Sustained Response of Ibrutinib in a Patient with Waldenstrom Macroglobulinemia Presenting with Myasthenic Crisis as a Paraneoplastic Neurological Syndrome: A Case Report and Review of Literature

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ABSTRACT

Paraneoplastic syndrome is a broad spectrum of signs and symptoms due to neoplasm, attributed to substances produced by tumor cells, or in response to it. Myasthenia gravis (MG) is a well-known paraneoplastic neurological syndrome (PNS), frequently associated with thymic abnormalities, but rarely reported in patients with lymphoplasmacytic lymphoma.

This study presents the case of a 52-year-old Indonesian male patient who was diagnosed with Waldenstrom macroglobulinemia (WM), a rare B-cell neoplasm, after developing a new onset of MG with myasthenic crisis. the patient's MG features improved with Ibrutinib as a treatment targeted toward cancer. This is the first case report presenting the treatment response of Ibrutinib in WM with myasthenic crisis. The literature was reviewed to explain the possibility of MG as a paraneoplastic syndrome of WM and the treatment response of Ibrutinib for this patient, as well as summarizing previous case reports of concomitant MG and WM.

MG should be considered a paraneoplastic malignancy syndrome, including WM, during diagnostic workup. Ibrutinib should also be considered when available to patients, due to its adequate response in both previously treated and treatment naïve patients.

***Keywords**: Paraneoplastic, Myasthenia Gravis, Ibrutinib, Waldenstrom Macroglobulinemia.*

INTRODUCTION

Paraneoplastic syndromes are a broad spectrum of signs and symptoms that occur as a consequence of neoplasm. These syndromes are not caused by the tumor but are attributed to substances produced or as a response. Paraneoplastic neurological syndrome (PNS) occurs due to cross-reactivity between immune system components directed to tumor cells and the nervous system. It often precedes the diagnosis of systemic cancer, assisting the diagnosis of malignancy in earlier stages.

Myasthenia gravis (MG), an autoimmune-mediated disease affecting the neuromuscular junction is a well-known PNS associated with thymic abnormalities. However, in the last 50 years, very few published reports of myasthenic patients with monoclonal gammopathy have been published. Only 5 cases were associated with Waldenstrom Macroglobulinemia (WM). We present a case of a 52-year-old male patient who was diagnosed with WM, following a new onset of MG with a myasthenic crisis.

CASE ILLUSTRATION

A 52-year-old male patient was admitted to our emergency unit due to a myasthenic crisis with dyspnea and respiratory failure. He was transferred from another hospital and was already intubated when presented to our facility. Two days before admission, he had worsening symptoms of dyspnea and generalized weakness. Over the last five months, the patient experienced generalized weakness, intermittent shortness of breath, and slurred speech, as well as swallowing difficulties. These symptoms more often occurred with moderate physical activity and improved with rest. Ptosis, diplopia, and weakness of limbs were absent. Past and familial medical history was unremarkable. The patient had not been diagnosed with myasthenia gravis until the onset of the myasthenic crisis.

On admission, the patient was alert and mechanically ventilated. His vital signs were (on norepinephrine 0.05 mcg/kg/min). Neurological examinations revealed normal motor strength on all four limbs and reduced physiological reflexes on both lower limbs. Other physical examinations were unremarkable. The repetitive nerve stimulation (RNS) test illustrated a decremental response of compound muscle action potential (CMAP) amplitude at the trapezius and deltoid muscle with 19.3% and 23.4% reduction between the first and fourth train, respectively. Single fiber electromyography (EMG) was not performed because of the electric artifact in the intensive care unit (ICU) ward. Nerve conduction studies (NCS) showed no electrophysiological evidence of peripheral neuropathy. Anti-acetylcholine receptor (AChR) antibody as an essential biomarker was undetected. Regardless of the negative anti-AChR antibody, an initial diagnosis of myasthenic crisis in MG was made based on the clinical picture, considering a proportion of patients could have other autoantibodies, such as anti-muscle tyrosine kinase (MuSK) or anti-lipoprotein-related protein 4 (LRP4), or are seronegative. Anti-MuSK or anti-LRP4 antibodies were not tested since they were unavailable in the facility.

