A retrospective analysis of endocrinopathies in 136 Chinese patients with POEMS syndrome

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Abstract

Background: POEMS syndrome is a rare multisystem disease but with a wide spectrum of clinical endocrinopathies. The patients with POEMS syndromes may present with one or more hormone disorders during disease course, but such phenomenon has usually been underestimated. In this report, the prevalence and clinical characteristics of Endocrine abnormalities in a large Chinese cohort with POEMS syndromes were summarized.

Methods: Retrospective review of patients with a definite diagnosis of POEMS syndrome in our hospital between January 2000 and January 2020 were performed. The clinical data about endocrine abnormalities were extracted from their medical records and analysis.

Results: This study comprised 136 patients (95 male, 41 female) with a median age of 48(40-56) years old. The endocrine abnormalities were more common (127 cases, 93.38%) in patients with POEMS syndromes. The prevalence of single endocrinopathy and multiple endocrinopathies was 12.60% (16/127 cases) and 87.40% (111/127) respectively. The most frequent endocrinopathy was hypogonadism (98/136, 72.06%), followed by hypothyroidism (83/136, 61.03%), hypocalcemia (50/136, 36.76%), hyperprolactinemia (47/136, 34.56%), abnormal glucose metabolism (41/136, 30.15%) and adrenal insufficiency (41/136, 30.15%). In POEMS syndromes, nearly most of endocrine organs could be involved. In patients with multiple endocrinopathies, the percentage of 2, 3, 4, 5 and 6 kind of endocrine axes involved were 29.92%(38/127), 30.71%(39/127), 17.32%(22/127), 7.09%(9/127) and 2.36%(3/127), respectively. It results in complex clinical presentation of hormone disorders, including overt or subclinical situation.

Conclusions: In Conclusion, this study provides an overview of the abnormalities observed in a large series in China. Endocrinopathy manifestations in POEMS syndromes are more frequent, and its clinical complicity should be paid more attention to. To patients with definite diagnosis of POEMS syndromes, early and thorough endocrine evaluation should be performed.

Background

POEMS syndrome is a really rare paraneoplastic syndrome due to plasma cell disorder, characterized by polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes^[1]. Its prevalence is only 0.3 per 100,000 according to a national survey in Japan in 2003^[2]. In China, there have been some small series and many isolated case reports about this rare disorder, with limited information about systematically studies^[3].

The pathogenesis of POEMS syndrome has not been well understood, but more and more evidences indicate that the high levels of serum vascular endothelial growth factor (VEGF) correlates with disease activity. It can induce rapid and reversible increase in vascular permeability, playing an important role in angiogenesis^[4].

Endocrinopathy is a very important feature of POEMS syndrome, which presented in about 84% patients with this paraneoplastic syndrome in some series. But usually it has been poorly understood. Hypogonadism (55–89%) is the most frequent endocrine disorder, followed by thyroid abnormalities, glucose metabolism abnormalities, hypocalcemia, adrenal insufficiency, et al. Some patients with POEMS syndrome even suffered from multiple endocrinopathies, with 3 or 4 endocrine axes involved meantime or successively^[5].

Until now, there have been few reports about the prevalence and comprehensive clinical spectrum of endocrinopathy manifestations in POEMS syndrome in China. In this article, we reviewed such issues in a large Chinese cohort with POEMS syndrome in our hospital in recent 20 years.

Methods

Participants

This retrospective observational study was conducted in PLA General hospital. A total of 136 with POEMS syndrome were included between January 2000 and January 2020. All the patients fulfilled the diagnostic criteria defined by Dispenzieri^[1], with two mandatory criteria (polyneuropathy and monoclonal plasma cell proliferating disorder), at least one major criterion (sclerotic bone lesion, Castleman disease or VEGF elevation) and one minor criterion (organomegaly, edema, endocrinology, skin change, papillary edema or thrombocytosis). Because of the high prevalence of diabetes mellitus (DM) and thyroid abnormalities, these diagnoses alone were not sufficient to meet the minor criterion. We analyzed the medical records of these patients regarding their endocrinopathies at the time of diagnosis of POEMS syndrome. DM and hypothyroidism were not attributed to POEMS syndrome unless these reportedly occurred months to years after the onset of another or more features of POEMS syndrome.

Statistical analysis

Data are presented as number (%), mean $\pm$ standard deviation or median (interquartile range). SPSS (version 13.0, IBM Corporation, Somers, NY, USA) was used for statistical analysis.

Results

Totally, 136 patients with POEMS syndromes were enrolled in this report. The median age was 48(40-56) years and the ratio of male/female was 2.32 (95 cases/41 cases). It is showed the information about endocrinopathies evaluation was incomplete in many patients' medical record, so the true prevalence of endocrinopathies might be under underestimated.

