

## Successfully Treated Waldenstrom Macroglobulinemia with Nine-year Follow-up: “Case Report and Review of Neurologic Manifestations”

Melanie Leigh D Supnet<sup>1</sup>, James Daniel H Villanueva<sup>2</sup>, Laurence Adlai Morillo<sup>3</sup> and Raymond L Rosales<sup>1,2\*</sup>

<sup>1</sup>Department of Neurology and Psychiatry, University of Santo Tomas Hospital, Manila, Philippines

<sup>2</sup>Department of Internal Medicine, Metropolitan Medical Center, Philippines

<sup>3</sup>Department of Internal Medicine, Section of Hematology, University of Santo Tomas Hospital, Philippines

\*Corresponding author: Rosales RL, University of Santo Tomas Hospital, Manila, Philippines, Tel: 639209195184; E-mail: rrosalesmd88@gmail.com

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### Abstract

Waldenström's Macroglobulinemia (WM) is a rare disease, accounting for approximately 6% of all B cell lymphoproliferative disorders, with clinical features that are due to either infiltration of neoplastic cells or properties of the circulating IgM. This case report documents a Filipino-Chinese woman who had constellation of anemia, thrombocytopenia, cranial and spinal involvement, and sensory-motor polyneuropathy. Further evaluation showed clear pattern of WM demonstrated by IgM monoclonal gammopathy, presence of plasmacytoid cells on bone marrow aspirate and biopsy, and presence of B-cell markers on flow cytometry. Regimen of dexamethasone, rituximab and cyclophosphamide was given every 21 days for six courses. Follow-up studies showed negative results in serum protein and IgG electrophoresis. Repeat electrodiagnostic studies showed improved demyelinating neuropathies of the affected nerves and repeat neuroimaging showed reduction in size of the previously noted intracranial nodules and clearing of the spinal cord lesions. Appropriate treatment and follow up is very important in treating patients with WM. This report documents a serially monitored patient who remained in remission for nine years after prompt initiation of treatment. A review focusing on the neurologic sequel of WM was then performed.

**Keywords:** Waldenstrom's macroglobulinemia; Cranio-Spinal involvement; Peripheral Neuropathy; Case report

### Introduction

Waldenström macroglobulinemia (WM) also known as "lymphoplasmacytic lymphoma (LPL)," is a rare malignancy of the lymphoplasmatoid cells that secrete monoclonal IgM paraproteins [1,2]. It usually affects those in the 6th decade of life, with a male predominance and highest incidence among Caucasians with an incidence of 1000-1500 new cases of WM every year in the USA [3]. The overall incidence of WM is approximately 3 per million persons per year and accounts for approximately 1% to 2% of hematologic cancers [4,5]. The 5-year relative survival (RS) of patients who are diagnosed with WM starting in 2000 is 78% and 10-year RS is 66% [3]. Few studies were done regarding its incidence in Asia, and in a latest demographic data by the Surveillance, Epidemiology and End Results database (SEER) in 1992-2001 the incidence of WM among males is 0.29 per 100,00 persons per year and for females it is 0.27 [6].

WM's common presentations are blood hyperviscosity, cytopenias lymphadenopathy, and hepatosplenomegaly. Patients may develop immune-mediated peripheral neuropathy, which may be a result of paraprotein directed against myelin-associated glycoprotein (anti-MAG) or glycolipids [7]. The most common entity is a distal, symmetric, chronic demyelinating peripheral neuropathy, which occurs in nearly half of the patients and hyperviscosity-related nervous system disorders are encountered in up to a third. Other neurological complications, such as encephalopathy or myelopathy caused by direct tumor infiltration, paraprotein deposition or autoimmune phenomena, are rare. Findings of tumor infiltration with evidence of

hyperglobulinemia describe the presence of Bing Neel syndrome which is a rarely documented condition [8].

