

## CASE REPORT

### POEMS syndrome

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#### Abstract

POEMS syndrome is the syndrome of **P**olyneuropathy, **O**rganomegaly, **E**ndocrinopathy, **M**onoclonal protein and typical **S**kin changes. A 65-year-old lady presented with the 2-day-history of inability to walk, 4-month-history of progressive worsening of muscle weakness of both lower limbs and 1-year-history of progressive worsening of bilateral numbness of lower limbs. Nerve conduction study revealed generalized sensorimotor demyelinating polyneuropathy. She was initially treated as chronic inflammatory demyelinating polyradiculoneuropathy with intravenous immunoglobulin (IVIG) and high-dose prednisolone. However, she had no significant neurological improvement despite getting standard therapy. In addition to peripheral neuropathy, the presence of hepatosplenomegaly, skin changes, polycythaemia and thrombocytosis prompted for further investigations. She was diagnosed as POEMS syndrome based on the presence of two mandatory major criteria [polyneuropathy, monoclonal plasma cell proliferative disorder (lambda)], one major criterion (sclerotic bone lesions) and three minor criteria (organomegaly, skin changes and thrombocytosis/polycythaemia). She received treatment with melphalan and prednisolone. She achieved clinical improvement and partial response (haematologic and radiological) after six cycles of therapy. We highlight the awareness of this rare syndrome, for patients presenting with peripheral neuropathy and not responding to its standard therapy, by recognizing other associated clinical manifestations and proceeding further diagnostic work-up.

*Keywords:* POEMS syndrome, monoclonal plasma cell proliferative disorder, peripheral neuropathy

#### INTRODUCTION

POEMS syndrome is the syndrome of **P**olyneuropathy, **O**rganomegaly, **E**ndocrinopathy, **M**onoclonal protein and typical **S**kin changes.<sup>1</sup> The International Myeloma Working Group (IMWG) criteria for diagnosis of POEMS syndrome requires the presence of both of the mandatory major criteria, one of the three other major criteria, and one of the six minor criteria.<sup>2,3</sup> Mandatory major criteria include polyneuropathy and monoclonal plasma cell proliferative disorder (almost always lambda). Other major criteria include sclerotic bone lesions, Castleman disease and elevated levels of vascular endothelial growth factor (VEGF). Minor criteria include organomegaly (splenomegaly, hepatomegaly or lymphadenopathy), extravascular volume overload (oedema, pleural effusion or ascites),

endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic), skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomas, plethora, acrocyanosis, flushing, white nails), papilloedema and thrombocytosis/polycythaemia.<sup>1-3</sup> POEMS syndrome is also known as osteosclerotic myeloma, Takatsuki syndrome and Crow-Fukase syndrome. POEMS syndrome is a rare paraneoplastic disorder secondary to a plasma cell dyscrasia.<sup>4</sup>

In this case report, we reported the clinical presentation and diagnostic approach for a patient with POEMS syndrome. Recognition of associated clinical manifestations of POEMS syndrome and evaluation for further diagnostic work-up would be the key element in order to get the early diagnosis and proper treatment of this rare entity 'POEMS syndrome'.

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## CASE REPORT

A 65-year-old Malay lady, with dyslipidemia, presented with the 2-day-history of inability to walk, 4-month-history of progressive worsening of muscle weakness of both lower limbs and 1-year-history of progressive worsening of bilateral numbness of lower limbs. Symptoms started as prickling sensation (paresthesia) over the soles, which progressed to numbness of the feet, and then, progressed to muscle weakness of lower limbs (ascending pattern). And then, she also had numbness over both upper limbs. She had significant weight loss (approximately 20 kg within 1 year) and loss of appetite.

Upon physical examination, she was thin and plethoric. Multiple red papules over the trunk and limbs were noted. Neurological examination showed bilateral lower limb muscle weakness and symmetrical peripheral neuropathy, which were evidenced by the findings of muscle power of 3 out of 5 for both lower limbs, absent reflexes (knee, ankle), downgoing planter responses and reduced sensation up to knee level for both lower limbs (in stocking distribution pattern). There were reduced sensation over the fingers of both hands up to wrist level (in glove distribution pattern) and wasting of the small muscles of the hand. On examination of abdomen, there were hepatosplenomegaly (liver was palpable 4 finger-breadth below the right costal margin and spleen was palpable 1 finger-breadth below the left costal margin).