83.16 % (79/95) male patients had hypogonadism. Erectile dysfunction (88.61%, 70/79) and gynecomastia (12.66%, 10/79) were common findings in male patients with hypogonadism. The testosterone was 5.73 ± 4.17 (normal range 8.40-28.70 nmol/L) in all male cases with POEMS, much lower than the same-aged male. Follicle-stimulating hormone (FSH) and Luteinizing hormone (LH) in 78

cases were in normal range except for 1 case with low level of these two hormones, which indicated secondary hypogonadism. In premenopausal female, irregular menses (94.74%, 18/19) were the frequent symptoms and 7 patients even presented with amenorrhea at last. Some cases presented with secondary hypogonadism (14.63%, 6/41). Mild hyperprolactinemia were detected both in male (32.63%, 31/95) and female (39.02%, 16/41). Female patients with mild hyperprolactinemia had no galactorrhea. No therapy were performed on such mild hyperprolactinemia in male or female.

30.15% patients had abnormal glucose metabolism (41/136), including 7.35% patients (10/136) with impaired glucose tolerance, and 22.79% (31/136) with overt DM. As for impaired glucose tolerance and mild type 2 DM, lifestyle interventions can keep blood glucose well controlled. Hypoglycemia medicines or/and insulin were administrated to DM patients with serious hyperglycemia (61.29%, 19/31).

Hypothyroidism was also a common endocrine disorder (61.03%, 83/136). 33.82% (46/136) patients had overt hypothyroidism and 16.18% (22/136) had subclinical hypothyroidism, meanwhile 11.03% (15/136) patients had secondary hypothyroidism. The patients with overt hypothyroidism always presented with tiredness, loss of appetite and mild edema. Most of the patients were treated with *levothyroxine*, no matter primary or secondary.

The prevalence of primary adrenal insufficiency was 30.15% (41/136), including 8.82% (12/136) in overt group (elevated ACTH level and decreased free cortisone level) and 21.32% (29/136) in subclinical group (isolated elevated ACTH levels with cortisol rhythm disorder). ACTH stimulation test were not carried out in our series, which might omit some patients with adrenal insufficiency. Glucocorticoid were usually administrated in these patients with POEMS syndrome, meanwhile resulting in remission of adrenal insufficiency.

Hypocalcaemia adjusted with albumin was also common, with a prevalence of 36.76% (50/136). Parathyroid hormone(PTH) were not routinely measured in this series. In these 50 cases, available serum PTH levels in 14 cases were 48.04 ± 21.17 (normal range 15.0-65.0 pmol/L) and other 36 cases had not serum PTH measured. This indicated that calcium abnormalities was also a characteristic endocrinopathy in POEMS, but such conditions had always been underestimated.

29.92%(38/127) patients had two endocrine abnormalities and the most frequent was hypothyroidism combined with hypogonadism (8/38). Also 30.71%(39/127) patients had three endocrine abnormalities, and the most frequent was hypothyroidism combined with hypogonadism and hyperprolactinemia(8/39), as well as hypothyroidism combined with hypogonadism and abnormal glucose metabolism (8/38). The percentage of 4, 5 and 6 kind of endocrine axes involved were 17.32%(22/127), 7.09%(9/127) and 2.36% (3/127), respectively. In patients with multiple endocrinopathies, the clinical manifestations were even more complicated.

Discussion

The prevalence of POEMS is really much lower in China, as reported in other countries. To our knowledge, this series about patients with POEMS syndrome is the largest one in China. It showed that endocrinopathy is a central feature of this disorder and should be paid more attention to than before.

The proportion of each endocrinopathy and multiple endocrinopathies in our Chinese series are slightly different compared with those data from Mayo Clinical report (Table 1)^[5]. Of the 136 patients with POEMS syndrome, 93.38% of patients had one endocrinopathy, with hypogonadism as the most frequent endocrine abnormality, followed by hypothyroidism, hypocalcemia, hyperprolactinemia, abnormal glucose metabolism, and lastly by adrenal insufficiency. No other hypopituitarism was recorded in these patients, except for 7 patients with secondary hypogonadism and 15 patients with secondary hypothyroidism. The multiple endocrinopathies should also be emphasized. In POEMS syndromes, nearly most of endocrine axis had the possibility of being involved, resulting in complex clinical presentations of hormone disorders. The percentage of 2, 3, 4, 5 and 6 kind of endocrine axes involved were 29.92%, 30.71%, 17.32%, 7.09% and 2.36%, respectively. These endocrine abnormalities can seriously affect the patient's quality of life, and sometimes even lead to emergencies, if they cannot be diagnosed in time and treated properly.

