

COMPLICATIONS IN WALDENSTRÖM MACROGLOBULINEMIA

by Rafat Abonour, MD



Dr. Rafat Abonour

What are the complications encountered by patients diagnosed with Waldenström macroglobulinemia? This is the question asked by all WM patients when confronting their diagnosis. Answer: there are a number of possible complications caused either by tumor infiltration in the bone marrow and/or by an abnormal level of IgM in the blood, also referred to as abnormal macroglobulinemia.

Symptoms Attributable to Tumor Infiltration

Extensive bone marrow infiltration by the abnormal Waldenström cells leads to reduction in bone marrow function and, consequently, reduced production of red blood cells. Progressive anemia is in fact the most common indication for initiation of treatment. Bone destruction, however, which is common in multiple myeloma, is very uncommon in WM.

Abnormal Waldenström cells can also infiltrate other organs, including the lymph nodes, liver, and spleen. Lymph node infiltration may be of little consequence (except that it is esthetically disturbing), or it may result in significantly enlarged nodes that cause obstruction of the bowel, blood vessels, or airways. An enlarging spleen can reduce the capacity of the stomach, and this in turn may result in a false sense of satiety. In this case one eats less, with subsequent weight loss. Other rare forms of infiltration have been reported in the lungs, bowels, stomach, head and the orbit (eye cavity). Bing-Neel syndrome is seen when long-standing, sluggish circulation causes blood vessels to leak Waldenström cells into the space surrounding the vessels. Such patients will complain of headache, vertigo, impaired hearing, ataxia (uncoordinated muscle movement), nystagmus (uncoordinated eye movement), diplopia (double vision), and, eventually, will succumb to coma.

Symptoms Attributable to Circulating IgM

In general, patients with WM bleed more easily either because IgM interferes with clotting factors or because IgM has the effect of coating the platelets, consequently making them less effective.

Hyperviscosity results from the increased level of IgM in the blood stream. Because IgM is a large protein, an increased amount of monoclonal IgM leads to greater vascular resistance, higher viscosity, and slower blood flow to vital organs. Symptoms of hyperviscosity are evident in only 10% to 30% of patients with WM. The most common complaints are fatigue, bleeding from the gums and nose, and retinal bleeds which can lead to blurred vision or even loss of vision. In more advanced cases, patients may experience headache, vertigo, nystagmus, dizziness, sudden deafness, diplopia, or ataxia. Untreated advanced hyperviscosity can lead to confusion, dementia, stupor, stroke, or coma.

Symptoms of hyperviscosity usually appear when the normal serum viscosity of 1.4 to 1.8 cP (centi-Poise) reaches 4 to 6 cP (corresponding to a serum IgM level of at least 3 g/dL). There are huge variations in the threshold from an asymptomatic status to one showing the effects due to hyperviscosity. Some patients with a large amount of IgM (approaching 5-7 g/dl) remain symptom-free, while others exhibit symptoms at much lower levels.

Cryoglobulinemia, the formation of cryoglobulins in the blood, is another complication related to IgM. Cryoglobulins are serum proteins or protein complexes of IgM that undergo reversible precipitation at low temperatures. While this complication may be detected in 20% of WM patients, fewer than 5% present with symptoms from cryoglobulinemia such as Raynaud syndrome (blue and painful finger tips in cold weather), joint pain, purpura (purple or red spots under the skin), skin ulcers, or kidney damage.

Finally, IgM can bind to red blood cells at cold temperatures and produce a condition called cold agglutinin disease. This happens in about 10% of WM patients and leads to chronic red blood cell destruction, resulting in various degrees of anemia.

Symptoms Attributable to Tissue Deposition of IgM

IgM deposition can occur in the kidneys presenting as excess protein leakage by the kidneys, in the intestine leading to diarrhea, and in skin seen as rash or nodules.

Symptoms Attributable to Autoantibody Activity of IgM

Although IgM is intended to be our first line of defense against bacteria and other foreign insults, in WM the serum IgM most often has no specific target. In rare cases IgM can react with the patient's own normal protein, leading to various forms of autoimmune disease. In fewer than 10% of WM patients the IgM reacts with specific red blood cell antigens at temperatures below 37°C to produce a chronic red blood cell reduction and symptoms of anemia.

Peripheral neuropathies have been reported in 15% to 30% of patients with WM. The most commonly encountered symptomatic neuropathy in WM is symmetric multiple nerve involvement; other forms include cranial nerve palsies and single nerve damage. In approximately 50% of these patients, the IgM reacts with MAG, a myelin protein forming a protective coating on the nerves. Most patients with anti-MAG antibodies present with sensory complaints of numbness, paresthesias (tingling or pin pricks), imbalance, and gait ataxia caused by defective sense of position. In some patients with WM, the protein produced can be degraded and tends to deposit in tissues. This protein is called amyloid protein. Autonomic symptoms are the hallmark of amyloid polyneuropathy and consist of postural hypotension, diarrhea, impotence, and bladder dysfunction.

Symptoms Attributable to Fatigue

While fatigue is one of the most distressing symptoms associated with cancer and cancer treatment, it is frequently underreported by patients and overlooked by health care providers.

The causes of fatigue include anemia, loss of muscle mass, defective muscle energy metabolism, and/or abnormalities in the generation or use of ATP (the body's prime phosphate energy source). Neurophysiologic skeletal-muscle changes and chronic stress response are other variables encountered. In addition, systemic inflammatory response, poor nutrition, disrupted sleep, hormonal changes (for example, premature menopause), and direct central nervous system toxicity (that is, drugs which cross the blood-brain barrier, cranial irradiation). Inactivity can induce muscular wasting; prolonged rest can lead to further loss of physical strength and endurance.

How can a WM patient counter the impact of fatigue? Exercise! Many fatigued patients have difficulty believing that exercise will improve their symptoms. But patients who exercise during or after the completion of treatment have significantly reduced fatigue and emotional distress, decreased sleep disturbance, improved functional capacity, and better quality of life.

Dr. Rafat Abonour, Associate Professor of Hematology/ Oncology, is Director of the Plasma Cells Disorders Program at Indiana University. The author of numerous articles, his clinical and research activities are focused on translational research in the areas of hematologic malignancies and bone marrow/stem cell transplantation. His work on gene transfer into hematopoietic stem cells in the setting of stem cell transplantation gained national interest when the efficient transfer of the multi-drug resistant gene-1 into autologous CD34+ cells was established.

Dr. Abonour's current efforts are disease-focused and centered on incorporating novel therapy in the management of rare plasma cell disorders such as Waldenström macroglobulinemia and amyloidosis. As an active member of the Eastern Cooperative Oncology Group, Dr. Abonour is the chair of a study looking at rituximab in combination with chemotherapy in the treatment of Waldenström macroglobulinemia.

An avid runner, Dr. Abonour practices what he advocates when he urges cancer patients to combat fatigue by embracing a regular exercise program.

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