

Case Report

POEMS syndrome associated with Castleman disease, hyaline vascular type: a rare case report

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Abstract:

POEMS (Peripheral Neuropathy, Organomegaly, Endocrinopathy, Monoclonal Gammopathy, and Skin changes) syndrome, a rare paraneoplastic disease, presents multisystemic disorder related to underlying plasma cell dyscrasia. Approximately 10-30% of patients with POEMS are associated with Castleman disease. Castleman disease has a wide variety of presentations ranging from simple B-symptoms to various autoimmune symptoms or a frank POEMS syndrome. The spectrum of disease may overlap between osteosclerotic myeloma (OSM), Castleman disease and POEMS syndrome. Herein, we reported a 68-year-old Thai woman who presented with generalized lymphadenopathy compatible with Castleman disease together with a new onset of ascites, splenomegaly, polyneuropathy and history of arterial thrombosis. Accordingly, the diagnosis was POEMS syndrome with Castleman disease. Treatment with cyclophosphamide, thalidomide and dexamethasone (CTD) regimen was used. Clinical symptoms of extravascular volume overload (ascites and legs edema) gradually improved after 2 cycles of CTD regimen.

Keywords : ● POEMS syndrome ● Castleman disease ● Polyneuropathy ● Monoclonal gammopathy
● Ascites

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รายงานผู้ป่วย

POEMS syndrome associated with Castleman disease, hyaline vascular type: a rare case report

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บทคัดย่อ

กลุ่มอาการ POEMS (Peripheral Neuropathy, Organomegaly, Endocrinopathy, Monoclonal Gammopathy, and Skin changes) เป็นกลุ่มอาการที่เป็นผลตามมาของโรคมะเร็ง (paraneoplastic disease) ที่พบได้ไม่บ่อย ซึ่งผู้ป่วยมักมีอาการแสดงที่ผิดปกติในหลายระบบ โดยเป็นผลมาจากโรคที่เกิดจากความผิดปกติของเม็ดเลือดขาวชนิดพลาสมาเซลล์ประมาณร้อยละ 10 ถึง 30 ของผู้ป่วยกลุ่มอาการ POEMS มักพบว่ามีความสัมพันธ์กับโรค Castleman ร่วมด้วย ซึ่งทั้งสองโรคจัดอยู่ในกลุ่มโรคที่พบได้น้อยเนื่องจากพบว่ามีอุบัติการณ์การเกิดโรคอยู่ที่ประมาณ 0.3-0.5 ต่อ 100,000 ประชากรต่อปี โดยโรค Castleman มีอาการแสดงที่ค่อนข้างหลากหลาย ตั้งแต่ ไข้ น้ำหนักลด เหงื่อออกตอนกลางคืน (B symptoms) อาการแสดงทางโรคภูมิคุ้มกันทำลายตนเอง จนไปถึงกลุ่มอาการ POEMS ซึ่งขอบเขตของการแสดงอาการของกลุ่มอาการในแต่ละระบบนั้นมีความคาบเกี่ยวกันระหว่างโรค osteosclerotic myeloma (OSM) โรค Castleman และ POEMS syndrome ด้วยเหตุนี้คณะผู้รายงานจึงได้รายงานตัวอย่างผู้ป่วยหญิงไทยอายุ 68 ปี ตรวจพบน้ำในช่องท้องครั้งแรกต่อม่านน้ำเหลืองโตทั่วตัว ผลชิ้นเนื้อเข้าได้กับโรค Castleman ม้ามโต อาการประสาทอักเสบหลายตำแหน่ง และมีประวัติเส้นเลือดแดงอุดตัน ผู้ป่วยรายนี้ได้รับการวินิจฉัยโรค Castleman และมีอาการของ POEMS ร่วมด้วยซึ่งผู้ป่วยได้รับการรักษาด้วยยาเคมีบำบัดสูตร Cyclophosphamide, Thalidomide และ Dexamethasone (CTD) หลังการรักษาด้วยสูตรการรักษา CTD ไปแล้วสองรอบ พบว่าผู้ป่วยมีน้ำในช่องท้องและขาบวมทั้งสองข้างลดลง

คำสำคัญ : ● POEMS syndrome ● Castleman disease ● Polyneuropathy ● Monoclonal gammopathy
● Ascites

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2563;30:307-13.

