Six-year course of POEMS Syndrome: a case report

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ABSTRACT

We reported a case of polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome diagnosed 6 years after the onset of the initial symptoms, when all the typical features had finally developed. The patient was a 54-year-old woman who initially presented with tonsillitis and enlarged cervical lymph nodes, and was treated with tonsillectomy and lymph node resection. Three years later, she presented with recurrent cervical lymphadenopathies (diagnosed as Castleman’s disease), multiple osteoblastic lesions, and weakness of both lower extremities. After another three years without adequate treatment, the patient showed progressive limb weakness (which proved to be polyneuropathy), generalized edema, splenomegaly, and hypertrichosis. We performed serum electrophoresis, and its findings indicated immunoglobulin G (IgG) monoclonal gammopathy, which finally established a diagnosis of POEMS syndrome. In this report, we provide a brief review of POEMS syndrome and a critical retrospective evaluation of the delay in diagnosis of this patient.

POEMS syndrome is a monoclonal plasma cell proliferative disorder (M), with combination of peripheral neuropathy (P) and other paraneoplastic features in multiple organs or systems, such as organomegaly (O), endocrinopathy (E), skin changes (S)—that is, POEMS—osteosclerotic lesions, papilledema, edema, effusions, ascites, and thrombocytosis. This syndrome has a chronic disease course, and its presentation is probably due to the overproduction of pro-inflammatory cytokines in the plasma cells [1]. Although several studies reported about the POEMS syndrome previously, including a large series of study containing 99 patients [2], these literatures emphasized on the overall clinical, laboratory, and image presentation. The evolution of tissue changes and clinical course of POEMS syndrome are not well-described. Herein, we reported a case with the typical presentations of POEMS syndrome, focusing on the evolution of the disease and the imaging presentations. We also performed a review of the literature regarding POEMS diagnostic criteria, and indicated the major conditions identified in differential diagnoses for the syndrome.

CASE REPORT

A 54-year-old woman presented to our institution with dysphagia for 2 weeks and left neck swelling for 5 years. She reported no significant medical history. Physical examination revealed an enlarged left tonsil, as well as elastic, moveable, and non-tender masses in the left upper neck. She denied weight loss, neurologic deficit, fever, or recent airway infection.

Computed tomography (CT) of the head and neck confirmed the presence of an enlarged, enhanced left tonsil, as well as elastic, moveable, and non-tender masses in the left upper neck. She denied weight loss, neurologic deficit, fever, or recent airway infection.

The patient thus received left tonsillectomy and resection of the enlarged lymph nodes. The pathology report revealed chronic tonsillitis with granulated tonsil tissue, and follicular hyperplasia with progressive transformation of germinal centers (PTGCs) of the lymph nodes. No evidence of malignant or premalignant features was found in all the resected specimens. After the surgery, the patient was followed up regularly at the outpatient clinic of our hospital for a year and no apparent evidence of tumor recurrence was noted.
Three years post-surgery, the patient returned to our institution, reporting progressive bilateral lower extremity weakness of one-year duration. Physical examinations revealed recurrent masses in the left lower neck, but no tonsil involvement. A CT scan of the head and neck showed multiple enlarged lymph nodes in the left neck (Fig. 2a) and multiple newly appearing osteoblastic lesions in the cervical vertebrae (Fig. 2b). Magnetic resonance imaging (MRI) of the lumbar spine was performed to investigate the lower limb weakness. It revealed a moderate degree of degenerative spinal stenosis, and multiple osteoblastic nodules with intermediate to low signal intensity on both T1-weighted and T2-weighted images (Fig. 3a-3b). Laboratory complete blood count investigation revealed thrombocytosis, with a platelet count of 896,000/μL, whereas the other value of blood count are within normal limit.

We then performed an excisional biopsy of the cervical lymph nodes, as we suspected metastatic lymphadenopathy and vertebral tumors. The pathology report indicated follicular hyperplasia with interfollicular plasmacytosis of the lymph node, suggesting plasma cell-type Castleman's disease. After the biopsy procedure, however, the patient was lost to follow-up at our hospital.

Three years elapsed, and the patient presented to our institution again with generalized edema and progressive bilateral lower limb weakness. Physical examination revealed hypertrichosis on both thighs. Subsequent abdominal CT study showed splenomegaly, ascites (Fig. 3c-3d), progressive enlargement of the left neck masses, and osteoblastic lesions in the vertebrae. Nerve conduction velocity (NCV) and electromyography (EMG) studies reported diffuse sensorimotor polyneuropathy of all limbs. Electrophoresis of the serum revealed immunoglobulin g (IgG) λ monoclonal gammopathy. The combined information from clinical, imaging, and laboratory studies over six years allowed us to establish a diagnosis of POEMS syndrome in this patient.

