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ORIGINAL ARTICLE

A retrospective analysis of endocrinopathy manifestations in 136 Chinese patients with POEMS syndrome

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Abstract

OBJECTIVE: POEMS syndrome is a rare multisystemic disease, with a wide spectrum of clinical endocrinopathies. Patients with POEMS syndrome may present with one or more hormone disorders during the disease course, but such phenomenon has usually been underestimated. In this report, we analyzed the prevalence and clinical characteristics of endocrine abnormalities in a large Chinese cohort with POEMS syndrome.

METHODS: This retrospective review was performed in patients with a definite diagnosis of POEMS syndrome who were hospitalized in our hospital between January 2000 and January 2020. The clinical data about endocrine abnormalities were extracted from their medical records and analyzed.

RESULTS: This study comprised 136 patients (95 male, 41 female) with a median age of 48(40-56) years old. Endocrine abnormalities were frequent (127 cases, 93.38%) in patients with POEMS syndrome. The prevalence of single endocrinopathy and multiple endocrinopathies were 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 patients with multiple endocrinopathies, the prevalence of 2, 3, 4, 5, and 6 kinds 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. Such hormone disorders cause complex clinical presentations, including overt or subclinical situations.

CONCLUSION: Endocrinopathy manifestations in POEMS syndrome are more frequent, and its clinical complicacy should be emphasized in differential diagnosis. For patients with a definite diagnosis of POEMS syndrome, an early and thorough endocrine evaluation should be performed.

INTRODUCTION

POEMS syndrome is a rare paraneoplastic syndrome due to plasma cell disorder, characterized by polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes (Dispenzieri, 2017). The prevalence is only 0.3 per 100,000 according to a national survey in Japan in 2003 (Suichi *et al.* 2019). In China, there have been some small series and many isolated case reports about this rare disorder, with limited information about systematical studies (Wang *et al.* 2019).

The pathogenesis of POEMS syndrome has not been well understood, but increasing evidence indicate that high levels of serum vascular endothelial growth factor (VEGF) correlate with disease activity. It can induce rapid and reversible enhancement in vascular permeability, which plays an important role in angiogenesis (Corlan *et al.* 2017; Bianco *et al.* 2019).

Endocrinopathy is one important feature of POEMS syndrome, which presents in 84% patients with this paraneoplastic syndrome in some series. Hypogonadism (55-89%) is the most frequent endocrine disorder, followed by thyroid abnormalities, glucose metabolism abnormalities, hypocalcaemia, adrenal insufficiency, *et al.* Some patients with POEMS syndrome even suffer from multiple endocrinopathies, with 3 or 4 endocrine axes involved meantimely or successively (Gandhi *et al.* 2007). However, this issue has usually been poorly understood.

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 who were hospitalized 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 enrolled between January 2000 and January 2020. The study was approved by the Ethics Committee of PLA General Hospital. Informed consents were obtained from all patients prior to the use of their data and images for publication. All patients fulfilled the diagnostic criteria defined by Dispenzieri (Dispenzieri, 2017), 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 clinical records of various endocrinopathies in these patients at the time of confirmed diagnosis. Only when DM and hypothyroidism occurred months to years after other endocrinopathies of POEMS syndrome, these two features were attributed to POEMS syndrome.

Statistical analysis

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

RESULTS

General information

From January 2000 to January 2021, a total of 136 patients diagnosed with POEMS syndrome in our hospital were included in this study. The median age was 48(40-56) years and the ratio of male/female was 2.32 (95 cases/41 cases). The initial presentations included numbness and weakness of lower limbs (106/136, 77.94%), edema (47/136, 34.56%) and skin pigmentation (43/136, 31.62%), and endocrine and metabolic abnormalities (21/136,15.44%). The departments in which patients initially looked for medical care were Neurology department (89/136, 65.44%), Hematology Department (13/136, 9.56%) and Endocrinology Department (10/136, 7.35%). Additionally, some cases were administrated in other departments. 52.94% (72/136) of patients with POEMS syndrome were treated with multi-disciplinary team (MDT) including endocrinology. The time interval from presentations onset to diagnosis was 412 days (198-1,055 days), which indicated that delay in diagnosis was more common. It was shown that the information about endocrinopathies evaluation was incomplete in many patients' medical records, so the actual prevalence of endocrinopathies might be underestimated.