Introduction

POEMS (Peripheral Neuropathy, Organomegaly, Endocrinopathy, Monoclonal Gammopathy, and Skin changes) syndrome, also known as osteosclerotic myeloma, Crow-Fukase syndrome, and Takatsuki syndrome¹⁻⁴, is a rare paraneoplastic disease associated with underlying plasma cell dyscrasia⁵. Castleman disease, also known as angiofollicular lymph node hyperplasia, is a rare lymphoproliferative disorder. Approximately 11-30% of patients with POEMS syndrome received a diagnosis with Castleman disease¹⁰. However, several case reports showed controversy in pathogenesis of Castleman disease variants of POEMS that may or may not be associated with a clonal plasma cell dyscrasia⁶⁻⁹.

The pathogenesis of POEMS and Castleman disease variants of POEMS remains unclear. To date, overproduction of vascular endothelial growth factor (VEGF) and interleukin-6 (IL-6), expressed on osteoblast, plasma cell, macrophage, bone tissue, tumor cells, and megakaryocytes/platelets has been proposed.⁹

The POEMS syndrome is associated with multiple organ injury such as extravascular volume overload, polyneuropathies, papilledema, organomegaly, thrombosis etc.^{1,3,9} As a result, making an early diagnosis is challenging. Herein, we report a patient with Castleman disease variant of POEMS presenting rare clinical manifestations including new onset ascites and history of arterial thrombosis.

Case report

A 68-year-old Thai female was admitted for an evaluation of generalized lymphadenopathy together with a new onset of ascites, hepatosplenomegaly, and polyneuropathy.

Approximately 7 years prior to admission (PTA), the patient began to develop numbness at both feet without other neurological symptoms. Three years PTA, she had progressive numbness and weakness at all extremities and was diagnosed with chronic inflamma-

tory demyelinating polyneuropathy (CIDP) confirmed by electromyography. Two and one half years PTA, she developed right-sided hemiparesis and was diagnosed with acute ischemic stroke confirmed by noncontrast CT brain scan. Approximately 10 months later, she had fully recovery from right hemiparesis after rehabilitation therapy. Seven months PTA, she developed progressive polyneuropathy, abdominal distension, bilateral legs edema, and lymphadenopathy at the right groin. She had primary hypothyroidism treated by L-thyroxine for 3 years.

The physical examination revealed frank ascites, hepatosplenomegaly, pitting edema on both legs, polyneuropathy with hyporeflexia at all extremities, papilledema of both eyes, and 3 cm. rubbery consistent, moveable and not tender lymphadenopathy at the right groin

An initial investigation revealed thrombocytosis as shown in complete blood count (Hb 12.8 g/dL, Hct 39.1%, WBC 8.2 x10⁹/L, neutrophil 63.5%, lymphocyte 28.5%, monocyte 6.3%, eosinophil 1%, and platelet 510 x10⁹/L). Her blood chemistry, electrolyte, and serum creatinine were within normal range. The only abnormal liver function test (LFT) was hypo-albuminemia (2.48 g/dL). A monoclonal gammopathy at β 1 zone was detected by serum protein electrophoresis (SPEP). An IgA lambda monoclonal gammopathy was detected by serum immunofixation. The Kappa/lambda light chain ratio was 2.4 (normal range approximately 0.26 to 1.65).



Figure1 Chest X-ray showed bilateral pleural effusion.



Figure 2 A & B CT whole abdomen with contrast (delayed phase) showed hepatosplenomegaly, ascites and osteosclerotic bone lesion at L1 vertebrae.

A computerized tomography of chest and whole abdomen revealed markedly diffused ascites, bilateral pleural effusion, hepatosplenomegaly and multiple enlarged lymph nodes at the bilateral common/internal/external iliac, para-aortic and inguinal regions. Multiple ill-defined osteolytic lesions were observed at the right ilium, right ischium and osteosclerotic lesion at antero-superior aspect of L1 vertebral body. (Figure 2)

Electroneuromyography revealed peripheral neuropathy; mixed sensorimotor, demyelination, and axonopathy.

Inguinal lymph node biopsy was performed and histopathology showed reactive follicular and inter-follicular lymphoid hyperplasia suggesting Castleman disease, hyaline vascular type. Stainings for HHV8 and EBER were negative.

Bone marrow aspiration and biopsy showed normocellular marrow with multi-lineage maturation. No atypical plasma cell and lymphoid infiltration were found.

