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CASE REPORT

Peripheral Neuropathy: Clinical Diagnosis of POEMS Syndrome and Treatment with Radiotherapy

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ABSTRACT

POEMS syndrome is a rare paraneoplastic syndrome of plasma cell dyscrasia. Since this is a potentially fatal and devastating disease, prompt diagnosis and appropriate treatment is essential. This report is of a young woman who presented with peripheral polyneuropathy that was treated as chronic inflammatory demyelinating polyneuropathy for 18 months before a diagnosis of POEMS syndrome was made when endocrinological and dermatological manifestations arose. Due to repeated failure in obtaining histological confirmation from the isolated sclerotic vertebra, the diagnosis was made clinically. External radiotherapy, using the intensity modulating technique, was given to 45 Gy in 25 fractions. The intention of this report is to raise awareness of the clinical recognition of POEMS syndrome and the role of radiotherapy in the treatment.

Key Words: *Paraneoplastic syndromes; POEMS syndrome; Polyneuropathies; Radiotherapy*

INTRODUCTION

POEMS syndrome is a rare paraneoplastic syndrome of plasma cell dyscrasia. The term was first coined by Bardwick et al in 1980 to represent polyneuropathy (P), organomegaly (O), endocrinopathy (E), M-proteins (M), and skin changes (S).[1] Although not all features are required for the diagnosis of POEMS syndrome, a minimum of 2 major criteria, including sensorimotor peripheral neuropathy and evidence of a monoclonal plasmaproliferative disorder, and 1 minor criterion, including bone lesion, Castleman disease, organomegaly, endocrinopathy, oedema, or skin changes, are needed to distinguish the condition from neuropathy associated with monoclonal gammopathy of undetermined significance.[2]

The cause of POEMS syndrome is unknown. Cytokines, especially vascular endothelial growth factor (VEGF), have been implicated in the pathogenesis of the disease.[3-5] In a study conducted at the Mayo clinic, the median survival of patients with POEMS was 165 months.[2] The number of POEMS features does not affect survival.[2,6] Localised disease is treated with radiotherapy, while widespread osteosclerotic lesions should be managed by systemic treatment.[7] Although oncologists often depend on histology for confirmation of malignancy before starting definitive treatment, including radiotherapy or chemotherapy, obtaining histology for plasma cell dyscrasia may not be possible.

This report is of a young woman who presented with peripheral polyneuropathy that was treated as chronic inflammatory demyelinating polyneuropathy (CIDP) for 18 months before a diagnosis of POEMS syndrome was made when endocrinological and dermatological manifestations arose.

CASE REPORT

A 28-year-old woman presented with numbness and progressive bilateral lower limb weakness in 2004. Physical examination showed absent ankle jerks, hypotonia, and decreased distal power. Routine blood tests were normal except for persistent mild thrombocytosis. Immune markers and serum plasmaphoresis were normal. Magnetic resonance imaging (MRI) of the spine demonstrated abnormal clumping and dural adhesion of the nerve roots of the cauda equina, abnormal contrast enhancement of nerve roots, and a T1-weighted and T2-weighted hypointense lesion at L3, which was thought to be a bone island (Figure 1). Sural nerve