Nerve conduction study/electromyography (NCS/EMG) of bilateral median, ulnar, sural, common peroneal and tibial nerves were performed. Findings were consistent with generalized axonal sensorimotor polyneuropathy. Needle EMG showed chronic denervative changes of the tested muscles. Distal motor latency (DML) were mildly prolonged in bilateral median, ulnar nerves and absent in bilateral common peroneal, tibial nerves. Compound muscle action potential (CMAP) amplitude were reduced in bilateral median, ulnar nerves and absent in bilateral common peroneal, tibial nerves. Motor conduction velocities (MCV) were reduced in bilateral median, ulnar nerves and absent in bilateral common peroneal, tibial nerves. F wave latency were absent in bilateral median, ulnar, common peroneal and tibial nerves. Distal sensory latency (DSL) were absent in bilateral median, ulnar and sural nerves. Sensory nerve action potential (SNAP) amplitude were absent in bilateral median, ulnar, sural, common peroneal and tibial nerves.

Lumbar puncture was performed and cerebrospinal fluid (CSF) analysis showed raised CSF total protein (654 mg/L), raised CSF albumin (423 mg/L) and no CSF white cells (polymorphs 0/cmm, lymphocyte 0/cmm). CSF cytology result was negative for malignancy.

She was initially treated as chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) with intravenous immunoglobulin (IVIg) (0.4 g/kg/day for 5 days) and high-dose prednisolone (1 mg/kg/day). However, she did not show significant neurological improvement.

In view of no significant neurological improvement despite getting the standard therapy, together with significant weight loss and her old age, investigations to screen for malignancy were carried out. Blood investigation for tumour markers and mammogram revealed no abnormalities. Skin biopsy showed acquired tufted angioma. Full blood count showed polycythaemia (haemoglobin 17.4 g/dL, haematocrit 0.51 l/L) and thrombocytosis (platelet  $634 \times 10^9/L$ ). Peripheral blood film revealed normocytic normochromic and slightly packed red cells, no Rouleaux formation, adequate and unremarkable white cells, plentiful platelets, no leucoerythroblastic picture and no blasts.

In addition to peripheral neuropathy, the presence of polycythaemia, thrombocytosis, hepatosplenomegaly as well as skin changes prompted the attending neurologist to consider POEMS syndrome as a working diagnosis, and hence the patient was referred to haematology team for further diagnostic work-up.

The result of serum and urine protein electrophoresis showed monoclonal IgG lambda (serum paraprotein 6.9 g/L and urine paraprotein 12.5 mg/L). Hence, further investigation i.e. bone marrow biopsy examination was performed to look for monoclonal plasma cell proliferative disorder. Bone marrow aspirate and trephine biopsy result revealed plasma cell neoplasm, as evidenced by presence of clonal plasma cells expressing lambda light chain restriction (no abnormal finding in cytogenetic analysis) (Fig. 1).

Hence, she had 2 mandatory major criteria of POEMS syndrome.

Normal serum calcium level and renal function test were noted. Serum lactate dehydrogenase (LDH) level was high (554 U/L). She had no evidence of endocrinopathy (thyroid function test and random serum cortisol level revealed no abnormalities).

