OPEN ACCESS

Saudi Journal of Medicine

Abbreviated Key Title: Saudi J Med
ISSN 2518-3389 (Print) |ISSN 2518-3397 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Case Report

POEMS Syndrome: A Case Report and Literature Review

Imane Benbella[1,4], Houda ElAsri[1,4,*], Safaa Rifai[1,4], Mustapha Mahmoud[1,3,4], Fatima El Boukhrissi[2,4]

[1]Biochemistry Unit, University Hospital Hassan II, Fès, Morocco
[2]Biochemistry Unit, Military Hospital Moulay Ismail, Meknès, Morocco
[3]Head of the Biochemistry Unit, University Hospital Hassan II, Fès, Morocco
[4]Faculty of Medecine, Pharmacology and Dental Médecine, university Sidi Med Ben Abdellah, Fès, Morocco

DOI: 10.36348/sjm.2022.v07i01.015 | **Received:** 07.12.2021 | **Accepted:** 12.01.2022 | **Published:** 30.01.2022

***Corresponding Author:** Houda ElAsri
Biochemistry Unit, University Hospital Hassan II, Fès, Morocco

Abstract

POEMS syndrome is a rare paraneoplasic syndrome associated to a plasma cell proliferative disorder, which is characterized by the presence of peripheral neuropathy (P), organomegaly (O), endocrinopathy (E), monoclonal gammopathy (M) and skin change (S). Because of the rarity of this disease, the small number of cases described in the literature and the polymorphism of the clinical manifestations, the diagnosis of POEMS syndrome remains difficult. The prognosis of the disease is related to the early onset of specific treatment. We hereby present a clinical case of POEMS syndrome in a 41-year-old woman revealed by a polyneuropathy, in order to highlight the diagnostic problems and to raise awareness of this syndrome.

Keywords: POEMS syndrome, monoclonal gammopathy, vascular endothelial growth factor, polyneuropathy, case report.

INTRODUCTION

POEMS syndrome is a rare paraneoplasic syndrome associated to a plasma cell proliferative disorder. It is characterized by the presence of peripheral neuropathy (P), organomegaly (O), endocrinopathy (E), monoclonal gammopathy (M) and skin change (S). Atypical clinical presentations are possible, sometimes accompanied by severe visceral damage, particularly neurological and renal. The polymorphism of the clinical manifestations makes the diagnosis difficult and delays the treatment.

We hereby present a case of POEMS syndrome revealed by a polyneuropathy. Our objective is to highlight the diagnostic problems and to raise awareness of this syndrome.

CASE REPORT

A 41-year-old woman was admitted at the neurology department, following a 03 months history of progressive fatigue and numbness in the lower extremities, weight loss, and chronic bilateral temporo-occipital cephalalgias.

The physical examination revealed a peripheral neurogenic syndrome of the lower limbs associated with sphincter disorders, a paroxysmal facial erythema related to rosacea and bilateral papillary edema. Superficial lymph nodes were not palpable.

The laboratory examination found normal cardiac, liver, and renal functions. A complete blood count showed white blood cells of 8170/mm³, hemoglobin of 13.5g/dL and platelet count of 349000/mm³.No significant abnormalities were found on the peripheral blood smear and the PT/aPTT (Prothrombin Time/Activated Partial Thromboplastin Time)levels were within normal limits. The glucose level was normal with HbA1C of 5.2%. Thyroid function test showed TSHus (ultra-sensible thyroid-stimulating hormone) of 4.48uUI/Ml (0.35-4.94) and anti-thyroid peroxidase (anti-TPO) antibodies of 186.40 UI/mL (<5.61). Vitamin B12 dosage was of 100 pg/dL (180-360) with normal anti-parietal cell antibodies and intrinsic factor blocking antibodies. Hepatitis serology showed HBsAg (-), HBsAb(+) and HBcAb (+).VEGF (Vascular Endothelial Growth Factor) level was high at 265.46 pg/mL (<211.65). Serum protein electrophoresis

showed an increase in the beta2 region (Figure 1) and the immunofixation examination revealed a monoclonal IgAλ (ImmunoglobulinAλ) peak (Figure 2).The immunoglobulin free light chains dosage was normal. The cerebrospinal fluid cytobacteriological analysis and electrophoresis were normal.

