

POEMS Syndrome: A Case Report from Punjab

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ABSTRACT The present case showed M protein spike with varying type of plasma dyscrasias, ascites, gynaecomastia, impotence and mild acanthosis. POEMS syndrome is a rare multisystem disorder involving polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes. It usually manifests in 5th-6th decade of life with a mean survival period of 8 years. We report a case of a 56 years old male surviving more than 15 years with POEMS syndrome. The pathophysiology and genetics of POEMS syndrome is not well understood. An underlying plasma cell disorder is believed to be responsible for it.

INTRODUCTION

POEMS syndrome is rare multisystem disorder, first described in 1956 by Crow and then in 1968 by Fukase. The name POEMS was given to it by Bardwick and co-workers in 1980 based on its five features, viz., Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy and Skin changes. It is also known as Crow-Fukase Syndrome (Nakanishi et al. 1984); EP Syndrome; Polyneuropathy-organomegaly-endocrinopathy-M protein-skin lesion, Shimpo syndrome (Shimpo 1968); or Takat-Suki syndrome (Bitter et al. 1985). It is more prevalent in men with male to female ratio of 2.5:1 and usually manifests in 5th-6th decades of life (Chan et al. 2006). Its inheritance is uncertain (Winter and Baraitser 2000) and its pathophysiology is also not well understood.

CASE REPORT

A 56 year old male was presented with ascites, anasarca, sensory loss, gradual loss of power in the limbs and hyperpigmentation over the chest. His oedema had started 15 years ago, initiating from feet it slowly had progressed upwards; sometimes it worsened but was partly controlled after hospitalization. Around that time patient also started having gradual sensory and power loss over the extremities. During early stages of manifestation the patient was able to walk with support but was unable to walk when presented. Hyperpigmentation over the chest started as a small spot and then the number and size of the

spots increased. There was a history of sudden onset of impotence, gynaecomastia, respiratory distress and fever. The patient also had history of intermittent claudication, but there was no history of sudden loss in appetite or urinary insufficiency.

Upon examination the oedema was of pitting and the deep tendon sensitivity to painful stimulus was increased. The clubbing was noted in the fingers. The flexion deformities were seen in toes and feet. The hyperpigmented area over the chest was painful to touch and hepatosplenomegaly was also present (Fig.1). The power was grade IV/IV in the upper limbs and III/IV in the lower limbs (Fig. 2). Deep tendon reflexes were absent in the lower limbs and were suppressed in the upper limbs. No lymphadenopathy was seen in the patient.

The X-ray chest showed expanding osteolytic lesion on the sternum in the hilar region and consolidation in the right lower lobe along with the pleural effusion. The CT scan showed large well-developed hypodense lesions in the left frontal lobe and also in the left parietal lobe. Both these lesions were causing dilation of the adjacent sulcal spaces and ipsilateral ventricles. All these symptoms were indicative of encephaloma due to the old infarct.

All the blood tests were normal except for the increase in the platelet count which was 5,67,000. The serum creatinine was mildly increased and the urine showed presence of the albumin (which had been there since the onset of disease). CSF examination showed the presence of globulins. However, the levels of IL-6, VEGF, IL-1 β , TNF- ∞ were not measured in serum or CSF.

In skin biopsy, the epidermis showed irregular thickening with mild acanthosis, many pigment containing melanophages were present in the

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upper dermis and melanin was also present in the keratinocytes. Skin adenexal structures were present in the dermis amidst the collagen bundles. The lymph-node biopsy showed reactive lymphadenitis. The bone marrow taken from the lesion in the sternum was diagnosed as plasmocytoma.

The nerve conduction studies showed reduced conduction in the right peroneal nerve and the right posterior tibial nerve.

The patient had been given prednisolone, endoxain and antibiotics for some time and had also received radiation therapy for the lesion in the sternum; but with poor outcome.

DISCUSSION

POEMS syndrome stands for Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy and Skin changes. All five systems should show symptoms for the absolute diagnosis of POEMS syndrome but there is a great diversity in the symptoms presented by the patients of POEMS syndrome (Soubrier et al. 1994). However, most of the authors agree that at least 3 out of the 5 systems should be involved, of which various combinations have been described. Prognosis of the patients irrespective of the systems involved remains unchanged (Miralles et al. 1992). Our case exhibited typical involvement of all five systems.

Polyneuropathy is the most common symptom (Mullai et al. 2001), which involves both sensory and motor nerves and is bilaterally symmetrical in distribution, it spreads from distal end to proximal end in extremities. Associated cranial and autonomic nerves are not involved. EMG shows signs of both demyelination and axonal degeneration and the deep tendon reflexes may vary (Nakanishi et al. 1984; Miralles et al. 1992). Our case had also reported gradual progress of sensory and motor loss from distal to proximal end. Neuropathologically, segmental demyelination, particularly in the proximal segment of peripheral nerve trunk, is the primary process. Axonal degeneration and marked endoneurial edema are also characteristic for this syndrome so are the focal excessive myelin outfoldings with globular features corresponding to periodicity and paranodal enlargement of myelin (Koike and Soube 2000).

Hepatosplenomegaly was present but lymphadenopathy was absent in our case. Frizzera

et al. (1988) reported that organomegaly involving the spleen and lymph nodes may show normal histology or features of Castleman's disease (giant angiofollicular hyperplasia and multicentric plasma cell variant). The lymph node biopsy in our case showed reactive lymphadenitis.

