AMYLOIDOSIS ASSOCIATED WITH WALDENSTRÖM DISEASE OR IgM-MGUS

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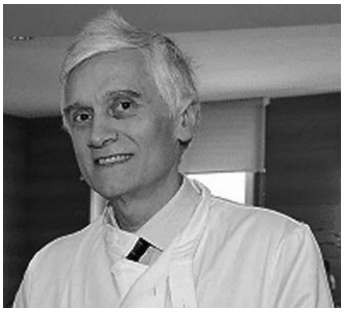

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Dr. Giampaolo Merlini of the Amyloidosis Research and Treatment Center, Foundation IRCCS Policlinico San Matteo, Department of Molecular Medicine, University of Pavia, Pavia, Italy, is a world authority on amyloidosis. While IgM amyloidosis occurs infrequently in Waldenstrom's macroglobulinemia patients, it is a serious complication and one that every Waldenstrom's patient needs to be aware of.

What is amyloidosis?

Proteins are the engine of life in all living organisms. In order to function properly, proteins need to be assembled, or folded, in the right way. We now recognize almost 30 proteins that are, or may become, "misfolded" and "sticky" through aging or through mutations and form aggregates that are toxic for tissues, causing severe and progressive organ dysfunction. These aggregates of misfolded and sticky protein can then organize into very fine needles, called fibrils, which deposit and accumulate in organs and further impair organ function. These fibrillary deposits have a fatty-like appearance and are called amyloid, hence the term amyloidosis to indicate the diseases characterized by such deposits. For instance, one of these proteins, called beta-protein, which is produced in the brain, can aggregate and form plaques of amyloid deposits causing progressive loss of the brain cells (neurons) and of the cognitive functions as observed in Alzheimer's disease.

The amyloid associated with WM and IgM-MGUS is the result of misfolded proteins from the immune system produced in the following manner. Some of the cells involved in the body's defense, namely the B-cells and the plasma cells, generate proteins referred to as antibodies or immunoglobulins that are constructed against ever-changing targets, including bacteria, viruses, toxins, etc. To continuously adapt our defenses against such new threats, the structure of an immunoglobulin needs to be modified. Modification of an immunoglobulin is accomplished by mutation.

Each immunoglobulin is composed of two heavy chains and two light chains that are bound together to form a structure capable of recognizing specific targets. The engineering of these immunoglobulins depends on very sophisticated cellular mechanisms and requires the production of an excess of light chains that can be released in the blood as free light chains. In rare cases, the mutations required for tuning the body's defenses may result in light chains that have an altered structure or misfolding. Such misfolded proteins become sticky and toxic, and they accumulate in different body sites as amyloid deposits, ultimately leading to dysfunction of vital organs. This type of amyloidosis is named light chain amyloidosis (AL), also known as primary amyloidosis. AL or primary amyloidosis is the most common form of the amyloidoses that affect several organs (referred to as systemic amyloidoses), with approximately 10 new patients per million per year.

How frequently is amyloidosis associated with Waldenström macroglobulinemia or with IgM-MGUS?

AL amyloidosis can complicate Waldenström macroglobulinemia and IgM-MGUS. This occurs when the free light chains produced by the lympho-plasmacellular clone, which underlies both WM and IgM-MGUS, turn out to be misfolded. However this is an uncommon event, and in fact IgM-associated amyloidosis represents only 5 to 6% of all cases of AL amyloidosis, with a yearly expected incidence of 0.6 cases per million. On the other hand, when an IgM-associated amyloidosis arises, it may become necessary to modify the treatment and monitoring of the underlying disease. Therefore the possibility of developing an IgM-associated amyloidosis should always be taken into account when monitoring patients with Waldenström macroglobulinemia or IgM-MGUS.

The IgM-associated amyloidosis presents distinct features when compared to non-IgM associated amyloidosis: 1) the concentration of the circulating free light chains is lower, 2) the heart is less frequently and less severely involved, and 3) the amyloid is frequently localized in the lung and in lymph nodes.