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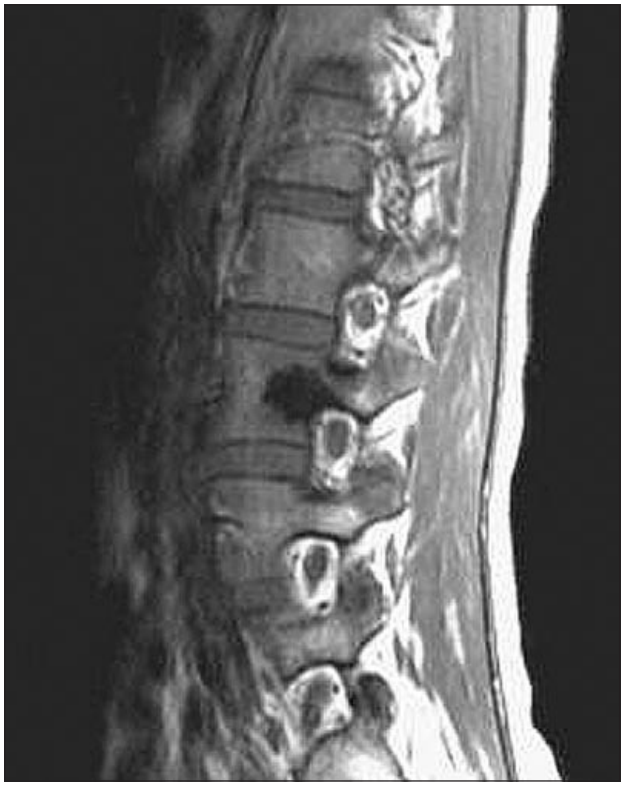

Figure 1. Sagittal magnetic resonance imaging showing a T1-weighted hypodense lesion at the L3 vertebra.

biopsy showed mixed demyelination and axonal degeneration. Nerve conduction tests showed absent motor and sensory potentials in the lower limbs and slowing of motor and sensory conduction velocity in the upper limbs. Both results were consistent with CIDP. Plasmaphoresis, methylprednisolone, immunoglobulin, and azathioprine were given, but lower limb power continued to deteriorate with an ascending pattern. Upper limb power was also affected.

Approximately 12 months after onset, the patient started to develop skin pigmentation and hirsutism, especially over the lower limbs. Amenorrhoea was apparent. With evolving neurological, endocrinological, and dermatological symptoms and signs, the possibility of POEMS was considered 18 months after disease presentation.

Further examination with skeletal survey revealed a sclerotic focus over the right posterior half of the L3 vertebra (Figure 2); a finding that was already present on the MRI as T1-weighted and T2-weighted hypointensities, and thought to be a bone island at the time. Repeated fine-needle aspiration biopsy and open biopsy of the sclerotic bone lesion were performed, but the specimens were inadequate for diagnosis. Bone marrow examination showed plasmacytosis with some clonal

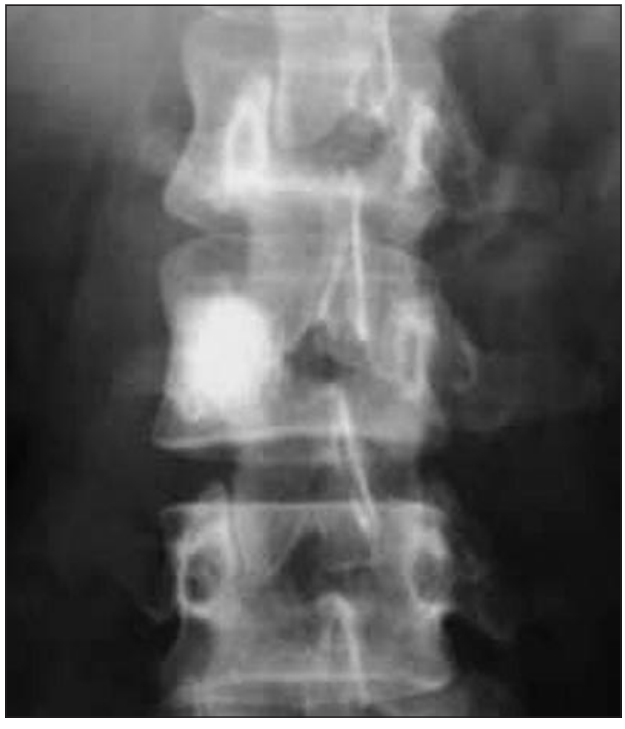

Figure 2. Plain X-ray of the lumbar spine showing a focal sclerotic lesion at the posterior half of the vertebral body, involving a pedicle with non-aggressive features.

plasma cells, but the findings were considered non-specific. Urine protein electrophoresis showed monoclonal band, and urine immunofixation-typed free-λ light chain of 0.03 g/24 hours. Positron emission tomography-computed tomography showed hepatosplenomegaly.

