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LATE (AND RARE!) COMPLICATIONS OF WALDENSTRÖM MACROGLOBULINEMIA

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Classification of Waldenström Macroglobulinemia

Waldenström macroglobulinemia is a form of malignant lymphoma. The technical terminology is lymphoplasmacytic lymphoma. Physicians who specialize in the field classify lymphoma into three types: low-grade, intermediate-grade, and high-grade. The grading assigned to a specific lymphoma reflects how biologically aggressive it is. Waldenström macroglobulinemia is referred to as a low-grade lymphoma. Low-grade means that the tumor tends to grow slowly, that very few of the cells are actually dividing at any one time, and that the genetics of the lymphoma are favorable.

With current technology, it is possible to analyze the genes and chromosomes of patients with Waldenström macroglobulinemia and other types of lymphoma. In many lymphomas, it is possible to find genes that predict for resistance to chemotherapy, poor response to rituximab, or rapid regrowth of the lymphoma after chemotherapy is administered. The gene abnormalities that predict this type of poor outcome following chemotherapy are only rarely seen in Waldenström macroglobulinemia. As a result, patients with Waldenström tend to have high response rates and a long duration of response; and in this regard, the genetics are “favorable.”

In fact, if one took a single Waldenström cell and placed it under the microscope for inspection, it would be difficult to identify that single cell as cancerous. A diagnosis of Waldenström can be established because there is a high percentage of these cells in the bone marrow. A biopsy is always required to establish a diagnosis of Waldenström. This most commonly occurs through the bone marrow, but occasionally a diagnosis can be made by biopsy of a lymph node. Virtually all patients with Waldenström require a bone marrow examination. Waldenström cells may be diffuse throughout the marrow or they may be grouped in clusters.

The low-grade designation is very good news for Waldenström patients, and this favorable biology is a major reason why the outcomes with treatment are so favorable. Typically, effective therapy shrinks the Waldenström population and can allow for years of durable response because the tumor regrows very slowly after a treatment is halted.

Large Cell Transformation (Richter’s Syndrome)

Another reason why Waldenström macroglobulinemia is classified as low-grade is that as the cell evolves from its parentage it becomes progressively more mature. Waldenström cells develop in one of two ways. In the first, a Waldenström cell divides and forms two Waldenström cells. This is not the only possible way in which Waldenström cells develop. In fact, most Waldenström cells are incapable of dividing or divide very infrequently, perhaps not even annually.

The other way a Waldenström cell can develop is from a more primitive lymphoma cell that “grows up.” This really means that the cell matures from a more primitive “parent.” Waldenström cells can be found in the bone marrow, liver, spleen, and lymph nodes. The cells, actually as they grow, will exit the bone marrow, undergo processing in lymph nodes, and then return to the bone marrow. The standard for the Waldenström cell is to start as a less mature cell and become progressively more mature with time. This maturation is an inherent property of all cells of the body. Unfortunately, in a small proportion of patients with Waldenström who have typically lived with the disease for many years, the Waldenström cell may lose its ability to mature from an immature parent B-cell into the more mature Waldenström cell. In general, as a cell matures, it shrinks in size from a larger cell to a smaller, more compact cell. In instances where genetic changes occur that prevent the maturation of the Waldenström cell, development will sometimes stop at an intermediate stage where the cell is referred to as a “large cell.”

Dr. Richter of the University of Minnesota first recognized this blockage in maturity of the lymphoma cell at a point when it does not mature beyond the large cell stage. Initially this block in maturity was erroneously supposed to represent a transformation of the lymphoma to a new type. But what actually occurs is a block in the ability of the lymphoma cell to mature. This block, which is referred to as large cell transformation, now bears the name of the doctor who recognized it and is referred to as Richter’s transformation or Richter’s syndrome. The most common type of lymphoma associated with intermediate maturity is diffuse large-cell B-cell lymphoma (DLBCL). All types of lymphoma, not only Waldenström, can undergo Richter’s transformation to DLBCL.

Large cell transformation (Richter’s syndrome) represents a change in the biologic behavior of Waldenström lymphoma. The resulting large cells tend to have more genetic abnormalities, and they tend to have a faster growth rate. As a consequence, when large cells develop, they require a more aggressive form of treatment. Treatment of patients with Richter’s syndrome usually requires some chemotherapy medications that are not often used in the treatment of Waldenström macroglobulinemia. Since all the Waldenström’s cells do not transform, patients have coexistent Waldenström and DLBCL.

Moreover, one possible complication arises because many patients have been exposed to various treatments over the years for their Waldenström. For such patients there is the potential for inherent chemotherapy resistance.