The patient was treated with therapeutic plasma exchange (TPE) along with oral pyridostigmine 60 mg 3 times daily and oral prednisolone 20 mg once daily for his myasthenic crisis. His condition gradually improved 2 weeks after taking the medication and five rounds of TPE, thus the patient was extubated. Upon admission, the patient's Myasthenia Gravis composite score (MGCS) was 22, which significantly decreased to 6 when discharged from the hospital. The reduction in MGCS signifies a positive response to the combined treatment of TPE, pyridostigmine, and prednisolone administered during the patient's care.

Several examinations were conducted throughout the patient's hospitalization. Laboratory data showed moderate normocytic anemia, with a Hb level of 9,7 g/dL. Serum protein electrophoresis indicated a monoclonal spike over gamma fraction (**Figure 1**) and a band of mu heavy and kappa light chain in serum immunofixation (**Figure 2**). The patient had high IgM levels of 588 mg/dl (normal value of 40-320 mg/dl). Whole-body Positron Emission Tomography (PET) – CT scan was unremarkable. Bone marrow biopsy showed hypercellular bone marrow with an evident population of CD20-positive small lymphocytes, mixed with CD138 and CD38-positive population of plasma cells. Immunophenotyping from bone marrow aspiration demonstrated the following antigenic expression pattern: CD5 (-), CD10 (-), CD23 (-), CD25 (-), CD 43 (-), CD200 (-), CD19 (+), CD20 (+), LAMBDA (+). A diagnosis of Waldenstrom Macroglobulinemia was made based on the demonstration of elevated serum IgM, IgM monoclonal protein on immunofixation, and histological evidence of bone marrow infiltration by clonal lymphoplasmacytic cells. Based on the

Revised International Prognostic Score System of Waldenstrom Macroglobulinemia (rIPSSWM) following the parameters of B2 microglobulin 2.46 mg/dL, albumin 2.50 g/dL, LDH 107 IU/L, and age <65 years old, the patient was considered as low risk. The estimated 3-year WM-related mortality for this stage is 10%.

Following discharge, the patient attended follow-up consultations at the outpatient neurology and hematology clinic. The patient was administered Rituximab at a dose of 375 mg/m2 on day 1 of weeks 1 through 4, as per the guidelines outlined in the iNNOVATE study, and also received oral ibrutinib at a dose of 420 mg per day. Treatment for MG consisted of pyridostigmine and prednisolone, which was tapered off after the improvement of MG symptoms. Due to the coronavirus pandemic, the intravenous Rituximab treatment during weeks 17-20 was omitted, and ibrutinib monotherapy was continued. The patient responded well to Ibrutinib treatment with sustained clinical remission of MG, no new symptoms, or signs of active WM disease, no significant adverse events, and a good quality of life throughout the treatment. In the last evaluation after 9 months of Ibrutinib, the laboratory parameters showed significant improvements, where IgM levels decreased from 588 to 382 mg/dL and Hb levels increased from 9.7 to 13.9 g/dL. The patient died nine months later due to respiratory failure after contracting COVID-19. There was no autopsy, and at the time of death, MG and WM remained in clinical remission.

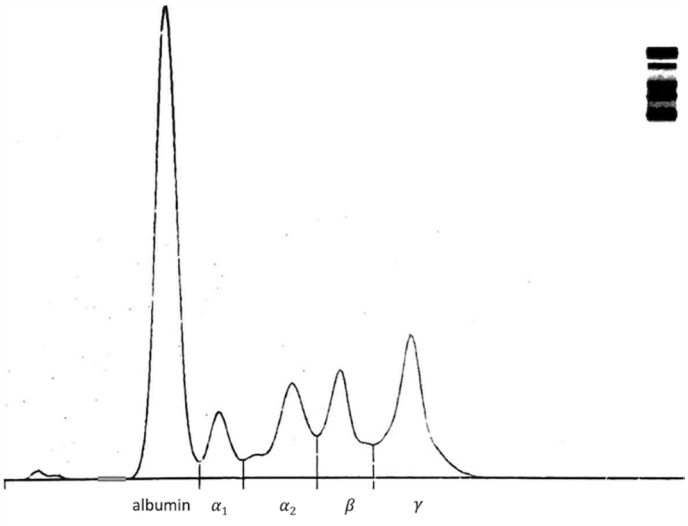

Figure 1. Serum protein electrophoresis-monoclonal spike over gamma fraction.

