A CASE REPORT OF POEMS SYNDROME:

A DIAGNOSTIC CHALLENGE

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ABSTRACT

Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Gammopathy, and Skin Changes (POEMS) syndrome is a rare multiorgan disease that is characterized by polyneuropathy in the setting of a plasma cell disorder. The pathogenesis of the syndrome is unknown but overproduction of vascular endothelial growth factor (VEGF) is said to be responsible for most of the symptoms. There is no standard treatment for POEMS syndrome; however, there are emerging therapies, including radiation therapy, alkylator based therapies, and corticosteroids, that have shown to be beneficial.

We present a case of a 34-year-old woman who came in due to ascites associated with upper and lower extremity weakness, paresthesia, skin changes, and polycythemia. Criteria for POEMS syndrome were fulfilled and serum electrophoresis revealed the presence of M protein, thus confirming the diagnosis. After treatment combination of prednisone and melphalan, the patient's clinical status improved markedly. High degree of clinical suspicion may significantly alter the course of the disease.

Keywords: *Monoclonal gammopathy, Polyneuropathy, Vascular Endothelial Growth Factor, Melphalan*

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OBJECTIVES

1. To present a case of a 34 year-old female who presented with ovarian tumor, polyneuropathy, skin changes, and polycythemia;
2. To review the incidence of Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Gammopathy, and Skin Changes (POEMS) syndrome and its clinical manifestations; and
3. To discuss the rarity, pathogenesis, management, and prognosis of the case.

INTRODUCTION

Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome is a rare multisystemic disease that occurs in the setting of a monoclonal plasma cell disorder.[1] Exact incidence and prevalence are not known. The only estimates are from Japan where the prevalence has been reported to be about 1 in 330,000 with a male predilection of 2.5:1.[2] The syndrome commonly presents in the fifth to sixth decade. At present, there has been no reported case of POEMS in the Philippines.

Mandatory criteria for the diagnosis of POEMS syndrome include chronic polyneuropathy and monoclonal plasma cell disorder. Other supporting conditions include sclerotic or lytic bone lesions, skin changes, papilledema, polycythemia and thrombocytosis.[3]

Due to its rarity, the diagnosis is often delayed and the condition mistaken for another neurologic condition. We present a case of a 34-year-old woman who was initially admitted as a case of ovarian new growth but eventually diagnosed with POEMS syndrome. The challenges in the diagnosis and management of her case were also discussed.

CASE PROTOCOL

This is a case of a 34-year-old female, married from South Cotabato, who was referred due to paresthesia and extremity weakness.

Three years prior to admission, the patient had onset of paresthesia and weakness of bilateral lower extremities, gradually progressing to include the upper extremities. She was initially managed as a case of acute inflammatory demyelinating polyneuropathy and was started on prednisone, which provided temporary relief; however, symptoms recurred upon tapering off the steroids.

Two years prior to admission, the patient had worsening of her upper and lower extremity weakness; hence, further work up was done.

The magnetic resonance imaging (MRI) of the brain was unremarkable. Electromyelogram (EMG) revealed absence of both motor and sensory evoked responses, and reduced to absent motor unit action potentials (MUAPs) consistent with chronic inflammatory polyneuropathy (*Figure 1*). However, patient was lost to follow up and only tolerated the above condition.

