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Case Report

Anti-MAG Antibody Neuropathy Treated Successfully with Pomalidomide and Dexamethasone: A Case Report

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A B S T R A C T

Anti-myelin-associated glycoprotein (MAG) neuropathy is a rare, immune-mediated demyelinating condition. It is characterised by an association with an IgM monoclonal gammopathy and the presence of pathogenic anti-MAG antibodies. Research into this field began in the 1980s. Initial therapeutic approaches aimed to reduce the M protein concentration using treatments such as plasma exchange, steroids, chlorambucil, azathioprine and cyclophosphamide. Some patients experienced partial benefit, indicating that mechanisms beyond damage solely caused by elevated M protein are involved. Consequently, immune-directed therapies, such as IVIg and rituximab, have demonstrated some efficacy in this patient group. Some case reports suggested the use of Lenalidomide as a potential therapeutic option. This is the first case report showing the successful use of pomalidomide in anti-MAG neuropathy.

Keywords: Anti-myelin-associated glycoprotein, MAG antibodies, Rituximab

1. Introduction

Peripheral neuropathy is a well-recognised manifestation of paraproteinemia, commonly referred to as paraproteinemic neuropathy (PPN). Studies have shown that paraproteins are present in 3% to 4% of individuals over the age of 50 years, more than 5% of those over 70 years and in approximately 3% to 5% of patients with chronic peripheral neuropathy[1]. Peripheral neuropathy associated with an IgM monoclonal gammopathy is characterised by a distal, acquired, demyelinating and symmetric pattern, often referred to as Distal acquired demyelinating symmetric (DADS) neuropathy with M-protein (DADS-M). This condition most frequently presents in elderly men as symmetric, distal neuropathy that primarily targets large sensory nerve fibres, leading to sensory ataxia. Although anti-MAG antibodies are found in about 50% of these patients, their presence or absence does not appear to correlate with the severity or specific type of neuropathy experienced[2].

2. Case Summary

A 65-year-old male with a known case of hypertension and a history of occasional alcohol consumption presented with an insidious onset and gradually progressive imbalance while walking for 6 years. He also complained of tremors in both

hands, symmetrical and progressive over the last 6 years. He had paraesthesia's and numbness of both feet with slipping of footwear. On examination, he was found to have wasting of the small muscles of the hands with mild weakness. Power was normal (5/5) across all 4 limbs except at the ankle, where it was 3/5. He had b/l foot-drop and coarse kinetic symmetrical tremors involving both upper limbs at the distal joints. Romberg's test was positive, along with positive cerebellar signs and an ataxic high-stepping gait.

His investigations showed near normal blood counts (Hb-11.1gm%; TLC- 11,360; Plts: 271000), ESR -12 mm. Metabolic parameters were normal except for mild hypoalbuminemia (3.3 g/dl) and elevated LDH (509). TSH and Vit B12 were normal. MRI Brain and Lumbo-sacral spine showed generalised brain atrophy, chronic ischemic changes and degenerative changes in the spine. Cerebrospinal fluid examination demonstrated a mild increase in proteins. Nerve conduction studies revealed bilateral symmetrical sensorimotor demyelinating and axonal neuropathy. His serum protein electrophoresis was suggestive of an M Band (0.33 gm%), which on immunofixation electrophoresis showed IgM Kappa subtype. Bone Marrow Aspiration and Biopsy showed a Hypercellular marrow with trilineage hematopoiesis. His anti- MAG antibody was found to be positive. He was diagnosed with Anti-MAG positive Sensory Ataxic Neuropathy. He was treated with pulse doses of methyl prednisolone (1gm for 5 days) followed by oral prednisolone in tapering doses. He developed mild breathlessness and was found to have ischemic changes on ECG. His Coronary angiography revealed stenosis of the Left Anterior Descending (LAD) and Left Circumflex (LCx) arteries. He underwent Percutaneous Transluminal Coronary Angioplasty (PTCA). Following the interruption of his neuropathy treatment due to the procedure, the patient was referred back to the neurologist. He was then started on Injection Rituximab, receiving two 1 g doses 15 days apart. The patient was followed up monthly for 4 months without any evidence of improvement.

