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Case Report

A Case of POEMS Syndrome and Associated Endocrinopathies: Hypogonadism and Subclinical Hypothyroidism

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Abstract: POEMS is a rare paraneoplastic syndrome characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes. Castleman disease (angiofollicular lymph node hyperplasia) and elevation of serum vascular endothelial growth factor (VEGF) are associated features as well. Pathogenesis of POEMS syndrome is still unclear, although a loss of balance between proinflammatory and anti-inflammatory cytokines is considered the underlying pathophysiology. Hypogonadism is the most common endocrinopathy encountered in POEMS syndrome. We report the case of a 45-year-old man with history of hypogonadism who developed Castleman disease. He was eventually diagnosed with POEMS syndrome upon developing polyneuropathy, his VEGF levels were elevated, and additionally, he was found to have subclinical hypothyroidism. Clinical and biochemical response to therapy and the course of his disease are presented. With treatment and normalization of his VEGF levels, his repeat thyroid function testing showed a decrease in his thyroid stimulating hormone levels to normal range. His hypogonadism continued to require testosterone replacement therapy. A potential role of cytokines and angiogenic factors in the development of the disease including the endocrinopathy component, is discussed. It is unclear whether VEGF has a role in the etiopathogenesis of the endocrinopathies or perhaps it is simply a marker of disease activity, with a low disease activity correlating with the recovery of the thyroid function. Further studies are needed to elucidate the underlying mechanisms, although we suspect it likely involves, at least in part, inflammatory cytokines and angiogenic factors.

Keywords: POEMS; Castleman disease; hypogonadism; subclinical hypothyroidism; endocrinopathy; vascular endothelial growth factor; interleukin-6, cytokines; angiogenic factors; polyneuropathy; monoclonal plasma cell disorder

1. Introduction

POEMS (acronym: Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal plasma cell disorder, Skin changes) is a rare paraneoplastic syndrome characterized by an underlying monoclonal plasma cell disorder. Another defining characteristic of the syndrome is polyneuropathy, often first experienced as distal sensory loss which can eventually progress to motor disability [1]. Diagnosis of the syndrome requires the presence of three major criteria, with the monoclonal plasma cell disorder and polyneuropathy being mandatory major criteria, and one minor criterion (see Table 1). It is often associated with Castleman disease, a lymphoproliferative disorder

which presents as either unicentric or multicentric lymphadenopathy with a spectrum of clinical presentations ranging from asymptomatic to severe B-symptoms, cytopenias, and endocrinopathies [2].

Table 1. POEMS Syndrome diagnostic criteria.

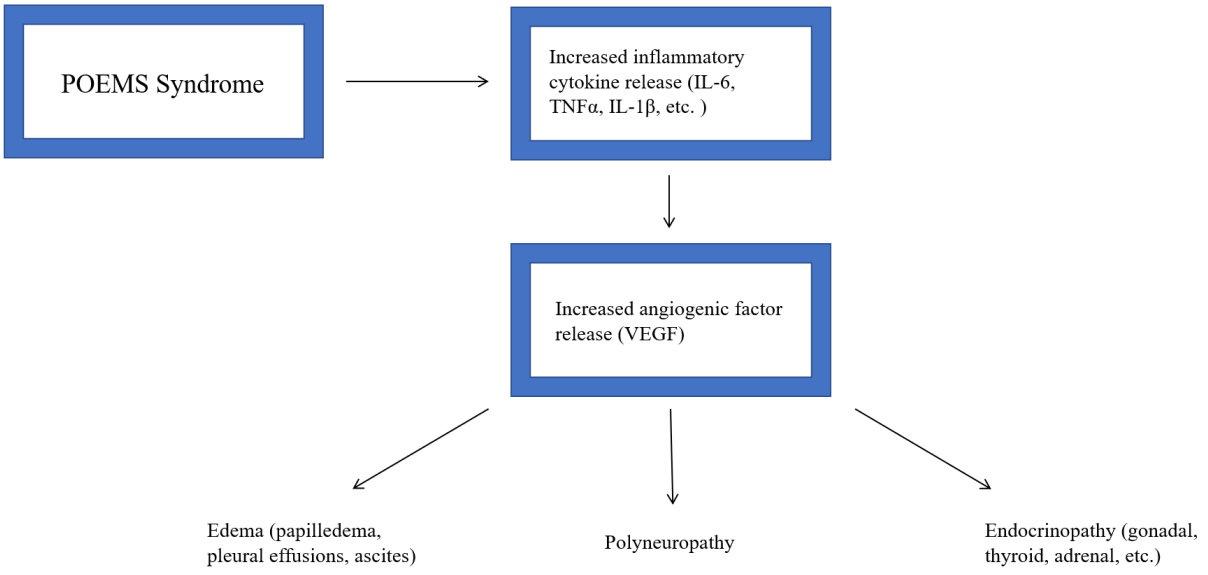
POEMS Syndrome Diagnostic Criteria	
Mandatory Major Criteria	• Polyneuropathy • Monoclonal plasma cell-proliferative disorder
Other Major Criteria (at least one)	• Castleman disease • Sclerotic bone lesions • Elevated VEGF level
Minor Criteria (at least one)	• Endocrinopathy (e.g., pituitary, adrenal) • Extravascular volume overload (e.g., pleural effusion, ascites) • Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy) • Skin changes (e.g., hyperpigmentation, plethora) • Papilledema • Thrombocytosis/polycythemia