Purine nucleoside analogs such as fludarabine and cladribine have been implicated as a potential risk factor for the development of Richter’s transformation. Fortunately, the risk is low and it often occurs late. Patients and their physicians should discuss this risk before reaching a decision to proceed with fludarabine or cladribine therapy. The treatment is highly effective in the management of Waldenström, and all treatments carry side effects and toxicities, so that a risk-versus-benefit assessment is warranted. Caution should be exercised when considering purine nucleoside analogs as a treatment option.

Large cell transformation can also occur in Waldenström patients who have never been treated. Fortunately, this is such a rare occurrence that it usually is not a critical factor when decisions are made concerning treatment selection for patients. Cancer cells are genetically unstable and, thus, can change over time. Therefore, it is possible for lymphomas to change from low-grade (Waldenström) to intermediate-grade (DLBCL) even in the absence of therapy. However, this risk is only for a very small percentage of patients.

Signs of large-cell transformation may include a sudden enlargement of a single lymph node or the development of nighttime fevers or drenching sweats. The blood test for lactate dehydrogenase (LDH: part of routine blood chemistry) can rapidly rise. In all instances, a biopsy is required to establish the presence of large-cell transformation. Oftentimes, a PET (positron emission tomography) scan will show enhanced uptake in a transformed lymph node. Fortunately, diffuse large-cell B-cell lymphoma is a highly treatable form of lymphoma and can be controlled.

Central Nervous System Lymphoma (Bing-Neel Syndrome)

When Waldenström cells move out of the bone marrow they tend to collect in certain organs, usually limited to the bone marrow, liver, spleen, and lymph nodes throughout the course of the disease. The presence of Waldenström is generally restricted to these organs because the cells have a peculiar “stickiness” that keeps them within those specific sites. In rare instances late in the disease, the Waldenström cells can lose their sticky quality and begin to involve other organ systems. When this occurs the disease is referred to as ‘extramedullary disease.’ Occasionally, Waldenström cells can invade the central nervous system (CNS), which describes the brain, spinal cord, and meninges (the membranes that cover the brain and spinal cord). The development of Waldenström macroglobulinemia cells in the central nervous system was first described by Drs. Bing and Neel and carries their names as the Bing-Neel syndrome. A more accurate description would be CNS involvement with Waldenström macroglobulinemia.

Central nervous system involvement with Waldenström macroglobulinemia comes in two forms. The first is in the form of actual tumors that develop within the brain substance and cause problems such as seizures or paralysis. These tumors are typically treated with radiation therapy directly to the tumors combined with chemotherapy designed to cross into the central nervous system.

The second form of central nervous system involvement is in the form of meningitis, in which case individual cells involve the central nervous system without causing tumors. This spinal inflammation, due to the Waldenström cell accessing the central nervous system, can cause damage to the cranial nerves in the form of headaches, confusion, neck stiffness, and sporadic loss of motor function. Other symptoms can include facial paralysis, drooping eyelid, double vision, or swallowing with difficulty. These are changes associated with damage to the cranial nerves in the brainstem of the central nervous system. Rarely, the cranial nerves that control vision (cranial nerve II) and hearing (cranial nerve VIII) can be involved leading to visual or hearing loss.

This “lymphomatous meningitis” is a very dangerous complication of Waldenström and requires aggressive therapy to eradicate it. The treatments for Bing-Neel syndrome include radiation to the central nervous system and chemotherapy directly administered into the spinal fluid space. Oftentimes, intravenous chemotherapy in high doses that can cross into the spinal fluid will be concomitantly administered to help promote control of the disease. The usual chemotherapy agents are generally not usable because the central nervous system is a “protected site” where chemotherapy will not cross over. Physicians refer to a “blood-brain barrier” to indicate that medications administered through the bloodstream generally cannot access the central nervous system because of this protective barrier. For this reason, the chemotherapy may have to be administered directly into the spinal canal. Bing-Neel is rare and, as a consequence, for the management of Bing-Neel it is wise to turn to a team with experience in this syndrome. Such a team generally will include both a neurologist specializing in malignancy as well as a Waldenström expert.

Conclusion

Although both Richter's syndrome and central nervous system lymphoma are serious complications of Waldenström macroglobulinemia occurring late in the course of the disease, both complications are treatable. And, fortunately, both are so rare that most oncologists, even those whose practices include a number of Waldenström patients, never see these complications during their entire career. The complications of Waldenström, both Richter's transformation and Bing-Neel, are generally not seen early in the course of Waldenström and almost never when patients have it for a short period of time. Typically these developments occur when one has had the disease for many years, usually but not exclusively, after extensive therapy.

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