

# Not the final diagnosis: from Addison's disease to POEMS syndrome: a case report and literature review

Journal of International Medical Research

49(12) 1–10

© The Author(s) 2021

Article reuse guidelines:

[sagepub.com/journals-permissions](https://sagepub.com/journals-permissions)

DOI: 10.1177/03000605211066239

[journals.sagepub.com/home/imr](https://journals.sagepub.com/home/imr)

Xiaoxi Xie<sup>1</sup> , Rao Li<sup>2</sup>, Yongxia Lu<sup>3</sup>, Xuan Li<sup>4</sup>,  
Pu Kuang<sup>5</sup>, Chunhui Wang<sup>1</sup>, Nanwei Tong<sup>6</sup> and  
Qingguo Lü<sup>6</sup>

## Abstract

We report the case of a 47-year-old male patient with pigmentation of the head, face and hands, who was initially diagnosed as having primary adrenal insufficiency (Addison's disease). Laboratory testing, imaging and physical examination revealed subclinical hypothyroidism, high circulating prolactin and oestradiol concentrations, gynaecomastia, lymphadenopathy, splenomegaly and weakness of both lower limbs. These findings led us to consider whether a single or multiple diseases were present in this patient. Indeed, Addison's disease can represent one aspect of a wider systemic disease. Therefore, we performed further examinations, and found high serum M protein (5.1%) and vascular endothelial growth factor [1005.30 pg/mL (normal range 0 to 142 pg/mL)] concentrations. As a consequence, we diagnosed polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes (POEMS) syndrome. Consequently, when a single disease cannot fully explain the multiple symptoms and signs of one patient, clinicians should consider the possibility of the presence of a wider syndrome and undertake more detailed diagnostic testing.

<sup>1</sup>Department of Gastroenterology, West China Hospital of Sichuan University, Chengdu, China

<sup>2</sup>Department of Endocrinology and Metabolism, West China Hospital of Sichuan University/West China School of Nursing, Sichuan University, Chengdu, China

<sup>3</sup>Department of Endocrinology and Metabolism, Chengdu Seventh People's Hospital, Chengdu, China

<sup>4</sup>Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, MS, USA

<sup>5</sup>Department of Haematology, West China Hospital of Sichuan University, Chengdu, China

<sup>6</sup>Department of Endocrinology and Metabolism, West China Hospital of Sichuan University, Chengdu, China

### Corresponding author:

Qingguo Lü, Department of Endocrinology and Metabolism, West China Hospital of Sichuan University, no. 37 GuoXue Lane, Chengdu 610041, China.  
Email: 364167902@qq.com



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative

Commons Attribution-NonCommercial 4.0 License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

**Keywords**

Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes syndrome, Addison's disease, skin pigmentation, M protein, vascular endothelial growth factor, hypothyroidism

Date received: 12 April 2021; accepted: 22 November 2021

**Introduction**

Primary adrenal insufficiency (PAI), also called Addison's disease, is the clinical manifestation of chronic glucocorticoid and/or mineralocorticoid deficiency that results from damage to the adrenal cortex, and may lead to a life-threatening adrenal crisis or have other potentially serious consequences<sup>1</sup> in some severe cases. There are a number of potential causes and contributors to Addison's disease, including infection (most commonly tuberculosis in China), autoimmune diseases, adrenal resection, neoplastic and genetic disorders (most commonly in children), and other iatrogenic conditions, such as the side effects of anticoagulants and novel anti-cancer target spot inhibitors.<sup>2</sup> Therefore, the cause of the disease should initially be sought, to facilitate aetiologically-focused treatment, but glucocorticoid/mineralocorticoid replacement therapy should also be provided.<sup>3</sup>

POEMS syndrome is a rare systemic disease that is caused by clonal plasma cell proliferation, and is named after its features: polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes. The prevalence of the syndrome was found to be 0.3 per 100,000 in a large national survey in Japan conducted in 2003<sup>4</sup> and it is approximately 2.5 times commoner in men than women. The median age of onset is usually 50 to 60 years of age.<sup>5</sup> Because of its gradual onset, patients with POEMS syndrome

may be asymptomatic or present with symptoms related to nervous system and multi-endocrine dysfunction. Therefore, the condition may not be diagnosed at an early stage, which seriously affects the prognosis of the patients.