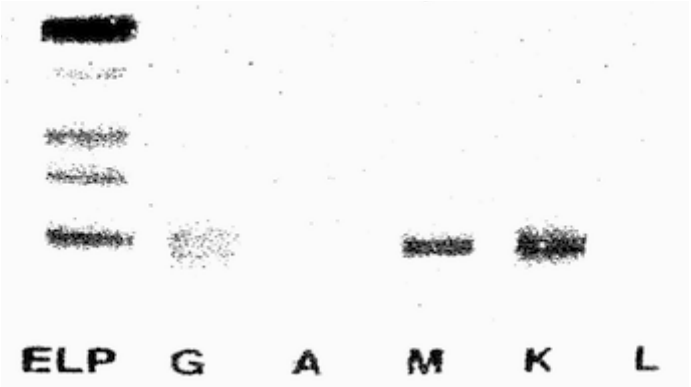

Figure 2. Immunofixation electrophoresis-IgM kappa monoclonal gammopathy.

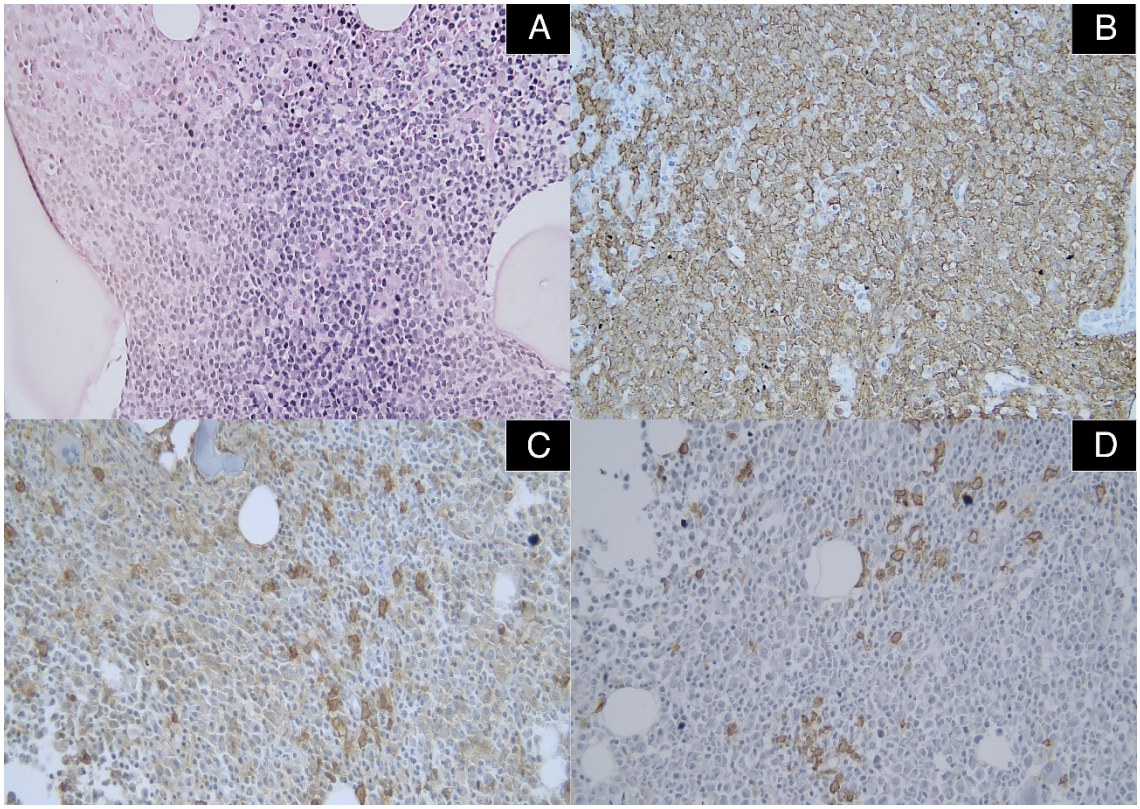

Figure 3. A. Hypercellular marrow with increased small lymphocytes admixed with plasma cells (Hematoxylin & Eosin, 400x) B. CD 20 positive (IHC, 400x) C. CD 38 only positive in small reactive T lymphocytes (IHC, 400x) C. CD 138 showed positive in plasma cells (IHC, 400x).