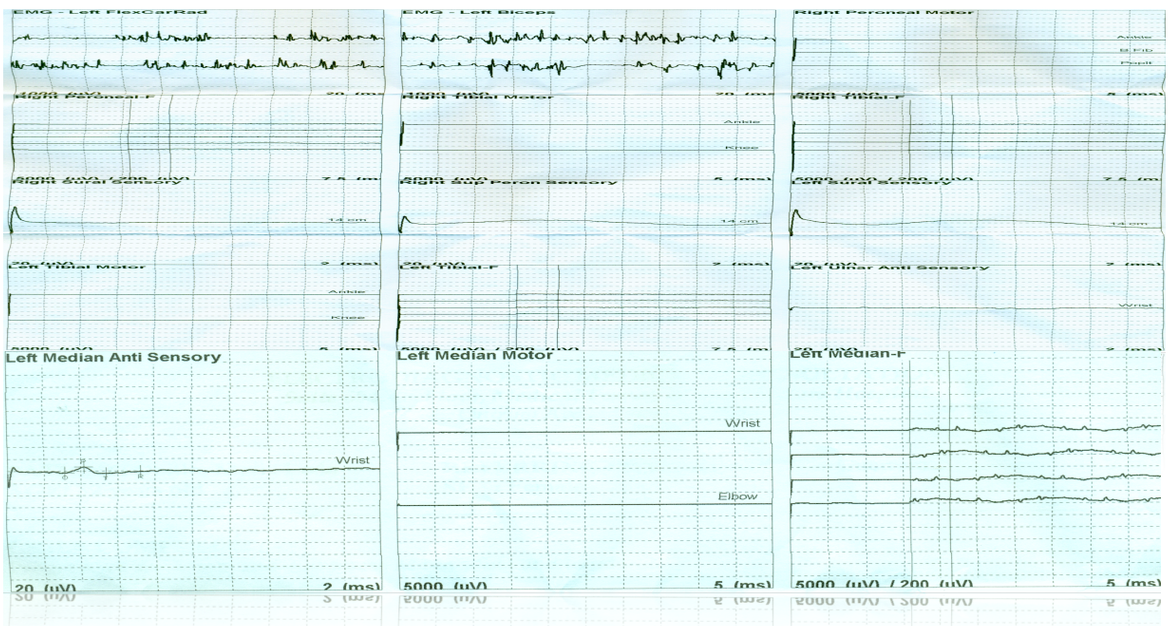


Figure 1. Electromyogram showing absence of motor evoked and sensory evoked responses.

Seven months prior to admission, she noted to have facial plethora and darkening and thickening of her skin. Serial complete blood count (CBC) revealed persistent erythrocytosis and thrombocytosis. The Janus kinase-2 (JAK-2)

immunoassay test was negative. Nevertheless, she was managed as a case of polycythemia vera. She was prescribed with hydroxyurea and managed with intermittent phlebotomy.

Five months prior to admission, there was note of ascites and amenorrhea. The ultrasound of the whole abdomen revealed cholelithiases with cholecystitis, moderate splenomegaly, moderate ascites, and a right ovarian mass. She was advised surgery; hence, she was admitted for cholecystectomy and salpingo-oophorectomy. She was referred to the Internal Medicine service because of the persistent extremity weakness, paresthesia, erythrocytosis and thrombocytosis.

The past medical, personal and social, and family medical histories were unremarkable. The patient had intermittent episodes of dyspnea on exertion and two-pillow orthopnea. The patient did not report any other associated symptoms.

The patient was examined awake with stable vital signs. The skin was dry, thickened and hyperpigmented (*Figure 2A*).



Figure 2. On physical examination, the patient had hyperpigmented and thickened skin **(A)**, clubbing of the nails on both hands **(B),** Ascites (**C)**, and Bipedal edema **(D)**.

The patient had anicteric sclerae and pinkish palpebral conjunctivae with no conjunctival injection. Pulmonary findings were unremarkable. The cardiac examination revealed an adynamic precordium and regular rhythm. The abdomen was distended with positive shifting dullness and fluid wave test (*Figure 2C*). The liver and spleen were difficult to palpate due to the ascites. Grade 1 bipedal edema was noted (*Figure 2D*).

Visual acuity test revealed an impaired vision: 20/20-2 on the right eye (OD) and 20/20-1 on the left eye (OS). On fundoscopy and slit lamp test, retinal veins were engorged and tortuous, optic disk was swollen and hyperemic, and retinal hemorrhages were also noted around the disk (*Figure 3*). These findings were consistent with papilledema.

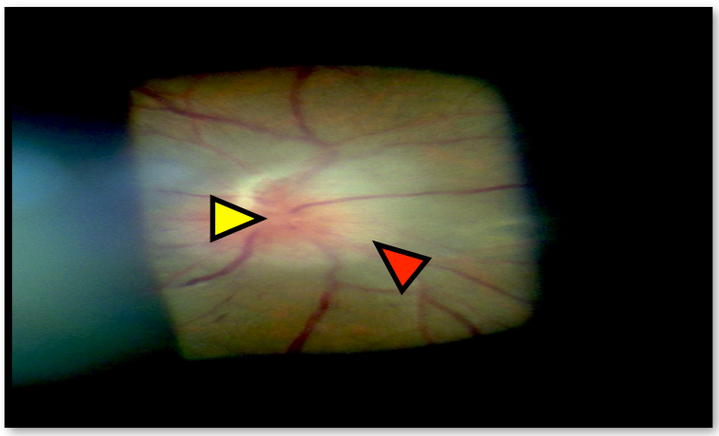


Figure 3. The slit lamp examination showed indistinct optic disk margin (red arrowhead) and hyperemia (yellow arrowhead)

The manual motor strength testing (MMT) was 2/5 on both lower extremities and 3/5 on both upper extremities. Pathologic reflexes and meningeal signs were absent. Deep tendon reflexes were hyporeflexic (1+) on all test points.