With fulfilment of the major and minor criteria for POEMS syndrome, including polyneuropathy, presence of λ light chain, sclerotic bone lesion, organomegaly, endocrinopathy, and skin changes, radiotherapy was planned for localised bone disease.

The target volume for irradiation was the L3 vertebra with a 1-cm margin. Critical organs included the spinal cord, kidneys, and small bowel. Intensity-modulating radiotherapy was used instead of the classical posterior wedge pair technique to ensure dose conformity to the target volume and minimise the dose to the critical organs, particularly the kidneys, while encompassing the lateral processes of the L3 vertebra and the tumour margins. The dose consisted of 45 Gy in 25 fractions given over 5 weeks. Menstruation returned 1 month after commencement of radiotherapy and muscle power was stabilised for 1 year after the course of radiotherapy. A persistent but decreasing quantity of urine free-λ light chain of 0.01 g/24 hours was present in subsequent urine protein electrophoresis and immunofixation.

DISCUSSION

Diagnosis of POEMS syndrome in the early stage is often difficult, especially when any sclerotic bony lesion is not obvious and clues to multiple system involvement are not apparent. The median time between onset of symptoms and diagnosis has been reported to be 15 months.[2]

The differential diagnoses for peripheral neuropathy include Guillain-Barré syndrome, CIDP, vasculitic neuropathy, and paraprotein-associated neuropathy. POEMS syndrome is categorised as a paraprotein-associated neuropathy. Also in this category are diseases such as multiple myeloma, Waldenström's macroglobulinaemia, primary amyloidosis, cryoglobulinaemia, and lymphoma.[8] An estimated 10% of idiopathic polyneuropathies are of this type.[9]

All patients with POEMS syndrome have peripheral neuropathy, often as the predominant symptom. Peripheral neuropathy can mimic inflammatory polyneuropathy, not only in clinical presentation but also in radiological, pathological, and nerve conduction findings. In POEMS syndrome, the motor involvement follows the sensory symptoms. The sensorimotor components are distal, symmetrical, and progressive with proximal spread.[10] Nerve conduction studies and electromyelography demonstrate a polyneuropathy with prominent demyelination, as well as features of axonal degeneration, which are similar to those of CIDP. Biopsy of the sural nerve usually shows both axonal degeneration and demyelination.[11] Suarez et al are investigating the distinctions in the natural histories of POEMS syndrome and CIDP, and the outcomes and further analysis are pending.[12] Scarlato et al compared POEMS nerves with normal control nerves.[13] VEGF was highly expressed in blood vessels of POEMS nerves and some non-myelin–forming Schwann cells. Together with the high-serum VEGF found in patients with POEMS in this[13] and other studies,[3,14] it has been proposed that endothelial injury is directly or indirectly caused by abnormal activation of endothelial cells by VEGF. Hypertrophy and proliferation of endothelial cells lead to secondary microangiopathy and further hypoxia and stimulation of VEGF. The increase of VEGF is not found in acute or chronic inflammatory demyelinating polyneuropathy,[4] monoclonal gammopathy of undetermined significance,[5,13] or multiple myeloma.[5] Hence, the rise in VEGF may have a diagnostic role. Pathogenesis of POEMS polyneuropathy has not been fully understood, and the actions of other cytokines including interleukin-6 and tumour necrosis factor-α may contribute. Furthermore, the source responsible for the excessive production of VEGF has not been identified.

Before immunohistology can provide a definitive diagnosis of POEMS syndrome, the presence of paraproteins needs to be determined. The monoclonal protein is not large and is missed by protein electrophoresis in nearly one-third of patients, if serum electrophoresis alone is used.[2] This patient underwent repeated serum protein electrophoresis with negative results, and it was not until POEMS syndrome was considered that the urine samples were used for immunofixation. Thus, serum and urine protein electrophoresis, together with immunofixation, are recommended for the investigation of peripheral neuropathy, especially for unexplained or refractory disease.