The patient received chemotherapy and was followed up regularly at the outpatient clinic for one year. The disease has stabilized during this period.

**DISCUSSION**

POEMS syndrome represents a constellation of polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes. Although the syndrome was first described by Crow in 1956 [3], the acronym "POEMS" was formally suggested in 1980 [4]. POEMS syndrome is rare, and its actual prevalence is unclear. According an investigation of 99 patients in 2003, the median age is 51 years, and the prevalence among men is higher than that among women (63:37) [2].

The etiology of POEMS syndrome is unclear. It is considered a paraneoplastic syndrome resulting from an underlying plasma cell proliferative disorder. Chronic overproduction of pro-inflammatory and other cytokines (e.g., vascular endothelial growth factor), probably by plasma cells, seems to play an important role in the pathogenesis of the clinical symptoms. The manifestations of microangiopathy, generalized edema, pleural effusions, increased vascular permeability, neovascularization, polyneuropathy, pulmonary hypertension, leukocytosis, and thrombocytosis may result from the effects of these cytokines [5].

Our patient initially presented with tonsillitis and enlarged cervical lymph nodes with PTGCs. Lymph nodes with PTGCs indicated a reactive status caused by non-specific etiologies. Enlarged lymph nodes, caused by either non-specific reactive change or Castleman’s disease, are one of the presentations of POEMS syndrome. That being said, no previous literature reported the relationship between tonsillitis and POEMS syndrome, and thus it is unclear whether our patient’s tonsillitis and reactive lymph nodes were merely incidental episodes, or truly represented the initial presentations of POEMS syndrome.
The long clinical course in our case provides an example of how POEMS syndrome may develop from ambiguous clinical manifestations (i.e., tonsillitis and reactive cervical lymph nodes), to more clear yet inadequately specific symptoms and signs (bilateral weakness of lower extremities, plasma cell type Castleman’s disease, sclerotic bone lesions, and thrombocytosis), and eventually to the accurate diagnosis of the disease with the additional manifestations of fluid overload (ascites, generalized edema), 4-limb polyneuropathy, organomegaly, and skin change (hypertrichosis).

The diagnosis of POEMS syndrome is made according to the criteria revised by Dispenzieri in 2007 [6], including two mandatory major criteria, three major criteria, and several minor criteria (Table 1). The mandatory major criteria include polyneuropathy and monoclonal plasma cell proliferation; the major criteria include sclerotic bone lesions, Castleman’s disease, and elevated levels of vascular endothelial growth factor (VEGF); and the minor criteria include organomegaly, extravascular volume overload, endocrinopathy, specific skin lesion, papilledema, and specific hematologic changes. A defined diagnosis can be established when the patient meets both of the mandatory major criteria, at least one of the three major criteria, and at least one of the six minor criteria. Our patient presented with polyneuropathy, IgG λ monoclonal gammopathy, multiple sclerotic bone lesions, multicentric Castleman’s disease, splenomegaly, hypertrichosis, and thrombocytosis, which were compatible with the diagnostic criteria of POEMS syndrome.

Since not all features are required to make the diagnosis, several retrospective series and case reports have investigated the clinical presentation of POEMS syndrome. Table 1 also illustrates the frequency of respective clinical features in POEMS syndrome reported in six of the largest series [7]. Except for polyneuropathy and

Figure 2

Figure 2. A post-contrast enhanced head and neck CT image in the coronal view three years after initial treatment. a. Soft tissue window revealed multiple enlarged cervical lymph nodes in level III-IV of the left neck (thick arrow). b. and c. Bone window showed multiple new osteoblastic nodules (thin white arrows), which were not found in the previous head and neck CT.
POEMS syndrome

monoclonal plasma cell proliferation, which are the mandatory diagnostic features of POEMS syndrome, almost all of the patients studied presented with osteosclerotic lesions. Symptoms showing a high incidence also included organomegaly, endocrinopathy, and specific skin changes.

Some presentations of POEMS syndrome can be revealed using imaging studies, including the bone lesions, hepatomegaly, splenomegaly, enlarged lymph nodes, and signs of fluid overload (pleural effusion, ascites, and generalized edema). Generally, only some of these features are revealed simultaneously using image studies, except in the late stage of the disease. In addition to metastasis, the combination of enlarged lymph nodes and osteoblastic lesions is a good diagnostic clue indicating POEMS syndrome, according to Bonekamp et al [8].

There is not yet a standard treatment for POEMS syndrome. The choice of treatment strategy depends upon whether the patient has limited or widespread bone lesions [9]. For patients with widespread bone lesions, as the patient reported here, systemic chemotherapy with agents similar to those used for multiple myeloma is the preferred treatment. Autologous hematopoietic cell transplantation can also be considered for younger patients. On the other hand, for patients with limited disease, usually defined as fewer than 3 solitary osteosclerotic myelomas, irradiation therapy at a dose of 40 to 50 Gy is the recommended treatment.