An electroneuromyography disclosed a demyelinating sensitivo-motor polyradiculoneuropathy with secondary axonal degeneration.

The CT (Computed Tomography) scan showed a floating internal jugular vein thrombosis. An MRI (Magnetic Resonance Imaging) was conducted and revealed multiple inflammatory lesions of the cerebral white matter. The cervical ultrasound evaluation showed Hashimoto's thyroiditis. Cardiac, renal and abdominal ultrasound was normal.

POEMS syndrome was diagnosed using a combination of history and examination results according to the 2014 update on diagnosis, risk-stratification and management of POEMS syndrome [1]. The presence of polyneuropathy (demyelinating in the majority of cases of POEMS syndrome), monoclonal plasma cell disorder (IgA λ), high levels of VEGF, papilledema, thyroidal endocrinopathy, skin alterations, low vitamin B12 values, thrombotic diatheses and weight loss supported the diagnosis of POEMS syndrome. Subsequently, the patient received a dexamethasone bolus and hydrocortisone and was lost to follow-up.

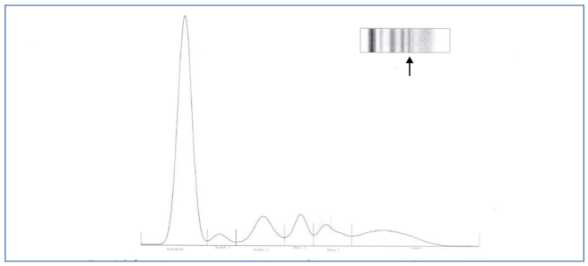

Fig-1: Serum protein electrophoresis showing a monoclonal band in beta region

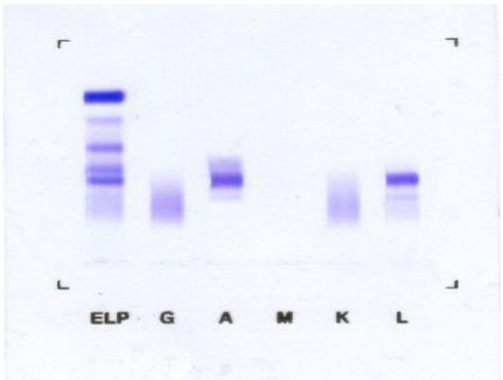

Fig-2: Immunofixation electrophoresis showing a band in beta region consisting of IgAλ.

DISCUSSION

According to early reports in the literature, it was believed that POEMS syndrome is more common in people of Japanese descent and that the prevalence in Japan is approximately 0.3 per 100.000 [2]. However, there has been recently multiple case series published from around the world [3-5].

Although the exact mechanism behind the pathogenesis of POEMS syndrome is uncertain, cytokines may play a significant role [6]. Increased production of proangiogenic and proinflammatory cytokines such as interleukin-1 (IL-1), IL-6, IL-12, tumor necrosis factor (TNF), and specifically vascular endothelial growth factor 165 (VEGF165) are critical elements in its pathophysiology [7-9]. VEGF, expressed by the plasmacytes and other cells such as macrophages, osteoblasts and megakaryocytes, targets the endothelial cells and is responsible for a quick and reversible increase in vascular permeability [9]. The rise of VEGF serum levels might cause some clinical manifestations of POEMS such as edema, neuropathy, organomegaly, increasing of microvascular permeability of the blood vessels with endometrial edema [7, 9].