Finally, the diagnosis of Castleman disease variant of POEMS syndrome was made. She received systemic treatment with cyclophosphamide and dexamethasone (Cy-dex regimen) for 1 cycle then continued treatment with cyclophosphamide (500 mg/m², days 1, 8, 15, 22), thalidomide (50 mg/day, days 1-28) and dexamethasone (20 mg/day, days 1, 8, 15, 22) (CTD regimen). After 2 cycles of CTD regimen, clinical symptoms of ascites and bilateral legs edema improved. Currently, she received

3rd cycle of CTD regimen and has no immediate adverse event from the treatment.

Discussion

POEMS syndrome is a rare paraneoplastic disease and causes multi-systemic disorders that relate to underlying plasma cell disorder.⁹ The diagnosis is based on clinical presentation and laboratory features that require 2 mandatory major criteria, including polyneuropathy and monoclonal gammopathy, 1 of the 3 other major criteria, and 1 of the 6 minor criteria⁹ (Table 1). In several case reports, the diagnosis was delayed as a result from a lack of physician's experience due to a very rare disease presented with multi-systemic disorders. So far, the most common misdiagnosis is chronic inflammatory demyelinated polyneuropathy (CIDP) among patients presenting polyneuropathy. POEMS syndrome has also been reported largely in France, the US, China, and India^{9,11-14}. The prevalence of POEMS syndrome in Japan is approximately 0.3 per 100,000¹⁵. POEMS syndrome should be distinguished from Castleman disease variants of POEMS syndrome, in which clonal plasma cell dyscrasia is undetected in bone marrow^{8,9}.

Castleman disease, also known as angio-follicular lymph node hyperplasia, is a nonclonal lymphoproliferative disorder. It was first described by Dr. Benjamin Castleman in the 1950s. The diagnosis of Castleman

Table 1 Criteria for the diagnosis of POEMS syndrome

Mandatory major criteria	1. Monoclonal plasma cell-proliferative disorder (almost always λ) 2. Polyneuropathy (typically demyelinating)
Other major criteria (one required)	3. Sclerotic bone lesions 4. Castleman disease 5. Vascular endothelial growth factor (VEGF) elevation
Minor criteria (one required)	6. Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy) 7. Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic) 8. Extravascular volume overload (edema, pleural effusion, or ascites) 9. Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangioma, plethora, acrocyanosis, flushing, white nails) 10. Papilledema 11. Thrombocytosis/polycythemia
Other symptoms and signs	Clubbing of fingers, weight loss, hyperhidrosis, pulmonary hypertension/restrictive lung disease, thrombotic diatheses, diarrhea, and low vitamin B12 levels

Modified from Dispenzieri A. *Am J Hematol.* 2017;92:814-29.

disease depends on pathological findings, i.e., reactive proliferation in the lymphoid tissues. Clinical features are divided as localized and multicentric subtypes.¹⁶

Pathogenesis of POEMS syndrome and Castleman disease remains unclear⁹. At presentation, overproduction of VEGF and IL-6 has been proposed. VEGF plays a central role in the pathophysiology of POEMS syndrome but IL-6 is a main pathophysiology of Castleman disease⁸⁻⁹. Excessive production of IL-6 induces a pro-inflammatory cytokine, leading to severe constitutional symptoms and induces the secretion of VEGF. Excessive production of VEGF increases angiogenesis and vascularization which present in the lymph nodes of patients with Castleman disease¹⁷.

We report a patient who presented with all features of POEMS syndrome and Castleman disease, including polyneuropathy, IgA lambda monoclonal gammopathy, pathological lymph node compatible with hyaline-vascular type Castleman disease, sclerotic bone lesion, splenomegaly, pleural effusion, ascites, bilateral legs edema, hypothyroidism, papilledema, and thrombocytosis. Our patient fulfilled 2 mandatory major criteria, 2 other major criteria, and 5 minor criteria. History of ischemic stroke is a very rare thrombotic complication of POEMS

syndrome. We can differentiate our patient's diagnosis from other clonal plasma cell disorders by the presence of less than 5% immature plasma cells in bone marrow biopsy and no evidence of extramedullary plasmacytoma.