DISCUSSION

Myasthenia gravis is an autoimmune disease in which autoantibodies target the components of the postsynaptic endplate, causing impairment of neuromuscular transmission Fluctuating muscle weakness and fatigability due to dysfunction of the neuromuscular junction are the primary symptoms of the disease. Approximately 80% of patients produce autoantibodies to the acetylcholine receptor (anti-AChR), while the rest produce other autoantibodies, such as anti-MuSK and anti-LRP4, or are seronegative. MuSK and LRP4 are responsible for the clustering of the AChR in the postsynaptic membrane by assembly and activation of the agrin-LRP4-MuSK Complex.[1] Our patient was seronegative for anti-AChR. We did not further test the patient for anti-MuSK. The diagnosis of MG was based on the patient's symptoms, RNS, and treatment response to TPE for a myasthenic crisis, which was deemed sufficient.

Waldenstrom macroglobulinemia (WM) is an indolent non-Hodgkin lymphoma characterized by bone marrow infiltration of small lymphocytes and an IgM monoclonal gammopathy.[2] Patients with WM present with anemia, thrombocytopenia, hepatosplenomegaly, lymphadenopathy, or hyperviscosity. The patient's laboratory studies, bone marrow pathologic examinations, and immunophenotyping were consistent with the criteria for WM, as defined by the 2017 World Health Organization classification of tumors of the hematopoietic and lymphoid tissue.[3]

The patient in our case report represents a unique manifestation of illness in which there was an acute and time-related correlation in the onset and resolution of MG after the administration of Ibrutinib and Rituximab for the treatment of WM. Clinical suspicion suggests a plausible association between the two pathologies, as MG represents a paraneoplastic syndrome of WM.

Paraneoplastic neurological syndromes (PNS) result from cross-reactivity between tumor-directed antibodies and components of the nervous system.[4] A well-known form of PNS of the neuromuscular junction is

myasthenia gravis (MG), with Lambert-Eaton myasthenic syndrome (LEMS) being the other.[5] The diagnosis of LEMS was excluded since the patient did not exert pathognomonic symptoms, such as proximal weakness and autonomic dysfunction. It is important to note that most MG cases are non-paraneoplastic, with around 90% of cases not being associated with any underlying malignancies. MG is a paraneoplastic syndrome when related to thymoma and very rarely associated with other carcinomas.[5] However, there are multiple published case reports suspecting MG as a paraneoplastic syndrome of various malignancies other than lymphoma.

A search of available reports was performed in PubMed and EMBASE using the terms "myasthenia gravis" and "lymphoplasmacytic lymphoma" or "Waldenstrom macroglobulinemia". Papers were reviewed by two of the authors (A.M.L and G.A). Data from patients and important points from the studies are summarized (**Table 1**). There are 5 reported cases in the literature, with WM and MG,[6–10] before the approval of ibrutinib for Waldenstrom macroglobulinemia treatment. In cases reported by Lin et al.[7], Valles-Antuna et al.[8], and Malkan, et al.[9], the patient initially presented with clinical symptoms of MG, without any suspicion of an underlying malignancy. WM was diagnosed simultaneously or within a short period after a workup for diagnosis of MG. In a case reported by Rezania et al.[10], the patient was diagnosed with WM six years before the first onset of MG. AChR antibodies were present in two cases, and MuSK antibodies were detected in another. Meanwhile, four of the case reports described the treatment choices of WM given to the patients. Rituximab was administered in two cases, and R-CHOP chemotherapy and chlorambucil were given in the remaining cases. In the report by Valles-Antuna et al.[9], treatment of WM with Rituximab was associated with an improvement of MG symptoms and anti-MuSK titers.

