

Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy and Skin abnormalities (POEMS) Syndrome in a Filipino Nurse Returning to Work Following Bortezomib Treatment: A Case Report



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ABSTRACT

POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes) also known as Crow-Fukase syndrome or Takatsuki syndrome is a rare and disabling paraneoplastic syndrome that frequently occurs in the fifth or sixth decade of life without a known standard first-line therapy. A 34-year-old Filipino male nurse, who presented with gradually progressive distal lower extremity weakness and sharp shooting pain in bilateral legs accompanied by mild joint effusion on the left knee, hypertrichosis, bilateral conjunctival injection, and gynecomastia underwent extensive workup and was diagnosed with POEMS syndrome. Complete blood count revealed erythrocytosis and thrombocytosis with elevated serum VEGF (vascular endothelial growth factor) and elevated monoclonal serum free lambda light chains. The electrophysiologic studies revealed chronic demyelinating sensorimotor polyneuropathy while bone marrow core biopsy and bone marrow aspirate smear immunohistochemical staining showed it to be positive for lambda and

CD138. He had an initial unsuccessful treatment course with melphalan and prednisone. Hence, bortezomib and dexamethasone were given which gave significant improvement in symptoms from the overall neuropathy limitation score of 5 to 1.

Key words: POEMS syndrome, Crow-Fukase syndrome, Takatsuki syndrome, Bortezomib, Dexamethasone.

INTRODUCTION

POEMS syndrome is a rare monoclonal gammopathy. Between 2007 to 2020, among southeast Asian countries which include the Philippines, there are only a few published studies. Overall, the ratio of male and female cases was equal, unlike other countries which reported male predominance. The median age of onset was during the fifth decade of life. Owing to the rarity of this disease, there are no standard treatments, but numerous therapeutic options have been reported. Most of the cases used a combination of melphalan and steroids as first-line treatment, which provided good outcomes.[1] Worldwide, recent studies presented that classic chemotherapy which is an alkylator-based therapy,

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melphalan, was the least effective with only 20% complete remission rate. The proteasome inhibitor, bortezomib, achieved a 69% complete remission rate described as an improvement in clinical symptoms and serum-free light chain response without the appearance of its adverse effect (eg, neuropathy). Thus, utilization of bortezomib as front-line monotherapy appears to be tolerated and highly effective.[2]

In relapse cases, other treatment options were tested in which the combination of bortezomib and dexamethasone was given together with daratumumab, an immunomodulatory drug[3] or cyclophosphamide. On the other hand, other publications reported the use of bortezomib and dexamethasone only as a first-line regimen for newly diagnosed POEMS syndrome and a majority of these patients include Chinese males in their fifth decade of life. Hematologic response evaluation was based on light chain amyloidosis response criteria and neurological disability assessed through the Overall Neuropathy Limitations Scale (ONLS).[4]

Our aim is to present a case report of a documented Filipino man with POEMS syndrome that achieved significant improvement following bortezomib use. We are unaware of similar reports from the Philippines, specifically alluding to the present case. Also, the implemented treatment is highlighted given that this Filipino nurse was able to return to his work needed during the pandemic times.

CASE PRESENTATION

A 34-year-old Filipino male was admitted to our institution due to a 3-month history of gradual progressive distal lower extremity weakness described as difficulty during ambulation in which the patient cannot clear his feet off the ground accompanied by minimal erythematous, tender, sharp shooting pain on the left knee and dull aching pain on bilateral legs with a pain scale ranging from 7-9/10. The patient was initially admitted at a hospital in the United Arab Emirates where he was diagnosed and treated as a case of Guillain-Barre syndrome and given intravenous immunoglobulin with no improvements noted. He was also seen by a hematologist-oncologist due to the finding of erythrocytosis and thrombocytosis on complete blood count. It revealed an RBC count of $5.72 \times 10^6/\mu\text{L}$ (reference range 4.5-5.5) and a platelet

count of $891 \times 10^9/\text{L}$ (reference range 150-410). He was given aspirin 80 mg/tab 1 tab once a day and he underwent phlebotomy but he was lost to follow-up.

In the interim he revealed persistence of lower extremity weakness and pain and hence consulted a neurologist in the Philippines. Upon admission, the patient was wheelchair-bound, awake, oriented to three spheres, and had intact cognitive functions. There were no cranial nerve deficits noted.

