

Utility of osteosclerotic lesion biopsy in diagnosis of POEMS syndrome

A case report

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Abstract

Rationale: We report a case of successful diagnosis of POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome based on monoclonality that was confirmed by an osteosclerotic lesion biopsy in a patient without pathognomonic symptoms or monoclonal gammopathy, probably because of comorbidities, which included systemic lupus erythematosus, rheumatoid arthritis, and Sjögren syndrome.

Patient concerns: A 57-year-old woman presented with an approximately 2-year history of numbness in the toes that had gradually spread, along with muscle weakness in both arms and legs. She had been receiving immunosuppressant and corticosteroid therapy since being diagnosed with systemic lupus erythematosus and Sjögren syndrome at the age of 31 years and rheumatoid arthritis at the age of 44 years. Neurological examination revealed predominantly distal hypoesthesia and weakness in a typical stocking-and-glove pattern. Immunoelectrophoresis revealed elevated polyclonal immunoglobulin, which was attributed to her known underlying disease.

Diagnoses: Biopsy of an osteosclerotic lesion confirmed proliferation of monoclonal plasma cells, leading to a diagnosis of POEMS syndrome.

Interventions and outcomes: Lenalidomide therapy was started after the diagnosis and the patient had a favorable outcome.

Lessons: Osteosclerotic lesion biopsy can be useful for diagnosis of POEMS syndrome in difficult cases.

Abbreviations: CT = computed tomography, FLC = free light chain, MRI = magnetic resonance imaging, POEMS = polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes, RA = rheumatoid arthritis, SLE = systemic lupus erythematosus, SS = Sjögren syndrome, VEGF = vascular endothelial growth factor.

Keywords: osteosclerotic lesion, POEMS syndrome, rheumatoid arthritis, Sjögren syndrome, systemic lupus erythematosus

Editor: Zelena Dora.

Authorship: DH, HA, SN, and TS examined the patient, drafted the manuscript, and created the figures. MH performed the pathological examination. YH helped draft the manuscript. All authors read and approved the final manuscript.

The Human Research Ethics Committee of St. Marianna University Hospital provided a waiver considering that approval is not necessary for a single case report. Written informed consent was obtained from the patient.

The patient provided written informed consent for publication of clinical details and images. A copy of the consent form is available for review by the journal editor.

All relevant data are contained in the manuscript.

The authors declare that they have no competing interests.

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Medicine (2017) 96:41(e8188)

Received: 20 June 2017 / Received in final form: 24 August 2017 / Accepted: 8 September 2017

<http://dx.doi.org/10.1097/MD.00000000000008188>

1. Introduction

POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome is a rare disorder with signs and symptoms that vary from one body site to another.^[1] There are about 340 people with POEMS syndrome in Japan, indicating a prevalence of approximately 0.3 per hundred thousand population.^[2] Furthermore, there is a few cases frequency of POEMS syndrome with collagen disease.^[3–5] Proliferation of monoclonal plasma cells within an intramedullary plasmacytoma likely contributes to the pathology of POEMS syndrome. The condition is characterized by increased production of M-protein to a detectable level, an abnormal λ/κ free light chain (FLC) ratio, and obvious monoclonality (monoclonal gammopathy confirmed by immunoelectrophoresis).^[1] Painless osteosclerotic lesions that are visible on plain skeletal radiography are also characteristic of POEMS syndrome. We report here a case of successful diagnosis of POEMS syndrome based on monoclonality (proliferation of monoclonal plasma cells) that was confirmed by an osteosclerotic lesion biopsy in a patient without pathognomonic symptoms or monoclonal gammopathy, probably because of comorbidities, which included systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and Sjögren syndrome (SS). Lenalidomide therapy was started after the diagnosis and the patient had a favorable outcome.

Table 1

Laboratory data on admission.

