Dr. Morie A. Gertz

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by Morie A. Gertz, MD

In the following article written for the Torch *readership, Dr. Morie Gertz discusses amyloidosis in WM. This rare complication of our disease is linked to the abnormally high level of the IgM protein found in the bloodstream of WM patients. While Dr. Gertz here limits his discussion to IgM- associated amyloidosis, the reader should understand that amyloid deposits can develop from a significant number of proteins in addition to IgM and can afflict patients in many diseases other than WM. The symptoms in such cases, however, are the same as those described below when the disease is IgM-related.*

In Waldenström macroglobulinemia, the symptoms in virtually all patients are derived from the growth of the malignant Waldenström cells in the bone marrow, lymph nodes, liver, and spleen. The growth of these malignant cells is responsible for the most common findings in Waldenström's: anemia leading to fatigue, lymph gland enlargement, and enlargement of the liver and spleen, sometimes associated with weight loss. The monoclonal IgM, which is a hallmark of Waldenström macroglobulinemia, does not play a role in producing symptoms in most patients. The IgM is a useful measure of a patient's course as it indicates a response to treatment when declining, or stability when showing slight variations, or, when rising, evidence of progressive disease.

In rare instances, the IgM protein itself is responsible for symptoms. When the IgM level is very high, the blood can become syrupy and thick, and this is the hyperviscosity syndrome that requires plasma exchange. When the IgM binds to a nerve, it can cause damage to the nerve, leading to numbness, tingling, and weakness in the feet and lower legs. This is so-called peripheral neuropathy. Occasionally, the IgM protein leads to amyloidosis, the subject of this review.

All proteins, including the Waldenström's protein, are biodegradable and recyclable. The life of the IgM protein in the circulation is roughly 6 weeks. After 6 weeks, the protein goes to the recycling center of the human body, is degraded, and then the breakdown products are used for the production of new IgM protein. Occasionally, the IgM protein misfolds and, therefore, becomes non-recyclable and non- biodegradable. As a consequence, it can build up in the circulation and deposit in the tissues, causing organs to malfunction.

When the IgM protein misfolds and is no longer amenable to the recycling processes of the human body, it is carried in the blood to different tissues in the body and deposited there. It is now referred to as an amyloid deposit. Amyloid typically deposits in the tissue of the heart, liver, kidney, nerve, and lung. In each of these organs, the deposits of amyloid can cause those organs to malfunction.

When depositing in the kidney, amyloid causes the kidney to leak protein into the urine with resultant swelling in the lower extremities, a rise in the serum cholesterol, and eventual damage to the purifying function of the kidney. When amyloid deposits into the heart, it causes the heart to function poorly and become less efficient. The resultant impairment of heart function leads to exertional fatigue, shortness of breath, and ultimately heart failure. Deposits in the nerve can resemble IgM-associated neuropathy with numbness and tingling, burning, and lower extremity weakness. Deposits in the lung can cause shortness of breath and interfere with oxygen flow from the atmosphere into the bloodstream. Amyloid deposits in the liver can cause enlargement of the liver with the resultant loss of appetite, fatigue, weight loss, and distaste for specific foods.

Amyloid deposits are never normally found in the body. Their presence always indicates an abnormal process. The disorder is rare. It affects 8 out of one million people yearly. In the case of IgM-associated amyloid, the protein is produced by the Waldenström cell and, although it can affect anyone, the majority of patients are over age 60 with an average age at diagnosis of 67. Two-thirds of the patients we see are men. Although amyloid is an abnormal protein, diet and the amount of protein eaten play no role in the development of the disease; and no links have been found with stress, occupation, or environmental exposure. It is not infectious or contagious. The reasons why the amyloid protein cannot be broken down by the body are not well understood, but research studies are underway at Mayo Clinic to try and understand what is unique about the amyloid protein that prevents it from being removed by the body. The symptoms of amyloid include swelling, weakness, weight loss, shortness of breath, diarrhea, easy bruising of the face or eyelids, tongue enlargement, and dizziness upon standing. Some of these symptoms are also seen in Waldenström macroglobulinemia, and caution is required to distinguish the two disorders.

Amyloid needs to be treated because it can irreversibly damage the heart and the kidney. Patients who develop severe kidney damage from amyloid may require dialysis treatment for support. Patients whose hearts become involved can have serious problems related to the reduced pumping action of their heart resulting in fatigue and loss of energy. The most common symptom of heart amyloid is shortness of breath with the slightest physical activity. It is difficult to climb stairs, and blood pressure often will fall. This needs to be distinguished from the fatigue and shortness of breath associated with Waldenström, which are usually due to anemia.

The diagnosis of amyloidosis is fundamentally different from the diagnosis of Waldenström macroglobulinemia. While the diagnosis of Waldenström is based on bone marrow findings or the size of the IgM protein, neither are predictors for the presence of amyloid. The first suspicions of amyloidosis are based on symptoms, and then specialized biopsies and specialized staining techniques are required to confirm a diagnosis. Most patients with Waldenström need not be concerned with the possibility of amyloidosis. However, for patients whose symptoms include numbness in their feet, unexplained weight loss, leaking of protein into the urine, or evidence of heart malfunction, amyloidosis should be suspected as the cause. Biopsy of the bone marrow, skin, or the fat can be used to demonstrate amyloid deposits.

The prognosis of amyloid is dependent on the extent of heart involvement and generally is a more serious condition than Waldenström's macroglobulinemia. The typical evaluation of a patient with amyloid includes measurements of proteins that reflect the efficiency of heart function, as well as ultrasound of the heart.

The treatment of amyloidosis is different from Waldenström. A biopsy is always required to establish the diagnosis. It cannot be done with x-rays or scans. There is no smoldering phase of amyloidosis; and at diagnosis, virtually all patients require some form of therapy. Watch and wait does not apply to most patients with amyloidosis. For a subset of patients, high-dose chemotherapy and autologous stem cell transplant is an appropriate technique. For others, more traditional chemotherapy akin to that used in Waldenström macroglobulinemia is appropriate. One specific regimen cannot be recommended and evaluation of therapy options has to be done in consultation with a physician experienced in the management of amyloidosis.

The treatment is usually designed to limit production of the amyloid protein. Measurements of the light chain in the blood are performed on a regular basis to assess the impact of therapy. As in all patients with Waldenström, the IgM level is measured on a serialized basis as well. Supportive care is important. Well-balanced nutrition is important for the body's energy supply. Specialized diets may be required, and dietary restrictions are common. Sufficient sleep is essential. Strenuous activities need to be avoided, although activity is beneficial. In general, amyloid does not increase the risk of getting infections, but direct exposure to people with known infections is not recommended. If there are questions about the diagnosis or treatment, your healthcare provider or amyloid specialists at Mayo Clinic would be happy to perform an evaluation.

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