Both mandatory criteria are required along with at least one other major criterion and one minor criterion to confirm a POEMS syndrome diagnosis. VEGF = vascular endothelial growth factor.

The pathogenesis of POEMS syndrome is still unclear, although a loss of balance between proinflammatory and anti-inflammatory cytokines resulting in increased angiogenic factor secretion is thought to be the most likely underlying pathophysiology [3,4]. In fact, serum levels of proinflammatory cytokines such as interleukin 1β, interleukin-6 (IL-6) and tumor necrosis factor α were found to be higher in patients with POEMS compared to patients with multiple myeloma, with the reverse being the case for levels of transforming growth factor β1, an antagonistic cytokine [4]. Tomasso et al. also found that serum IL-6 and vascular endothelial growth factor (VEGF) levels were found to both correlate with level of disease activity, with decreases in levels noted after autologous stem cell transplant (ASCT) was performed for therapy of advanced disease [5].

VEGF is suspected to be the dominant pathogenic factor in POEMS syndrome (Figure 1). It is thought that elevated VEGF, which occurs as part of the elevation of proinflammatory cytokines, causes neoangiogenesis and vascular permeability which results in some clinical features of POEMS including edema, pleural effusions, ascites, and pulmonary hypertension. Increased endoneural microvascular permeability is also thought to contribute to blood-nerve barrier dysfunction causing polyneuropathy [6].

Figure 1. Proposed mechanism contributing to POEMS syndrome's clinical presentation involving inflammatory cytokine release and subsequent over secretion of angiogenic factors.



IL-6 = interleukin-6, TNFα = tumor necrosis factor α, IL-1β = interleukin-1β, VEGF = vascular endothelial growth factor.

One of the other prominent, yet poorly understood, features of POEMS syndrome is its various co-occurring endocrinopathies. It has been suggested that VEGF overexpression in POEMS syndrome may also affect endocrine axes because of the disruption in the local balance of angiogenic factors which possibly play a role in the regulation of hormone secretion in endocrine glands [3]. The most common endocrinopathy encountered in POEMS syndrome is primary or secondary hypogonadism, which often presents with gynecomastia and erectile dysfunction in this context [3,7]. Here we present a case of POEMS syndrome with associated Castleman disease and hypogonadism treated with testosterone supplementation.

2. Case Presentation

A 45-year-old male presented to his primary care physician with complaints of persistent neck lymphadenopathy despite multiple courses of antibiotics associated with fatigue and mild night sweats. He underwent an initial MRI which revealed multiple enhancing neck masses on the right measuring up to 4 cm from the angle of the mandible. His subsequent excisional lymph node biopsy showed atrophic germinal centers surrounded by expanded mantle cells with "onion skinning" of mantle zone lymphocytes along with marked paracortical plasmacytosis with a predominance of lambda positive plasma cells compared to kappa plasma cells. Overall, these findings were consistent with plasma cell variant multicentric Castleman disease. His initial protein electrophoresis and bone marrow biopsy were both unremarkable along with most of his remaining workup including human herpesvirus-8 (HHV-8) and human immunodeficiency virus (HIV) infection, complete blood count, erythrocyte sedimentation rate, and lactate dehydrogenase (LDH).

He underwent CT chest, abdomen, and pelvis which did not reveal any lymphadenopathy, although it did show sclerotic bone lesions in the pelvis and lumbar vertebrae with the largest lesion at the L5 vertebra, with focal uptake noted at the L5 lesion on subsequent bone scan. A fine-needle aspiration and core biopsy were performed of the L5 bone lesion, with pathology revealing a lambda-positive plasma cell proliferation consistent with a plasma cell neoplasm. At this point, he was also beginning to experience fatigue, night sweats, and weight loss and was thus started on 8 cycles of weekly rituximab with subsequent resolution of his night sweats. Due to concerns for risk of pathologic fracture in the context of new back pain, he underwent radiotherapy to the L5 lesion.

