CASE REPORT

Polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes (POEMS syndrome): a paraneoplastic syndrome

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Abstract

POEMS syndrome (Crow-Fukase syndrome) is a rare paraneoplastic disorder. It is characterized by peripheral neuropathy, elevated vascular endothelial growth factors (VEGFs), monoclonal gammopathy, sclerotic bone lesions and Castleman disease. Other important clinical features are organomegaly, edema, ascites, papilledema, endocrinopathy, skin changes and thrombocytosis. A high index of suspicion, a detailed clinical history and examination followed by appropriate laboratory investigations like VEGF level, radiological skeletal survey and bone marrow biopsy are required to diagnose POEMS syndrome. We report a case of POEMS syndrome who presented with insidious onset, progressive sensorimotor polyneuropathy, pedal edema, ascites, hepatomegaly, skin changes and hypothyroidism. X-ray of the pelvis showed osteosclerotic lesions. Immunoelectrophoresis using the immunofixation method revealed lambda chain monoclonal gammopathy. The patient was given radiotherapy, followed by a combination therapy of melphalan and dexamethasone. We emphasize the importance of recognizing a challenging diagnosis of a rare disease, which is shown to be treatment responsive.

INTRODUCTION

The POEMS syndrome is a rare paraneoplastic disorder of plasma cells, which was first described in 1956 by Crow and later by Fukase in 1968 [1]. The acronym ‘POEMS’ was given by Bardwick and co-workers in 1980 on the basis of five characteristic features: peripheral polyneuropathy, lambda-chain monoclonal gammopathy, organomegaly, skin changes and endocrinopathy [1]. It is more prevalent in men (male-to-female ratio of 2.5 : 1) and usually manifests in fifth to sixth decades of life. Its pathophysiology is poorly understood.

CASE REPORT

A 40-year-old male presented with progressive weakness, tingling and numbness in lower limbs for 2 years. He noted lower limbs swelling and skin changes over the face, hands and feet for 1 year. He also gave a history of erectile dysfunction and loss of libido for past 6 months. There was no history of bone pain or drug abuse. He had no previous history of tuberculosis, diabetes mellitus or hypertension.

On physical examination, bilateral pedal edema was present (Fig. 1a and b). Skin was thickened and hyperpigmented over...
the face, fingers of the hands and shin (Fig. 1a–d). Bilateral gynaecomastia and testicular atrophy were also present. Abdominal examination showed hepatomegaly and ascites. Higher mental functions were normal. Examination of the fundi revealed bilateral papilledema, but otherwise cranial nerve examination was unremarkable. Muscle power in upper limbs was normal and predominant distal weakness [Medical Research Council (MRC) grade 4/5 at hip joints and 4-/5 at ankle joints] was present in lower limbs. Deep tendon reflexes in the upper limb were diminished (+1) including biceps, triceps and supinator and absent in lower limbs (knee and ankle). All modalities of sensations including pain, touch, temperature, vibration and joint position senses were impaired below knees. Romberg’s sign was positive.

Full blood count, liver and renal function tests, muscle enzymes (creatine phosphokinase), serum ferritin and vitamin B12 level were normal. Serum total protein was 7.1 g/dl, albumin 3 g/dl, globulin 4.1 g/dl and A : G ratio 1 : 1.3. Fasting and postprandial blood sugar levels were normal. Thyroid function tests revealed hypothyroidism (TSH level: 16.62 mIU/l and normal TSH level 0.4–4 mIU/l). Luteinizing hormone and testosterone levels were 15 (1.8–8.6 IU/l) and 111 (300–1000 ng/dl), respectively. Antinuclear antibody, rheumatoid factor, enzyme-linked immunosorbent assay test for human immunodeficiency virus, serology for hepatitis B and C were negative. Abdominal ultrasonography showed hepatomegaly (16 cm), moderate ascites and multiple enlarged mesenteric lymph nodes along the iliac vessels. Fine-needle aspiration cytology of mesenteric lymph node was inconclusive. Ascitic fluid was an exudate (SAAG < 1.1). Ascitic fluid adenosine deaminase level was normal and no malignant cells were observed. Abdominal ultrasonography showed hepatomegaly (16 cm), moderate ascites and multiple enlarged mesenteric lymph nodes along the iliac vessels. Fine-needle aspiration cytology of mesenteric lymph node was inconclusive. Ascitic fluid was an exudate (SAAG < 1.1). Ascitic fluid adenosine deaminase level was normal and no malignant cells were observed.

Neurophysiological studies showed sensorimotor demyelinating and axonal type polyneuropathy in both upper (median and ulnar nerves) and lower limbs (peroneal, tibial and sural nerves). Cerebrospinal fluid (CSF) analysis was normal. X-ray of the pelvis showed multiple osteosclerotic lesions involving head of left femur and right iliac crest (Fig. 2). X-ray of the skull and spine was normal. The serum protein electrophoresis showed gamma globulinemia with no monoclonal M spike. Immuno-electrophoresis using the immunofixation method revealed a monoclonal IgG lambda band. The bone marrow biopsy from right iliac crest showed large atypical plasma cells in the range of 6–8% (Fig. 3). The patient was diagnosed with POEMS syndrome. He was given radiotherapy, followed by a combination therapy of melphalan (16 mg/m²) and dexamethasone. At 6 months and 1-year follow-up, the patient has no worsening of symptoms.