Studies showed that VEGF levels are more likely to be 5-10 times higher in POEMS syndrome compared to healthy controls or patients with other disorders [9]. Therefore, VEGF level could be used as biomarkers for the monitoring of this disease. It could also be used for the differential diagnosis of POEMS syndrome with other pathologies such as multiple myeloma (MM), monoclonal gammopathy of undetermined significance (MGUS) and amyloidosis [9]. A VEGF value greater than 1000pg/ml is deemed pathological. Nonetheless, the different reference ranges for VEGF (normal and pathologic; in serum or plasma) are yet to be defined. Moreover, the ex vivo platelet activation during the clotting process or the presence of thrombocytosis in some patients causes a release of platelet derived VEGF, thus affecting the serum VEGF levels [9].

Our patient was a female of 41 years old. However, POEMS syndrome seems to be more common in males in their fifth or sixth decade of life as shown in the diagnosis criteria published in 2003 by Despenzieri and al. at the Mayo Clinic on the basis of clinical and laboratory features [10]. Indeed, the diagnosis of the POEMS syndrome is based on a combination of clinical and biological features (table 1). It requires the presence of one of the two mandatory major criteria, one of the three other major criteria and at least one of the six minor criteria [11].

Table-1: Criteria of the diagnosis of POEMS syndrome (2014)[1].

Mandatory major criteria	1-Polyneuropathy (typically demyelinating) 2- Monoclonal plasma cell-proliferative disorder (almost always λ)
Other major criteria (one required)	3- Castleman disease. 4-Sclerotic bone lesions. 5-Vascular endothelial growth factor elevation.
Minor criteria	6-Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy). 7-Extravascular volume overloads (edema, pleural effusion, or ascites). 8- Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic). 9- Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, and flushing, white nails). 10- Papilledema. 11- Thrombocytosis/ polycythemia.
Other symptoms and signs	Clubbing, weight loss, hyperhidrosis, pulmonary hypertension/restrictive lung disease, thrombotic diatheses, diarrhea, low vitamin b12 values.

According to a review of POEMS syndrome based on large retrospective datasets, the polyneuropathy is the main feature of the syndrome [10, 12-16]. Patients usually appear with a subacute, symmetrical, distal sensorimotor neuropathy that is often painful. It usually begins as a sensory neuropathy and progresses to motor symptoms. The lower limbs are affected earlier, and more severely, than the upper limbs. Clinical examination may reveal distal wasting, weakness and sensory loss affecting both large and small fiber sensory modalities [7, 17-20].

Electrodiagnostic studies show a length-dependent sensorimotor neuropathy, typically demyelinating, with axonal degeneration [18-20].

As many as three-fourths of patients have organomegaly [6], but other series suggest that it occurs in only one-fourth of patients [10, 14]. Any or all of the liver, spleen, and lymph nodes can be enlarged. Clinical and radiological studies have shown that imaging, especially computed tomography, is more sensitive in identifying organomegaly compared to clinical examination [19]. Most commonly, extravascular overload manifests as peripheral edema, but pleural effusion, ascites, and pericardial effusions are common [11].In our case, neither a clinical nor a radiological sign of organomegaly or extravascular volume overload was found.

Endocrinopathy is a fundamental feature of POEMS syndrome, but the mechanisms are not yet well understood [21]. In one series of 170 patients with POEMS syndrome [9,16], approximately 84% of patients had a recognized endocrinopathy, with hypogonadism being the most common endocrine abnormality, with low levels of testosterone and erectile dysfunction in more than 70% of male patients [9]. Other endocrine abnormalities could be found such as thyroid abnormalities, or glucometabolism abnormalities. Ghandi and al, found that patients with POEMS syndrome often have an impaired fasting glucose concentration, impaired glucose tolerance, or diabetes [22]. However, given the high prevalence of diabetes and hypothyroidism in the general population, some authors do not include those abnormalities in the diagnostic criteria of POEMS syndrome [9]. The adrenal insufficiency is another endocrine abnormality that can be found in POEMS patients. Therefore, it is important not to overlook subclinical adrenal insufficiency because patients can develop an adrenal crisis [1].