His associated POEMS syndrome diagnosis was not confirmed until roughly a year after his initial excisional lymph node biopsy, when he began to experience progressive peripheral neuropathy starting in his distal lower extremities eventually extending to his mid-calf over a period of one and a half years without any upper extremity or motor involvement. A repeat serum protein electrophoresis at this point detected the presence of two monoclonal bands (IgA lambda and possibly IgG lambda). He also had a vascular endothelial growth factor (VEGF) level drawn which was elevated at 217 pg/mL (VEGF ELISA, reference range: 31–86 pg/mL). At this point, it was recommended to collect stem cells for ASCT. He was also started on lenalidomide and dexamethasone combination therapy after which he was noted to have improvement in his adenopathy and neuropathy symptoms. His repeat VEGF level 6 months after initiating combination therapy showed a decrease to 43 pg/mL, and further to less than 31 pg/mL after 2 years of lenalidomide therapy. The patient eventually underwent ASCT, 10 years after diagnosis, due to concern regarding progression of clinical disease with favorable effect noted.

Prior to his onset of lymphadenopathy, he had been on testosterone injections which were stopped at the time Castleman disease was diagnosed. Due to progression of gynecomastia and worsening depressive symptoms, he was restarted on testosterone injections about five years after his Castleman's diagnosis with improvement noted. Unfortunately records regarding his testosterone levels upon initial diagnosis are scant, however years later, he was re-tested after yet another interruption in his testosterone therapy with total testosterone levels of less than 100 ng/dL and follicular stimulating hormone (FSH) and luteinizing hormone (LH) levels in high-normal range (FSH: 16.75 and 13.82 mIU/mL (Range: 1.27–19.26 mIU/mL), LH: 7.32 and 8.63 mIU/mL (Range: 1.24–8.62 mIU/mL)) suggestive of possible secondary hypogonadism versus a mixed primary and secondary hypogonadism given his transiently elevated LH levels. DXA scan was normal, except for the unusually high level of bone density in the lumbar region due to osteosclerosis.

His other endocrinopathy workup included a hemoglobin A1c in prediabetes range and normal prolactin and cortisol levels. His initial thyroid function test was suggestive of subclinical hypothyroidism, with a thyrotropin or thyroid-stimulating hormone (TSH) at level of 6.25 mIU/mL (Range: 0.4–4.0 mIU/mL), and a normal free thyroxine was normal at level of 1.2 ng/dL (Range 0.8–1.8 ng/dL). However, repeat thyroid levels drawn after initiation of lenalidomide treatment denoted normalization of his TSH levels and remained so. Long term, hemoglobin A1c values fluctuated between normal and prediabetes, 5.0% to 6.1%.

3. Discussion

This case depicts a patient with an initial diagnosis of Castleman's disease via an excisional lymph node biopsy with an eventual diagnosis of associated POEMS syndrome after the development of the characteristic polyneuropathy symptoms along with monoclonal bands noted on protein electrophoresis. It is interesting to note that while he was found to have sclerotic bone lesions upon initial workup, which are often found in POEMS syndrome and considered a major criterion for diagnosis, the onset of the characteristic polyneuropathy formally establishing the POEMS diagnosis did not occur until about one year later.

As mentioned earlier, the etiology of endocrinopathies in POEMS syndrome and Castleman disease remains unclear. Prior studies attempting to elucidate any inciting mechanism have found no pathologic characteristics of endocrine glands on autopsy in POEMS syndrome patients including light chain deposition disorders [8], and there is no known circulating antibody that has been detected against any circulating hormones or endocrine receptors to explain this phenomenon [9]. In addition, the pattern of endocrinopathies is not always consistent between different individuals with POEMS syndrome or Castleman disease. The most common endocrinopathy seen in POEMS syndrome is hypogonadism, which can be of a primary or secondary hypogonadism pattern [7]; both seemed to be present in our patient. Other endocrinopathies that can occur include thyroid abnormalities, which can present as either a subclinical hypothyroidism or overt primary hypothyroidism, and hyperprolactinemia [3]. Although adrenal insufficiency is rarer, it has been detected in POEMS patients [7].

As stated previously, the prevailing theory regarding the etiology of POEMS syndrome is that of an inflammatory cytokine and angiogenic factor-mediated process resulting in the development of not only the underlying POEMS syndrome and Castleman's disease, but also the associated endocrinopathies [3]. Since angiogenesis is important towards hormone secretion regulation, a disruption in angiogenic factor concentrations could possibly affect endocrine function [10]. Supporting this theory is a study by Yang et al. [11], who found that in patients with primary or subclinical hypothyroidism due to POEMS syndrome, many showed improvement in their thyroid function (as indicated by thyroid stimulating hormone, free thyroxine, and free triiodothyronine levels 1 month after discontinuing levothyroxine) after completing POEMS syndrome therapy. In addition, patients who had a documented complete VEGF response (that is, a decrease in VEGF levels to normal concentrations) had a significantly higher rate of thyroid response to treatment compared to those who did not exhibit a complete response (89.8 versus 66.2%) [11]. Abnormal glucose metabolism, found in our patient, is common in POEMS endocrinopathy, but its inclusion as part of the syndrome is debatable [7]. The high prevalence in the general population and the number of patients on glucocorticoids at the time of diagnosis of POEMS are confounding factors. However, Ghandi et al. [3] were able to establish a temporal relationship between glucose intolerance and POEMS syndrome in their series, having ruled out glucocorticoid use at the time of testing.