Positron Emission Tomography/Computed tomography (PET/CT) scan showed active

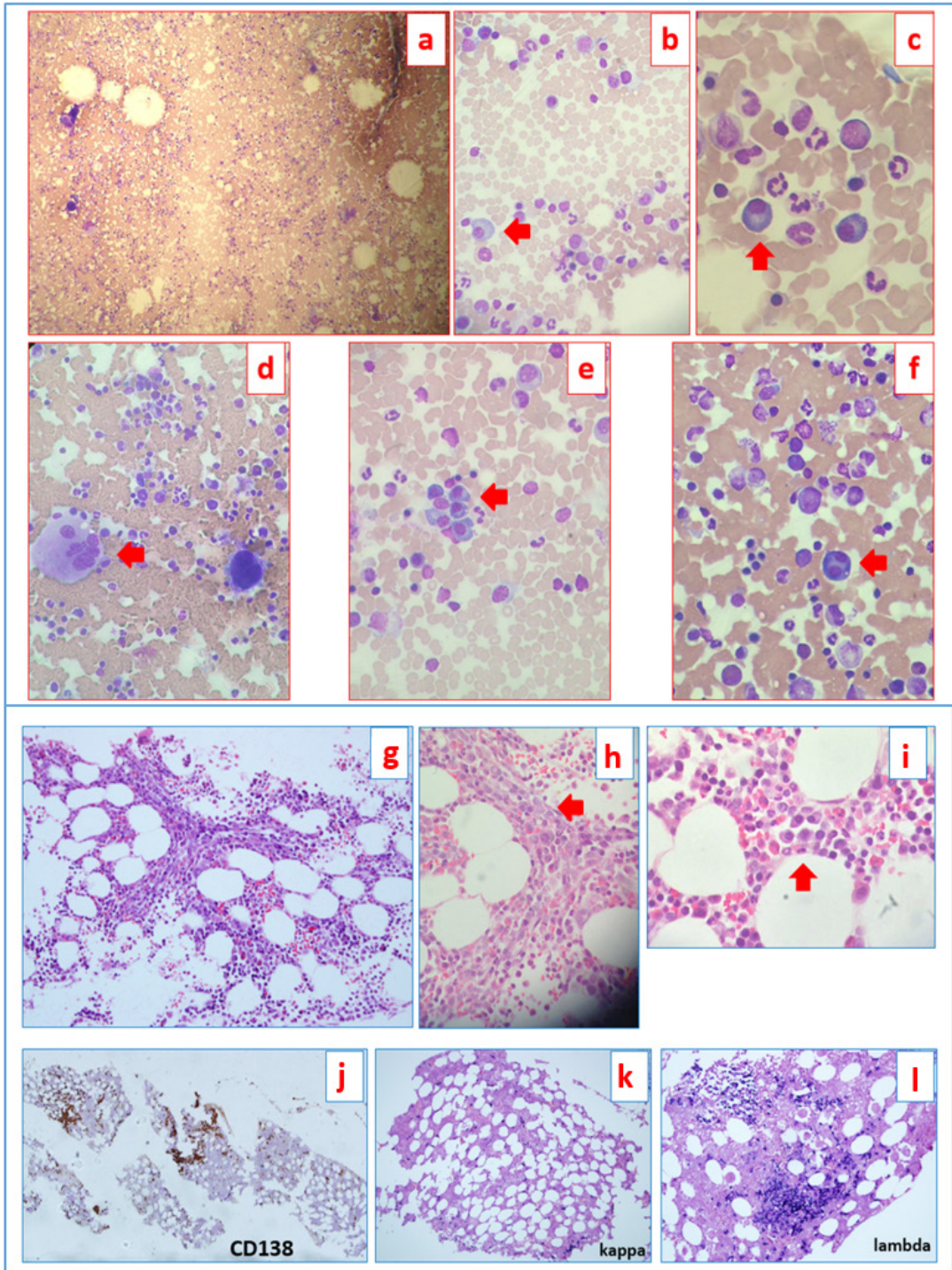


FIG. 1: Bone marrow biopsy examination. Bone marrow aspirate findings showing trilineage dysplasia with 6% of plasma cells: (a) MGG (May-Grünwald Giemsa) stain x10 (b) abnormal plasma cell (arrow) MGG stain x40 (c) abnormal plasma cell (arrow) MGG stain x40 (d) abnormal megakaryocyte (arrow) MGG stain x40 (e) abnormal plasma cells (arrow) MGG stain x40 (f) binucleated plasma cell (arrow) MGG stain x40. Bone marrow trephine biopsy findings showing features consistent with plasma cell neoplasm with lambda light chain restriction (g) increased number of plasma cells forming a cluster. H&E x10 (h) cluster of plasma cells (arrow). H&E x20 (i) abnormal plasma cells (arrow). H&E x20 (j) CD138 positive. x10 (k-l) lambda light chain restriction (in-situ hybridization). x20