Complete blood count (CBC) revealed slightly elevated hemoglobin (156 g/L) and platelet count (446 x 10^3/uL). The prothrombin time (PT) and activated partial thromboplastin time (aPTT) were within normal range. The liver function test, bilirubin levels, fasting blood sugar, creatinine, blood urea nitrogen, serum electrolytes, urinalysis and hepatitis profile were unremarkable -- except for hypoalbuminemia (27.58 g/L). The thyroid-stimulating hormone (TSH) was slightly elevated (4.62 uIU/ml) while free thyroxine (fT4) level was normal (9.45 pmol/L),

which is compatible with subclinical hypothyroidism. The CA-125, lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR) and beta human chorionic gonadotropin (beta-HCG) were normal.

The 12-lead electrocardiogram (ECG) revealed sinus rhythm. Chest radiograph was unremarkable. Computed tomography (CT) scan of the whole abdomen revealed calculus cholecystolithiasis with sludge formation and splenomegaly (*Figure 4A*).

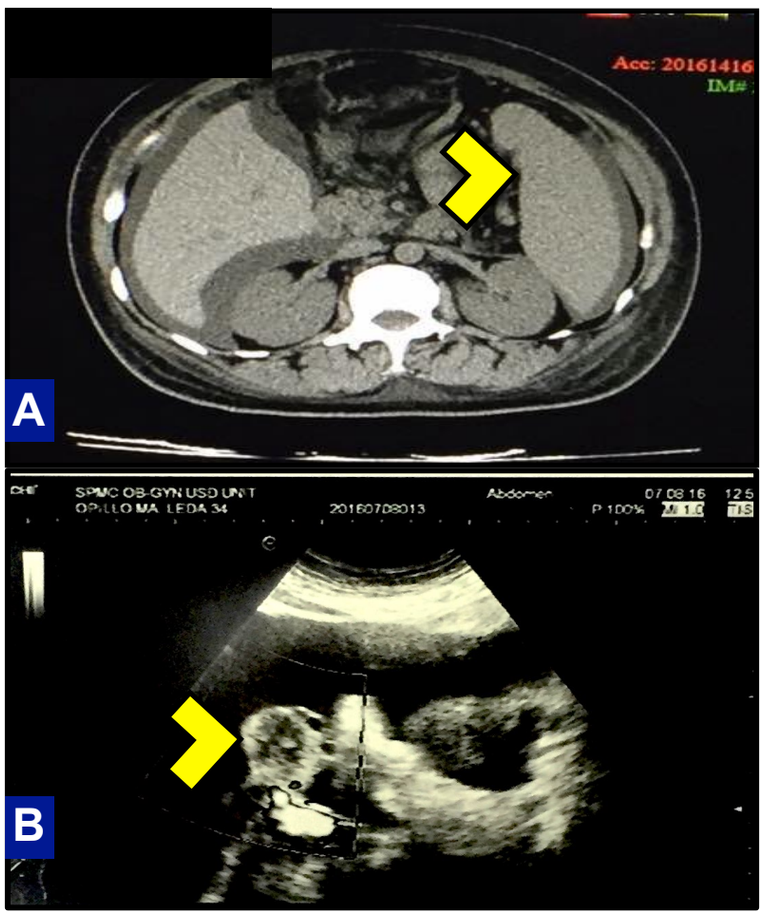


Figure 4. Diagnostic imaging included CT Scan (A) which showed splenomegaly (red arrowhead), and transvaginal sonography (B) which revealed mass on the right ovarian stroma (red arrowhead)

Transvaginal sonography (TVS) revealed a lesion within the right ovarian stroma suggestive of an endometrial or follicular cyst versus a small epithelial tumor and massive ascites (*Figure 4B*).

Peripheral blood smear (PBS) revealed megakaryocytes with hyperchromatic and hyposegmented nuclei (*Figure 5*).