Hematological Data		Biochemical and Serological Data		Urinalysis	
WBC	5100/ μ L	K	4.9 mEq/L	KL-6	377 U/mL
Neut	50.5 %	Cl	102 mEq/L	β 2-MG	3.7 mg/L
Lym	39.6 %	Ca	8.6 mg/dL	IL-6	3.5 pg/mL
Mono	8.9 %	UN	14.7 mg/dL	VEGF (plasma)	879 pg/mL
Eo	1.5 %	Cre	0.85 mg/dL	ANA	(-)
Ba	6.0 %	CRP	0.11 mg/dL	MAG	(-)
RBC	$38.3 \times 10^5/\mu$ L	CK	11 U/L	ACE	6.1 U/L
Hb	12.2 g/dL	Glucose	110 mg/dL	Free T ₃	1.2 pg/mL
Hct	36.5 %	BNP	25.9 pg/mL	Free T ₄	9.8 pg/mL
Plt	$44.6 \times 10^3/\mu$ L	FLC		PTH-intact	59.0 pmol/L
		κ chain	77.6 mg/L	LH	29.6 mIU/mL
		λ chain	60.5 mg/L	FSH	65.7 mIU/mL
		κ/λ ratio	1.28	PRL	22.5 ng/mL
TP	6.0 g/dL	IgG	1408 mg/dL		
Protein fraction		IgA	471 mg/dL		
alb	54.6 %	IgM	64 mg/dL		
α 1-globulin	2.9 %	IgD	2.5 mg/dL		
α 2-globulin	8.0 %	M protein	(-)		
β -globulin	10.8 %	MMP-3	156.6 ng/mL		
γ -globulin	23.7 %	SS-A	2 \times		
Alb	3.2 g/dL	SS-B	4 \times		
AST	15 U/L	IgG4	98 mg/dL		
ALT	17 U/L	CH 50	40.2 U/mL		
LDH	112 U/L	ds-DNA-IgG	9.6 IU/mL		
ALP	234 U/L	sIL-2R	380 U/mL		
Na	144 mEq/L				

β 2 MG = β 2 microglobulin, ACE = angiotensin-converting enzyme, ANA = anti-nuclear antibody, B-J protein = Bence-Jones protein, Ccr 24 h = 24-hour creatine clearance, CSF = cerebrospinal fluid, ds-DNA-IgG = anti-double stranded DNA antibody, FLC = free light chain, FSH = follicle stimulating hormone, IL-6 = interleukin-6, LH = luteinizing hormone, MAG = anti-myelin associated glycoprotein antibody, MMP-3 = matrix metalloproteinase-3, PRL = prolactin, PTH = parathyroid hormone, sIL-2R = soluble interleukin-2 receptor, SS-A = anti-Sjögren syndrome related antigen type A, SS-B = anti-Sjögren syndrome related antigen type B, VEGF = vascular endothelial growth factor.

2. Case report

A 57-year-old right-handed woman was admitted to our department of neurology with numbness and weakness of both arms and legs. Her past medical history included SLE and SS diagnosed at the age of 31 years, RA diagnosed at the age of 44 years, atherothrombotic brain infarction (with no sequelae), aortic valve stenosis, and spinal canal stenosis (L4/5) diagnosed at the age of 56 years, and right-sided deep vein thrombosis diagnosed at the age of 57 years. She reported drinking socially and denied smoking. Her family history was unremarkable. She was taking prednisolone 7 mg, azathioprine 75 mg, aspirin 100 mg, edoxaban 30 mg, lansoprazole 15 mg, polaprezinc 150 mg, pregabalin 100 mg, and eldocalcitol 0.75 μ g daily.

She had noticed episodes of numbness in the toes on both sides that started in around May 2014, but did not seek treatment because she suspected they were attributable to her known pre-existing disease. The numbness then spread to the ankles and by late October 2015 was accompanied by pain in the soles of both feet. By late January 2016, the numbness extended to below the knees and involved the area distal to the wrists; plantar flexion and dorsiflexion of the right ankle became difficult. This progressed to difficulty in plantar flexion and dorsiflexion of the left ankle joint and in palmar flexion and extension of both wrists in February 2016. The patient then developed edema in the lower extremities bilaterally and was admitted to our hospital for further examination and treatment in April 2016.

On admission, height was 158 cm, body weight was 42 kg, blood pressure was 126/86 mm Hg, pulse rate was regular at 86 beats/min, body temperature was 36.8°C, and respiratory rate was 16 breaths/min. Physical examination revealed a systolic

murmur (Levine grade IV/VI) in the second intercostal space at the right sternal border, edema in the lower extremities bilaterally, finger joint deformities, and angiomas on the chest and back. The patient was lucid and neurological examination revealed no cranial nerve abnormalities. Motor system examination confirmed distal muscle weakness in all extremities (upper and lower extremity strength score by manual muscle testing 5-/4 and 2/1, respectively; right and left grip strength, 12 and 8 kg, respectively). Tendon reflexes were absent in all extremities and pathological reflexes were negative. Sensory system examination revealed numbness in the areas distal to both wrists and knees, pain in the areas distal to the ankles bilaterally, and superficial and deep sensory impairment in the affected areas, particularly in the lower extremities. The patient could stand briefly but with considerable unsteadiness and could not walk unaided. There were no autonomic disorders, such as urinary disorder or orthostatic hypotension. Overall Neuropathy Limitation Scale^[6] score was 8.

