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Letters to the Editor

Monoclonal Gammopathy of Neurological Significance: A Case Report and Insights on Treatment

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To the editor.

Monoclonal gammopathy (MG) is a frequently detected clonal B cell or plasma cell disorder, traditionally considered a premalignant condition preceding non-Hodgkin lymphomas (NHL) and Multiple Myeloma (MM). However, it is long known that MG can cause organ damage independently from tumor growth: the best-known instances are AL amyloidosis and IgM-associated peripheral neuropathy. Nowadays, these clinical entities are classified as monoclonal gammopathies of clinical significance (MGCS).[1-3]

Here we describe a case of a 61 years old male with monoclonal gammopathy IgM kappa and sensorimotor polyneuropathy (PN), unresponsive to high-dose corticosteroids and high-dose intravenous immunoglobulins (IVIGs) in February 2023. Blood count, renal function, calcium levels, kappa/lambda free light chain ratio, and cerebrospinal fluid physical-chemical examination showed no abnormalities. Bence-Jones proteinuria was absent. A total body CT scan with contrast medium revealed hepatomegaly (LD right lobe 18 cm) with steatosis and no other abnormalities. A high titer (72142 BTU) of anti-myelin-associated glycoprotein antibodies (anti-MAG) and a positivity for anti-sulfatide IgM antibodies were reported. Bone marrow needle aspiration and biopsy showed a small lymphoplasmacytic clone (< 5%). Therefore, a diagnosis of monoclonal gammopathy of neurological significance (MGNS) was made. Then, a cycle of four weekly doses of Rituximab (RTX) (375 mg/m² IV) was administered, with initial symptomatic and biochemical response (58773 BTU) followed by a flare-up (75000 BTU) confirmed by worsening of electroneuromyographic evaluation. Subsequently, in May 2023, 5 sessions of plasmapheresis (PE) were performed (45058 BTU). Hence, 4 monthly RTX (375 mg/m² IV), each preceded by 2 PE sessions, were performed with a clinical improvement but no biochemical (59000 BTU) or electromyographic response (**Figure 1**). After 18 months of follow-up, the patient maintained clinical improvement and biochemical stability.

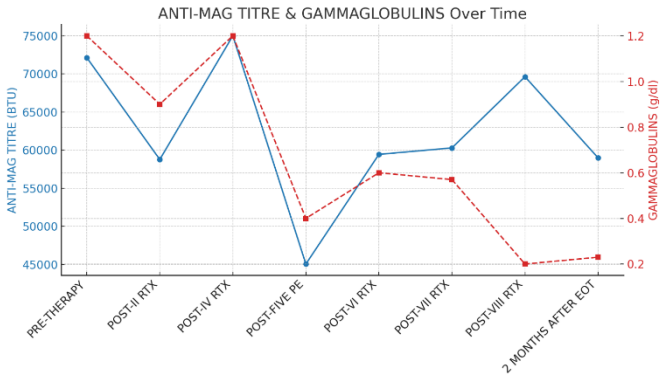

Figure 1. Anti-MAG titre and gammaglobulins trend.

PE was performed using the Fresenius continuous filtration system, exchanging one blood volume per session with human serum albumin in saline.

MGNS is defined as a PN caused by a monoclonal gammopathy without a diagnosis of malignancy (e.g., Waldenström Macroglobulinemia), which means it is a diagnosis of exclusion. They are classified on the basis of the type of monoclonal protein (IgM vs IgG/IgA) and the type of neurological damage (demyelinating, axonal, mixed).[4] Generally, PN is sensory rather than motor, symmetrical, length-dependent, and of slow progression in the context of IgM paraproteinemia, which can be indistinguishable from chronic idiopathic demyelinating polyneuropathy (CIPD). A nerve biopsy should be performed to assess the causality link between MG and the PN; however, it is not routinely performed as it is associated with permanent sensory or motor deficits and pain in the area distal to the biopsy.

The most common form is the IgM-related MGNS, in which anti-MAG, anti-ganglioside, and/or anti-sulphate-3-glucuronyl paragloboside antibodies can be

found. It's characterized by demyelinating PN. Rarely, it can cause a syndrome characterized by chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins, and disialosyl antibodies (CANOMAD).[5]

There is no consensus or guidelines on the treatment of MGNS. IVIGs and corticosteroids proved of no or little help, as did alkylating agents and nucleoside analogs.[4-6] It is long known that PE and RTX are useful in the management of MG-associated PN. PE is useful for managing acute symptoms, reducing rapidly the titre of paraprotein, and RTX can lead to a functional benefit of variable duration in 30-50% of patients.[4-7]

A recurrent somatic point mutation of the myeloid differentiation factor 88 (MYD88) gene, leading to an amino acid change from leucine to proline (L265P), is present in 50% of cases of MGNS.[8] This mutation is present in > 90% of cases of Waldenström Macroglobulinemia (WM), too, underlying the presence of biological similarities between the two entities.[4] As in WM, Bruton kinase inhibitors (BTKi) could be a potential therapeutic strategy. In small case series, promising results with ibrutinib and acalabrutinib were reported. In particular, a recent prospective single-arm trial enrolling 7 patients showed that the combination of acalabrutinib and rituximab could be promising (86% hematologic responses, 57% neurological improvement).[9] For these reasons, in the absence of standardized treatment regimens, it is recommended to follow WM guidelines.[4-5,10-12]

MGNS represents a novel entity and an unmet clinical need without a codified therapy. The available therapies have not been particularly effective, as shown in our experience. BTKi could be promising drugs in this setting, as in WM.

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