In the present case report, we describe a middle-aged male patient who presented with pigmentation of the head, face and hands, and was initially diagnosed as having Addison's disease. After excluding other causes of adrenocortical damage, it was found that the serum concentrations of myeloma (M) protein and vascular endothelial growth factor (VEGF) were high. On the basis of these and the findings of other haematological and bone marrow examinations, a diagnosis of POEMS syndrome was made. The purpose of the report is to aid clinicians' understanding of POEMS syndrome and increase awareness regarding approaches to the diagnosis of systemic diseases.

**Case report**

A 47-year-old male patient presented to the outpatient clinic of the Department of Endocrinology and Metabolism, West China Hospital of Sichuan University with a 2-year history of pigmentation of the head, face and hands, fatigue, and hyperhidrosis. Analysis of his circulating hormone concentrations revealed his cortisol concentration at 08:00 to be 421.5 nmol/L (normal range 147.3 to 609.3 nmol/L) and his

adrenocorticotrophic hormone (ACTH) concentration to be 29.18 pmol/L (normal range 1.01 to 17.18 pmol/L). Six months prior to presentation, his symptoms had become more severe and were accompanied by weakness and symmetrical pitting oedema of both lower extremities. The patient had also experienced low appetite, poor sleep, a loss of 5 kg in mass, and hyposthenia during the preceding 6 months. The patient was born and lived in Nanbu County and was a high-school teacher. He stated no knowledge of any relevant family history or the occurrence of analogous problems in his local area. He had not knowingly been exposed to toxic or radioactive substances and he had no history of smoking or alcohol consumption. Moreover, the patient had no history of hepatitis, tuberculosis or other serious infectious diseases.

Physical examination revealed a body temperature of 36.4°C, heart rate of 83 beats/minute, respiratory rate of 20 breaths/minute, blood pressure of 103/67 mmHg, height of 166 cm, body mass of 65 kg, body mass index (BMI) of 23.59 kg/m<sup>2</sup> and waist circumference of 93 cm. The patient displayed a normal level of consciousness. His body hair was sparse, and skin pigmentation of the face, back of the hands and palms (shown in Figure 1), and especially of the areolae, was apparent (shown in Figure 2). Nodules were palpable in the upper inner quadrants of both breasts, and these were firm, mobile, clearly demarcated, and approximately 2 cm in diameter. Lymph nodes of approximately 1 cm in diameter were palpable in both armpits and in the groin, and these were hard, clearly demarcated and mobile. He had oedema of the eyelids and pitting oedema of both lower extremities. Cardiopulmonary and abdominal examinations revealed no abnormalities. The patient's muscle strength in his upper and lower limbs was grade 5.

Physiological reflexes were present and pathological signs were not elicited on neurological examination. The examinations performed in this patient were approved by the Ethics Committee of West China Hospital, Sichuan University, and the patient provided his written informed consent.

The principal laboratory test results for the patient are shown in Table 1. His free testosterone (FT) concentration was estimated using his total testosterone, sex

**Table 1.** Laboratory data for the patient.

Test item	Test value	Reference range
<b>Haematology</b>		
HGB, g/L	136	130–175
PLT, 10 <sup>9</sup> /L	242	100–300
<b>Blood biochemistry</b>		
Na, mmol/L	144	137–147
K, mmol/L	4.04	3.50–5.30
GLU, mmol/L	5.66	3.90–5.90
<b>Thyroid function</b>		
TSH, mU/L	4.47	0.27–4.20
FT4, pmol/L	16.6	12.0–22.0
<b>Sex hormones</b>		
LH, IU/L	8.7	1.7–8.6
FSH, IU/L	6.3	1.5–12.4
PRL, ng/mL	21.7	4.6–21.4
E2, pmol/L	245	41–158
TT, nmol/L	12.0	8.7–31.5
FT, nmol/L	0.203	–
DHEA-S, μmol/L	2.11	1.20–8.98
<b>PRA, AT-II and ALD</b>		
PRA, pmol/L per hour	2.84	1.19–1.87
ALD, nmol/L	0.239	0.125–0.486
<b>Cortisol and ACTH</b>		
ACTH (08:00), pmol/L	25.0	1.1–17.2
PTC (08:00), nmol/L	240.0	133.0–537.0