The presence of the urinary free-λ light chain was important for the diagnosis for this patient, since histology was not conclusive despite repeated fine-needle aspiration cytology and biopsies obtained for plasma cell dyscrasia. Oncologists often rely on histology for confirmation of malignancy before starting definitive treatment. Plasma cell dyscrasia is not a malignancy with readily obtainable histology, thus recognising its paraneoplastic manifestation as POEMS syndrome is crucial, as this provides evidence of the underlying disease. A treatment plan can then be implemented to manage the underlying disease.

Treatment for POEMS syndrome is not standardised. In general, localised disease is treated with radiotherapy, while widespread osteosclerotic lesions should be managed by systemic treatment.[7] Hence, distinguishing between localised or systemic plasma cell dyscrasia should be done before deciding the treatment. Clear diagnostic criteria were published by the International Myeloma Working Group in 2003.[15] Solitary plasmacytoma is defined as an entity with a single area of bone destruction due to clonal plasma cells, no M-protein in serum and/or urine (a small M-component can be present), bone marrow biopsy findings inconsistent with multiple myeloma, normal skeletal survey, and absence of end-organ damage such as hyper-calcaemia, renal failure, anaemia, or additional lytic bone lesions.[15] Therefore, when classifying the underlying plasma cell disorder, investigations including histology of any lesions, bone marrow examination, skeletal survey, and blood tests are important.

At investigation of this patient, the only sclerotic lesion found was located at the L3 vertebra. The radiotherapy technique for solitary plasmacytoma was used. Most experts recommend doses of 40 Gy to 50 Gy, encompassing all disease with a margin of healthy tissue.[7] Stabilisation or improvement of symptoms are expected for 50% of patients after radiotherapy and responses are often not apparent until 3 to 6 months after treatment.[2] In this patient, the return of menstruation occurred during the course of radiotherapy and the neuropathy stabilised for 1 year after completion of radiotherapy. Skin changes were also alleviated. In view of the high possibility of clinical response, radiotherapy should be considered as a first-line treatment for patients with POEMS syndrome with a dominant sclerotic lesion.

Corticosteroids, alkylating agents, and high-dose chemotherapy with autologous stem-cell support may be considered as systemic treatments for patients with diffuse sclerotic lesions, absence of bone lesions, or who have no demonstrated disease stabilisation 3 to 6 months after completing radiotherapy.[11] The good clinical results obtained for treating multiple myeloma suggest that thalidomide, lenalidomide, and bortezomib may contribute an antineoplastic effect and antiangiogenic action. However, since thalidomide and lenalidomide cause 18%[16] and 5% to 11%,[17] respectively, of any grade of peripheral neuropathy, these agents should be used with caution for POEMS syndrome.[11] In view of the high-serum VEGF levels found in POEMS patients, bevacizumab has been considered for treatment. Three patients with POEMS syndrome have been given bevacizumab, 2 of whom showed dramatic response,[18,19] while 1 had no clinical improvement and subsequently died of capillary leak syndrome 5 weeks after the last bevacizumab infusion.[20] In the absence of adequate clinical experience, bevacizumab should only be considered for selected patients with close monitoring for potential side effects. Plasmaphoresis, cyclosporine, and azathioprine are ineffective without prednisolone. No response has been observed with intravenous immunoglobulin.[2] In this patient, plasmaphoresis, immunoglobulin, and azathioprine were used initially for the treatment of presumed CIDP with limited success.

Early recognition of POEMS syndrome in patients with peripheral neuropathy is important. Serum and urine protein electrophoresis and immunofixation should be performed to identify the associated paraproteins. Radiotherapy resulted in disease stabilisation for this patient with POEMS syndrome with a localised lesion. A localised field of radiotherapy should be considered as first-line treatment for patients with a solitary sclerotic bony lesion.

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