The motor examination revealed bilateral lower extremity weakness with more pronounced distal musculature weakness. The bilateral ankle dorsiflexion and plantar flexion had a manual muscle grade of 0-1/5, while bilateral knee flexion and extension had a manual muscle grade of 3+/5 and lastly, bilateral hip abduction, adduction, flexion, and extension had a manual muscle grade of 4+/5. On the other hand, there are good manual muscle grades on all major muscle groups of bilateral upper extremities. There was no spasticity, rigidity, atrophy, fasciculations, or tremor. An impaired position sense on bilateral lower extremities and impaired vibratory sense on bilateral medial malleoli were also noted. The sensation was intact to light touch, pain, and temperature. The patient had generalized areflexia with an ONLS of 5 (arm scale 0/5 and leg scale of 5/7). He required a wheelchair to travel up to 10 meters but was able to stand and walk up to 1 meter with the help of one person. On general physical examination, there was bilateral conjunctival injection and hypertrichosis on bilateral lower legs (Figure 1).

An initial work-up was done which included whole body positron emission tomography with a finding of hypermetabolic focus along the upper paravertebral left lung field/pleural thickening (non-specific) (Figure 2) and irregular/non-homogenous hypermetabolic activity along the bone marrow of the axial and appendicular skeleton, which was also a non-specific finding in the absence of a known malignancy (may be compatible with blood disorder) (Figure 3). A serum-free light chain panel was also done which showed free kappa light chain of 8.10 mg/L (reference interval 7.1-22.49 mg/L), free lambda light chain of 55.3 (reference interval 8.8-23.26 mg/L), and free kappa/lambda light chain ratio of 0.146 (reference interval 0.57-1.25) suspicious for low-level monotype serum-free lambda light chains based on a free lite ratio (Figure 4). An



Figure 1. Case of POEMS: Hypertrichosis on bilateral lower legs

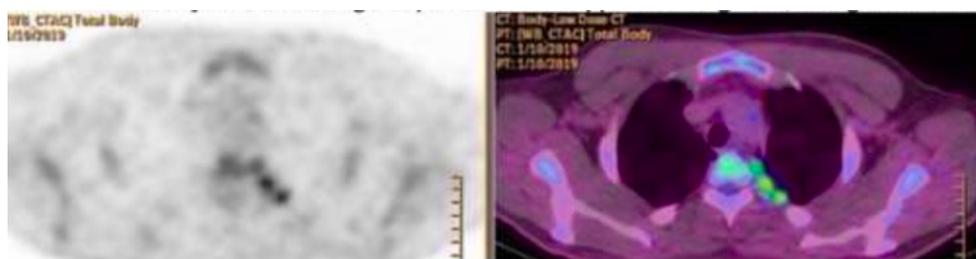


Figure 2. Case of POEMS: Fluorodeoxyglucose (FDG) uptake along the paravertebral upper lung field along thickened pleura

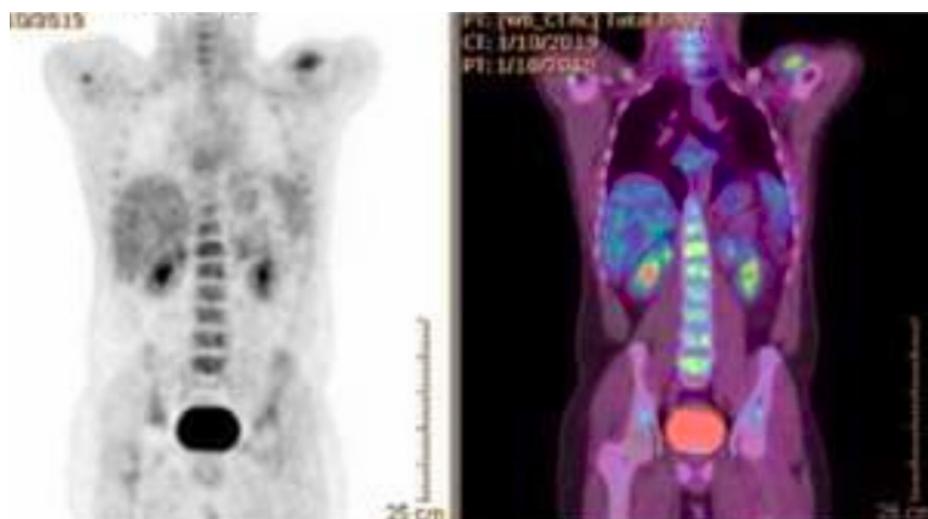


Figure 3. Case of POEMS: Inhomogeneous/irregular fluorodeoxyglucose (FDG) uptake along the spine and pelvic bone marrow. Inhomogeneous uptake in the ribs, right humeral head, left pubic bone, sacrum, and right femur