HGB, haemoglobin; PLT, platelet count; GLU, glucose; TSH, thyroid-stimulating hormone; FT4, free tetraiodothyronine; LH, luteinising hormone; FSH, follicle-stimulating hormone; PRL, prolactin; E2, estradiol; TT, total testosterone; FT, free testosterone; DHEA-S, dehydroepiandrosterone sulfate; PRA, plasma renin activity; AT-II, angiotensin II; ALD, aldosterone; ACTH, adrenocorticotrophic hormone; PTC, plasma total cortisol.

hormone-binding globulin (SHBG) and albumin concentrations, and this approach closely mirrors the results of equilibrium dialysis<sup>6</sup>. An ACTH stimulation test was performed to further evaluate the patient's adrenal reserve. Two hundred and fifty micrograms of ACTH were intravenously injected and the patient's serum cortisol concentration was then measured 0, 30 and 60 minutes later. As shown in Table 2, the peak concentration of cortisol was below 500 nmol/L, suggesting insufficient adrenal reserve. Therefore, a diagnosis of Addison's disease was considered.

Infection, autoimmune diseases, adrenal resection, and neoplastic and genetic disorders can all cause Addison's disease.<sup>7,8</sup> The findings of a large study conducted at a single centre in China (131 cases) showed that adrenal tuberculosis was the most frequent cause of Addison's disease, accounting for 32.1% (42/131) of cases.<sup>8</sup> In the present case, there were no definite findings of active tuberculosis in the chest, abdomen or other parts of the body of the patient, and adrenal-enhanced computed tomography (CT) revealed bilateral adrenal hyperplasia. We have not been able to locate reports of any other similar cases of POEMS syndrome. The patient may have been manifesting hyperplasia in compensation for insufficient adrenocortical reserve, but the evidence regarding tuberculosis was not definitive. In addition, the anti-adrenal autoantibody titre should be measured to

exclude the possibility of autoimmune damage to the adrenals.

The patient's symptoms improved after replacement therapy with prednisone 2.5 mg *per os* daily. However, a series of clinical features and test results in the present patient could not be explained by Addison's disease alone, including his gynecomastia, lymphadenopathy, splenomegaly, oedema of the lower limbs, and high oestradiol and prolactin concentrations. For example, some physiological factors, including dietary, sleep, emotional and environmental problems, can induce hyperprolactinemia. Therefore, it is reasonable to question whether a single disease could have fully explained all the patient's symptoms.

To identify any other causes of the patient's symptoms and signs, we conducted a series of further relevant examinations. The results of pituitary-enhanced magnetic resonance imaging and bone scanning were negative. Pulmonary CT revealed nodules in the lower lobe of the right lung and enlargement of the axillary lymph nodes. Ultrasonographic examination of his abdomen and breasts revealed splenomegaly (5.2-cm thickness) and gynecomastia. Ultrasonographic cardiography showed the presence of a small amount pericardial effusion and an ejection fraction of 67%. Electroneuromyography identified polyneuropathy of both lower extremities. Serum protein electrophoresis (SPE) showed that M protein accounted for 5.1% of the total, and immunofixation electrophoresis revealed a monoclonal IgA  $\lambda$  peak, with an immunoglobulin (Ig)A concentration of 24.99  $\mu$ mol/L (normal range 5.23 to 18.13  $\mu$ mol/L) and a light-chain  $\lambda$  concentration of 7.03 g/L (normal range 3.80 to 6.50 g/L). Bone marrow smear and biopsy showed that plasma cells accounted for 2.5% of the total blood cell count. His serum VEGF concentration was 1005 pg/mL (normal range 0 to 142 pg/mL). Chest CT revealed no osteosclerosis. On the basis