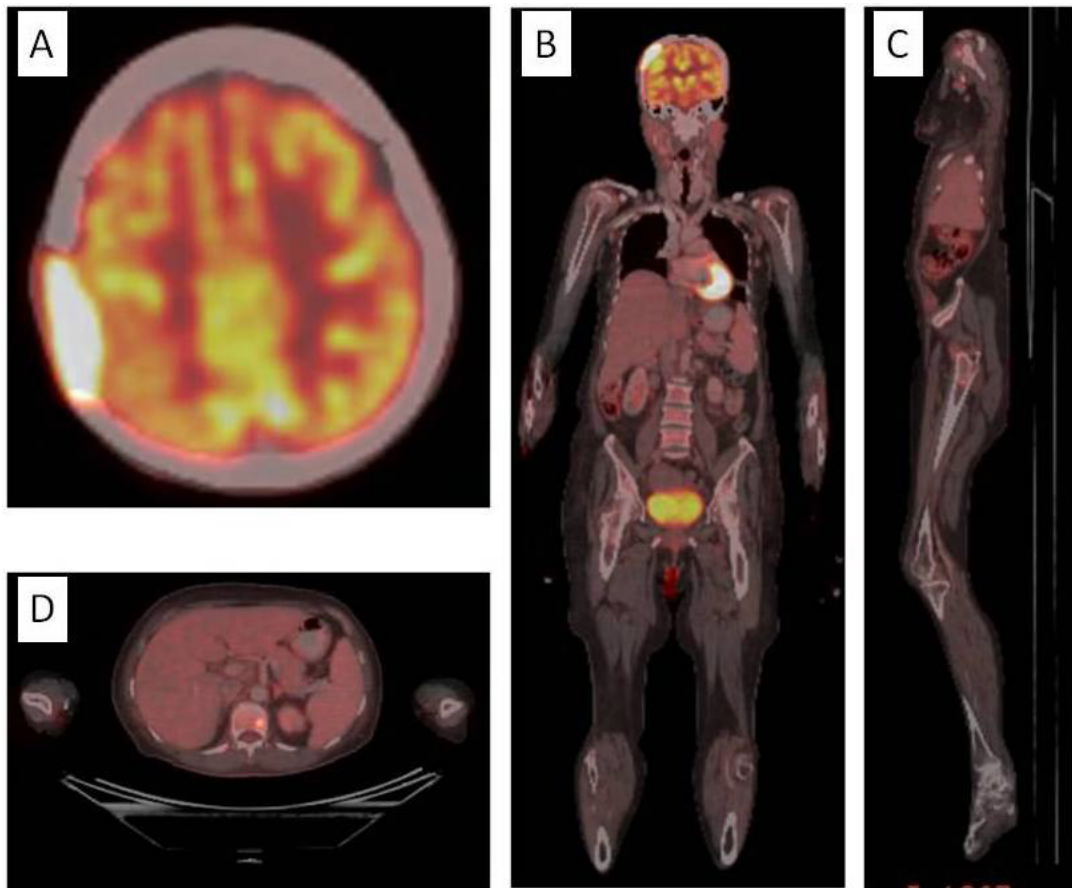


FIG. 2: PET/CT scan. (A) Large hypermetabolic soft tissue expansile mass destroying right parietal bone (5.3 x 2 x 4.6 cm,  $SUV_{max}$  23.8). (B) & (C) Multiple hypermetabolic osteosclerotic lesions involving axial and appendicular skeleton, mildly hypermetabolic cervical, axillary, mediastinal nodes. (D) Hepatomegaly (22 cm,  $SUV_{max}$  2.3), borderline splenomegaly (12 cm,  $SUV_{max}$  2.3)

disease: (1) large hypermetabolic soft tissue expansile mass destroying right parietal bone (5.3 x 2 x 4.6 cm, metabolic tumour volume (MTV) 18.91 cm<sup>3</sup>, maximum standardized uptake value ( $SUV_{max}$  23.8, Deauville 5), (2) multiple hypermetabolic osteosclerotic lesions involving axial and appendicular skeleton, (3) mildly hypermetabolic cervical, axillary, mediastinal nodes, (4) hepatomegaly (22 cm,  $SUV_{max}$  2.3) and borderline splenomegaly (12 cm,  $SUV_{max}$  2.3) (Fig. 2). Magnetic resonance imaging (MRI) brain showed the expansile intramedullary right parietal bone lesion, diffuse pachymeningeal enhancement and left parietal subdural effusion (0.6 cm in thickness). Biopsy of the bone lesion was not performed because the patient was not keen on the procedure.