Exhausted both financially and morally, the patient and his relatives declined any further diagnostic evaluations. Given the lack of therapeutic alternatives, a trial of low-dose immunomodulatory therapy was initiated. The patient was started on pomalidomide 2 mg daily along with dexamethasone 20 mg once weekly. After 1 month of treatment, he demonstrated early symptomatic improvement, able to stand and ambulate a few steps with support. Over the subsequent four months, his neurological function continued to improve and he was able to walk independently without support. Dexamethasone was discontinued after one year, while pomalidomide 2 mg was continued as monotherapy. Two years into treatment, the patient remains functionally independent. At the last follow-up, he was able to independently climb stairs, walk without assistance and perform all activities of daily living. His most recent immunofixation electrophoresis results continue to show an IgM Kappa level of 0.27 g%.

3. Discussion

Anti-MAG antibody neuropathy typically presents as a chronic, slowly progressive, large-fibre sensory-motor polyneuropathy, most commonly starting in the lower extremities. Clinical features often include sensory ataxia, leading to gait imbalance and the development of action-induced tremor in the fingers and hands in some patients. The condition predominantly affects elderly males. The initial symptom is usually the neuropathy itself. Neurological signs develop gradually over one to two decades, sparing the cranial nerves and progress slowly, leading to cumulative disability over the years[3].

The pathophysiology of Anti-MAG neuropathy is largely attributed to IgM antibody-mediated damage to the myelin glycoprotein, causing thinning of the myelin and widening of the myelin lamellae. The link between this condition and IgM monoclonal gammopathy is thought to arise from both B-cell clonal proliferation and accompanying autoimmune processes[4].

Therapeutic strategies in anti-MAG neuropathy have traditionally focused on immune-directed treatments like corticosteroids, IVIg and plasma exchange with variable and often transient benefit. Cytotoxic agents such as chlorambucil, cyclophosphamide and fludarabine can reduce IgM production but are associated with significant toxicity, limiting their long-term use[5]. Rituximab, a CD20-directed monoclonal antibody, has been the most widely studied agent; however, observational studies suggest some benefit in approximately 30-50% of patients. In a double-blind, placebo-controlled study, an improvement of at least 1 point in the INCAT lower limb disability scores was observed in 4 out of 13 patients after 8 months. However, this change, which was the study's aim for detecting a change of 1 or more, did not achieve statistical significance[6].

Immunomodulatory drugs (IMiDs) have a biologically plausible role in paraproteinemic neuropathies due to their antiplasma cell activity, inhibition of pro-inflammatory cytokines and suppression of monoclonal immunoglobulin production. Lenalidomide has previously been explored in anti-MAG neuropathy, with early case reports suggesting benefit[7,8]. It also showed a response in combination with rituximab[9]. However, a recent phase 1 study demonstrated limited clinical efficacy and a higher-than-expected incidence of venous thromboembolism, raising concerns regarding its long-term safety in this population. These findings underscore the need for alternative agents with improved tolerability[10].

Pomalidomide, a third-generation IMiD, has enhanced immunomodulatory potency with a more favourable toxicity profile compared to earlier agents. Although data on pomalidomide in anti-MAG neuropathy are lacking, its efficacy in other monoclonal gammopathy–associated conditions and its ability to suppress IgM-producing clones provide a strong mechanistic rationale for its use. Pomalidomide exerts its effects through multiple mechanisms, including directly inhibiting tumour cell proliferation and inducing apoptosis and enhancing the immune system's ability. Additionally, pomalidomide interferes with the tumour supportive microenvironment, including stromal cells that shield myeloma cells from immune responses. These multifaceted actions make pomalidomide an effective therapeutic option in treating resistant or relapsed myeloma. Evidence supports the effectiveness and tolerability of pomalidomide-dexamethasone combination in patients who have already been treated with lenalidomide and bortezomib[11]. Expert guidelines recommend the standard starting dose for this therapy is 4 mg of pomalidomide, taken on days 1-21 of each 28-day cycle, along with a weekly dose of 40 mg of dexamethasone. However, a phase 2 trial with 35 patients per

cohort demonstrated an overall response rate (ORR) of 49% in the 2-mg group and 43% in the 4-mg group, with no clear advantage of the higher dose. The 6-month overall survival rate was 78% for the 2-mg group and 67% for the 4-mg group[12].

In this context, the present case is notable for the magnitude and durability of neurological improvement achieved with low-dose pomalidomide and dexamethasone. The patient demonstrated early symptomatic improvement within one month, followed by sustained functional recovery over several months, eventually regaining full independence in ambulation and activities of daily living. In conclusion, this case provides preliminary evidence that pomalidomide, in combination with dexamethasone, may represent a promising and well-tolerated therapeutic option in selected patients with refractory anti-MAG neuropathy.

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