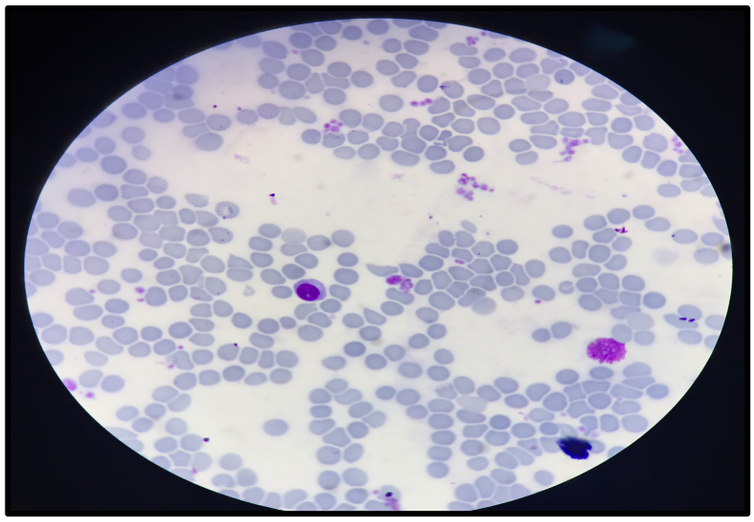
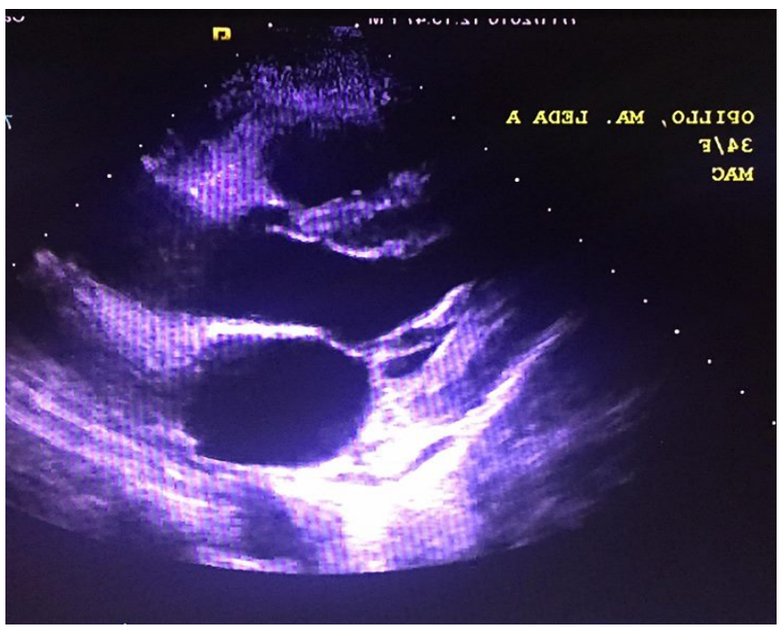


Figure 5. Peripheral blood smear showing normocytic, hyper chromic with no inclusion bodies seen, no immature white blood cells, no dyspoetic cells with predominance of segments. Presence of increase platelets some seen in clumps.

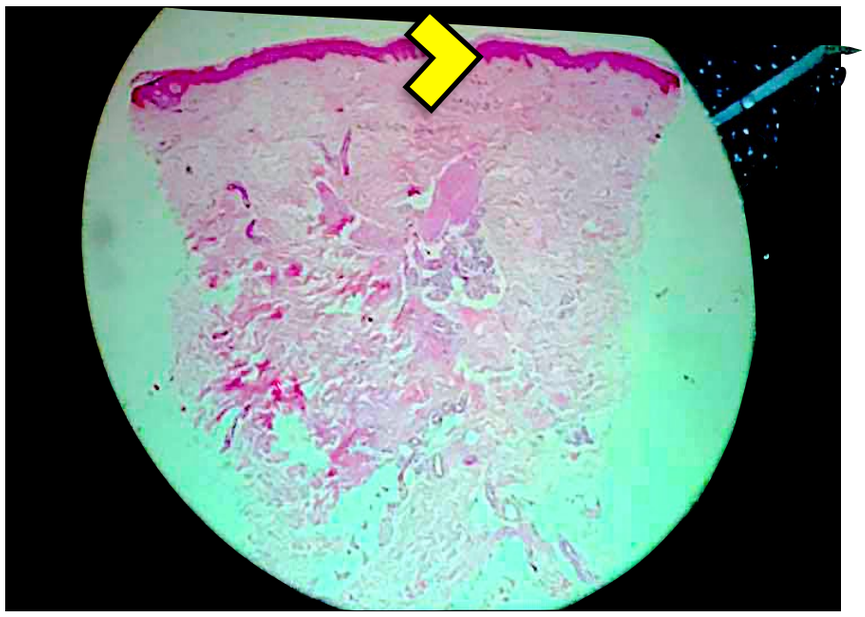
Two-dimensional echocardiography (2D Echo) did not reveal significant hypertrophy, wall motion abnormalities, cardiac masses or congenital heart disease (*Figure 6).*