Approximately 10-30% of patients with POEMS have co-existing Castleman disease^{8,9,17}. Clinical presentations of Castleman disease are diverse and range from B-symptoms, generalized lymphadenopathy, various autoimmune symptoms to a frank POEMS syndrome^{9,18}. The spectrum of disease may overlap between osteosclerotic myeloma (OSM), Castleman disease, and POEMS syndrome (Figure 3).^{9,18} To date, the association between Castleman

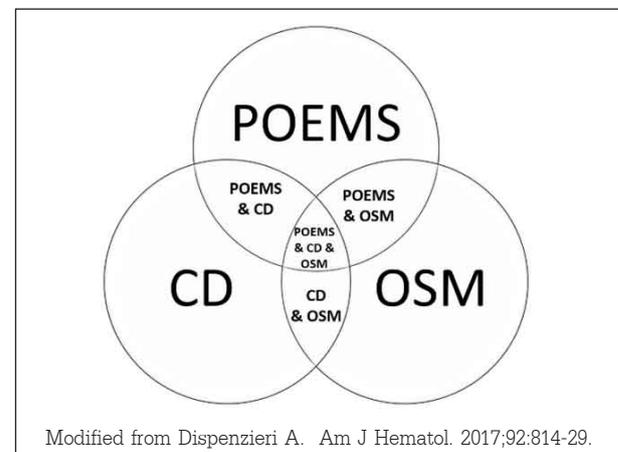


Figure 3 Spectrum of disease: osteosclerotic myeloma (OSM) to POEMS to Castleman disease (CD).

disease and POEMS syndrome is not fully understood¹⁸; however, overproduction of IL-6 and VEGF plays a central role in the pathophysiology of both diseases.^{5,8,9,17} Among patients with Castleman disease variant of POEMS, peripheral neuropathy is typically mild or absent, whereas patients with POEMS have a severe progressive polyneuropathy with marked motor and sensory component^{9,17,18}. The classification between standard POEMS syndrome and Castleman disease variant of POEMS depends on peripheral neuropathy and clonal plasma cells. Without both of peripheral neuropathy and clonal plasma cells, patients can be classified as Castleman disease variant of POEMS if they have other POEMS features.⁹

Treatments of POEMS syndrome and Castleman disease variant of POEMS should differ. The treatment of POEMS syndrome can be divided in 2 targets: targeting the underlying clone and targeting the osteosclerotic bone lesion^{8,9}. If the bone marrow study does not show clonal plasma cell, radiation therapy is a preferred strategy. In other words, when clonal plasma cells are detected, systemic therapy is a preferred strategy (Figure 4)^{8,9,17}. In case of POEMS syndrome, systemic therapy regimens using multiple myeloma and AL amyloidosis are advised⁹. Other promising treatments including lenalidomide, thalidomide, bortezomib, anti-VEGF, anti-TNF, and anti-IL6 antibodies reported effectiveness.^{8,12,14-17} In this case, Castleman disease variant of POEMS differs in treatment strategy. Anti-IL6 antibodies and rituximab are recommended frontline treatments for the case of Castleman disease variant

of POEMS.^{8,9,17} Instead of using anti-IL6 antibodies or rituximab as the first-line therapy, we chose CTD regimen for our patient because she could not access to these antibodies.

In conclusion, discrimination between POEMS syndrome with Castleman disease and Castleman disease variant of POEMS syndrome depends on clinical presentations, laboratory investigations, and histopathology. The diagnosis of POEMS syndrome requires polyneuropathy and monoclonal gammopathy. On the contrary, the Castleman disease variant of POEMS syndrome lacks evidence of clonal plasma cells and polyneuropathy; however, many of other features of POEMS syndrome are presented.

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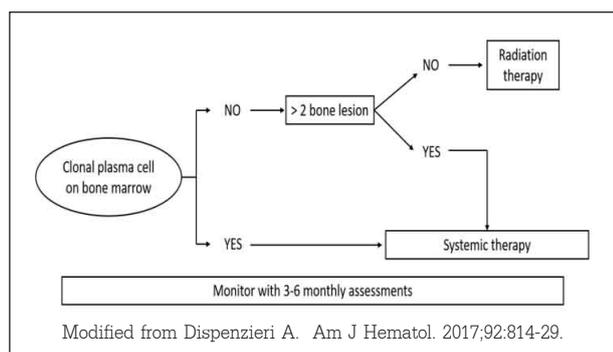


Figure 4: Algorithm for the treatment of POEMS syndrome

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