POEMS syndrome with vascular transformation of the lymph node sinuses: A case report

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Abstract. POEMS syndrome is a rare multisystem disorder associated with the clinical signs of polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes. However, there is often a delay in the diagnosis due to a lack of overall consideration of the symptoms collectively. For this reason, POEMS syndrome is frequently mistaken for other diseases, such as chronic inflammatory demyelinating polyneuropathy. The present study reports the case of a 40-year-old female patient, who presented with a progressive lack of strength in the lower limbs and a unilateral cervical lump. The patient's enlarged cervical lymph nodes were mistaken for local hemangioma. However, subsequently POEMS syndrome with vascular transformation of the lymph node sinuses (VTS) was diagnosed. The patient received glucocorticoid treatment (20 mg prednisone acetate, daily), which is ongoing. The most recent follow-up examination revealed that the patient's strength had improved and at the time of writing the patient remained alive. The study discusses the clinical manifestations, auxiliary examinations and reason for the misdiagnosis. Hematoxylin and eosin staining and cluster of differentiation 31 immunostaining were adopted to identify the VTS. To the best of our knowledge, this is the first report of POEMS syndrome with VTS.

Introduction

POEMS syndrome, a term coined by Bardwick in 1980 (1), is a rare multisystem disorder associated with the clinical signs of polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes (2). However, there is often a delay in diagnosis due to a lack of overall consideration of the symptoms (3). Early diagnosis is critical for POEMS patients to increase survival and reduce the morbidity rate. However, POEMS syndrome is frequently mistaken for other diseases due to its rarity and complex multisystemic manifestations, such as chronic inflammatory demyelinating polyneuropathy (CIDP); it has been reported that ~60% of patients were misdiagnosed as CIDP (4). POEMS treatment is similar to that administered for patients with suspected myeloma. Radiation therapy is administered for isolated plasma cell tumors. At present, no placebo-controlled studies investigating POEM treatments have been performed, however, systemic treatment may be effective. Currently, the main treatments for POEMS syndrome are limited to the administration of alkylating agents, such as cyclophosphamide, in combination with peripheral blood stem cell transplantation or lenalidomide combined with dexamethasone (4). The estimated median survival time of patients with POEMS syndrome is 14 years (4).

Vascular transformation of the lymph node sinuses (VTS) is a histopathological entity first described by Haferkamp *et al* (5) in 1971. Obstruction of the efferent lymph node vessel or lymph node venous flow is believed to play an important pathogenetic role in the development of VTS (6). The present study reports the case of a patient with enlarged cervical lymph nodes, initially misdiagnosed as local hemangioma. The clinical manifestations, diagnostic procedure, auxiliary examinations and reason for misdiagnosis are also discussed.

Case report

On July 29th, 2013, a 40-year-old female presented to Tianshi Shangke Hospital (Lishui, China) with a cervical lump, which was soft without tenderness. An enhanced computed tomography scan of the neck revealed multiple enlarged venous blood vessel masses in the right side of supraclavicular area and upper mediastinum. On September 28th, 2013, the patient was admitted to Changhai Hospital (Shanghai, China) with progressive lack of strength in the lower limbs and a unilateral cervical lump which had been apparent for 8 months. Prior to admission to Changhai Hospital, the patient had experienced thigh numbness. However, as walking, urination, squatting and standing without assistance were unaffected, no special

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Table I. Symptoms relevant to POEMS in the present patient.

Symptom	Evidence
Polyneuropathy	Progressive lack of strength and numbness in the lower limbs
Organomegaly	Lymph node enlargement
Endocrinopathy	Pitting edema in the ankles[a]. Prolactin level of 38.44 μg/l (normal range, 1.39-24.20 μg/l) and adrenocorticotropic hormone level of 75.78 pmol/ml (normal range, 4.00-22.00 pmol/ml)
Monoclonal gammopathy	Bone marrow puncture revealed a predominance of lymphocytes
Skin changes	Skin color of the patient deepened as the disease progressed

[a]This symptom was potentially induced by vascular endothelial growth factor (VEGF), which is known to target endothelial cells and induce a reversible and rapid increase in vascular permeability. Therefore, a high level of VEGF can lead to edema.

