

## HOW IS WALDENSTRÖM'S MACROGLOBULINEMIA DIAGNOSED?

by Morie A. Gertz, MD, MACP



Dr. Morie A. Gertz

*On June 16, Dr. Morie A. Gertz became Chairman of the Department of Internal Medicine at Mayo Clinic in Rochester, MN, capping a distinguished career of twenty-five years. The Torch takes this opportunity to offer congratulations to Dr. Gertz on behalf of the entire IWMF membership.*

*Dr. Gertz serves on the IWMF Scientific Advisory Committee and is a frequent and popular speaker at the IWMF educational forums where he shares his wide experience as a WM specialist at Mayo Clinic. In the following article Dr. Gertz continues the series Doctor on Call with a discussion of factors involved in accurate diagnosis of Waldenström's macroglobulinemia.*

The official designation of Waldenström's macroglobulinemia requires two components. The first is the presence in the serum of a monoclonal IgM protein, the so-called "macroglobulin protein." The second is the presence of an abnormal cell population. The abnormal cells, the so-called "lymphoplasmacytic cells," are in the bone marrow and are responsible for the production of the IgM protein. Waldenström's macroglobulinemia is a "lymphoplasmacytic" or low-grade lymphoma, and the percentage of abnormal cells in the bone marrow by visual estimate must exceed 10% in order for Waldenström's macroglobulinemia to be established.

The presence of a diagnosis, however, is not necessarily an indication for therapy. Variability in the degree of infiltration and sampling variation are also to be considered. It is possible to have the bone marrow show 5% lymphoplasmacytic cells in one area and 10% in another. Therefore, the driver for consideration of therapy is not merely the presence of bone marrow involvement and an IgM protein but rather the clinical manifestations resulting from the protein and marrow abnormalities. In the absence of anemia, glandular enlargement, or symptoms of malignant lymphoma, observation (so-called 'watch and wait') may be appropriate, even with established Waldenström's macroglobulinemia. It bears emphasis that the symptoms of Waldenström's macroglobulinemia merit intervention and not simply its presence. Many patients question why, when an early diagnosis of cancer is so heavily emphasized in the media, early intervention is not indicated. The reason is because the disease in its current form is not curable, and the goals of effective therapy are improvement in symptoms. In the absence of symptoms, active intervention may not be warranted. At Mayo Clinic, the size of the IgM protein is not used as a determinant of the need for therapy. There are supporters of the concept that if the IgM is >5000 this, in and of itself, is an indication for therapy. In my own personal experience, I have followed patients with IgM levels as high as 9000 who did not require therapy for up to a year. Realistically, however, the higher the IgM monoclonal protein is, the more likely it is that therapy will be required. Nonetheless, there are substantial numbers of patients who have extreme elevation of the IgM but no symptoms to warrant therapy.

The converse is also true. There are unique situations when the IgM protein level is very small, the infiltration in the bone marrow is minimal, yet therapy is required. There are four specific syndromes that mandate therapy despite the fact that the Waldenström's macroglobulinemia itself has a minimal impact. These four syndromes are amyloidosis, cryoglobulinemia, cold agglutinin disease, and progressive peripheral neuropathy secondary to IgM monoclonal gammopathy. Amyloidosis results from deposits of the IgM protein or fragments into the tissues of the kidney, heart, liver, or nerve, causing these to malfunction. Cryoglobulinemia represents the depositing of the IgM protein in the lining of blood vessels, causing them to become inflamed. This typically can cause a rash on the legs and changes to the kidney and to the liver. Even when the IgM level is as low as 200, treatment may be required. Cold agglutinin disease represents an IgM protein leading to the destruction of red blood cells that can cause anemia severe enough to warrant blood transfusions even when the IgM levels are small. Finally, the presence of progressive peripheral neuropathy may require therapy no matter what the level of the IgM protein is if the neuropathy itself is reaching a point where it is impacting on an individual's quality of life.