When should one suspect the presence of amyloidosis?

Primary amyloidosis can target practically all organs, except the brain. The kidney is involved in two-thirds of amyloidosis patients, characterized by loss of proteins in the urine, which becomes foamy, by swelling of the legs, and by eventual damage to the purifying function of the kidney. The heart is involved in almost half of the patients who develop shortness of breath during their usual activities, difficulties in climbing the stairs, fatigue, low blood pressure, and swelling of the legs. The nerves are affected in more than one quarter of patients, with tingling, numbness, burning, loss of sensitivity to hot or cold at the feet and legs, and, as the neuropathy progresses up to the knee, it may extend to the arms starting from the fingers. The amyloid can also damage the autonomic nervous system that regulates certain functions, such as bowel movements and erectile function in men, resulting in diarrhea or constipation and impotence. The lung and the upper respiratory passages can be involved by amyloid deposits with possible obstruction of the airways and reduced blood oxygenation contributing to shortness of breath. In one-fifth of patients, the lymph nodes can slowly become enlarged because of the amyloid deposition. The tongue can also become enlarged and stiff and show tooth impressions. Amyloid deposits in the liver can cause enlargement of the liver with possible compression of the stomach and loss of appetite. In a few patients, the amyloid deposits in the blood vessels make them fragile with easy bruising and purple spots that vanish in a few days, particularly around the eyes and at the base of the neck.

As described, the clinical manifestations are very diverse and can mimic common conditions in the elderly, such has cardiac failure or kidney and nerve dysfunction in patients with diabetes, making amyloidosis a difficult entity to be recognized. This holds especially true for amyloidosis associated with Waldenström macroglobulinemia, since some manifestations of amyloidosis are already part of the clinical picture of Waldenström macroglobulinemia (for example fatigue and shortness of breath due to anemia or peripheral neuropathy due to the antibody activity of the IgM versus certain components of the nerve tissue). Therefore patients and physicians should be especially alert in order to detect promptly any clinical manifestations possibly related to amyloidosis.

Is it possible to diagnose the presence of amyloid early, before severe organ damage has occurred?

Most of the clinical manifestations described above appear when the damage to the target organ is already advanced and sometimes irreversible. Manifestations of nerve involvement may appear rather early, but the heart (the most crucial organ on which our survival depends) and the kidneys are usually damaged silently until they become unable to function properly and become symptomatic. Fortunately, we can monitor both the heart and kidney functions using widely available biomarkers that can detect promptly the damage caused by the amyloid process, even several months before the appearance of symptoms. When the heart is stressed, it produces a hormone called “B natriuretic peptide” (BNP) and its fragment called NT-proBNP, which we can measure in the blood. It is now well established that these markers are extremely sensitive to cardiac amyloid infiltration, which they can detect in the very early stage, even though the markers can also be indicative of other primary cardiac diseases, such as atrial fibrillation or coronary disease. We would recommend that BNP or NT-proBNP be measured at least once a year, particularly in individuals with IgM monoclonal protein and high levels of free light chains in the blood with an abnormal free light chain ratio. If the level of these biomarkers is elevated, a careful evaluation by a cardiologist and echocardiography can help to detect possible early amyloid cardiac damage. Effective therapies can then be started promptly. Kidney involvement can be detected early by measuring both the level of albumin in the urine and the level of serum creatinine and then estimating the creatinine clearance by employing an established formula. These measurements should also be performed at least once a year in individuals with a serum monoclonal IgM.