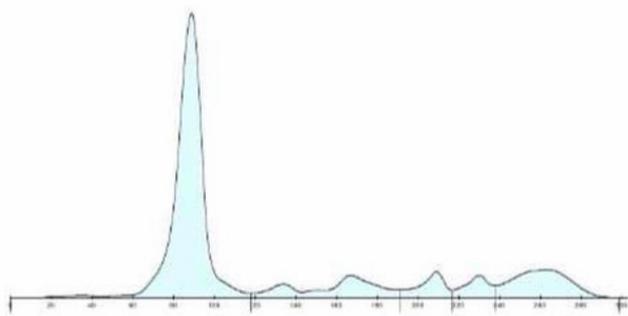


Figure 4. Serum electrophoresis (pre-treatment in a case of POEMS)

electrophysiologic study revealed chronic bilateral sensorimotor demyelinating polyneuropathy. The serum vascular endothelial growth factor (VEGF) level was also elevated at 3660 pg/ml (cut off value 1040 pg/ml). The bone marrow core biopsy and bone marrow aspirate smear immunohistochemical stain results showed positive for lambda and CD138 supporting the diagnosis of lambda light chain restricted plasma cell myeloma. He was started with melphalan 2 mg/tab 3 tabs TID, prednisone 50 mg/tab 1 tab OD, gabapentin 100 mg/tab 1 tab TID, and aspirin 80 mg/tab 1 tab OD. The patient was discharged stable after five days of hospital stay. The patient noted improvement in symptoms as he reported the ability to lift his foot off the ground only requiring minimal assistance to ambulate within the first three months. No other signs and symptoms were noted such as joint pain, edema, hyperpigmentation, plethora, acrocyanosis, and difficulty breathing.

After six months of regular follow-up and continuous medications, the patient had gynecomastia with a noted breast mass on the right. Excision of the breast mass was done which revealed no atypical plasma cell proliferation present. There was also a recurrence of the weakness of bilateral legs and feet described as a frequent tendency to fall and difficulty ambulating requiring maximal assistance. An elevated lambda chain was noted. Hence, melphalan and prednisone were discontinued. The patient was started on bortezomib 2.3 mg/m² SC weekly, dexamethasone 4 mg/tab 2 tabs twice a day, and omeprazole 40 mg/tab 1 tab once a day for 12 months.

Follow-Up and Outcomes

The patient showed clinical improvement and hematologic response after administration of

bortezomib and dexamethasone. He was able to ambulate independently with support using bilateral ankle-foot orthosis. There was still no reported numbness, joint pains, edema, hyperpigmentation, plethora, acrocyanosis, and difficulty breathing. The manual muscle grade of bilateral hip abduction, adduction, flexion and extension, knee flexion and extension are 5/5 while bilateral ankle dorsiflexion and plantar flexion are 3+/5 and 4+/5, respectively with ONLS of 1 (arm scale 0/5 and leg scale of 1/7). The serum light chain revealed negative for monoclonal serum-free light chains which showed free kappa light chain of 12.7 mg/L (reference interval 7.1-22.49 mg/L), free lambda light chain of 13.4 (reference interval 8.8-23.26 mg/L), and free kappa/lambda light chain ratio of 0.947 (reference interval 0.57-1.25). There was no hypertrichosis and gynecomastia. His ability to walk, climb, and run was affected but his gait did not look abnormal.