There is one syndrome closely resembling Waldenström's macroglobulinemia that has tricked me in the past, and this is splenic marginal zone lymphoma. Whenever I see the spleen disproportionately enlarged in a patient with Waldenström's macroglobulinemia, I always raise this question to ensure that I am making an accurate diagnosis. Therefore, although the diagnostic criteria for Waldenström's macroglobulinemia are relatively simple, the disease can easily be confused with other syndromes, and it takes experience to exclude syndromes associated with IgM monoclonal protein that require therapy. It also requires experience to know when not to treat Waldenström's macroglobulinemia even when a diagnosis is established and the disease is felt to be smoldering.

Why is Waldenström's macroglobulinemia misdiagnosed? Oftentimes, when physicians see a patient with a monoclonal protein they do not do the immunofixation necessary to separate an IgG and IgA from an IgM protein, and the patient may be mislabeled as having multiple myeloma. It is not until the protein is correctly labeled as IgM that the possibility of Waldenström's macroglobulinemia is entertained. Moreover, 1% of patients with multiple myeloma actually have IgM multiple myeloma, which can easily be confused with Waldenström's macroglobulinemia by an inexperienced physician. Although there is an IgM protein in the blood, the bone marrow clearly does not show lymphoplasmacytic lymphoma but shows the classic plasma cells associated with multiple myeloma. Fortunately, this is a rare syndrome.

What type of testing is required? For the majority of patients, the key studies include the blood counts, a 24-hour urine protein, quantitative immunoglobulins, measurements of liver and kidney function, and a CT scan of the abdomen to assess for nodes that cannot be palpated on routine physical examination, as well as to estimate spleen size. In our experience, the most common symptom of patients with Waldenström's macroglobulinemia is slowly progressive fatigue, difficulty climbing stairs, and shortness of breath with exertion. From a clinical standpoint, multiple myeloma does not resemble Waldenström's macroglobulinemia. The only similarity is the presence of an abnormal protein in the blood. Otherwise, multiple myeloma is different, and the experienced hematopathologist can make the distinction by looking at the cells in the bone marrow responsible for the production of the protein. There are specific cell markers that differentiate the Waldenström's cell from other cells in the bone marrow. Waldenström's cells are lymphocytes and express both CD19 and CD20 as well as surface IgM, which are markers of lymphocytes. Waldenström's cells are typically negative for the markers of

CD5, CD10, and CD23. Multiple myeloma, on the other hand, is typically CD20 negative and expresses CD138 and 138 with cytoplasmic immunoglobulin. Technically-adept immunopathology laboratories will routinely do these types of marker studies to help distinguish Waldenström's from other forms of bone marrow cancer.

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*Author of more than 300 publications, Dr. Gertz has participated in numerous clinical trials in the course of his research directed to multiple myeloma, amyloidosis, and Waldenström's macroglobulinemia. In recognition of his contribution to the understanding of these diseases, Dr. Gertz advanced to professor at the Mayo College of Medicine and to the chairmanship of the Division of Hematology at Mayo Clinic. In 2002 he was awarded the Mayo Distinguished Clinician Award for his contributions to patient care.*

*Other leadership positions filled by Dr. Gertz at the Mayo Clinic include President of the Mayo Rochester Staff and service on the Mayo Clinic Rochester Executive Board.*

*Dr. Gertz is a fellow of the American College of Physicians, a member of the Myeloma Subcommittee of the Eastern Cooperative Oncology Group, and a member of several professional organizations. He is currently the treasurer of the International Society of Amyloidosis and serves on three journal editorial boards.*

*In 2007 at the Fourth International Workshop on Waldenström's Macroglobulinemia, Dr. Gertz received the Robert A. Kyle Award in recognition of his role in advancing the understanding of this rare cancer.*

This article was published in the IWMF *Torch*, ([Fall 2008](#)) pages 3-5.