The etiology of WM is unknown, but there are reports of multigenerational clustering and familial patterns which indicate the possibility of a single genetic defect. The most recurrent genetic defect observed is the deletion in Chromosome 6q, which is responsible for tumor suppression [5,6]. Some somatic mutations are also documented as part of the pathogenesis of WM, the most common is MYD88 followed by CXCR4WHIM mutation [7]. Other studies suggest a monocytic lymphocytic component is almost always detected, typically with high levels of surface CD19, CD20 and immunoglobulin light chain expression [9,10]. In the past, there was no first line therapy proposed for the treatment of WM, however single-agent alkylators (e.g. Chlorambucil) or nucleoside analogs (e.g. Fludarabine) were the standard choices for first-line therapy [11]. With the advancement of science, emergence of other novel alternatives for treatment of WM has emerged, and anti-CD20 monoclonal antibody Rituximab, being one of those [12]. Dimopoulos and co-workers [11] reported on the use of the DRC (dexamethasone, rituximab, cyclophosphamide) regimen in previously untreated patients with symptomatic WM. In this study, we will show documented evidence that a patient treated with DRC regimen may achieve complete remission.

### Presenting Concerns

The subject of this report is a 63-year-old, right-handed, single, non-diabetic and non-hypertensive Filipino-Chinese female who had several admissions starting August 2005 because of anemia and thrombocytopenia, and was managed as a case of dengue. She also had complaints of recurrent fever, abdominal pain and dyspnea. Further evaluation showed presence of pleural effusion on the right lung. Three

months after, she developed sub-acute, slowly progressive numbness of distal extremities and right hemiparesis. Correlations of the finding of anemia, Central Nervous System (CNS) involvement demonstrated by cranial MRI, peripheral neuropathy seen through nerve conduction studies and IgM-Kappa on serum protein electrophoresis, WM was considered.

Most patients diagnosed with WM have symptoms attributable to tumor infiltration or to presence of monoclonal serum protein (or both). Extensive bone marrow infiltration leads to cytopenias and progressive anemia that was the initial presentation of our patient. Symptoms of abdominal pain and presence of pleural effusion may be attributed to diffuse lymphoplasmacytic infiltration of the pulmonary parenchyma and malignant infiltration of the stomach and bowel. The larger size and increased concentration of the monoclonal protein leads to an increase in vascular resistance and viscosity, which explains the constitutional symptoms and neurologic manifestations.

In July 2007, the patient received regimen of DRC. Because WM is a chronic, indolent, lymphoproliferative disorder, the patient was closely monitored for nine years.

### Clinical Findings

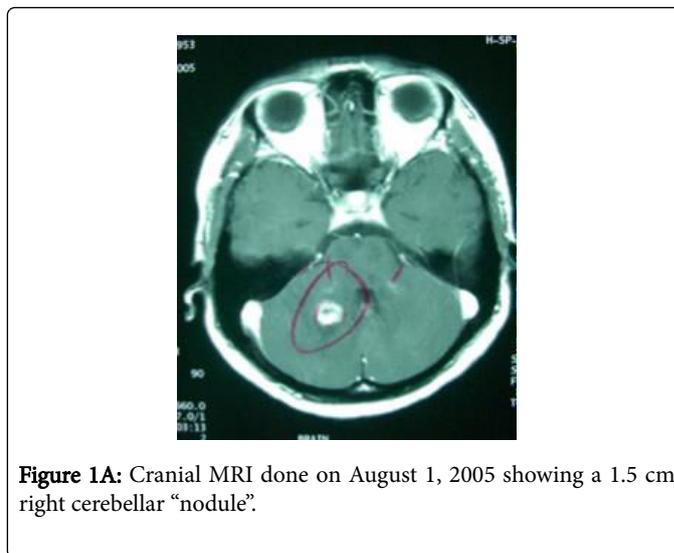
The patient initially had episodes of generalized weakness and anorexia. She presented with a peripheral neuropathy described as numbness of the distal upper and lower extremities gradually progressing to involve only the left side of the face and right upper and lower extremity. No motor weakness was noted initially however few months after, she noted stiffness of the right lower extremities and worsening of penmanship. She complained of sudden buckling of her knees and difficulty hoisting her. Neurologic examination showed a facial asymmetry (larger left palpebral fissure and shallowness of left nasolabial fold), 20% sensory deficit on left V1, V2, V3 and right upper and lower extremities, difficulty on tandem gaiting with normoreflexive deep tendon reflexes on both upper and lower extremities. Nystagmus or skewed deviation was not observed. Pathologic reflexes and meningeal irritation signs were not evident.