**Table 2.** Fast ACTH stimulation testing results.

Timing of measurement	Plasma cortisol (nmol/L)
Before ACTH	226
30 minutes after ACTH	345
60 minutes after ACTH	327

Note: A peak cortisol concentration <500 nmol/L at the 30- or 60-minute time point indicates adrenal insufficiency. ACTH, adrenocorticotropic hormone; PTC, plasma total cortisol.

of the above symptoms, signs and auxiliary examination data, we considered a diagnosis of POEMS syndrome, and the patient was transferred to the Department of Haematology, where he was treated with lenalidomide 25 mg (D1-21) in combination with dexamethasone 40 mg on days 1, 8, 15 and 22. After three courses of chemotherapy, the skin colour, breasts and lymph nodes of the patient gradually returned to normal (shown in Figure 3), his VEGF concentration decreased to 470 pg/mL, his M protein proportion on SPE was 0% and he was weakly positive for IgA  $\lambda$  immunoglobulin on immunofixation electrophoresis.

## Discussion

In 1980, Bardwick *et al.* combined the initials of five of the main clinical features of the syndrome (polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes) and christened it POEMS syndrome. It is a rare paraneoplastic syndrome that results from a clonal plasma cell disorder.<sup>9</sup> Other features of the syndrome involve papilloedema, extravascular volume overload, sclerotic bone lesions and thrombocytosis/erythrocytosis. POEMS syndrome has a variety of clinical characteristics, and we show a comprehensive summary of the clinical features of POEMS syndrome, derived from several large retrospective series conducted in various countries,<sup>10–17</sup> in Table 3. The diagnostic criteria for POEMS syndrome were updated by Dispenzieri in 2019 (shown in Table 4<sup>18</sup>). The patient described in this report displayed two mandatory major clinical criteria, a third major criterion, in the form of high circulating VEGF concentration, and several minor criteria (including splenomegaly, lymphadenopathy, oedema of the eyelids and lower extremities, endocrinopathy and skin pigmentation). Therefore, the diagnostic criteria of POEMS syndrome were fulfilled. In addition, the absence of evidence obtained from

**Table 3.** Prevalences of the documented features of POEMS syndrome, as recorded during several large retrospective case series.

Clinical characteristic	Percentage <sup>a</sup>
Polyneuropathy	96–100
Organomegaly	50–92
Hepatomegaly	23–82
Splenomegaly	22–74
Lymphadenopathy	26–75
Endocrinopathy	61–90
Thyroid dysfunction	17–73
Adrenal dysfunction	16–22
Glucose intolerance	3–41
Gonadal dysfunction	22–71
Extravascular volume overload	29–88
Peripheral oedema	24–91
Ascites	6–62
Pleural effusion	3–46
Hydropericardium	28–65
Monoclonal plasma cell dyscrasia	73–100
IgG $\lambda$	22–54
IgA $\lambda$	41–71
IgM $\lambda$	0
Biclonal	0–4
IgG $\kappa$	1–2
IgA $\kappa$	0–4
Bone lesions	27–97
Skin changes	46–90
Hyperpigmentation	25–72
Hypertrichosis	17–66
Thickening	5–56
Haematological abnormalities	
Polycythaemia	4–19
Thrombocytosis	12–88
Others	
Weight loss	37–53
Fatigue	22–31
Hyperhidrosis	12–20
Clubbing of the fingers	5–32
Papilloedema	21–64

Note: <sup>a</sup>Percentages are based on the total number of patients across the case series.

lymph node biopsy does not exclude the possibility of POEMS syndrome with Castleman disease.<sup>19</sup>