F**igure 6.** 2D Echocardiogram showing a normal result

Skin biopsy revealed presence of basket woven stratum corneum overlying a mildly atrophic epidermis with basal layer hyperpigmentation and focal basal vacuolar alteration and basement membrane zone thickening. The dermis reveals moderately dense perivascular predominantly lymphocytic inflammatory infiltrates

with rare eosinophils as well as scattered melanophages which is consistent with interface dermatitis (*Figure 7*)



F**igure 7.** Skin biopsy revealing presence of basket woven stratum corneum with no amyloid deposits highly suggestive of Interface dermatitis

Due to findings of chronic polyneuropathy, organomegaly, subclinical hypothyroidism, polycythemia and skin changes, POEMS syndrome was highly considered. Further workup to establish a plasma cell disorder was done to confirm the diagnosis.

The skeletal survey revealed lytic bone lesions in the right acromion process and supraglenoid tubercle (*Figure 8*).

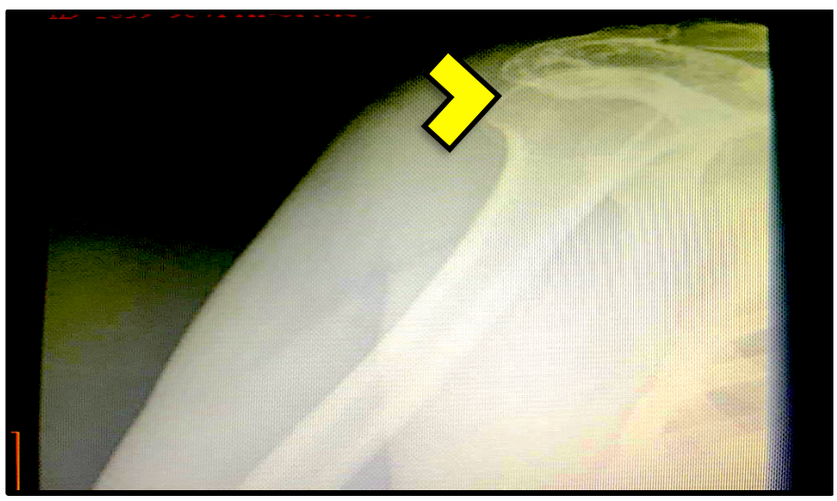


Figure 8. *Work up included Skeletal survey which revealed lytic lesion in the right acromion process and supraglenoid tubercle*

Serum electrophoresis revealed a presence of a small monoclonal band at the gamma region with a monoclonal peak concentration of 0.2% (0.01 g/dL). This is consistent with presence of M protein, confirming the diagnosis of POEMS syndrome. Serum immunotyping electrophoresis revealed findings consistent with a polyclonal gammopathy with detection of IgG-Kappa and IgG-Lambda immunoglobulins (*Figure 9*)