### Diagnostic Focus and Assessment

WM is a chronic, indolent lymphoproliferative disorder with spectrum of clinical manifestations. Performing protein electrophoresis, immunoglobulin quantitation and hyperviscosity measurements are critical in patients who present with unexplained fatigue, weakness, neurologic symptoms and neuropathies because hyperviscosity symptoms can be life threatening as with our patient. To establish the WM diagnosis, an IgM monoclonal protein and BM lymphoplasmacytic lymphoma (LPL) infiltration must be present [13].

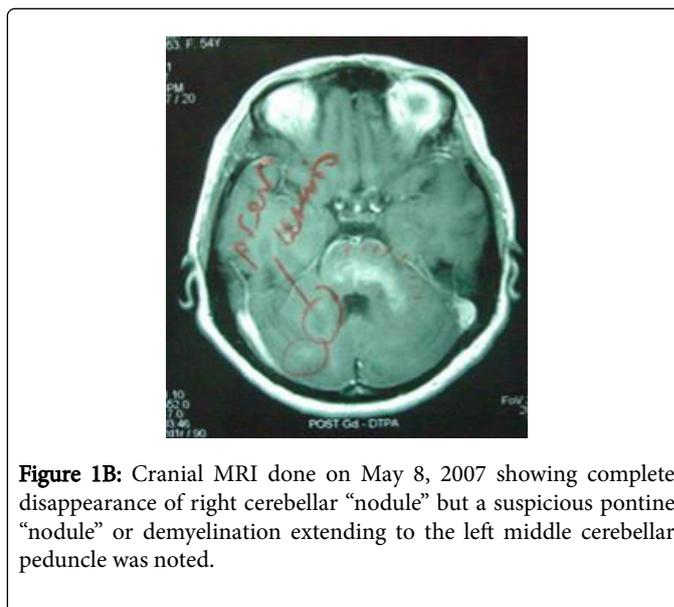
The World Health Organization (WHO) Lymphoma Classification [14,15] the consensus group formed at the Second International Workshop on Waldenström's macroglobulinemia [16] and Mayo Clinic [17] attempted to better define WM in recent years. Although the respective definitions of the diagnostic criteria for WM by these groups are not identical, all groups recognize WM as lymphoplasmacytic lymphoma associated with an IgM monoclonal protein in the serum.

A cranial MRI was requested in August 1, 2005 showing a 1.5 cm "nodule" at the right cerebellum in which demyelinating plaque was initially considered elsewhere (Figure 1A).



**Figure 1A:** Cranial MRI done on August 1, 2005 showing a 1.5 cm right cerebellar "nodule".

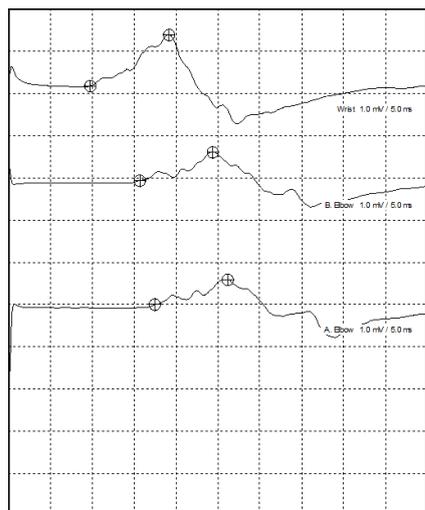
Intravenous methylprednisolone at 1g/day was given for five days which was shifted to oral form and subsequently tapered. A repeat cranial MRI done 2 months after steroid therapy showed marked reduction in size of the "nodule". Demyelinating disease was considered during that time. A year after, the patient had episodes of fever, body malaise and anorexia. Complete blood count showed anemia and thrombocytopenia. It was also during this time that she complained of numbness on the left side of her face and right distal extremities. She soon developed ascending weakness that was worse on the right. Nerve Conduction Studies (NCS) and visual evoked potential studies done elsewhere showed unremarkable results. Repeat cranial MRI done last May 8, 2007 revealed complete disappearance of the right cerebellar "nodule". However, multiple contrast-enhancing abnormalities, extending horizontally across the posterior half of the pons and into the middle cerebellar peduncles bilaterally, with left greater than the right were appreciated (Figure 1B).