Clinical manifestations of abnormal endocrine metabolism

About 83.16 % (79/95) male patients had hypogonadism. Erectile dysfunction (88.61%, 70/79) and gynecomastia (12.66%,10/79) were common complaints 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 the normal range except for 1 case with low levels of these two hormones, which indicated secondary hypogonadism. In premenopausal females, irregular menses (94.74%, 18/19) were the frequent symptoms and 7 patients even presented with amenorrhea lastly. Some cases presented with secondary hypogonadism (14.63%, 6/41). Mild hyperprolactinemia were detected both in males (32.63%, 31/95) and females (39.02%, 16/41). Female patients with mild hyperprolactinemia had no galactorrhea. No therapies were performed for such mild hyperprolactinemia in males or females.

Tab. 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)	79/95 (83.16%)	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.

About 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. Lifestyle interventions could keep blood glucose well controlled in most of these patients. Hypoglycemia medicine or/and insulin were prescribed 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 presented with tiredness, loss of appetite, and mild edema. Most of these patients with hypothyroidism were prescribed with levothyroxine.

The prevalence of primary adrenal insufficiency was 30.15% (41/136), including 8.82% (12/136) with overt presentation (elevated plasma ACTH levels and decreased serum free cortisone levels) and 21.32% (29/136) with subclinical presentation (isolated elevated plasma ACTH levels with serum free cortisol rhythm disorder). Glucocorticoids were usually administrated in these patients with POEMS syndrome, which had adrenal insufficiency relieved.

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

About 29.92% (38/127) patients had two endocrine abnormalities and the most frequent was hypothyroidism combined with hypogonadism (8/38). Moreover, 30.71% (39/127) patients had three endocrine abnormalities. The most frequent was hypothyroidism combined with hypogonadism and hyperprolactinemia (8/39), followed by hypothyroidism combined with hypogonadism and abnormal glucose metabolism (8/39). The percentage of 4, 5, and 6 kinds 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 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 indicates that endocrinopathy is also a central feature of this disorder and should be paid more attention to than before.

The proportions of each endocrinopathy and multiple endocinopathies in our Chinese series are slightly different compared with those data from Mayo Clinical report (Table 1) (Gandhi *et al.* 2007). Of the 136 patients with POEMS syndrome, 93.38% of patients had one endocrinopathy. Hypogonadism was the most frequent endocrine abnormality, followed by hypothyroidism, hypocalcaemia, hyperprolactinemia, abnormal glucose metabolism, and adrenal insufficiency. Except for 7 patients with secondary hypogonadism and 15 patients with secondary hypothyroidism, no other hypopituitarism was recorded in this series.

Multiple endocrinopahties should also be emphasized. In POEMS syndrome, nearly most of the endocrine axes have the possibility of being involved, resulting in complex clinical presentations of hormone disorders. The percentage of 2, 3, 4, 5, and 6 kinds 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 life quality and even lead to emergencies, if they could not be identified timely and treated properly.

Endocrinopathy is really a central feature of POEMS syndrome, but the pathogenesis has not been well understood. Increased levels of cytokines, particularly VEGF, have been reported to be an important pathogenic factor of POMES syndrome (Li *et al.* 2019). However, antibodies to hormones in serum or special hormone receptors in the endocrine glands have not been detected. The structure of endocrine glands is not impaired at autopsy. Endocrinopathy in POEMS syndrome maybe only a functional disorder, rather than structure impairment (Yang *et al.* 2016). It is hypothesized that overexpression of VEGF in POEMS syndrome might affect the endocrine axis and disrupt 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 disorder in POEMS syndrome. Gonad dysfunction is a serious problem that reduces patients' life quality and interpersonal relationships. In this series, 83.16 % male patients had hypogonadism and most of them complained of erectile dysfunction and gynecomastia. In premenopausal females, irregular menses (94.74%) and amenorrhea were the frequent symptoms. It was reported that an increased intracranial pressure in patients with POEMS syndrome could be detected, which was presumed to disrupt hypothalamic function and inhibit dopaminergic pathways and cause hypoprolacteinemia (Yang *et al.* 2016). Mild hyperprolactinemia were detected both in males (32.63%) and females (39.02%). Since the patient with mild hyperprolactinemia had no special symptoms, so administration with bromocriptine maybe unnecessary.