DISCUSSION

The POEMS syndrome is a rare, multiple system disorder, characterized by acronym: polyneuropathy (P), organomegaly (O), endocrinopathy (E), monoclonal or M-protein band (M) and skin changes (S). The diagnosis of POEMS syndrome is confirmed when both the mandatory major criteria (polyneuropathy and monoclonal plasma cell-proliferative disorder), one of the three other major criteria [Castleman disease, sclerotic bone lesions and elevated vascular endothelial growth factor (VEGF) level] and one of the six minor criteria (organomegaly, endocrinopathy, skin changes, extravascular volume overload, papilledema and thrombocytosis) are present [2]. The diagnosis of this rare disease is often delayed due to low index of suspicion. It is most commonly mistaken for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

Neuropathy is the most common presentation of POEMS syndrome (>90%) [2]. It is characterized by peripheral, symmetrical, ascending, sensorimotor polyneuropathy. Both demyelinating and axonal polyneuropathy are seen on electrodiagnostic studies as observed in our patient. The mechanism of neuropathy is still not known but the presence of anti-neural antibodies suggests an immune mediated pathology [3]. Endocrine dysfunctions are common in POEMS syndrome (60–80%) [4]. Primary gonadal failure (70%) is the most common endocrinopathy, followed by

Figure 1: Photographs of patient showing pitting edema over the left legs [thick arrow (a)]. Hyperpigmented skin is seen over the lower limbs, hands and face [thin arrows (a), (c) and (d)]. The photograph also showing abdominal distention (b). Free fluid was confirmed by abdominal ultrasonography.
POEMS syndrome

Viscera causing multiple organ dysfunction. However, histopathologic studies of affected organs and nerves do not support the hypothesis of deposition disorder. Increased levels of cytokines interleukin-1 beta (IL-1β), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α) and more specifically VEGF appear to play a pathogenic role [7].

Several studies have shown elevated serum or plasma VEGF levels in the POEMS syndrome. VEGF is a cytokine that increases microvascular permeability, thereby inducing edema, ascites and pleural effusions [8]. Though, serum or plasma VEGF is neither 100% sensitive nor specific for the POEMS syndrome, but it helps in differentiating POEMS syndrome from other plasma cell dyscrasias. It is also useful in monitoring disease activity during follow-up of the patient [9]. Unfortunately, measurement of serum VEGF level was not available at our center.

The patients of POEMS syndrome have solitary or multiple solitary plasmacytomas. Osteosclerotic lesions occur in ~95% of patients [10]. These lesions may be densely sclerotic, lytic with a sclerotic rim or mixed soap-bubble appearance. The bone marrow biopsy often shows clonal plasma cells and hyperplasia or clustering of megakaryocytes [10]. The monoclonal gammapathy is characteristic, which is almost always restricted to lambda-type monoclonal protein. It is found in >95% of patients [9]. It may be rarely found in urine and CSF.

The management of POEMS syndrome depends on whether disseminated bone marrow involvement is present or not [2]. In patients with an isolated bone lesion without clonal plasma cells (solitary plasmacytoma), radiotherapy is the recommended treatment [11]. Systemic therapy is reserved for disseminated bone marrow involvement. A recent study from China showed good results of a combination therapy of alkylating agents (melphan) with dexamethasone [12]. High-dose chemotherapy with peripheral blood stem cell transplant is also effective [13].

In view of multiple organ involvement including predominant demyelinating polyneuropathy, lambda-type monoclonal gammapathy, osteosclerotic bone lesions, extravascular volume overload (edema and ascites), papilledema, multiple endocrinopathies and skin changes, our patient was diagnosed with POEMS syndrome. Other close differential diagnosis such as CIDP, amyloidosis, monoclonal gammapathy of undetermined significance, tuberculosis and hemochromatosis were ruled out with appropriate investigations. The patient was treated with radiotherapy, followed by a combination therapy of alkylating agents, melphanal and dexamethasone.

To conclude, POEMS syndrome is a rare paraneoplastic disorder of plasma cells. The diagnosis is often challenging. A high index of suspicion, a detailed clinical history and examination followed by appropriate laboratory investigations like VEGF level, radiological skeletal survey and bone marrow biopsy are required to diagnose POEMS syndrome.

CONFLICT OF INTEREST STATEMENT
None declared.

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Figure 2: X-ray of the pelvis showing multiple sclerotic lesions over right iliac crest (thin arrow) and one large osteosclerotic lesion (thick arrow) over the neck of left femur.

Figure 3: Bone marrow smear in center reveals one large atypical plasma cell, which has prominent nucleoli and abundant cytoplasm. There is loss of normal nuclear configuration with a fraying border.
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