The M protein commonly found is an immunoglobulin G (IgG) or IgA and almost always of the lambda type [10]. It can be found either in serum and/or in urine with immunofixation tests [9]. The concentration of this protein is moderate with a median of 10mg/l. Bence Jones proteinuria is rarely found.

Around 25% of POEMS patients have a normal serum protein electrophoresis, the rest of the patients presents a polyclonal gammopathy patterns. Thus, the monoclonal plasma cell proliferative disorder may be overlooked in the absence of an immunofixation as part of the biological diagnostic investigations. In our case, the patient presented an anomaly in the serum protein electrophoresis. It was a band in the beta region which matched the IgAλ found in the immunofixation. Moreover, studies found that the immunoglobulin free light chains assay has limited value. Indeed, only 18% of cases have an abnormal ratio, even though 90% of POEMS patients have high immuglobulin free light chains [9].

Bone marrow usually contains less than 5% plasma cells, and, when clonal cells are found, they are almost always monoclonal lambda. Unfortunately, our patient did not benefit of a bone marrow aspiration or biopsy therefore the comparison of our case with the findings in the literature could not be conducted.

Translocations and deletion of chromosome 13 have been described, but hyperdiploidy was not seen [24]. A study conducted by Kang *et al*., found 20 newly diagnosed POEMS cytogenetic aberrations. Indeed, 14q32 (IGH) translocation was observed in 45% of the cases and included the t(4;14) and t(11;14) translocation

(15% and 25% of the cases, respectively). In addition, 25% of the patients presented deletions of 13q14 and 20% had an amplification of 1q21. No significant correlation between clinical features and cytogenetic abnormalities was observed, although patients with IGH translocations were more likely to exhibit papilledema [25].

A formal ophthalmologic examination should also be performed looking especially for papilledema which is present in at least one-third of patients. According to a study conducted by Despenzieri *et al*. at the Mayo Clinic, 67% of the patients had ocular signs and symptoms, the most common of which was papilledema in 52% of those examined. The most common ocular symptoms reported were blurred vision, diplopia, and ocular pain [11].

Given the patients' neurologic status, especially the motor impairment, most of them see their physical activities reduce, thereby the cardiovascular challenges and respiratory complaints are usually limited. Thus, in a series of 137 POEMS syndrome, the frequency of dyspnea, chest pain, cough and orhtopnea reported by the patients was 20%, 10%, 8%and 7% respectively. The pulmonary manifestations include pulmonary hypertension, restrictive lung disease, impaired neuromuscular respiratory function, and impaired diffusion capacity of carbon monoxide [26].

Table-2: Recommended minimum testing for diagnosis and evaluation of POEMS syndrome [1].

Test	Baseline	Every 3-6months	Yearly
Neurologic :			
*Detailed neurologic history (numbness, pain, weakness, balance, orthostasis) and examination (including fundoscopic examination).	X	Xɑ	X
*Electrophysiologic study (nerve conduction studies).	X	Xɑ	X
*Sural nerve biopsy.	Xɗ	_	_
Organomegaly/ Lymphadenopathy/ Extravascular volume overload :			
*Physical examination and CT scan documenting lymphadenopathy, organomegaly, ascites, pleural effusions, and edema.	X	Xɓ	Xɓ
Endocrinopathy:			
*History regarding menstrual and sexual function.	X	X	X
*Testosterone, estradiol, fasting glucose, glycosylated hemoglobin, thyroid-stimulating hormone, parathyroid hormone, prolactin, serum cortisol, luteinizing hormone.	X	Xɓ	Xɓ
*Follicule-stimulating hormone, adrenocorticotropin hormone,cortrosyn stimulation test.	Xɗ	Xɓ	Xɓ
Hematologic:			
*Serum protein electrophoresis and immunofixation.	X	X	X
*Affected quantitative immunoglobulin.	X	Xɗ	X
*Complete blood count (hemoglobin, platelets).	X	X	X
*24-h urine total protein, electrophoresis, and immunofixation.	X	_	X
*Vascular endothelial growth factor.			
*Bone marrow aspirate and biopsy (test for kappa/lambda by immunohistochemistry).	X X	X Xɔ	X _
Skin:			
*History and physical with attention to skin pigment, thickening, and texture; body hair quality and texture; color of distal extremities; and development of cherry angiomata.	X	X	X
Sclerotic bone lesions:			
*CT body bone windows and/or PET/CT.	X	_	Xɗ
Pulmonary function:			
*Pulmonary function tests.	X	Xɓ	Xɓ
*Echocardiography to assess right ventricular systolic and pulmonary artery pressures.	X	Xɓ	Xɓ