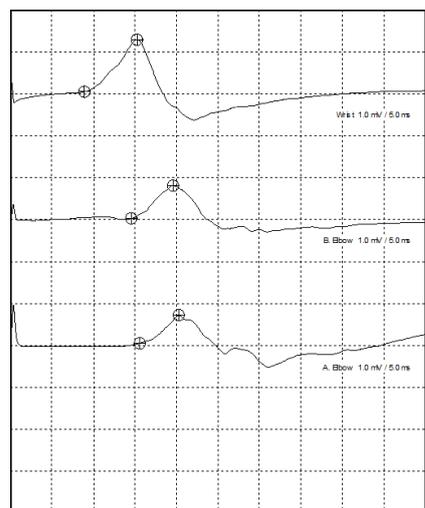
**Figure 1B:** Cranial MRI done on May 8, 2007 showing complete disappearance of right cerebellar "nodule" but a suspicious pontine "nodule" or demyelination extending to the left middle cerebellar peduncle was noted.

MRI of the thoracic spine also revealed signal abnormality and contrast enhancement from T3 cord level to the conus medullaris, and the main consideration was a demyelinating process. CSF analysis

revealed normal pressure but elevated protein at 90.6 mg/dL. CSF cytology showed acellular smears following cytopspin and CSF aquaporin-4 antibody was not detected. The neuropathic presentation of distal numbness persisted, and a repeat NCS, performed this time from our service, yielded mainly a demyelinating neuropathy. The NCS showed delayed distal latencies, and prolonged velocities of the motor median, ulnar, fibular and tibial nerves. There was wave dispersion upon stimulation of ulnar nerve and F-wave responses of the median, ulnar and tibial nerves were prolonged (Figures 2A and 2B).



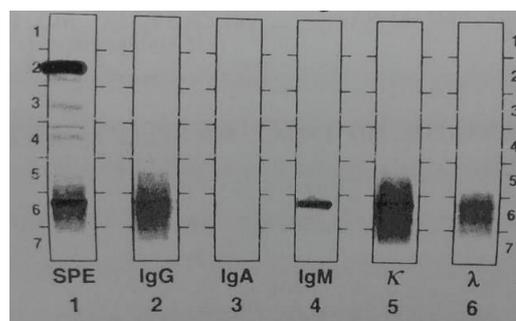
**Figure 2A:** NCS tracing showing wave dispersion along the ulnar nerve prior to treatment.



**Figure 2B:** NCS tracing showing improvement of wave dispersion along the ulnar nerve after the treatment.

Sensory studies did show prolonged conduction velocities of the ulnar, median and superficial fibular nerves. Electromyography did not show significant neurogenic changes, or myopathy.

Further work up was warranted because of the unusual clinical presentation and the CNS lesions demonstrated by MRI. Serum IgG and CSF IgG electrophoresis were done in May 2007, which showed elevated results 374 IU/mL (n.v. 90-187 IU/mL), and 17 mg/dL (n.v. 0.48- 5.86 mg/dL) respectively. There were noted distinct bands in IgM and Kappa light chain channels, indicative of IgM Kappa monoclonal gammopathy on both serum and CSF samples (Figure 3).



**Figure 3:** Serum protein electrophoresis done last May 18, 2007 showing distinct bands in the IgM and Kappa Light Chain channels, indicative of IgM Kappa monoclonal gammopathy.

The patient underwent bone marrow aspiration in June 2007, and aspirate was sent for flow cytometry. Results showed lymphoid population (1.26% of total population) showing moderately bright CD 45 expression, and low forward and side scatter expression. There was also expression of B-lymphoid markers bright CD20, moderately bright CD19 and CD 22, dim CD22 moderately bright partial CD10, and no significant expression of CD 23. There was bright expression of Kappa light chain surface immunoglobulin. Flow cytometric studies showed cytoplasmic membrane of the neoplastic lymphoid cells to express CD20, all of which are consistent with involvement of a B-cell neoplasm. Bone marrow aspiration biopsy was hypocellular and hypoparticulate, megakaryocytes were present, <1% were blasts, 70-80% granulocytic precursors, 15-20% normoblastic erythroid precursors, 10-15% lymphocytes and plasmacytoid lymphocytes, <1% monocytes (Figure 4).