Laboratory data on admission (Table 1) revealed elevated platelet count (446,000/ μ L), but the coagulation profile was normal. Total serum protein, albumin, and γ -globulin levels were normal (except for a slight increase in immunoglobulin A); antinuclear, anti-SS-A, and anti-SS-B antibody titers were increased 320-fold, 2-fold, and 4-fold, respectively. Serum matrix metalloproteinase-3 was 156.6 ng/mL (normal range 17.3–59.7 ng/mL) and immunofixation for M-protein was negative. Polyclonal gammopathy was confirmed by immunoelectrophoresis. Her κ and λ FLC levels were 77.6 mg/L (normal range 2.42–18.92 mg/L) and 60.5 mg/L (normal range 4.44–26.18 mg/L), respectively, and the κ/λ ratio was 1.28 (normal range 0.248–1.804). Metabolic and endocrine data and tumor

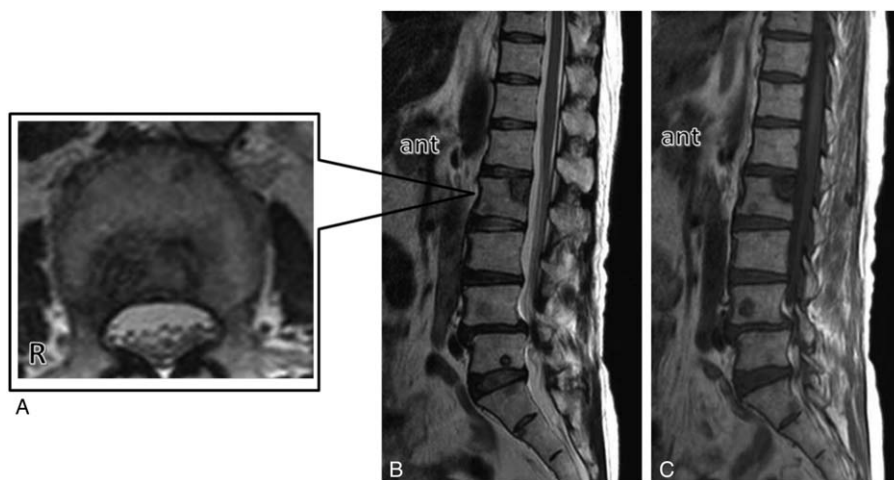


Figure 1. Spinal cord magnetic resonance image on admission. (A) Axial T2-weighted image of the second lumbar vertebra (1.5T; 3250ms, echo time 90ms) showing osteosclerotic lesions with high-density signals surrounded by low-density signals. (B) Sagittal T2-weighted image (1.5T; 456ms, echo time 10ms) of the lumbar vertebra showing multiple osteosclerotic lesions. (C) Sagittal T1-weighted image of the lumbar vertebra (1.5T; 519ms, echo time 15ms) showing multiple osteosclerotic lesions. ant=anterior, R=right.

marker levels were normal. Protein in cerebrospinal fluid had increased to 135.4mg/dL.

Electrocardiography showed sinus rhythm, heart rate of 86 beats/min, and normal R-R interval variability. Schellong test was negative. Plain chest radiography revealed no abnormalities and there were no acute lesions on plain magnetic resonance imaging (MRI) of the head. MRI of the lumbar spine showed forward slipping of the body of L4, spinal stenosis at L4/5, and osteosclerotic lesions in the bodies of L2, L4, L5, and S1 (low on T1-weighted and T2-weighted images and high on short-tau inversion recovery images; Fig. 1). Thoracoabdominal contrast computed tomography (CT) showed osteosclerotic lesions in the ribs, vertebral bodies, clavicles, and pelvis, and positron emission tomography-CT showed tracer accumulation in the area corresponding to an osteosclerotic lesion in the body of L2. There was mild pericardial effusion but no lymphadenopathy, hepatosplenomegaly, or accumulation of thoracoabdominal fluid. Bone scintigraphy demonstrated increased accumulation in the ribs on both sides and at several spinal levels. Transthoracic echocardiography revealed severe aortic valve stenosis with calcification and diffuse left ventricular hypertrophy, in good