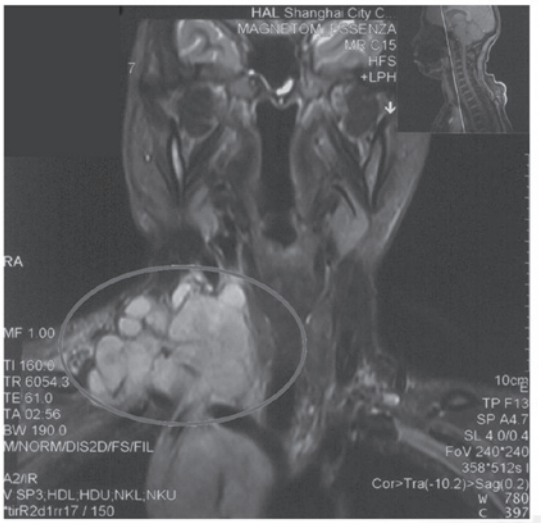

Figure 1. Enhanced magnetic resonance imaging scan showing a unilateral lesion in the cervical region (circle).

treatment had been offered. The symptoms persisted and subsequently progressed; 4 months after the onset of thigh numbness, the patient could no longer walk unaided. No headaches, photophobia, incontinence or coughing were reported throughout. The patient's medical history included no underlying health problems. Upon neurophysical examination on September 28th, 2013, motor strength and deep tendon reflexes were weak. Motor strength was rated at grade 4 (according to the Medical Research Council's Scale for Muscle Strength) (7) in the lower extremities, and soft pitting edema was observed in the ankles. Atrophy of the calf and thenar muscles and steppage gait were also present. On September 30th, 2013, possible metastases with a rich blood supply were observed on an enhanced magnetic resonance imaging scan of the region (Fig. 1). However, an ultrasound scan performed on the same day showed enlargement of the cervical lymph nodes. Subsequently, local hemangioma was misdiagnosed. On October 11th, 2013, a lumbar puncture was performed for a presumed diagnosis of peripheral neuropathy. Cerebral spinal fluid analysis showed an elevated protein level of 1.68 g/l (normal range, 0.15-0.45 g/l), a normal white blood cell count of 1/μl (normal, ≤5/μl), no malignant cells and a normal glucose level. A suspected diagnosis of CIDP was concluded. However, on October 12th, 2013, the patient's husband reported that the patient's skin color had become deeper as the disease had progressed.

Consequently, a series of auxiliary examinations were performed on the same day, concentrating on symptoms associated with POEMS syndrome, was performed. Table I shows the POEMS syndrome-related symptoms identified in the present patient. This included a predominance of lymphocytes observed on a bone marrow smear (Fig. 2).

To clarify the characteristics of the mass, a biopsy of the superficial lymph node was performed on October 23rd, 2013 (Fig. 3A). This was diagnosed as VTS (Fig. 3B and C) by hematoxylin and eosin staining and CD31 immunostaining as CD31 staining was observed in the blood vessels of the lymph node sinuses (Fig. 3D and E). However, the biopsy result did not account for all the symptoms that the patient possessed, such as the weakness in the lower limbs. The patient was administered glucocorticoids (20 mg prednisone acetate, daily). At the most recent follow-up examination, in December 2014, a slight improvement in the patient's symptoms was observed and at the time of writing the patient remained alive.

Discussion

POEMS syndrome is a rare condition characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin lesions (8). The diagnosis is based on a combination of clinical and laboratory features, and misdiagnosis may occur if the symptoms are not considered collectively. In the present study, the patient's clinical characteristics supported the diagnosis of POEMS syndrome based on the evidence described in Table I. It is often challenging to correctly diagnose this condition initially, as all of the typical features may not appear concurrently.

The mechanism of POEMS syndrome remains unclear (9), however, it has been reported that overproduction of vascular endothelial growth factor (VEGF) may be of great importance in the pathogenesis of polyneuropathy, due to the induction of angiogenesis. It has also been demonstrated that VEGF levels are higher in patients with POEMS syndrome compared with normal controls (10). Theoretically, these angiogenic factors may enter the regional lymph nodes and induce the changes associated with VTS.

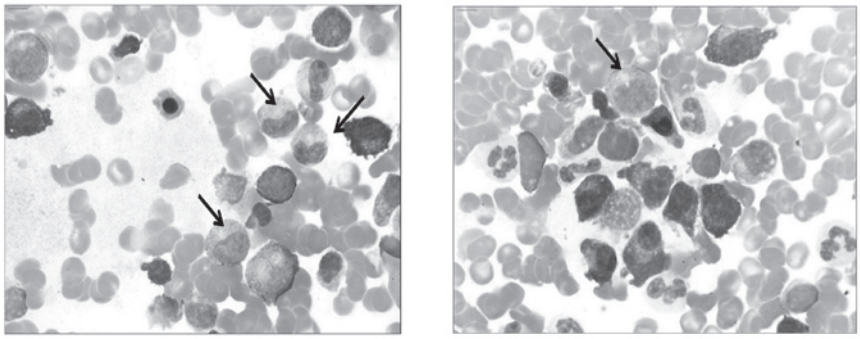

Figure 2. Bone marrow smear; arrows indicate the increased plasma cells (magnification, x100).