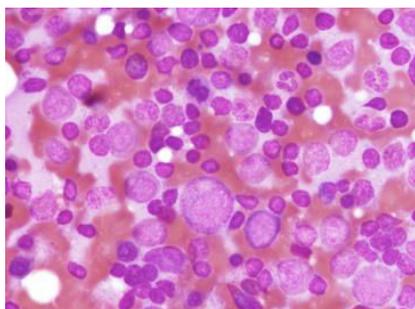
Correlating the findings of anemia, CNS involvement, peripheral neuropathy, IgM-Kappa on serum protein electrophoresis, lead to a diagnosis of WM.

### Therapeutic Focus and Assessment

The prognosis of patients with WM varies, with a median survival of 5 years and approximately 10% of patients are still alive at 15 years [18,19]. As for WM with CNS involvement the overall survival rate after diagnosis of was 71% at 5 years and 59% at 10 years [8]. Because of the heterogeneity of this disease, efforts have been made to define which patients require treatment. A consensus panel convened during the Second International Workshop on WM [20] agreed that initiation of therapy was appropriate for patients with constitutional symptoms such as fever, night sweats, fatigue due to anemia, or weight loss. Certain complications such as hyperviscosity syndrome, symptomatic sensory-motor peripheral neuropathy or symptomatic cryoglobulinemia may also be indications for therapy.

The choice of treatment should be guided by therapeutic goals for the patient to address the other complications of the disease. We

should also take into consideration the need for rapid disease control, risk of treatment-related neuropathy, immunosuppression, secondary malignancies, and potential for future Autologous Stem Cell Transplantation (ASCT) [7]. First line treatment for patients with no previous treatment yet suggested treatment includes Rituximab alone or rituximab with alkylators (bendamustine and cyclophosphamide), proteasome inhibitors, nucleoside analogs, and ibrutinib [8].



**Figure 4:** Bone marrow biopsy done last June 19, 2007 showing relatively polymorphous and hypercellular (60-70% cellularity). There are sheets and aggregates of neoplastic lymphoid cells consisting of mostly small to occasionally medium-sized lymphoid cells having coarse chromatin, inconspicuous nucleoli and scanty cytoplasm occupying 60-70% of the marrow space. There is erythrogranulopoiesis mainly in the uninvolved areas. Megakaryocytes are adequate ranging from small hypolobated to large multinucleated forms. Special stain shows mild reticulin fibrosis (Grade I-IV).

Dimopoulos and co-workers in 2009 [11] reported on the use of the DRC regimen in previously untreated patients with symptomatic WM. Because of the signs and symptoms that our patient presented, she was started on Dexamethasone 20 mg/IV in followed by Rituximab 375 mg/m<sup>2</sup>/IV in July 2007. Rituximab was mixed with normal saline to reach a final concentration of no more than 1 to 4 mg/mL and was administered intravenously. Cyclophosphamide 100 mg/m<sup>2</sup> twice daily, was administered orally on days 1 to 5 (total dose, 1,000 mg/m<sup>2</sup>). This regimen was repeated every 21 days for six courses. The Overall Response Rates (ORR) with R-CD (Rituximab with Cyclophosphamide and Dexamethasone or similar regimen is 80% to 90%, with a median Progression-Free Survival (PFS) of 3 years [7].

In this present WM case, there was noted marked subjective and clinical relief of numbness and weakness, including NCS documented improvement in neuropathic manifestations. There was no noted progression of the disease, and all baseline work ups remained normal, including bone scan, and renal function.

### Follow-up and Outcomes

As Early as November 2007, Serum IgG electrophoresis showed normal results, Serum IgG 111 IU/mL (nv 90-187 IU/mL). Follow up after each year showed negative results in serum protein and IgG electrophoresis (a total of 8 separate times). Follow-up NCS also showed improvement of demyelinating motor and sensory neuropathies of the affected nerves (a total of 9 NCS tests). There was reduction in size of the "nodules" previously described, while the spinal cord became clear, 1 year and 9 months from initial MRI lesion demonstration. In September of 2014, NCS studies (Figure 4), negated

the existence of a neither focal nor diffuse neuropathy, 7 years from initial findings of NCS demyelinating neuropathy. She became clinically asymptomatic from sensory and motor deficits spanning nine years from the time of diagnosis and treatment.

