CLINICAL VIGNETTE

AntiMAG-Associated Polyneuropathy

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Case

A 61-year-old woman presents with numbness, pain, and tingling in both of her arms and her legs that has been present her entire life. She states that, even in her youth, she assumed that this was just the way individuals were supposed to feel. She also reports numbness across the tops of her shoulders and down to her hands, and has felt tingling in her torso as well. She has found that her hand numbness has at times compromised her fine-motor skills and, especially in cold weather, substantially limited finger and hand function.

Evaluation revealed the presence of anti-Myelin-Associated-Glycoprotein (anti-MAG) associated polyneuropathy, and the patient was referred to Neurology for treatment and management. She underwent multiple courses of IVIg and methylprednisolone, neither of which provided her with significant relief from her neuropathic symptoms, did not significantly alter her anti-MAG IgM titer, and were associated with debilitating headaches and nausea. Additional testing revealed a monoclonal spike of 0.2g on serum protein electrophoresis, and she was referred to HemOnc for further care. On Serum Immunofixation, the M-spike was identified as monoclonal IgM kappa protein which, when taken in conjunction with a recent bone-marrow biopsy demonstrating MYD88 mutation, was concerning for Waldenstrom Macroglobulinemia. The patient's anti-MAG IgM titer and M-spike continued to be monitored along with symptoms for two years. Her symptoms continued to worsen in conjunction with a rising anti-MAG IgM titer, reaching a historical peak at 39273 Titer Units (TU) (Normal Range 0 – 999 TU). EMG studies confirmed severe sensorimotor polyneuropathy consistent with primary demyelination. However, on the basis of anit-MAG polyneuropathy alone, usage of Rituximab was initially rejected by the patient's insurance. A few month later with increasing concern for Waldenstrom in addition to the anti-MAG, the patient was finally started on her first course of Rituximab. in two months the patient's anti-MAG titer had fallen to 31492 TU, though she had not noticed any improvements in her neurologic symptoms. She continues to be monitored by both Neurology and Hematology/Oncology, and is scheduled to begin her next cycle of Rituximab this month.

Discussion

Anti-MAG neuropathy is a rare monoclonal gammopathy that arises from the presence of a pathological expansion of plasma cells or functional B-cells in the bone marrow, leading to the secretion of auto-reactive IgM paraprotein. This paraprotein binds with high affinity to the Human Natural Killer 1 (HNK-1) epitope of the 100 kDa myelin-associated glycoprotein, a transmembrane protein involved in maintenance of myelin-axonal interactions both centrally and peripherally. Binding of anti-MAG IgM to both MAG and sulfoglucuronyl glycosphingolipid (SGPG), another IgM target localized in peripheral myelin, leads to a Type II complement-mediated hypersensitivity reaction and autoimmune destruction of axons and ensheathing myelin alike.[1] Microscopic evidence of this deposition and destruction is present in the form of characteristic widening of myelin lamellae (WML) as visualized under immunofluorescence microscopy targeting IgM in nerve biopsies, as well as the presence of complement component C3d within the epineurium of peripheral nerves.[2] Clinically, this polyneuropathy can lead to a number of signs and symptoms including paresthesia, local anesthesia, muscle weakness, gait ataxia, and even tremor.[3,4]

The presence of serum paraprotein b associates the anti-MAG condition with other conditions on the spectrum of plasma cell dyscrasias. Typically, anti-MAG neuropathy is classified as associated with a "monoclonal gammopathy of undetermined significance" (MGUS), wherein the M protein maintains a relatively low serum concentration (< 3 g/dL), the underlying plasma cell occupies less than 5% of the bone marrow on aspiration, and there are no signs of systemic disease.[3] It is noted that MGUS is named as such for historical purposes and clearly in anti-mAG cases, the gammopathy is of **known** significance since it leads to polyneuropathy. In other cases, spikes on the serum protein electrophoresis (SPEP) distribution, particularly in the γ-band can be indicators of the co-occurrence of more severe dyscrasias such as Waldenstrom Macroglobulinemia (WM), as was the case with our patient. The M protein in the context of Waldenstrom has a very clear pathogenic role, leading to a number of hyperviscosity symptoms and elevated risk for venous thrombosis.

Guidelines for the treatment of anti-MAG neuropathy do not currently exist, and the standard treatment mechanisms for managing both acute and chronic gammopathies, namely IVIg, plasmapheresis, and corticosteroids, have demonstrated no consistent ability to improve the clinical condition of anti-MAG patients in cohort studies.[3] Even broadening the scope of treatment to immunomodulatory and suppressive therapies such as Interferon α and cyclophosphamide proved unfruitful in

randomized control trials.[5] Rituximab, an anti-CD20 monoclonal antibody immunotherapy, has been the most successful treatment for anti-MAG patients that has emerged over the last decade. Though initially indicated for the treatment of CD20+ leukemias and various autoimmune conditions, Rituximab has seen considerable off-label use in the experimental treatment of anti-MAG polyneuropathy. In fact, a number of case studies have reported significant reductions in anti-MAG antibody titer and, more importantly, clinical improvement of patients undergoing such therapy. Unfortunately, patient responsiveness to rituximab is quite variable, and multiple randomized control trial studies and literature meta-analyses have reported mixed findings, [4,5] with neuropathic pain and tremor even being exacerbated in a few rare cases of anti-MAG in association with the administration of rituximab. Nevertheless, randomized control trials and retrospective reviews published to date have demonstrated that anti-MAG patients on rituximab see improvement in Inflammatory Neuropathy Cause and Treatment (INCAT) and global impression of change scores over the course of 8-12 months following treatment.[4,6]

The patient received her first course of rituximab approximately in April of 2019 and a second cycle in July of 2019. Since then has been followed by both hematology and neurology with stabilization of her neuropathy, and with a significant decline in her Anti-MAG antibody (40,675 to 18,845). However, she has not seen a dramatic improvement in her symptoms.

Conclusion

Anti-Myelin-Associated Glycoprotein (anti-MAG) neuropathy is a polyneuropathy characterized by the presence of autoreactive monoclonal IgM antibodies that deposit in and destroy the myelin of peripheral nerves. The predominantly sensory neuropathy that arises has an insidious onset, and anti-MAG etiology is often not identified until antibody titers are incredibly high and significant loss of somatic sensation and emergence of neuropathic pain occur, as with our patient. Furthermore, the lack of standard, effective treatment guidelines for this rare condition posed a challenge from a medical management standpoint. Interestingly, anti-MAG polyneuropathy is, in rare cases such as ours, associated with other plasma cell dyscrasias. Early identification of the gammopathy, though difficult, is critical for mitigating the emergence of neuropathic symptoms that might not be reversible if the pathology has been present for a significant period of time, also the case with our patient. However, the co-occurrence of anti-MAG polyneuropathy and Waldenstrom Macroglobulinemia present in this patient creates a rare opportunity to employ immunomodulatory therapy to combat both conditions concurrently.

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