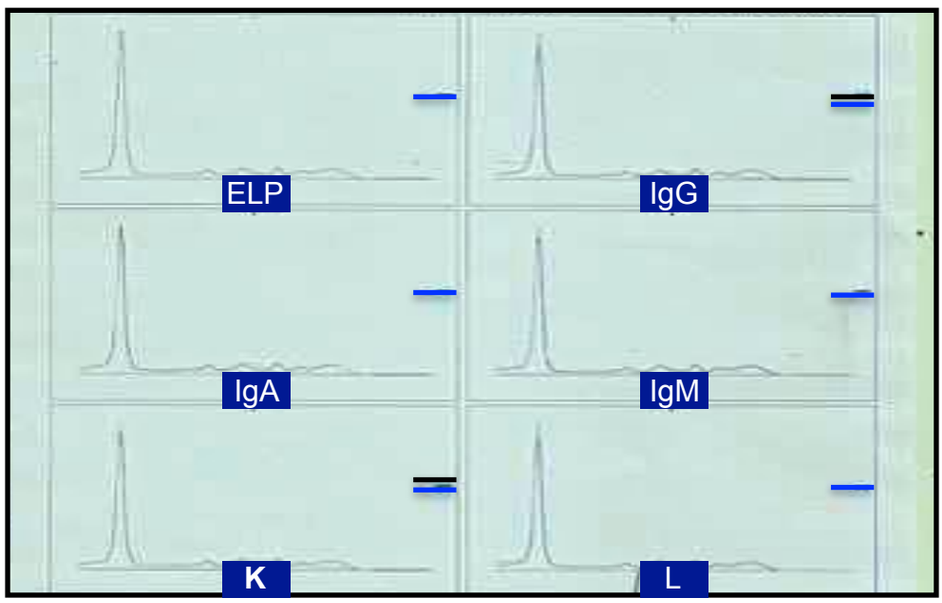


Figure 9. Serum immunotyping electrophoresis revealing findings of a polyclonal gammopathy with presence of IgG-Kappa and IgG-Lambda immunoglobulins (*Double Bands in K and IgG*)

The patient underwent bilateral salpingo-oophorectomy and cholecystectomy for the ovarian mass and cholelithiasis, respectively (*Figure 10*). On histopathology, presence of cells suggestive of a serous cyst adenoma. (*Figure 11)*.



Figure 10. Intraoperative findings showing a right ovarian mass located at the stroma

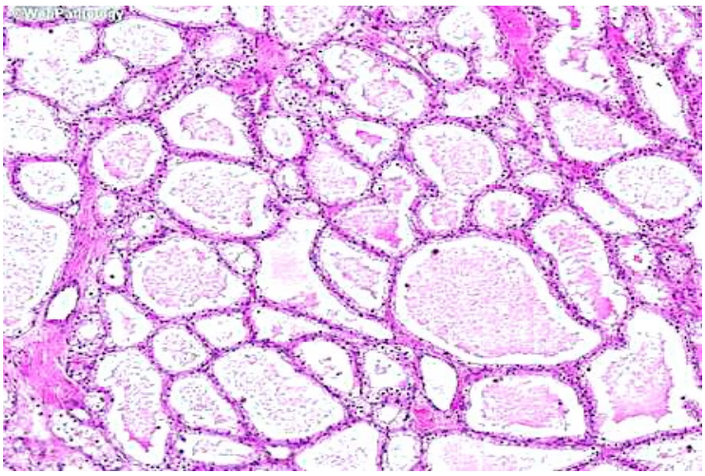


Figure 11. Histopathologic findings consistent with a cyst adenoma stroma consistent with serous cyst adenoma.

Intraoperative bone marrow aspiration and biopsy was also done which revealed unremarkable findings.

The patient was started on prednisone 20 mg 2 tablets daily and melphalan 16 mg daily for four days every 28 days. Presently, the ascites and edema were notably absent. The patient also had improved motor strength of 4/5 on all extremities. The patient underwent visual acuity test that revealed improved vision on both eyes reported as 20/20-1 OD and 20/20 OS.

DISCUSSION

In a patient presenting with chronic polyneuropathy coupled with other symptoms such as polycythemia and skin changes, the differential diagnosis include systemic disease conditions such as amyloidosis, scleroderma, and plasma cell dyscrasias.

Amyloidosis is multisystemic, rapidly progressive disease caused by the extracellular deposition of amyloids in tissues and organs and is characterized by cardiac, renal, and hepatic involvement,[4] 2D echo and ultrasound revealed no abnormalities in the heart, kidney, and liver. Moreover, the skin tissue biopsy revealed absence of overt thickening and collagen bundles in between spaces, making amyloidosis unlikely in this case.

Scleroderma is a chronic systemic autoimmune disease characterized by hardening of the skin and may also present with polyneuropathy.[5,6] However in our patient, raynaud's phenomenon, which is found in 70% of scleroderma cases,[7,8] was absent.

Plasma cell dyscrasias are conditions caused by the expansion of monoclonal bone marrow plasma cells.[9] It is characterized by lytic bone lesions and monoclonal immunoglobulins on serum electrophoresis. Our patient tested positive for M protein on serum electrophoresis.