POEMS syndrome involves multiple organs and it is caused by the proliferation

**Table 4.** Criteria for the diagnosis of POEMS syndrome.

Mandatory major criteria	1. Polyneuropathy (typically demyelinating)
Other major criteria (one required)	2. Monoclonal plasma-cell proliferative disorder (almost always $\lambda$ )
Minor criteria	3. Castleman disease
	4. Sclerotic bone lesions
	5. High vascular endothelial growth factor concentration
	6. Organomegaly (splenomegaly, hepatomegaly or lymphadenopathy)
	7. Extravascular volume overload (oedema, pleural effusion or ascites)
	8. Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid or pancreatic)
	9. Skin changes (hyperpigmentation, hypertrichosis, glomeruloid haemangiomas, plethora, acrocyanosis, flushing or white nails)
	10. Papilloedema
	11. Thrombocytosis/ polycythaemia
Other symptoms and signs	Clubbing, weight loss, hyperhidrosis, pulmonary hypertension/ restrictive lung disease, thrombotic diatheses, diarrhoea or low vitamin B12 concentration

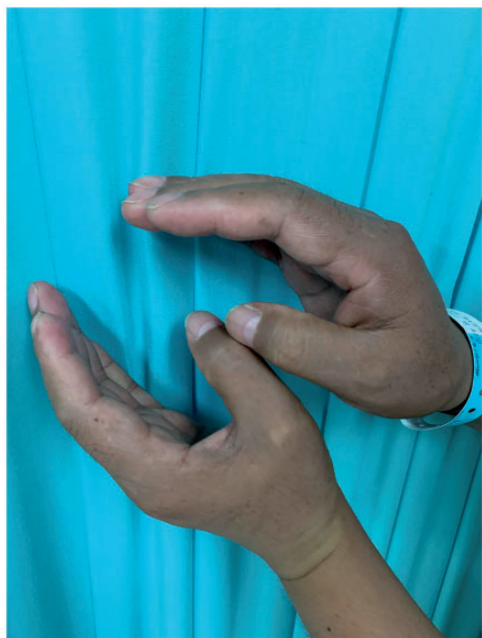
Note: A diagnosis of POEMS syndrome is made when both of the mandatory major criteria, one of the three other major criteria and one of the six minor criteria are met.

of monoclonal plasma cells. The pathogenesis of this syndrome is not well understood, but the greater production of VEGF and proinflammatory cytokines by plasma cells is a critical element.<sup>20-22</sup> VEGF is a regulator of angiogenesis and osteogenesis that targets endothelial cells and contributes to the ascites, oedema, organomegaly, pleural effusion and neuropathy that characterise the syndrome. VEGF concentration is also associated with disease progression,<sup>23</sup> therapeutic efficacy and survival.<sup>20</sup> However, anti-VEGF therapy alone does not achieve effective clinical remission,<sup>24</sup> suggesting that VEGF contributes to disease progression, rather than being a key cause of POEMS syndrome. Some previous studies have also shown that its pathogenesis may be associated with changes in other inflammatory factors, such as fibroblast growth factor, hepatocyte growth factor, tumour necrosis factor  $\alpha$ , interleukin-6, interleukin-12, hypoxia-inducible factor  $1\alpha$  and N-terminal peptide of type I collagen.<sup>25</sup>

Endocrinopathies are common in POEMS syndrome, but the exact mechanism is poorly understood. Monika *et al.* proposed that POEMS syndrome is an antibody-mediated immune disorder. Autopsy results suggest that specific antibodies binding directly to hypophyseal proteins may lead to endocrine disorders.<sup>26</sup> Gandhi *et al.* reported that 84% of 64 patients with POEMS syndrome had endocrine disease and 54% had multiple endocrine disorders.<sup>27</sup> Two large retrospective studies<sup>10,12</sup> showed that 67% to 84% of patients with POEMS syndrome had at least one endocrine system disorder. However, there have been few large-scale analyses of the deficiencies in adrenal function that account for a large proportion of the endocrine abnormalities in POEMS syndrome. We collated the relevant research reports and found that hypogonadism was the most common endocrine abnormality in POEMS syndrome.<sup>10,27,28</sup> Male patients tended to have erectile dysfunction and gynaecomastia, while



**Figure 1.** Pigmentation of the patient's areolae.



**Figure 2.** Pigmentation of the patient's hands.

amenorrhoea or menstrual disorders were typical features in female patients.<sup>28,29</sup> The second most common abnormality was adrenal insufficiency, followed by hypothyroidism and subclinical hypothyroidism, and finally diabetes or impaired glucose tolerance. Notably, Dispenzieri found that patients with POEMS syndrome and



**Figure 3.** Restoration of the normal skin colour of the patient's hands after three courses of chemotherapy.

impaired adrenocortical function had a higher mortality rate.<sup>29</sup> The present patient was ultimately diagnosed with POEMS syndrome following an initial diagnosis of Addison's disease.

