is described to be a sporadic disease of hypermutated genes resulting in malignant clones. The upregulation of some cytokines in the bone marrow, such as interleukin-6, B-lymphocyte stimulator (BLys), and CD40 ligand are thought to be responsible for the proliferation of the malignant cells. Numerous studies have also reported that there is a high familial predisposition in patients with WM. Up to 26% of patients with WM have a first- or second-degree relative with either WM or another B-cell disorder.

**Prognosis**

The International Staging System for Waldenstrom macroglobulinemia identified five factors that are associated with adverse prognosis: age older than 65, hemoglobin less than 11.5g/dL, platelet count less than 100K/µL beta-2-microglobulin greater than 3mg/dL, and monoclonal IgM concentration greater than 7g/L. Patients exhibiting 0 or 1 of the following factors are in the low-risk category with a median survival of 12 years. Patients possessing more than 2 of the risk factors are in the high-risk category and have a median survival of almost 4 years. Patients older than 65 years cannot be placed in the low-risk category. A previous study has shown that Waldenstrom patients were found to be at a higher risk of developing second hematologic malignancies. They demonstrated that the risk of second cancer in WM was 1.69 times higher than expected. Other studies have reported high incidence of the disease manifesting into diffuse large B-cell lymphoma and to myelodysplastic syndrome/acute myeloid leukemia. Researchers displayed concerns about the correlation between the significant risk of second cancers in WM patients and the therapy these patients undertake, such as nucleoside analogs and alkylating agents.

**Treatment Options**

Despite the advancement in medicine, there is yet to be a cure for WM. However, a number of biological therapies and chemotherapies are available for the
management of the cancer, which were derived from other lymphoproliferative disorders such as multiple myeloma and chronic lymphocytic leukemia. Clinical manifestations of WM, evidence of bone marrow infiltration, and characteristic immunophenotype of WM are important considerations for the initiation of therapy. Patients requiring the initiation of therapy commonly present with progressive anemia and cytopenias. Elevated serum IgM protein alone is not a strong indication for treatment. Hyperviscosity syndrome can be corrected by plasmapheresis, because 80% of IgM proteins are concentrated intravascularly. A single volume of plasmapheresis can decrease the serum IgM concentration by 40% and viscosity by up to 60%. Nucleoside analogues used as first-line treatment for WM that can be used singly or in combination with alkylating agents (chlorambucil) and rituximab are fludarabine and cladribine. Autologous or allogeneic stem cell transplant can be considered for qualified candidates with more serious hematologic malignancies or those in relapse stage.

Summary

Over the years, there has been significant advancement in the understanding of the pathogenesis and disease management of Waldenström macroglobulinemia to prolong survival rates. However, clinicians are still challenged with finding the most effective therapy for the increased incidence of second cancers in patients with Waldenström. Recent studies have also reported findings of poor treatment outcomes observed in Waldenström patients with familial predisposition. Future studies should focus on the development of more effective drug therapy of minimal toxicity to target WM patients with second malignancies and familial disease status.

References