In summary, the diagnosis of POEMS syndrome was made in this patient, based on the presence of two mandatory major criteria

[polyneuropathy, monoclonal plasma cell proliferative disorder (lambda)], one major criterion (sclerotic bone lesions) and three minor criteria (organomegaly, skin changes and thrombocytosis/polycythaemia).

Initially, she required weekly venesection for polycythaemia. Treatment with melphalan and prednisolone was started (melphalan 8 mg and prednisolone 60 mg for day 1 to 7, every 6-week-cycle). For neuropathic pain, she received medications such as gabapentin and pregabalin. She was referred for limb physiotherapy.

After 6 cycles of melphalan-prednisolone therapy, she achieved clinical improvement and partial response (haematologic and radiological). Clinically, paresthesia was improved with medication, however, NCS study did not show much improvement. Muscle power of lower limbs was improved, and she was able to walk with the support aid of walking frame. She

did not need venesection; and there was no more polycythaemia (haemoglobin 15 g/dL, haematocrit 0.45 l/L, platelet  $258 \times 10^9/L$ ). There was more than 50% reduction in paraprotein level (serum paraprotein 2.2 g/L and urine paraprotein 0 mg/L). PET/CT scan showed good metabolic response: (1) hypermetabolic soft tissue mass at the right parietal bone showed good response with reducing  $SUV_{max}$  (13.4 cf 23.8) and MTV (4.39 cf 18.91  $cm^3$ ), (2) multiple bone lesions involving the axial and appendicular skeleton became ametabolic except mild activity at the left transverse process of S1 vertebra, (3) the previous mild hypermetabolic activity of cervical and mediastinal nodes had resolved; the axillary nodes had minimal residual activity, (4) liver was still enlarged but reduced in size compared to previously (19.6 cm cf 22 cm) with physiological metabolic activity ( $SUV_{max}$  2.9); and spleen was not enlarged with physiological metabolic activity ( $SUV_{max}$  2.4).

## DISCUSSION

The patient presented with the typical clinical picture, i.e. peripheral neuropathy which is required for the diagnosis of POEMS syndrome and usually dominates the clinical picture. One of the differential diagnoses for peripheral neuropathy is chronic inflammatory demyelinating polyradiculoneuropathy (CIDP); and it is important to distinguish it from POEMS syndrome. Both CIDP and POEMS are characterized by subacute motor-dominant symmetric demyelinating polyradiculoneuropathy. Uniform demyelination and more severe axonal loss distinguish POEMS from CIDP.<sup>4</sup> A study by Nasu *et al* revealed that clinically, POEMS neuropathy more frequently showed severe leg pain (76% vs 7%;  $p < 0.001$ ), muscle atrophy (52% vs 24%;  $p = 0.005$ ) and distal dominant muscle weakness.<sup>5</sup> Nerve conduction study and electromyography can effectively distinguish POEMS from CIDP.<sup>4,5</sup> POEMS demonstrates greater axonal loss (greater reduction of motor amplitudes and greater number of fibrillation potentials), greater slowing of motor and sensory conduction velocities, less frequent temporal dispersion and conduction block, no sural sparing, and higher terminal latency indices.<sup>4</sup> These findings suggest that pathology of POEMS is uniform demyelination (diffusely distributed along the nerve) whereas pathology of CIDP is probably predominantly proximal

and distal.<sup>4</sup> Nerve biopsies can be helpful to distinguish POEMS from CIDP.<sup>6</sup> POEMS shows higher degree of axonal degeneration and more epineurial neovascularization whereas CIDP shows more endoneurial inflammation and more onion-bulbs.<sup>6</sup> These findings suggest that the mechanism in POEMS is paraneoplastic vasculopathy (associated with elevated VEGF levels) whereas the mechanism in CIDP is inflammatory demyelination.<sup>6</sup>

Another differential diagnosis which is important to distinguish from POEMS syndrome is multiple myeloma. In classical multiple myeloma, polyneuropathy is uncommon; bone lesions are osteolytic lesions but no sclerotic changes; there is target organ damage such as anaemia, hypercalcaemia, renal failure or pathologic fractures; and percentage of plasma cells is high in the bone marrow.