At the time of the initial diagnosis, she claimed that symptoms of pain, fatigue, discomfort and inconvenience, although not severely disabled, hampered her quality of life. She developed anxiety and depression which led to absenteeism and soon unemployment. At present, the patient claimed to have life satisfaction which encompasses health, family, social, and emotional well-being. The importance of early recognition, appropriate treatment, regular follow-up and remission of the disease, can potentially improve the patient's quality of life.

### Discussion

Neurological complications, which affect both the central and peripheral nervous system, may occur in the course of WM and are dominated by signs of hyperviscosity and the classic autoimmune neuropathies mediated by IgM. Peripheral neuropathy occurs in nearly half of the patients with this condition [21]. Direct CNS damage through a neoplastic lymphoplasmacytoid and plasma cells infiltration is rare. Bing-Neel syndrome, an under-recognized complication of WM, is a clinicopathological entity by which CNS is infiltrated by malignant cells [8]. In diffuse form, malignant cells of WM can infiltrate the leptomeningeal space, periventricular white matter or spinal cord, while tumoral form can be characterized by the presence of intraparenchymal mass or nodular lesions. CNS infiltrations may appear as contrast-enhancement and/or thickening of meningeal sheaths on computerized tomography or MRI, and must be distinguished from other cerebral diseases, such as glioblastoma multiforme, multifocal leukoencephalopathy, and primary central nervous system lymphoma [22].

The neurologic sequelae may be heterogenous depending on the area of involvement. Neurological presentations include alteration in sensorium, confusion, cognitive impairment, seizure, hemiparesis, ataxia, cranial nerve deficits, conus medullaris syndrome, cauda equina syndrome and peripheral neuropathy (Table 1).

The median survival of patient with WM is 5-6 years after initiating treatment [23]. A study by Kastiris and cohorts [24] found that since the late 20th century, there was no significant improvement in outcome of patients despite the evolution of treatment, including nucleoside analogues and other novel agents. Active treatment was indicated in this patient as she presented with clinical evidence of the adverse effects of the paraprotein such as hyperviscosity with neurologic complications as seen in the cranial MRI, peripheral neuropathy, symptomatic cryoglobulinemia and development of constitutional symptoms. Our patient received appropriate treatment and completed 6 cycles of chemotherapy consisting of combination of rituximab, dexamethasone and cyclophosphamide. This combination provides durable responses are indicated for most patients. Although currently, no randomized data determine the best option, therapy is decided based on patient age, performance status, aggressiveness of disease and paraprotein manifestations [25].

The effectiveness of chemotherapy is monitored with serum monoclonal IgM concentration on protein electrophoresis, along with evaluation for the signs or symptoms of active disease. The Third International Workshop on WM has formulated criteria to categorize response to treatment regimens [26]. Based on the response criteria,

our patient was categorized under complete response defined as disappearance of monoclonal protein by serum electrophoresis, absence of histologic evidence of bone marrow involvement, resolution of signs and symptoms attributable to WM.

Central	Neurological presentations
Cerebrum	Encephalopathy, cognitive impairment, seizures, hemiparesis, sensory deficit, motor deficit
Brainstem	Cranial nerve deficits
Spinal cord	Conus medullaris syndrome
Peripheral	
Cranial nerve	Ophthalmoplegia, facial palsy, dysarthria, dysphagia
Peripheral nerve	Demyelination, peripheral sensori-motor neuropathy
Roots	Cauda equina syndrome
Plexus	Pain, sensory deficit, motor deficit

**Table 1:** CNS and PNS manifestations of WM.

Appropriate treatment and follow up is very important in treating patients with WM. This present case report exemplifies the following clinical points: (1) WM lesions in the cranio-spinal axis may mimic a demyelinating disease, as in Multiple Sclerosis and Neuromyelitis Optica; (2) WM peripheral demyelinating neuropathy may mimic Guillain Barre Syndrome; (3) With prompt initiation of treatment with DRC regimen, complete remission may be achieved, and (4) Improvement in the quality of life of WM cases may be achieved following astute clinical, hematologic, radiologic and electrodiagnostic correlations and watchful follow-up observations over a long time.

### Informed Consent

The patient provided written permission for publication of this case report, including an approval from Institutional Review Board of Metropolitan Medical Center.

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