agreement with previous findings. Nerve conduction studies showed mildly decreased motor nerve conduction velocity and temporal dispersion in the upper extremities, with considerably decreased compound muscle action potential amplitude and motor nerve conduction velocity in the lower extremities (Table 2). Sensory nerve conduction velocity was markedly decreased and sensory nerve action potential amplitude was also considerably decreased in the lower extremities (Table 2). In short, the electrophysiological findings indicated polyneuropathy with demyelination in the upper extremities and both demyelination and axonopathy in the lower extremities. Furthermore, the terminal latency index^[7] was high in the median nerve bilaterally (0.44 on the right, 0.47 on the left). Needle electromyography showed no clear neurogenic pattern, but revealed fibrillation potentials at rest in the tibialis anterior and gastrocnemius muscles bilaterally. The patient declined a nerve biopsy.

The clinical course is shown in Fig. 2. CT-guided biopsy of a lesion in the L2 vertebra performed 12 days after hospitalization showed a marked increase in strongly CD138-positive plasma cells with clonality skewed toward λ light chains rather than κ light chains (Fig. 3). A repeat plasma vascular endothelial growth

Table 2

Nerve conduction study.

		DL (ms)	CMAP (mV)	MCV (m/s)	SNAP (μV)	SCV (m/s)
Median Nerve	R	4.2	6.9	38.8	12.0	42.1
	L	3.8	6.8	41.9	21.4	50.8
	Normal values	< 4.2	> 3.5	> 48.0	> 10.0	> 49.8
Peroneal Nerve	R	6.4	0.092	34.8		
	L	5.5	0.300	32.8		
	Normal values	< 5.5	> 2.5	> 40.0		
Tibial Nerve	R	10.1	0.053	28.5		
	L	7.3	0.170	27.6		
	Normal values	< 6.0	> 2.9	> 41.0		
Sural Nerve	R				3.1	36.5
	L				5.5	33.3
	Normal values				> 10.5	> 45.2

CMAP=compound muscle action potential, DL=distal latency, L=left, MCV= motor conduction velocity, R=right, SCV=sensory conduction velocity, SNAP=sensory nerve action potential.

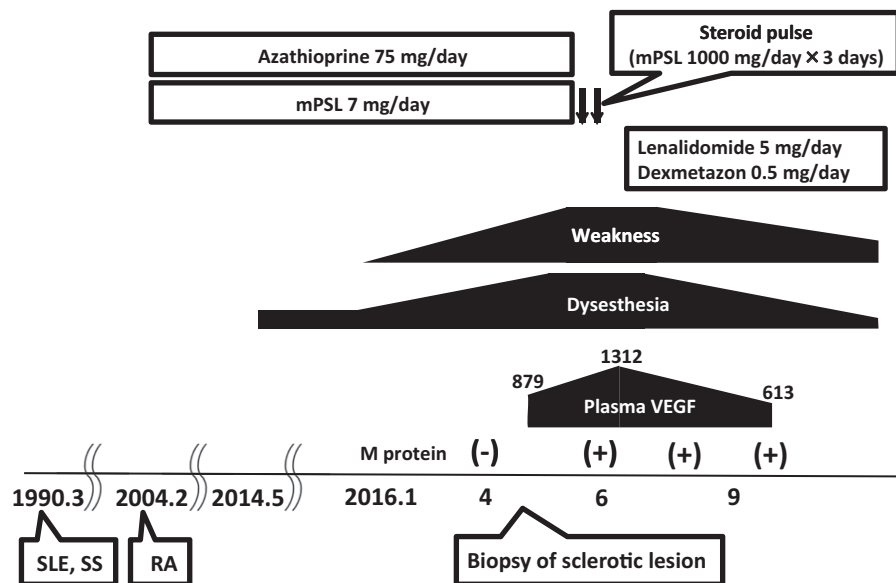


Figure 2. Clinical course. After treatment with lenalidomide and dexamethasone, her numbness, paresthesia, and weakness gradually improved and her serum VEGF level decreased. mPSL=methylprednisolone, RA=rheumatoid arthritis, SLE=systemic lupus erythematosus, SS=Sjögren syndrome.

factor (VEGF) level measured on day 25 of hospitalization showed elevation to 879 pg/mL (normal level <38.7 pg/mL). Fulfillment of the diagnostic criteria together with other findings prompted the diagnosis of POEMS syndrome. Two cycles of pulse corticosteroid therapy (methylprednisolone 1000 mg/day) started 45 days after hospitalization did not alleviate the patient’s neurological symptoms. Her plasma VEGF increased further to