ɑ: at 6 months and then yearly. ɓ: only if affected. ɔ: only to document complete response. ɗ: as clinically indicated.

Patients with POEMS syndrome are at increased risk for arterial and/or venous thrombosis. Nearly 20% of patients experience one of these complications, such as stroke, myocardial infarction, and Budd-Chiari syndrome. The median time between peripheral neuropathy symptom onset and the cerebrovascular event is 23 months (range, 0.5–64 months) [27, 28]. Risk factors for cerebral events included bone marrow plasmacytosis and thrombocytosis. Abnormalities in the coagulation cascade can also be associated with POEMS syndrome [29].

Patients with a monoclonal gammopathy and a length-dependent peripheral neuropathy (especially demyelinating), either low-resolution CT body with bone windows or PET/CT (Positron Emission Tomography/Computed Tomography) along with a VEGF level should be performed to screen for POEMS. If both are not consistent with the diagnosis, the patient either does not have POEMS syndrome or perhaps has very early disease [6].

Once the diagnosis is confirmed, a rigorous evaluation should be performed to define a baseline that will guide the future assessments (Table 3). After therapy has begun, monthly testing of VEGF and the monoclonal protein is recommended. When therapy is completed, VEGF and monoclonal protein testing can be done less frequently: every 3 months, and then every 3 to 6 months. Neurology testing and imaging are recommended at 6 months and then annually. For patients with complete hematologic response and complete VEGF and PET scan response, imaging can be performed less frequently [6].

Despite the presence of a link between decreased VEGF levels and a positive prognosis of the disease, successful results are more likely obtained using not only a VEGF antibodies treatment targeting VEGF, but also a treatment targeting the clonal plasma cell dyscrasia.

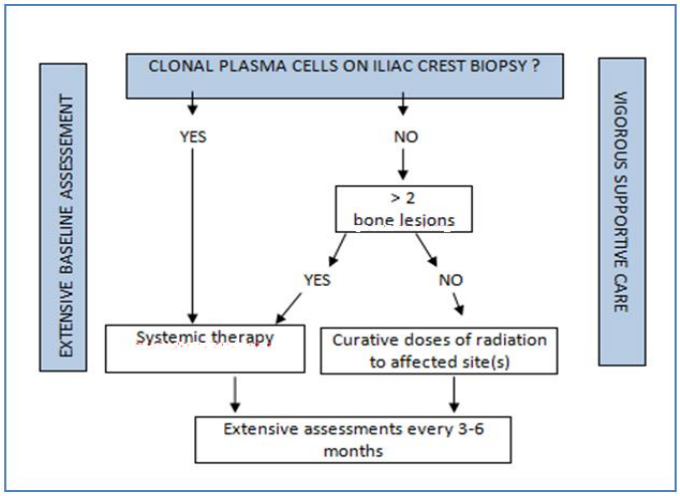

Fig-3: Algorithm for the treatment of POEMS syndrome [11].

A special attention should be paid to supportive care. Orthotics, physical therapy, and CPAP (continue positive airway pressure) all play an important role in patients' recovery.