Table 1
Endocrinological manifestations of our series (2000–2020) compared with mayo series(2000–2006)

Characteristic	Our series (2000–2020)	Mayo clinic series (2000–2006)
Total patients	136	64
Patients with endocrinopathy	127(93.38%)	54 (84%)
M/F	95/41	38/16
Median age (y) (IQR)	48(40–56)	50 (43–59)
Erectile dysfunction	70/95(73.68%)	23/38 (61%)
Hypogonadism (men)	75/95(78.95%)	26/33 (79%)
Gynecomastia (men)	10/95(10.53%)	10/38 (26%)
Hyperprolactinemia	47/136(34.56%)	10/35 (29%)
Hypothyroidism	83/136(61.02%)	28/48 (58%)
Glucose intolerance	41/136(30.15%)	24/50 (48%)
Adrenal insufficiency	41/136(30.15%)	6/9 (67%)
Hypocalcemia	50/136(36.76%)	14/51 (27%)
Evidence of multiple endocrine abnormalities	111/136(81.62%)	29/54 (54%)
*Data are number (percentage) of patients unless otherwise indicated.		
IQR = interquartile range.		

Endocrinopathy is a really central feature of POEMS syndrome, but the pathogenesis have not been well understood. Increased levels of cytokines, particularly VEGF, has been reported to be an important pathogenic factor of POMES syndrome^[6]. However, antibodies against hormones in serum or special hormone receptors in endocrine gland have not been detected. In fact, the structure of endocrine glands is not impaired at autopsy, which indicates that endocrinopathy in POEMS syndrome maybe only functional disorder, rather than structure impairment^[7]. It is hypothesized that overexpression of VEGF in POEMS syndrome might affect the endocrine axes because of a disruption of the local balance of angiogenic factors, which appears to be important in the regulation of hormone secretion in various endocrine glands.

Hypogonadism is the most common endocrine disorders in POEMS syndrome. In fact, Gonadal dysfunction is a serious problem that reduces patients' quality of life and interpersonal relationships. In this series, 83.16% male patients had hypogonadism and 88.61% reported erectile dysfunction. Gynecomastia (13.33%) was also a common finding in male patients with hypogonadism. The

testosterone was much lower than that in same-aged male. In premenopausal female, irregular menses (94.74%) and even amenorrhea in some patients were the frequent symptoms. Mild hyperprolactinemia were detected both in male (32.63%) and female (39.02%). An increased intracranial pressure in patients with POEMS syndrome could be detected. It was presumed to disrupt hypothalamic function and inhibit dopaminergic pathways, resulting in hypoprolactinemia^[7]. Since patient with mild hyperprolactinemia had no special symptoms, administration with Bromocriptine may be unnecessary.

7.35% patients (10/136) had impaired glucose tolerance, and 22.79% patients had overt DM. Since the insulin and C peptide secretion in fasting and postprandial were higher than normal range, which indicated that islet cell function were not obviously impaired. As for impaired glucose tolerance and mild type 2 DM, lifestyle interventions can keep blood glucose well controlled. Hypoglycemia medicines or/and insulin were administrated to diabetes mellitus with serious hyperglycemia. Usually, hyperglycemia would be more serious and high dose of insulin always needed when most of these POEMS patients were treated with high dose of corticosteroids on POEMS syndrome. Peripheral neuropathy is the most obvious symptom of POEMS syndrome. Patients with POEMS syndrome always complain numbness and pain in limbs. If hyperglycemia also coexist at the same time, they are frequently misdiagnosed as diabetic peripheral neuropathy (DPN). In fact, there are some differences between neuropathy of POEMS syndrome and DPN. A longer process and slower progress are features of DPN with axonal degeneration alone, while there is a combination of axonal and demyelinating lesions in POEMS syndrome^[8,9].

Thyroid is the common organ involved in autoimmune associated disease. Hypothyroidism is also a common endocrine disorder in POEMS. 61.03% patients had hypothyroidism, overt or subclinical. Since the symptoms of hypothyroidism are always non-specific, it is essential to thoroughly evaluate thyroid function. Therapy with levothyroxine can relieve these symptoms gradually. Some patients with POEMS syndrome had obvious pleural effusion and peritoneal effusion, which should be distinguished from serious hypothyroidism.

Adrenal insufficiency has ever been reported infrequently in patients with POEMS syndrome. In our report, The prevalence of primary adrenal insufficiency was 30.15% (41/136), including 8.82% (12/136) in overt group (elevated ACTH level and decreased free cortisone level) and 21.32% (29/136) in subclinical group (isolated elevated ACTH levels with cortisol rhythm disorder). However, ACTH stimulation test were not routinely carried out in our series, which might omit some patients with adrenal insufficiency. Systematic administration with glucocorticoid on POEMS syndrome can relieve the symptoms of adrenal insufficiency.