In the presence of clinical manifestations or increased level of cardiac and renal markers indicating the possible presence of light chain amyloidosis, rather simple diagnostic procedures should be promptly pursued. Since amyloidosis is characterized by the deposition of fibrillar protein, the diagnosis relies on the documentation of such deposits in tissues. The most accessible tissue is the fat around the navel that can be easily and painlessly aspirated using a fine needle. Specific staining can document the presence of the amyloid deposits in almost 90% of patients. In the remaining 10% who do not show deposits but have the disease (false negatives), it is possible to search for deposits using a biopsy of the labial salivary glands that identifies amyloidosis in an additional 5% of patients. Certain clinical centers may use rectal biopsy, and that is also useful. If all these biopsies are negative, while the clinical suspicion of amyloidosis is strong, then it is possible to biopsy the affected organ, usually the kidney or the heart.

Once the amyloid deposits have been documented, it is important to make sure that they are formed by light chains in order to institute the appropriate treatment. As reported above, a significant number of proteins can form amyloid deposits. For instance, in rare cases (approximately 5%) of patients with Waldenström macroglobulinemia, the amyloid deposits are not formed by light chains but by another protein called serum amyloid A (SAA) that increases markedly in the blood when there is a chronic inflammation. This type of amyloidosis (reactive or secondary amyloidosis) requires a distinct therapeutic and monitoring approach. Furthermore, in an elderly patient with isolated cardiac involvement and an IgM spike, it is wise to exclude amyloidosis related to aging (senile systemic amyloidosis) since it requires a different therapy. If the cardiac involvement is associated with involvement of the peripheral nerves, familial amyloid polyneuropathy (FAP) should be excluded. The determination of the type of protein constituting the amyloid deposits requires a specialized approach by amyloid referral centers, and your doctor should guide you in this process.

Is amyloidosis treatable?

Light chain amyloidosis is a treatable disease, with impressive survival benefit in responding patients. The most effective therapy, at present, is the suppression of the synthesis of the misfolded monoclonal lightchains through anti-clonal chemotherapy; hence the therapies used for Waldenström macroglobulinemia are also effective for the treatment of this severe complication. In the presence of amyloid, however, rapidly acting agents are preferred since it is vital to suppress the production of the toxic light chains as soon as possible. The intensity of the therapies may be limited by the presence of heart dysfunction caused by amyloidosis. In relatively young patients without significant heart damage, autologous stem cell transplantation may be considered. Treatment should be carefully monitored with frequent evaluation of the level of serum free light chains and of markers of heart (using NT-proBNP) and kidney (using urinary albumin level and serum creatinine) function.

In patients who achieve complete suppression of the amyloid light chains and improvement in the level of cardiac or renal biomarkers, survival is greatly extended. It is very important to sustain the function of the damaged organs with supportive therapy while chemotherapy is producing its beneficial effects. Coordinated collaboration of specialists is necessary to provide the best possible supportive care. Cardiologists and nephrologists know that patients with amyloidosis require particularly careful supportive measures. In patients with low blood pressure upon rising, the use of diuretics and antihypertensive drugs requires caution. The pain caused by the nerve involvement can be controlled by using pain medication. In patients who achieve a complete and durable response to chemotherapy but with end-stage renal failure, kidney transplantation may be considered.

What are the novel treatments for amyloidosis?

Although novel agents combined in chemotherapy regimens that are both rapid and effective have greatly improved the treatment of primary amyloidosis and significantly extended the rate of survival, the outcome is still suboptimal in most patients. Intense research is ongoing to develop new treatment approaches, targeting, for instance, the amyloid deposits and promoting their resorption by clearance mechanisms of the body. Several research groups are focusing on the mechanisms of cardiac damage by toxic light chains in

order to identify new therapeutic avenues that may reduce cardiac toxicity and accelerate recovery of heart function. It is expected that such novel remedies will soon be synergistically combined with anti-clonal therapy to further improve care for patients and possibly cure this complex but treatable disease. The key to improving the care of amyloidosis is early diagnosis followed by prompt, effective therapies. The widespread use of biomarkers may facilitate the early detection of organs damaged at an early stage of this disease and lead to their full recovery.

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