In view of the clinical symptomatology, multiple organ involvement and evidence of plasma cell dyscrasia, the diagnosis of POEMS syndrome was clinched, albeit after several months and misdiagnoses.

POEMS syndrome is a rare multisystemic disease that occurs in the setting of monoclonal plasma cell disorder. Exact incidence and prevalence are not known. The only estimates are from Japan where prevalence has been reported to be about 1/330,000 with a male predilection of 2.5:1.[1] The syndrome commonly presents in the fifth to sixth decade.[2] This patient, however, is a young 34-year-old female. At present, there is no reported incidence of POEMS in the Philippines.

The mandatory major criteria of polyneuropathy and monoclonal plasma cell proliferative disorder mostly of the lambda light chain type should be present for a case to qualify as POEMS syndrome.

The most common presentation of POEMS syndrome—is neuropathy, accounting for 90% of cases. [10-12] It occurs as a peripheral, symmetrical, ascending, sensorimotor polyneuropathy, which was notably exhibited by the patient.

M protein was also detected on serum electrophoresis, fulfilling another mandatory major criteria for POEMS syndrome. Monoclonal gammopathy is more common in POEMS (85%), while 7% may have polyclonal gammopathy. Serum immunotyping electrophoresis revealed polyclonal gammopathy with detection of IgG lambda and IgG kappa immunoglobulins.[1]

Other major criteria include sclerotic bone lesions, Castleman's disease, and an elevated level of vascular endothelial growth factor of at least three- to four-fold higher than the normal reference range. Lesions may be densely sclerotic or lytic with a sclerotic rim.[13,14] The skeletal survey of the patient revealed lytic bone lesions in the right acromion process and supraglenoid tubercle, fulfilling another major criteria of the syndrome.

The minor criteria for POEMS syndrome include organomegaly, extravascular volume overload, endocrinopathy, skin changes, papilledema and thrombocytosis or polycythemia.[15-17]

Organomegaly in POEMS may present as hepatomegaly or splenomegaly.[18] The latter was present the ultrasound of the patient. Endocrinopathies in POEMS are most commonly diabetes mellitus and gonadal dysfunction. The latter is usually manifested in women as irregular menses or galactorrhea. Others would have hyperthyroidism, hypothyroidism, and subclinical hyper or hypothyroidism.[1] The patient has subclinical hypothyroidism.

The pathophysiologic link between the assemblage of symptoms and the underlying disease is not well understood.[19] The syndrome has been linked to overproduction of certain cytokines specifically 1L-1 beta, TNF-alpha, and IL-6.[20] IL-6

is associated with disease activity with levels increased prior to clinical exacerbations.[21-23] Vascular endothelial growth factor (VEGF) is also increased in POEMS syndrome. Vascular endothelial growth factor (VEGF) is an endothelial cell specific mitogen and an angiogenic inducer. It is incriminated as a mediator of pathologic angiogenesis and is expressed in several tumors.[24] High levels of serum VEGF in POEMS syndrome is associated with severe endoneurial vessel involvement and nerve damage.[25-27]

The treatment in POEMS syndrome is not standardized although local irradiation and low-dose alkylator along with steroids had been the mainstay of the treatment. However, patients without bone lesions or those with widespread osteosclerotic lesions cannot be managed with local irradiation. The use of alkylator and corticosteroid regimen (melphalan and prednisone), such as in our patient, produces lesser toxicity but has a low response rate and short duration of response.[7,32] Other strategies have been used, including plasmapheresis, intravenous immunoglobulin, interferon alfa, corticosteroids, alkylators, azathioprine, autologous stem cell transplantation, tamoxifen, and transretinoic acid.[28-31]

CONCLUSION

We presented a case of a 34-year-old female who presented with chronic polyneuropathy which was later found out to be only a part of the syndrome, POEMS.

The diagnosis of POEMS syndrome is perplexing due to its evolving nature and diverse clinical manifestations especially in early stages when not every symptom has heralded.

In retrospect, focusing on a single symptom as an approach to a clinical condition may only serve to address a single problem of the patient but will not resolve its cause.

Careful history and physical examination, therefore, cannot be overly emphasized. The identification of important details and relating individual symptoms to the patient in totality will lead us to the right diagnosis, even in rare conditions such as POEMS syndrome.

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