Ankle foot orthotics helps increase mobility and reduces falls. Physical therapy can reduce the risk of permanent contractures and leads to improved function both in the long and short term. For those with severe neuromuscular weakness, CPAP and/or biPAP (bilevel positive airway pressure) contributes to a better oxygenation and eventually reduces the risk of complications associated with hypoventilation like pulmonary infection and pulmonary hypertension [11].

The prognosis of POEMS is good with a median survival of 13.8 years according to the Mayo Clinic series. The number of events is not correlated to survival. Death is not caused by the progression of plasma cell dyscrasia but is mainly due to cardiac, respiratory or infectious causes [10, 14].

CONCLUSION

POEMS syndrome is a serious disease which can compromise the functional and vital prognosis due to multiple organ failure, especially through renal, neurological and cardiac damages.

A monoclonal component should be seeked through an electrophoresis and immunoelectrophoresis in every patient with unexplained peripheral neuropathy, which can reduce the delay between the symptoms and the diagnosis.

REFERENCES

1. Dispenzieri, A. (2019). POEMS Syndrome: 2019 Update on diagnosis, risk-stratification, and management. *Am J Hematol, 94*; 812–827. https://doi. org/10.1002/ajh.25495.
2. Bardwick, P.A., Zvaifler, N.J., Gill, G.N., Newman, D., Greenway, G.D., Resnick D.L. (1980). Plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes: the POEMS syndrome. Report on two cases and a review of the literature. *Medicine (Baltimore) 59*(4):311–22 PMID: 6248720.
3. Dispenzieri, A., Kyle, R.A., Lacy, M.Q., Rajkumar, S.V., Therneau, T.M., Larson, D.R., Greipp, P.R., Witzig, T.E., Basu, R., Suarez, G.A. (2003). POEMS syndrome: definitions and long-term outcome. *BLOOD, 101*(7); 2496–506.