7.35% patients (10/136) had impaired glucose tolerance, and 22.79% patients had overt DM. The insulin and C peptide secretion in fasting and postprandial were higher than normal range, which indicated that islet cell functions were not surely impaired. Hypoglycemia medicine or/and insulin were only administrated to DM patients with serious hyperglycemia. However, when a high dose of corticosteroid was prescribed in these patients, hyperglycemia became more serious, and a high dose of insulin was needed. Peripheral neuropathy is the most obvious symptom of POEMS syndrome, so patients with POEMS syndrome always complain numbness and pain in limbs. If hyperglycemia also coexists at the same time, they are frequently misdiagnosed as diabetic peripheral neuropathy (DPN). There are some differences between the neuropathy of POEMS syndrome and DPN. Axonal degeneration progresses slowly in DPN, while the combination of axonal and demyelinating lesions often occurs in POEMS syndrome (Kourelis *et al.* 2016; Karam *et al.* 2015).

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

Adrenal insufficiency has ever been frequently reported in patients with POEMS syndrome. In our report, the prevalence of primary adrenal insufficiency was 30.15% (41/136), including 8.82% (12/136) with overt presentationand 21.32% (29/136) with subclinical presentation. However, ACTH stimulation tests were not routinely carried out in our series, which might underestimate the prevalence of adrenal insufficiency. Systemic administration of glucocorticoids for POEMS syndrome can relieve the symptoms of adrenal insufficiency.

Simple hypocalcaemias were common in POEMS in this series, with a prevalence of 36.76%. This indicated that calcium abnormality was also a frequent characteristic of endocrinopathy in POEMS but had always been overlooked for a long time. Regrettably, serum PTH were not routinely measured in this series. The available serum PTH in 14 cases with hypocalcaemia was in the normal range, which showed that the parathyroid functions were not impaired. In Mayo Clinic report, approximately one-third of patients had low serum 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 clinical practice, the evaluation of endocrinopathies were always incomplete and delayed for a long time. During the disease course, various endocrinopathies may occur in different stages (Gandhi *et al.* 2007). Moreover, several hormone disorders may present at the same time. All these disorders result in complicated clinical presentations, which have usually been misdiagnosed. Therefore, we suggest that all patients with POEMS syndrome should have a thorough and systematic endocrine evaluation at diagnosis.

After patients with POEMS syndrome are hospitalized, the definitive diagnosis always needs the clinical consultation of various specialists from neurology department, endocrinology department, hematology department, *et al.* We recommend that multiple discipline teams should be united in the management of POEMS syndrome. With this approach, the endocrinopathies could be toughly analyzed, correctly treated, and timely monitored in follow-up (Yang *et al.* 2016).

The present study has several limitations. As a retrospective medical record review, the inherent biases could not be precluded. The prevalence of endocrinopathies in our series is likely underestimated because some patients had incomplete endocrine evaluations, which had also been reported in Mayo clinical series (Gandhi *et al.* 2007). The actual prevalence of endocrinopathies may be higher than the data reported in this article, which must attract our more attention.

For patients with dominant sclerotic plasmacytoma, the first line therapy is irradiation. Patients with diffuse sclerotic lesions or disseminated bone marrow involvement should receive systemic therapy. Current systemic therapies include high-dose chemotherapy with autologous stem cell transplantation (ASCT), alkylator-based therapy, and therapy with novel agents. All three therapies can achieve acceptable remission rates and better survival (Ohwada *et al.* 2018; Kawajiri *et al.* 2018; Zhao *et al.* 2019).

Besides the therapy of POEMS syndrome, the treatment of endocrinopathies should be aimed at rectifying the disorder in hypogonadism, hypothyroidism, glucose metabolism, and calcium metabolism. For those with subclinical endocrinopathies, intensive monitoring or low doses of the corresponding hormones should also be prescribed.

It is reported that endocrine abnormalities can also get improvement after chemotherapy, including successful tapering 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) score increased from 12.9 to 20.5. Meanwhile, the total testosterone levels in males increased from 55 ng/dl to 624 ng/dl (Li *et al.* 2019).

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 that endocrinopathy manifestations in POEMS syndrome are more frequent and the clinical complicacy should be paid more attention to. For patients with a definite diagnosis of POEMS syndrome, an early and thorough endocrine evaluation should be performed.

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DECLARATION OF COMPETINGINTEREST

The authors declared that they have no competing interests.

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