1312 pg/mL and M-protein (IgG λ) became positive 57 days after hospitalization. Oral azathioprine was withdrawn and new treatment comprising lenalidomide 5 mg/day and dexamethasone 0.5 mg/day was started 64 days after hospitalization. The patient was discharged home after 76 days in hospital. The same treatment was continued after discharge. Her Overall Neuropathy Limitation Scale score improved from 8 to 3, the edema in her

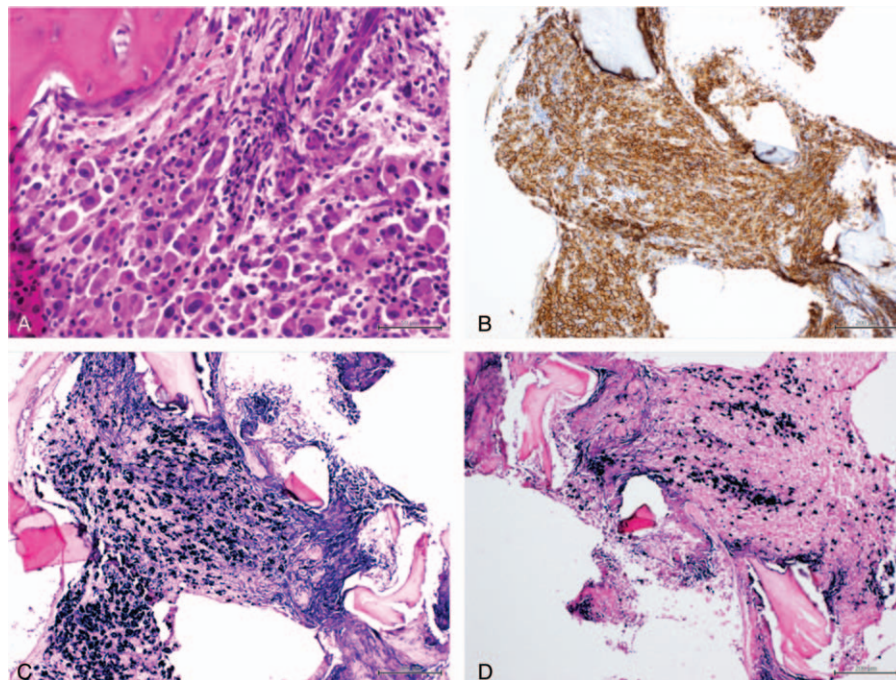


Figure 3. Biopsy specimen of a sclerotic lesion in the L2 vertebra. The specimen was obtained by computed tomography-guided needle biopsy of the lesion. (A) Sheets of mature-appearing plasma cells (hematoxylin-eosin staining, bar = 50 μm). (B) Plasma cells strongly positive for the plasma cell marker CD138 (bar = 200 μm). (C) In situ hybridization showing only rare plasma cells are positive for immunoglobulin λ light chain (bar = 200 μm). (D) In situ hybridization showing that plasma cells are rarely positive for immunoglobulin κ light chain (bar = 200 μm).

lower extremities resolved, and her plasma VEGF improved to 613 pg/mL. She is currently continuing the same treatment.