Peripheral neuropathy is usually the first symptom of POEMS syndrome, and can sometimes be the only feature of the disease.<sup>4</sup> The typical electrophysiological manifestations are demyelination and axonal degeneration. The severity of axonal loss in the upper and lower limbs varies significantly, but it tends to be more severe in the lower limbs.<sup>30</sup> The most common neurological symptoms are

subacute, symmetrical touch-evoked pain and hyperalgesia. These symptoms cannot be alleviated by plasma exchange or plasma immunoglobulin therapy, thereby distinguishing the syndrome from chronic inflammatory demyelinating polyneuropathy.<sup>31</sup> The patient described herein did not present with typical neurological signs, but electromyography showed polyneuropathy of his lower limbs. Therefore, in some patients with suspected POEMS syndrome, even though neurological signs are absent, electrophysiological examination should be performed.

POEMS syndrome is treatable.<sup>18</sup> The key to successful treatment is early recognition, rapid diagnosis and early intervention before the onset of irreversible neurological disease. The treatment of POEMS syndrome involves controlling the development of clonal hematologic diseases by targeting cytokines, such as VEGF and proinflammatory cytokines, and supportive care for the neurological and endocrine system disorders.<sup>32</sup> The evidence for the existing treatment regimens is derived from the results of large retrospective cohort studies and the key treatment modalities are chemotherapy and autologous stem cell transplantation (ASCT).<sup>33–35</sup> The chemotherapy regimens include melphalan in combination with dexamethasone, thalidomide/lenalidomide in combination with dexamethasone, and bortezomib in combination with cyclophosphamide and dexamethasone.<sup>33–38</sup> Bevacizumab is a monoclonal antibody that targets VEGF<sup>24</sup> and can be used in combination with other treatments, such as cyclophosphamide and dexamethasone.<sup>5</sup> Previous studies have shown that the short-term use of bevacizumab, alone or in combination with thalidomide, can act as a bridge to other treatments, such as ASCT.<sup>39</sup>

Currently, ASCT is the only treatment that induces nearly 100% remission of clinical symptoms. Systemic chemotherapy can

either be used as a long-term treatment or as a maintenance therapy to optimise the physical condition of patients for subsequent ASCT. The median survival time of patients with untreated POEMS syndrome is 33 months. Two recent studies conducted at the Mayo Clinic (N=291)<sup>40</sup> and by Wang *et al.* (N=362)<sup>41</sup> stratified the risk factors for POEMS syndrome and yielded 5-year overall survival rates of 79% and 84%, and 10-year overall survival rates of 62% and 77%, respectively. Three factors were associated with superior overall survival: youth, serum albumin concentration <481.5 µmol/L, and a complete haematological response to treatment.<sup>41</sup>

POEMS syndrome is a rare condition that involves multiple systems and is characterised by complex clinical manifestations. The present patient was first diagnosed with Addison's disease, but after further analysis of his clinical symptoms and signs and targeted auxiliary examinations, he was ultimately diagnosed with POEMS syndrome. The purpose of the present report is to improve awareness of the approaches required for the diagnosis of complex systemic diseases among clinicians in various specialties. Clinicians should involve paying more attention to basic questions, physical examination and the appropriate auxiliary examinations to reduce the incidences of misdiagnosis and missed diagnosis.

### Declaration of conflicting interest

The authors declare that there is no conflict of interest.

### Ethics statement

The manuscript was prepared and revised according to the CARE Checklist (2013).<sup>42</sup> Written informed consent was obtained from the patient for the publication of this report and any accompanying images, and the data were de-identified. The Medical Ethics Committee of West China Hospital of Sichuan




University exempts the report of a single case from the necessity for ethics approval.