PMID:12456500. https://doi.org/10.1182/blood-2002-07-2299.
4. Soubrier, M.J., Dubost, J.J., Sauvezie, B.J. (2011). POEMS syndrome: A study of 25 cases and a review of the literature. French Study Group on POEMS Syndrome. *Am J Med*, 1994; 97:543–553.
5. Li, J., Zhou, D.B., Huang, Z. (2011). Clinical characteristics and long-term outcome of patients with POEMS syndrome in China. *Ann Hematol, 90*; 819–826.
6. Angela, D., Taxiarchis, K., Francis, B. (2018). POEMS Syndrome: Diagnosis and Investigative Work-up. *Hematol OncolClin N Am*, *32*; 119–139. https://doi.org/10.1016/j.hoc.2017.09.010
7. Nasu, S., Misawa, S., Sekiguchi, Y. (2012). Different neurological and physiological profiles in POEMS syndrome and chronic inflammatory demyelinating polyneuropathy. *J Neurol Neurosurg Psychiatry*, *83*; 476–9.
8. D'Souza, A., Hayman, S.R., Buadi, F. (2011). The utility of plasma vascular endothelial growth factor levels in the diagnosis and follow-up of patients with POEMS syndrome. *Blood, 118*(17); 4663–5.
9. Nozza, A.(2017). POEMS SYNDROME: an Update. *Mediterr J Hematol Infect Dis*, 9(1): e2017051, DOI: http://dx.doi.org/10.4084/MJHID.2017.051
10. Dispenzieri, A., Kyle, R.A., Lacy, M.Q., Rajkumar, S.V., Therneau, T.M., Larson, D.R., Greipp, P.R., Witzig, T.E., Basu, R., Suarez, G.A. (2003). POEMS syndrome: definitions and long-term outcome. BLOOD, *101*(7); 2496–506. PMID:12456500. https://doi.org/10.1182/blood-2002-07-2299.
11. Dispenzieri, A. (2014). POEMS syndrome: 2014 Update on diagnosis, risk-stratification, and management. *American Journal of Hematology*, *89*(2), 213–223. doi:10.1002/ajh.23644
12. Takatsuki, K., Sanada, I. (1983). Plasma cell dyscrasia with polyneuropathy and endocrine disorder: Clinical and laboratory features of 109 reported cases. *Jpn J Clin Oncol*, 13; 543– 555
13. Nakanishi, T., Sobue, I., Toyokura, Y. (1984). The Crow-Fukase syndrome: A study of 102 cases in Japan. *Neurology, 34*; 712–720.
14. Soubrier, M.J., Dubost, J.J., Sauvezie, B.J. (1994). POEMS syndrome: A study of 25 cases and a review ofthe literature. French Study Group on POEMS Syndrome. *Am J Med, 97*; 543–553.
15. Li, J., Zhou, D.B., Huang, Z. (2011). Clinical characteristics and long-term outcome of patients with POEMS syndrome in China. *Ann Hematol. 90*; 819–826.
16. Ghandi, G.Y., Basu, R., Dispenzieri, A. (2007). Endocrinopathy in POEMS syndrome: The Mayo clinic experience. *Mayo ClinProc, 82*; 836–842.
17. Koike, H. (2008). Neuropathic pain correlates with myelinatedfibre loss and cytokine profile in POEMS syndrome. *J NeurolNeurosurg Psychiatry*, *79*; 1171–1179
18. Min, J.H., Hong, Y.H., Lee, K. (2005). W. Electrophysiological features of patients with POEMS syndrome. *ClinNeurophysiol, 116*; 965–968
19. Kulkarni, G.B. (2011). Clinicopathological profile of polyneuropathy, organomegaly, endocrinopathy, M protein and skin changes (POEMS) syndrome. *J ClinNeurosci*, 18:356–360
20. Liu, M. (2015). Motor nerve conduction study and muscle strength in newly diagnosed poems syndrome. Muscle Nerve, 51; 19–23
21. Li. (2019). Endocrine Manifestations in POEMS Syndrome: a case report and literature review. BMC Endocrine Disorders (2019) 19:33https://doi.org/10.1186/s12902-019-0355-6.
22. Huan, S., Xiaohong, J., Long, W., & Jiayan, Z. (2021). Missed diagnosis of POEMS syndrome with onset of progressive fatigue and numbness: a case report. *Journal of International Medical Research*, *49*(2) 1–10. DOI: 10.1177/0300060520986706
23. Caimari, F., Keddie, S., Lunn, M. P., D'Sa, S., & Baldeweg, S. E. (2019). Prevalence and course of endocrinopathy in POEMS syndrome. *The Journal of Clinical Endocrinology & Metabolism*, *104*(6), 2140-2146.
24. Dispenzieri, A. (2017). POEMS syndrome and Castleman's disease. In *Biology and management of unusual plasma cell dyscrasias* (pp. 41-69). Springer, New York, NY.
25. Kang, W. Y., Shen, K. N., Duan, M. H., Zhang, W., Cao, X. X., Zhou, D. B., & Li, J. (2013). 14q32 translocations and 13q14 deletions are common cytogenetic abnormalities in POEMS syndrome. *European journal of haematology*, *91*(6), 490-496.
26. Allam, J. S., Kennedy, C. C., Aksamit, T. R., & Dispenzieri, A. (2008). Pulmonary manifestations in patients with POEMS syndrome: a retrospective review of 137 patients. *Chest*, *133*(4), 969-974.
27. Lesprit, P., Authier, F. J., Gherardi, R., Bélec, L., Paris, D., Melliere, D., ... & Godeau, B. (1996). Acute arterial obliteration: a new feature of the POEMS syndrome?. *Medicine*, *75*(4), 226-232.
28. Dispenzieri, A. (2007). POEMS Syndrome. *Blood Rev, 21*(6); 285-299.
29. Saida, K., Kawakami, H., Ohta, M., & Iwamura, K. (1997). Coagulation and vascular abnormalities in Crow-Fukase syndrome. *Muscle & Nerve: Official Journal of the American Association of Electrodiagnostic Medicine*, *20*(4), 486-492.