DISCUSSION

The diagnosis of POEMS syndrome based on the current Dispenzieri diagnostic criteria requires the presence of both mandatory criteria (polyneuropathy and monoclonal plasma cell-proliferative disorder, almost always lambda restricted), and at least one major and one minor criterion. The major criteria include Castleman disease, sclerotic bone lesions, and VEGF elevation. On the other hand, the minor criteria include organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy), extravascular volume overload (edema, pleural effusion, or ascites), endocrinopathy (adrenal, pituitary, gonadal, parathyroid, thyroid, and pancreatic), skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomas, plethora, acrocyanosis, flushing, and white nails), papilledema, and thrombocytosis/polycythemia. Despite the availability of several criteria, diagnosing POEMS syndrome is challenging due to its multisystemic affection. Detailed history and examinations are essential since it is commonly misdiagnosed as chronic inflammatory demyelinating polyneuropathy.

The pathophysiology of POEMS syndrome remains unknown but high levels of pro-angiogenic, pro-inflammatory cytokines, and growth factors are found to be the hallmark of the disease. The symptoms of polyneuropathy and vascular leak in the form of edema and effusions are due to these factors

namely tumor necrosis factor-alpha (TNF-alpha), interleukin-1 (IL1), interleukin-6 (IL6), and VEGF.[5] Among these factors, VEGF may affect the blood-nerve barrier by increasing permeability, which eventually gives rise to edema and nerve damage due to increased endoneural pressure. Hence, it is considered as the primary factor responsible for a majority of symptoms. Serum VEGF is markedly elevated in this syndrome and that is why one of the treatment options was to target the suppression of VEGF.

Several studies denoted that serum VEGF levels can monitor disease activity and project functional outcome. Ideally, a change in therapeutic strategy should be considered if serum VEGF levels remained elevated after 6 months post treatment. It was found that 6 months are required to determine the effect of treatment because VEGF levels will reach a plateau over 6 months after treatment initiation and decrease afterwards. In relation to its outcome, there will be improvement in clinical symptoms and laboratory parameters at 12 months post treatment. [6] It correlated that normal VEGF levels can prolong remission rates and prevent disease relapses. However, other factors must still be considered and monitored since the suppression of VEGF alone by induction of an anti-VEGF monoclonal antibody, bevacizumab, does not appear to be fully effective in preventing relapses, especially in advanced cases.[7] This was also seen in patients subjected only to corticosteroids for treatment.[8]

There is no standard first-line therapy for newly-diagnosed POEMS syndrome but current treatment approaches provide a good prognosis based only on one randomized controlled study that has been completed. Treatment for newly diagnosed POEMS syndrome depends on the extension of disease. The current guidelines suggest that curative doses of radiation (40–50 Gy) are recommended in patients with isolated bone lesion without bone marrow clonal plasma cell involvement while systemic therapy is recommended in patients with disseminated disease (more bone lesions and/or bone marrow

plasmacytosis).[9] On the other hand, there are no established standards of care management in relapse cases of POEMS, though there are few cases that showed that bortezomib, a proteasome inhibitor, was effective and safe.

Bortezomib targets the ubiquitin-proteasome pathway. It decreases VEGF expression by downregulating several angiogenic cytokines, such as VEGFs, FGF-2, IGF-1, interleukins, and the expression of angiopoietins. Its antiangiogenic action is primarily due to the prevention of degradation of nuclear factor kappa-B kinase complex (IKK) inhibitor and resultant block of nuclear factor kappa light chain enhancer of activated B cells (NF- B) activity.[10]

In a study conducted in Shanghai Changzheng Hospital in China from December 2014 to May 2016, VEGF levels were determined before and after bortezomib treatment. Normal values of VEGF were defined as below 600 pg/ml and the response rate was determined after induction of bortezomib. The response rate was measured in terms of reduction of serum VEGF level. A majority of subjects showed complete response which was defined as a reduction of serum VEGF level to normal values. The reduction of serum VEGF levels coincided with improvement of the subject's ONLS from a score of 5 at the time of diagnosis to 3.[4] Thus, hematologic response evaluation was important in the assessment, including serum light chain levels and serum VEGF level.

CONCLUSION

We have documented a case of a Filipino male with confirmed POEMS syndrome or Crow-Fukase syndrome. The combination of bortezomib 2.3 mg/m² SC weekly and dexamethasone 4 mg/tab 2 tabs a day for 12 months are proven to be safe and responsive in improving symptoms in relapsed cases during early adulthood. The serum VEGF levels post-treatment must still be accounted to predict remission rates and plan future therapeutic goals and strategies.

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