### Funding

This work was funded by 1·3·5 project for disciplines of excellence—Clinical Research Incubation Project, West China Hospital, Sichuan University (grant number 2021HXFH040).

### ORCID iD

Xiaoxi Xie  <https://orcid.org/0000-0001-5538-4345>

### References

- Charmandari E, Nicolaidis NC and Chrousos GP. Adrenal insufficiency. *Lancet* 2014; 383: 2152–2167.
- Barthel A, Benker G, Berens K, et al. An Update on Addison's Disease. *Exp Clin Endocrinol Diabetes* 2019; 127: 165–175.
- Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2016; 101: 364–389.
- Nasu S, Misawa S, Sekiguchi Y, et al. Different neurological and physiological profiles in POEMS syndrome and chronic inflammatory demyelinating polyneuropathy. *J Neurol Neurosurg Ps* 2012; 83: 476–479.
- Keddie S and Lunn MP. POEMS syndrome. *Curr Opin Neurol* 2018; 31: 551–558.
- Keevil BG and Adaway J. Assessment of free testosterone concentration. *J Steroid Biochem Mol Biol* 2019; 190: 207–211.
- Betterle C, Presotto F and Furmaniak J. Epidemiology, pathogenesis, and diagnosis of Addison's disease in adults. *J Endocrinol Invest* 2019; 42: 1407–1433.
- Wang L, Lu L, Lu ZL, et al. Etiological composition and clinical features of primary adrenocortical hypofunction in China. *Natl Med J China* 2020; 100: 915–921.
- Bardwick PA, Zvaifler NJ, Gill GN, et al. 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)* 1980; 59: 311–322.
- Nakanishi T, Sobue I, Toyokura Y, et al. The Crow-Fukase syndrome: a study of 102 cases in Japan. *Neurology* 1984; 34: 712–720.
- Keddie S, Foldes D, Caimari F, et al. Clinical characteristics, risk factors, and outcomes of POEMS syndrome: A longitudinal cohort study. *Neurology* 2020; 95: e268–e279.
- Li J, Zhou DB, Huang Z, et al. Clinical characteristics and long-term outcome of patients with POEMS syndrome in China. *Ann Hematol* 2011; 90: 819–826.
- Dispenzieri A, Kyle RA, Lacy MQ, et al. POEMS syndrome: definitions and long-term outcome. *Blood* 2003; 101: 2496–2506.
- Cui RT, Huang XS, Shi Q, et al. POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes) syndrome in China. *Intern Med J* 2011; 41: 481–485.
- Pramanik R, Sharma A, Sharma A, et al. POEMS Syndrome: Indian Experience from a Tertiary-Care Institute. *Clin Lymphoma Myeloma Leuk* 2019; 19: e536–e544.
- Soubrier MJ, Dubost JJ and Sauvezie BJ. 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.
- Shim H, Seol CA, Park CJ, et al. POEMS Syndrome: Bone Marrow, Laboratory, and Clinical Findings in 24 Korean Patients. *Ann Lab Med* 2019; 39: 561–565.
- Dispenzieri A. POEMS Syndrome: 2019 Update on diagnosis, risk-stratification, and management. *Am J Hematol* 2019; 94: 812–827.
- Dispenzieri A and Fajgenbaum DC. Overview of Castleman disease. *Blood* 2020; 135: 1353–1364.
- D'Souza A, Hayman SR, Buadi F, et al. The utility of plasma vascular endothelial growth factor levels in the diagnosis and follow-up of patients with POEMS syndrome. *Blood* 2011; 118: 4663–4665.
- Kanai K, Sawai S, Sogawa K, et al. Markedly upregulated serum interleukin-12