Many endocrinal problems in the POEMS syndrome e.g., gynaecomastia and impotence in men, and amenorrhea in women are due to estrogen excess. Diabetes, hyperthyroidism, hyperprolactinemia and hypoparathyroidism, adrenocortical insufficiency have also been reported in POEMS syndrome (Gherardi et al. 1991; Mauvais-Jarvis et al. 1998). Gynaecomastia and impotence were present in our case also.

A monoclonal serum protein spike with varying types of plasma cell dyscrasias, was seen in our case. It ranged from a monoclonal gammopathy of unknown significance (MGUS) to plasmacytoma with osteolytic, osteosclerotic, or mixed bone lesions. The immunoglobulin subtypes, as seen in POEMS cases can be IgG or IgA (Bitter et al. 1985; Lacy et al. 1997). A case with Waldenström macroglobulinemia with IgM (Pavord et al. 1996) and another with polyclonal gammopathy (Mullai et al. 2001) have also been reported.

The hyperpigmentation over the chest was noted in the present case. According to Fishel et al. (1988) and Tsai et al. (2001) the skin changes usually observed in POEMS syndrome are hyperpigmentation, lichenification, hypertrichosis, sclerodermoid changes and glomeruloid hemangiomas. However, Calonje et al. (1997) observed that terry nails, clubbing, hyperhidrosis and Raynaud phenomenon may also be present. Skin biopsy may show inflammation, fibrosis, or non-specific changes. Our case showed clubbing, and in the skin biopsy the epidermis showed irregular thickening with mild acanthosis. Many pigment containing melanophages were present in the upper dermis and melanin was also present in the keratinocytes. The skin adenexal structures were present in the dermis amidst the collagen bundles.

The other non-specific symptoms in POEMS syndrome include, papilledema, anasarca, pleural effusion, ascites, fever, renal insufficiency, diarrhoea, generalized aches and pains, thrombocytosis, polycythemia, and vitamin B12 deficiency (Soubrier et al. 1994). A case with proptosis and papilloedema has been reported by Gandhi et al. (2000). Anasarca and ascites were seen in our case also.

The pathophysiology of POEMS syndrome is not well understood but Miralles et al. (1992) believe a plasma cell disorder to be responsible for the development of this syndrome. They suggested that minute changes in the vessel wall



Fig. 1. Hyperpigmented area over chest



Fig. 2. Flexion deformity of lower limbs

that lead to increased vascular permeability is the basic defect. However, the mechanism by which this occurs is unknown. Watanabe et al. (1996) reported significant elevations in vascular endothelial growth factor (VEGF) in such cases. Increase in VEGF has been postulated to lead to enhanced vascular permeability, which allows deposition of plasma cell-derived material; and the stimulated vascular proliferation is believed to result in some of the skin changes that are noted in these patients (Watanabe et al. 1998). A high concentration of VEGF in the platelets of POEMS syndrome cases was reported by Hashiguchi et al. (2000) who observed that it is the aggregation and adhesion of the platelets, containing excess VEGF, to the vascular endothelium that results in excessive physiological activities of VEGF. Michizono et al. (2001) further observed that the circulating levels of matrix metalloproteinases (MMP-1,-2,-3,-9) and tissue inhibitor of metalloproteinases (TIMP-1) were increased in POEMS syndrome patients and that the levels of TIMP-1 and VEGF were strongly related to each other.

The presence of globulins in cerebrospinal fluid was noted in our case. The elevated levels of cytokines, such as interleukin 1 β (IL-1 β), interleukin 6 (IL-6), and tumour necrosis factor- ∞ , (TNF- ∞) in serum have been recorded in most of the patients of POEMS syndrome. The increased levels of IL-6 have also been noted in CSF. The level of IL-6 is used to monitor the response to treatment and progress of disease. However, the serum levels of other growth factors, including epidermal growth factor (EGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF) are not increased in such patients (Soubrier et al. 1997).

POEMS syndrome is associated with Castleman disease and angioma formation, and a role of human herpes virus 8 (HHV-8) has also been postulated; although the early studies have failed to demonstrate any association (Papo et al. 1999).

Prognosis and Treatment

The median survival period for patients with POEMS syndrome is 8 years. The natural course of POEMS syndrome is chronic, with a reported median survival of a decade (8-13.8 y). The morbidity depends on the system and extent of its involvement (Chan et al. 2006). The treatment

consists of radiation and surgical resection of myeloma and bone lesion, a high dose of intravenous immunoglobulin (IVIg) (Koike and Soube 2000), steroids and PUVA for skin lesions in addition to chemotherapy (Schaller et al. 2001). Rovira et al. (2001) and Fujita et al. (2002) reported dramatic improvement in a patient with disseminated disease resistant to chemotherapy, with high dose of therapy (HDT) followed by autologous hematopoietic cell transplantation (AHCT). Physiotherapy is recommended if disability is caused by neuropathy. Imai et al. (2007) demonstrated that autologous peripheral blood stem cell transplantation can improve clinical symptoms and signs due to polyneuropathy in POEMS. The mainstays of therapy for patients with POEMS include irradiation, corticosteroids, and alkylator-based therapy, high-dose chemotherapy with peripheral blood stem cell transplantation (Dispenzieri et al. 2003; Dispenzieri 2005). The clinical remission for one patient was described by Kojima et al. (2006) who received high-dose chemotherapy with autologous CD34⁺-purged stem cells. Similarly clinical remission and correspondingly decreased VEGF serum concentrations of one patient with POEMS syndrome and renal lesions was reported by Sanada et al. (2006) after treatment with high-dose melphalan therapy followed by autologous blood stem cell transplantation.

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