Simple hypocalcaemia were also common in POEMS in this series, with a prevalence of 36.76%. This indicated that calcium abnormalities was also a frequent characteristic endocrinopathy in POEMS, but had always been underestimated for a long time. Unfortunately, Serum PTH were not routinely measured. The available serum PTH in 14 cases with hypocalcemia was in normal range, which indicated that the parathyroid function were not impaired. In Mayo clinic report, that approximately one third of patients in our series had low calcium levels.

According to the findings in our series and other large series, We can see that POEMS syndrome is a rare multisystem disease but with a wide spectrum of clinical endocrinopathies. In fact, the evaluation of endocrinopathies always incomplete and delayed for a long time. During the disease course, the various endocrinopathies may occur in different stage^[5]. Also, several hormones disorders may present at the same time. All these disorders results in the complicated clinical presentations, which is susceptible to be misdiagnosed. So we suggest that all patients with POEMS syndrome should have a thorough and systematic endocrine evaluation at diagnosis of this syndrome.

After patients with POEMS syndrome were hospitalized, the definite diagnosis always need the clinical consultation of various specialists from neurology department, endocrinology department, hematology department, et al. We recommend that the multiple discipline teams should be united in management of POEMS syndrome. With this approach, the endocrinopathies can be toughly analyzed, correctly treated and timely monitored in the follow up^[7].

The present study had several limitations. As a retrospective medical record review, the inherent biases could not be precluded. The prevalence of endocrinopathy in our series is likely underestimated because some patients had incomplete endocrine evaluations, which had been reported in Mayo clinical series^[5]. The actual prevalence of endocrinopathies may be much higher than the data reported in this article, which must attract our more attention.

For patients with a dominant sclerotic plasmacytoma, first line therapy is irradiation. Patients with diffuse sclerotic lesions or disseminated bone marrow involvement should receive systemic therapy. Current systematic therapies include high-dose chemotherapy with autologous stem cell transplantation (ASCT), alkylator-based therapy, and therapy with novel agents. All three treatments can achieve acceptable remission rates and survival^[10-12].

Besides therapies on POEMS syndrome, the treatment on endocrinopathies should be aimed at hormone supplement and/or rectifying the disorder in hypogonadism, hypothyroidism, glucose metabolism, and calcium metabolism. To those with subclinical endocrinopathies, the intensive monitoring or low dose of corresponding hormones should also be prescribed. With improvement of endocrinopathies the clinical satiation will also improve, resulting in a good base for future treatment on POEMS syndromes.

It reported that endocrine abnormalities can also improve after chemotherapy, including successful tapering off of thyroid replacement, androgen replacement, and corticosteroid replacement in at least one-third of the patients. In a single-center prospective study in China, 35 patients with newly diagnosed POEMS syndrome were treated with Lenalidomide and dexamethasone for 12 cycles. After treatment, the mean total female sexual function index (FSFI) score increased from 17.1 to 23.7 and the mean international index of erectile function (IIEF) scores increased from 12.9 to 20.5. Meanwhile the total testosterone levels in male increased from 55 ng/dl to 624 ng/dl^[6].

Conclusions

Endocrinopathies manifestation is an important component of the POEMS syndrome. This study provides an overview of the abnormalities observed in a large series in China. These findings should serve as a reminder for physicians caring for patients with POEMS syndrome that endocrinopathy manifestations in POEMS syndromes are more frequent, and its clinical complicity should be paid more attention to. To patients with definite diagnosis of POEMS syndromes, early and thorough endocrine evaluation should be performed.

Abbreviations

VEGF: vascular endothelial growth factor; DM: diabetes mellitus; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; ACTH: adreno-cortico-tropic-horone; PTH: Parathyroid hormone; DPN: diabetic peripheral neuropathy; ASCT: autologous stem cell transplantation; FSFI: female sexual function index; IIEF: international index of erectile function; PLA: People's Liberation Army; ENT:Ears, Nose, and Throat.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of PLA General Hospital.

Consent for publication

Informed consents were obtained from all the patients prior to the use of their data and images for publication.

Availability of data and materials

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declared that they have no competing interests.

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Authors' contributions

CZ collected the data. YS, CZ, and XLW participated in the analysis and the interpretation of the data, YS drafted the manuscript. QHG, JMB, ZHL, JTD, YMM and XLW critically revised the manuscript. All the authors read and approved the final article.

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Statement of authorship

The authors confirm that the manuscript has not been published or is under review for publication elsewhere.

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