- as a novel biomarker in POEMS syndrome. *Neurology* 2012; 79: 575–582.
22. Soubrier M, Dubost JJ, Serre AF, et al. Growth factors in POEMS syndrome: evidence for a marked increase in circulating vascular endothelial growth factor. *Arthritis Rheum* 1997; 40: 786–787.
  23. Zhao H, Cai H, Wang C, et al. Prognostic value of serum vascular endothelial growth factor and hematological responses in patients with newly-diagnosed POEMS syndrome. *Blood Cancer J* 2018; 8: 37.
  24. Sekiguchi Y, Misawa S, Shibuya K, et al. Ambiguous effects of anti-VEGF monoclonal antibody (bevacizumab) for POEMS syndrome. *J Neurol Neurosurg* 2013; 84: 1346–1348.
  25. Wang C, Zhou YL, Cai H, et al. Markedly elevated serum total N-terminal propeptide of type I collagen is a novel marker for the diagnosis and follow up of patients with POEMS syndrome. *Haematologica* 2014; 99: e78–e80.
  26. Reulecke M, Dumas M and Meier C. Specific antibody activity against neuroendocrine tissue in a case of POEMS syndrome with IgG gammopathy. *Neurology* 1988; 38: 614–616.
  27. Gandhi GY, Basu R, Dispenzieri A, et al. Endocrinopathy in POEMS syndrome: the Mayo Clinic experience. *Mayo Clin Proc* 2007; 82: 836–842.
  28. Kulkarni GB, Mahadevan A, Taly AB, et al. Clinicopathological profile of polyneuropathy, organomegaly, endocrinopathy, M protein and skin changes (POEMS) syndrome. *J Clin Neurosci* 2011; 18: 356–360.
  29. Lizis-Kolus K, Kowalska A and Nowakowska-Domagala M. [The POEMS syndrome with coexisting endocrinopathy—case report]. *Endokrynol Pol* 2007; 58: 238–243.
  30. Liu MS, Zou ZY, Guan YZ, et al. Motor Nerve Conduction Study and Muscle Strength in Newly Diagnosed Poems Syndrome. *Muscle Nerve* 2015; 51: 19–23.
  31. Mauermann ML. The Peripheral Neuropathies of POEMS Syndrome and Castleman Disease. *Hematol Oncol Clin N Am* 2018; 32: 153–163.
  32. Jaccard A. POEMS Syndrome: Therapeutic Options. *Hematol Oncol Clin North Am* 2018; 32: 141–151.
  33. Li J, Duan MH, Wang C, et al. Impact of pretransplant induction therapy on autologous stem cell transplantation for patients with newly diagnosed POEMS syndrome. *Leukemia* 2017; 31: 1375–1381.
  34. Autore F, Innocenti I, Luigetti M, et al. Autologous peripheral blood stem cell transplantation and the role of lenalidomide in patients affected by poems syndrome. *Hematol Oncol* 2018; 36: 392–398.
  35. Royer B, Merlusca L, Abraham J, et al. Efficacy of lenalidomide in POEMS syndrome: a retrospective study of 20 patients. *Am J Hematol.* 2013; 88: 207–12.
  36. Nozza A, Terenghi F, Gallia F, et al. Lenalidomide and dexamethasone in patients with POEMS syndrome: results of a prospective, open-label trial. *Br J Haematol* 2017; 179: 748–755.
  37. Misawa S, Sato Y, Katayama K, et al. Safety and efficacy of thalidomide in patients with POEMS syndrome: a multi-centre, randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2016; 15: 1129–1137.
  38. Cai QQ, Wang C, Cao XX, et al. Efficacy and safety of low-dose lenalidomide plus dexamethasone in patients with relapsed or refractory POEMS syndrome. *Eur J Haematol* 2015; 95: 325–330.
  39. Dietrich PY and Duchosal MA. Bevacizumab therapy before autologous stem-cell transplantation for POEMS syndrome. *Ann Oncol* 2008; 19: 595.
  40. Kourelis TV, Buadi FK, Kumar SK, et al. Long-term outcome of patients with POEMS syndrome: An update of the Mayo Clinic experience. *Am J Hematol* 2016; 91: 585–589.
  41. Wang C, Huang XF, Cai QQ, et al. Prognostic study for overall survival in patients with newly diagnosed POEMS syndrome. *Leukemia* 2017; 31: 100–106.
  42. Gagnier JJ, Kienle G, Altman DG, et al. The CARE guidelines: consensus-based clinical case reporting guideline development. *Headache* 2013; 53: 1541–1547.