Our case demonstrated a similar pattern to that observed by Yang et al. [11]. While this patient's initial endocrinopathy workup denoted a subclinical hypothyroid state alongside his known hypogonadism, with treatment and normalization of his VEGF levels, his repeat thyroid function testing showed a decrease in his thyroid stimulating hormone levels to normal range. It is also entirely possible that VEGF has no implication in the development of endocrinopathies and that it is simply a marker of disease activity, with low disease activity correlating with recovery of thyroid function.

In conclusion, POEMS syndrome and Castleman disease are rare, multisystem (albeit, the latter may be unicentric) processes which are still poorly understood. Further studies are needed to better elucidate the underlying mechanisms, although it likely involves, at least in part, inflammatory cytokines and angiogenic factors. Whether these factors are also responsible for the commonly associated endocrinopathies remains to be seen.

Author Contributions

K.L.Y.: Data collection, analysis, and interpretation, writing and editing of the manuscript, and illustration. S.T.O.: Conception and design, data collection, analysis, and interpretation, writing and editing of the manuscript, and supervision. Both authors have read and agreed to the published version of the manuscript.

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The authors omitted all identifying details about the patient in the report.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

Conflicts of Interest

The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

No AI tools were utilized for this paper.

References

1. Dispenzieri, A.; Kyle, R.A.; Lacy, M.Q.; et al. POEMS syndrome: Definitions and long-term outcome. *Blood* **2003**, *101*, 2496–2506. https://doi.org/10.1182/blood-2002-07-2299.
2. Lomas, O.C.; Streetly, M.; Pratt, G.; et al. The management of Castleman disease. *Br. J. Haematol.* **2021**, *195*, 328–337. https://doi.org/10.1111/bjh.17688.
3. Gandhi, G.Y.; Basu, R.; Dispenzieri, A.; et al. Endocrinopathy in POEMS syndrome: The Mayo Clinic experience. *Mayo Clin. Proc.* **2007**, *82*, 836–842. https://doi.org/10.4065/82.7.836.
4. Gherardi, R.K.; Bélec, L.; Soubrier, M.; et al. Overproduction of proinflammatory cytokines imbalanced by their antagonists in POEMS syndrome. *Blood* **1996**, *87*, 1458–1465.
5. Tomasso, A.; Innocenti, I.; Autore, F.; et al. VEGF and IL-6 Correlation in POEMS: A Potential Upcoming Marker of Active Disease and Early Autologous BMT Response. *Mediterr. J. Hematol. Infect. Dis.* **2022**, *14*, e2022007. https://doi.org/10.4084/MJHID.2022.007.
6. Pihan, M.; Keddie, S.; D'Sa, S.; et al. Raised VEGF: High sensitivity and specificity in the diagnosis of POEMS syndrome. *Neurol. Neuroimmunol. Neuroinflamm.* **2018**, *5*, e486. https://doi.org/10.1212/NXI.0000000000000486.
7. Caimari, F.; Keddie, S.; Lunn, M.P.; et al. Prevalence and Course of Endocrinopathy in POEMS Syndrome. *J. Clin. Endocrinol. Metab.* **2019**, *104*, 2140–2146. https://doi.org/10.1210/jc.2018-01516.
8. Gherardi, R.; Baudrimont, M.; Kujas, M.; et al. Pathological findings in three non-Japanese patients with the POEMS syndrome. *Virchows Arch A Pathol. Anat. Histopathol.* **1988**, *413*, 357–365. https://doi.org/10.1007/BF00783029.
9. Bardwick, P.A.; Zvaifler, N.J.; Gill, G.N.; 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* **1980**, *59*, 311–322. https://doi.org/10.1097/00005792-198007000-00006.
10. Góth, M.I.; Hubina, E.; Raptis, S.; et al. Physiological and pathological angiogenesis in the endocrine system. *Microsc. Res. Tech.* **2003**, *60*, 98–106. https://doi.org/10.1002/jemt.10248.
11. Yang, H.; Zhao, H.; Gao, X.; et al. Endocrine Evaluation in POEMS Syndrome: A Cohort Study. *Front. Endocrinol.* **2020**, *11*, 536241. https://doi.org/10.3389/fendo.2020.536241.