For our patient, she was treated with 6 cycles of melphalan-prednisolone therapy. She had clinical improvement and partial response (haematologic and radiological). From literature review, there are no randomized clinical trial data to direct the best therapy for POEMS syndrome.<sup>7</sup> The recommendations regarding treatment options are (1) radiation therapy (curative intent, to the affected sites, at the dose of 40 to 50 Gy) (Grade 1C) for limited disease (symptomatic patients with one to three isolated bone lesions and no evidence of bone marrow involvement), and (2) systemic therapy similar to treatment of multiple myeloma [chemotherapy, haematopoietic stem cell transplantation (HSCT)] (Grade 1C) for advanced disease (symptomatic patients with widespread osteosclerotic lesions or severe symptoms).<sup>7</sup> The preferred treatment regimen for systemic therapy is melphalan plus dexamethasone that has demonstrated good response rates [80.6% (25 out of 31 patients) achieved haematologic response including 12 (38.7%) complete remission and 13 (41.9%) partial remission] with acceptable toxicity profile.<sup>8</sup> Lenalidomide-based regimen may be an acceptable alternative,<sup>9</sup> but further studies are necessary prior to their routine use. Autologous HSCT following high-dose melphalan should be considered for younger transplant-eligible patients with widespread osteosclerotic lesions and/or severe symptoms, especially progressive neuropathy (Grade 2C).<sup>7</sup> In the largest series of study by Mayo Clinic (59 patients with POEMS syndrome treated with autologous HSCT using peripheral blood stem cells), clinical improvement was nearly universal in

these patients, maximal neurologic improvement was seen at three years post-transplant, five-year overall survival rate was 94 percent and five-year progression-free survival rate was 75 percent at a median follow-up of 45 months.<sup>10</sup> From literature review, there are a few reports that thalidomide-based therapy<sup>11</sup> and bortezomib-based therapy<sup>12-14</sup> show some activity, however, further larger studies are needed to explore the safety profile.

For paresthesia in our patient, she has received medications such as gabapentin and pregabalin. She has performed limb physiotherapy. The study by Dispenzieri A mentioned that the two best ways to approach the peripheral neuropathy are to target the clone and to perform physical therapy and occupational therapy intensively by the patient.<sup>7</sup> Painful peripheral neuropathy should be treated with drugs, such as gabapentin, pregabalin, amitriptyline, nortriptyline, duloxetine, topical lidocaine patches, and topical ketamine, lidocaine, and amitriptyline compounds.<sup>7</sup>

The cause of POEMS syndrome is unknown, although chronic overproduction of pro-inflammatory and other cytokines appears to be a major feature of this disorder. From literature review, the possible pathophysiology includes (1) chronic overproduction of pro-inflammatory cytokines such as vascular endothelial growth factor (VEGF), resulting in increased vascular permeability, microangiopathy, oedema, effusion, neovascularization, polyneuropathy, pulmonary hypertension, leukocytosis and thrombocytosis<sup>15,16</sup> (2) marked activation of cytokines such as interleukin-1 $\beta$  (IL-1 $\beta$ ), tumor necrosis factor alpha (TNF-alpha), and interleukin-6 (IL-6)<sup>16</sup> (3) weak or decreased TGF- $\beta$ 1 antagonistic reaction<sup>15</sup> and (4) elevation of circulating levels of matrix metalloproteinases (MMP-1, -2, -3, -9) and tissue inhibitor of metalloproteinases (TIMP-1)<sup>17</sup>. Platelets<sup>18</sup> or plasma cells<sup>19</sup> are major sources of VEGF, a potent inducer of increased vascular permeability. Elevated levels of VEGF decrease significantly in patients with POEMS syndrome following successful therapy.<sup>16</sup> For our patient, the measurement of VEGF level was not available.

The course of POEMS syndrome is chronic. Overall median survival was 13.7 years in the Mayo Clinic series<sup>1</sup> whereas median survival of those with clubbing or extravascular volume overload were 2.6 and 6.6 years, respectively.<sup>1</sup> Patients who received radiation therapy with a good response to treatment had superior survival.

### Conclusion

We highlight this rare syndrome to raise the awareness for full diagnostic work-up and prompt multidisciplinary approach in order to obtain an early diagnosis of the disease and management with the aim for reduced long-term irreversible morbidity.

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