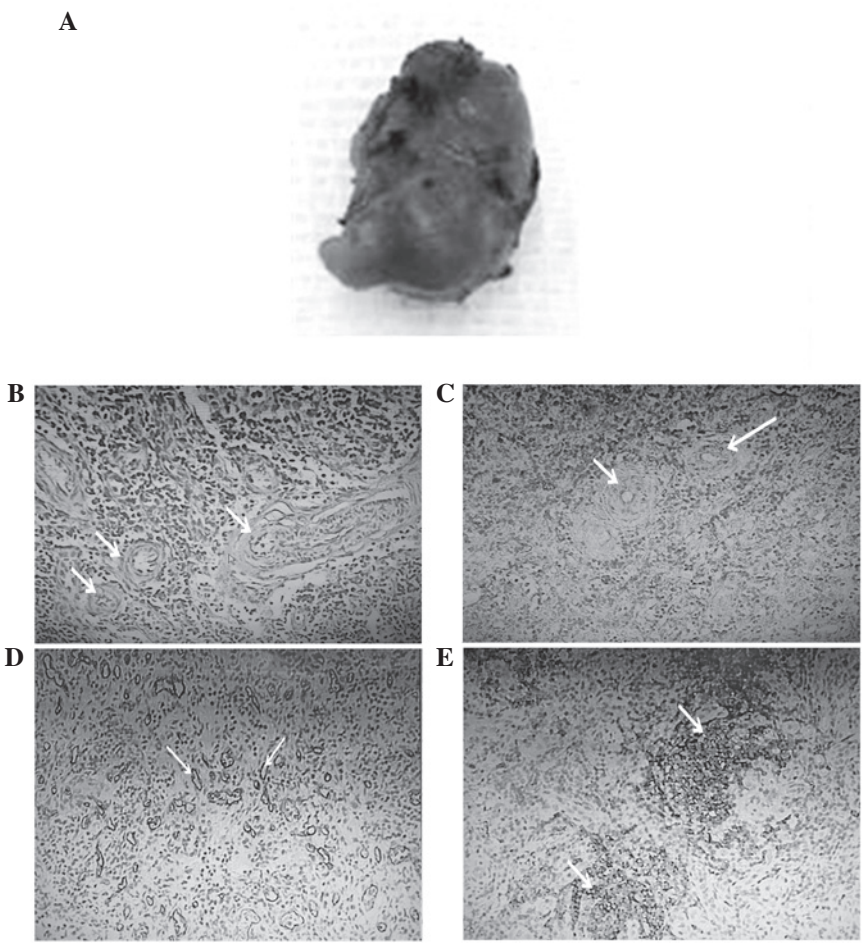

Figure 3. (A) Biopsy specimen of the diseased cervical lymphoid tissue, 0.5x1.1x2.1 cm in size. (B and C) Vascular transformations of the lymph node sinuses (arrows; hematoxylin and eosin stain; magnification, B, x40 and C, x10). (D and E) Cluster of differentiation 31 immunostaining of the vascular transformation of the lymph node sinuses (arrows) (magnification, D, x4 and E, x40).

VTS is a benign lymph node vascular hyperplastic lesion; although it is not a true tumor, it may be confused with cancerous tumors or metastases. VTS is considered to occur secondary to obstruction of the lymph node venous or efferent vessels (11,12). In the present case, abnormal clonal plasma cell proliferation, characteristic of POEMS, was identified in the bone marrow, suggesting a potentially severe outflow problem in the lymph circulation.

From a diagnostic perspective, a lump in the neck region may not appear to be associated with POEMS syndrome, a systemic disease; therefore, the monistic nature of this case was not initially apparent. When the case was considered as a whole, together with the local aspects, in the current patient, it was deduced that VTS of the bilateral cervical region was a regional lesion induced by the pathological changes associated with POEMS syndrome.

In conclusion, the current study presents a rare association of cervical lymph node enlargement due to VTS in a patient with POEMS syndrome which, to the best of our knowledge, has not previously been reported. This case highlights the

importance of detecting VEGF expression in patients with POEMS syndrome and we recommend that patients are followed up closely.

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