Table 1. Previous reports of patients with concomitant myasthenia gravis and Waldenstrom macroglobulinemia.

Case	Age/sex/Ab*	Case Features	Timing of diagnosis of MG to WM	Treatment and response
Bartoloni 1981 [6]	NA	IgM AChR receptor antibodies were not present	WM was diagnosed in patients with MG before thymectomy	NA
Lin 2001 [7]	78/M/+	WM with Myasthenia gravis of ocular type	WM was diagnosed during MG workup	Chlorambucil. MG responded well with a cholinesterase inhibitor and corticosteroid before starting treatment for WM
Rezania 2011 [10]	62/M/+	Initial presentation of MG including ptosis, diplopia, and leg weakness. The recurrence of WM was 10 years after the initial diagnosis.	MG was diagnosed 6 years after diagnosis and treatment of WM	First onset of WM: not responsive to rituximab, responded well to cladribine On onset of MG: pyridostigmine, rituximab. (Rituximab was omitted due to an allergic reaction). The patient responded well after the addition of Prednisone and cyclosporine
Malkan 2014 [9]	24/F/NA	Presented with chronic fatigue and nosebleeds. The patient had a history of thymectomy due to MG	WM was diagnosed after MG	R-CHOP chemotherapy and pyridostigmine
Valles-Antuna 2014 [8]	49/M/+ MusK	Presented with diplopia. Exacerbation after initial treatment requires mechanical ventilation. WM and MG have sustained remission in rituximab.	WM was diagnosed during MG workup	Rituximab, pyridostigmine and corticosteroid with excellent response. The patient remains stable after 6 years, without treatment.

The primary therapy for WM for this patient was Ibrutinib, a Bruton's Tyrosine Kinase (BTK) inhibitor, combined with Rituximab, a monoclonal anti-CD20 antibody. BTK is a non-receptor tyrosine kinase in the B-cell receptor signaling pathway, in which its activation promotes B-cell survival and differentiation.[11] Constitutively active BTK is found in 90% of WM patients with activating mutation of MYD88L^{265P12}. Therefore, BTK inhibitors were approved as a treatment for WM, considering the nature of the disease is a B-cell lymphoproliferative neoplasm. In the studies by Treon et al.[13] and Dimopoulos et al.[14] of symptomatic, previously treated WM patients (including rituximab-refractory patients), Ibrutinib 420 mg daily resulted in an excellent overall response rate of 90% in both studies. In another study by Treon et al.[15], involving treatment-naïve patients with WM, the administration of Ibrutinib at a daily dosage of 420 mg resulted in an overall response rate of 100%, with 83% of patients exhibiting a major response. This study also highlighted that after Ibrutinib treatment, median serum IgM levels declined, and hemoglobin levels increased. Meanwhile, the 18-month progression-free survival for treatment-naïve WM patients treated with Ibrutinib was 92% (95% CI, 73%-98%).[15] The iNNOVATE study, a randomized phase III trial compared the efficacy of rituximab + ibrutinib to that of rituximab in WM patients. The study had a follow-up period of 50 months, during which the progression-free survival (PFS) was not reached with rituximab + ibrutinib, compared to 20.3 months (13.0-27.6) with rituximab monotherapy.[16] The safety profile for Ibrutinib + rituximab was manageable, with the prevalence of grade 3 $\geq$ adverse events clinically decreased over time. Treatment for WM with Ibrutinib in our patient, who is treatment-naïve, resulted in a sustained decrease of IgM and absence of MG symptoms.

The reduction of serum IgM to the normal range with no new symptoms and signs of active disease indicated a very good partial response. This response was aligned with the criteria for a complete response in WM.[17]

CONCLUSION

The presented case underscores the significance of conducting a thorough workup for patients diagnosed with MG, given the potential association with an underlying malignancy. Further studies are required to establish a correlation between MG and WM as a paraneoplastic disorder, as several case reports have been published over the years. Ibrutinib should be considered when available to patients, due to adequate response in treated naïve patients.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICS STATEMENT

Informed consent was obtained from the patient to publish this case report.

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