The overall median survival time of POEMS syndrome is 13.7 years. Patients with limited bone lesions who receive irradiation therapy have remarkably better survival rates: a 97% 4-year overall survival rate and a 52% 4-year failure-free survival rate, according to the Mayo Clinic series. For patients who present with clubbed fingers or extravascular volume overload, however, the median survival drops to 2.6 and 6.6 years, respectively [7].

One of the important conditions in differential diagnoses of POEMS syndrome is multiple myeloma, especially the osteoblastic variant. The bone lesions of POEMS syndrome can be solitary or multifocal and most present either as a pure osteoblastic (47%) or a mixed osteoblastic and osteolytic pattern (51%). In contrast, only 1% to 8% of multiple

Figure 3. Magnetic resonance imaging (MRI) characteristics of bone nodules in the lumbar spine. A sagittal T1-weighted image (a), and a sagittal T2-weighted image (b), revealed multiple intraosseous low signal intensity nodules. Grade I spondylolisthesis of L5-S1 and protruded intervertebral discs between L3-4, L4-5, and L5-S1 were also noted. A post-contrast enhanced abdominal CT image (c and d) in the axial view revealed generalized subcutaneous edema, splenomegaly, and ascites in the pelvic cavity.
myeloma patients have osteosclerotic lesions [8]. Further, the presence of anemia, hypercalcemia, renal failure, and pathologic fractures may be observed in patients with multiple myeloma, but seldom occur in patients with POEMS syndrome.

Castleman’s disease is one of the presentations of POEMS syndrome. The morphologic classification of Castleman’s disease includes unicentric and multicentric forms; the histopathogenetic classification comprises hyaline vascular, plasma cell, and human herpes virus 8–associated types. About 15% of patients with POEMS syndrome present Castleman’s disease, usually the multicentric form [8]. Some patients may present with Castleman’s disease and many clinical features of POEMS syndrome without the monoclonal plasma cell proliferation or polyneuropathy, which are the mandatory diagnostic criteria for classic POEMS syndrome. The term Castleman’s disease variant of POEMS syndrome is used to describe this condition. Distinguishing between Castleman’s disease and classic POEMS syndrome is important due to their different treatment strategies [9].

Because the patient in this report had protruded discs in her lumbar spine, it can be difficult to determine whether her lower limb weakness was caused by radiculopathy or polyneuropathy. The symptoms of radiculopathy usually occur unilaterally with the involved area compatible with the dermatomal and myotomal distribution of the spinal nerve. In contrast, polyneuropathy often has symmetrical involvement, starting from the peripheral portion of the limb with sock distribution, which progresses ascendingly. Nerve conduction velocity and EMG studies can help to confirm the presence of polyneuropathy [10].

POEMS syndrome is thought to be a disease with a chronic course. The diagnostic accuracy depends on the presented manifestations of the affected subject. Because of the slow progression of the disease, the characteristic symptoms leading to the accurate diagnosis of POEMS may not appear simultaneously. This may mislead clinicians to diagnosis diseases that mimic POEMS, such as multiple myeloma, Castleman’s disease, or radiculopathy. Awareness of the classic clinical and image presentations of POEMS syndrome is essential to avoid delayed diagnosis. On image studies, the osteoblastic myeloma and the enlarged lymph nodes are the most important diagnostic hints that indicate POEMS syndrome. The retrospective nature of this case report indicates that further evaluation of the other clinical features of POEMS syndrome could be undertaken earlier when these two findings are present.

| Table 1. Diagnostic Criteria of POEMS Syndrome and Incidence of These Findings Based on 6 Large Retrospective Series |
|--------------------------------------------------|---------------------|
| **Mandatory major criteria (both required)**     | **Incidence %**     |
| Polyneuropathy                                   | 100                 |
| Monoclonal plasma cell proliferative disorder   | 100                 |
| **Other major criteria (one required)**          |                     |
| Sclerotic bone lesions                           | 27-97               |
| Castleman’s disease                              | 11-25               |
| Elevated levels of vascular endothelial growth factor (VEGF) | N/A               |
| **Minor criteria (one required)**                |                     |
| Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy) | 45-85               |
| Extravascular volume overload (edema, pleural effusion, or ascites) | 29-87               |
| Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic)* | 67-84               |
| Skin change (hypermigmentation, hypertrichosis, glomeruloid hemangioma, plethora, acrocyanosis, flushing, or white nails) | 68-69               |
| Papilledema                                       | 29-64               |
| Thrombocytosis or polycythemia                   | 54-88               |

* An endocrine disorder other than diabetes or hypothyroidism is required since these two disorders are common in the general population

* N/A: not available

REFERENCES