3. Discussion

Patients with POEMS syndrome present with various symptoms at different sites of the body. All patients with POEMS syndrome develop polyneuropathy, but organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes have been reported to occur in 45% to 85%, 67% to 84%, 24% to 54%, and 46% to 93% of patients, respectively.^[1] A diagnosis of POEMS syndrome requires fulfillment of 2 mandatory criteria, at least one of 3 other major criteria, and at least one of 6 minor criteria. The major mandatory criteria are plasma cell dyscrasia and polyneuropathy, and other major criteria include Castleman disease, sclerotic bone lesions, and elevated VEGF. Minor criteria include organomegaly, extravascular volume overload, endocrinopathy, skin changes, papilledema, and thrombocytosis/polycythemia.^[1] The mandatory major criteria of plasma cell dyscrasia and polyneuropathy, other major criteria of sclerotic bone lesions and elevated VEGF, and minor criteria of skin changes, extravascular volume overload, and thrombocytosis were fulfilled in this case. However, characteristic symptoms are often absent in the early stages, and subsequent delays in diagnosis and treatment can result in a poor prognosis. POEMS syndrome was not easily diagnosed in our case for the following reasons. First, the patient had multiple comorbidities (SLE, RA, SS, aortic stenosis, and deep vein thrombosis), symptoms of which overlap with the characteristic symptoms of POEMS syndrome (such as polyneuropathy, edema, and skin disorders). Second, M-protein, which is indicative of increased monoclonal immunoglobulin levels, was not detected, the λ/κ FLC ratio was normal, and immunoelectrophoresis did not indicate monoclonal gammopathy. Polyneuropathy, chronic inflammatory demyelinating polyneuropathy, amyloid neuropathies, diabetic polyneuropathy, connective tissue-related peripheral neuropathy, paraneoplastic syndrome, alcoholic neuropathy, celiac disease, neuropathy related to human immunodeficiency virus or hepatitis C virus infection, various drugs, thyroid disorders, paraproteinemia, sarcoid polyneuropathy, vitamin B12 deficiency, and hereditary diseases (e.g., Fabry disease and hereditary sensory autonomic neuropathy) were excluded by various laboratory findings. However, chronic inflammatory demyelinating polyneuropathy and connective tissue related peripheral neuropathy remained in the differential diagnosis. Ultimately, these neuropathies were ruled out by a high terminal latency index value^[7] on nerve conduction studies as well as the therapeutic effect of lenalidomide.

Proliferation of monoclonal plasma cells is usually evident in protein fractions recovered from patients with POEMS syndrome,^[8] but our initial findings of immunoelectrophoresis, FLC analysis, and M-protein detection did not support this. Aggarwal et al^[9] reported higher levels of both λ and κ FLC in patients with SLE or RA than in normal controls, and that testing for FLC in addition to testing C3, C4, and anti-ds-DNA antibody levels is useful for assessing disease activity in SLE. Similarly, the underlying SLE and RA in our patient might have caused the increase in polyclonal immunoglobulins, thereby masking apparent monoclonality. Therefore, osteosclerotic lesion biopsy to confirm abnormal proliferation of plasma cells with a predominance of monoclonal λ chains was critical in reaching the diagnosis of POEMS syndrome in this case. There have been a few previous reports of a patient with POEMS syndrome also

having SLE, SS, and RA,^[3–5] so the present case is valuable in demonstrating the utility of a diagnostic osteosclerotic lesion biopsy when immunoelectrophoresis for monoclonality is inconclusive. M-protein level is not very high in patients with POEMS syndrome, with a positive rate of only 24% to 54%,^[1] so the undetectable level of M-protein in our patient does not conflict with a diagnosis of POEMS syndrome.

Serum and plasma VEGF levels increase in POEMS syndrome, suggesting its usefulness in diagnosis and assessment of disease activity. D'Souza et al^[10] showed that a serum VEGF threshold of 200 pg/mL had a specificity of 95% and a sensitivity of 63% for differentiating POEMS syndrome from other diseases that also include elevated serum VEGF, such as RA, SLE, chronic inflammatory demyelinating polyradiculoneuropathy, and multiple myeloma. Plasma cells and platelets both secrete VEGF in POEMS syndrome, and serum levels are reportedly 10 to 50 times higher than plasma levels.^[11] The abnormally high plasma VEGF level in our patient supports a diagnosis of POEMS syndrome. Nevertheless, because there have been no prior reports of plasma VEGF levels in patients with POEMS syndrome and multiple underlying diseases such as SLE and RA, diagnostic osteosclerotic lesion biopsy was essential in diagnosing POEMS syndrome in the present case.

Standard treatment for POEMS syndrome has not yet been established, so we opted for lenalidomide because autologous stem cell transplantation and long-term thalidomide therapy were not realistic options in our patient because of the underlying connective tissue disease and the risk of neurological complications, respectively. A recent study showed that lenalidomide is effective and safe and has some neurological benefit in patients with POEMS syndrome.^[1] Indeed, lenalidomide therapy had a favorable outcome in the present case, including alleviation of neurological symptoms and decreased plasma VEGF levels.

POEMS syndrome is a rare disease that requires therapeutic strategies different from those used for other peripheral nerve disorders, and delayed diagnosis and treatment may have severe sequelae. Osteosclerotic lesion biopsy is recommended in the differential diagnosis of POEMS syndrome from other conditions, particularly in a patient with peripheral neuropathy and comorbid connective tissue disease who is unresponsive to treatment and in whom thorough systemic examination reveals an osteosclerotic lesion, but symptoms and investigations are not pathognomonic for POEMS syndrome.

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