POEMS syndrome: a significant clinical response to lenalidomide

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POEMS syndrome is a rare paraneoplastic syndrome. Diagnosis is made on the presence of 3 major criteria and 1 minor criterion. The major criteria for the syndrome are polyradiculoneuropathy, clonal plasma cell disorder, sclerotic bone lesions, elevated VGEF, and presence of Castleman disease. Minor criteria include organomegaly, endocrinopathy, characteristic skin changes, papilledema, extravascular volume overload, and thrombocytosis[1-4] (Table[3,4]). The cause of POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome is unknown. Increased levels of cytokines, more specifically VEGF, appear to play a pathogenic role in the disorder.[5,6] Although patients often have higher levels of IL-1β, TNF-α, and IL-6, increased levels of VEGF are most frequently found and they often decrease with successful therapy.[5,7]

Efficient treatment consists of irradiation for patients with localized solitary plasmacytomas and high-dose chemotherapy with autologous stem cell transplant for selected candidates.[8,9] Treatment with monoclonal VGEF antibodies is controversial.[10] Effectiveness of immunodulatory drugs (IMiDs) and proteasome inhibitors such as thalidomide and bortezemib has been reported, but their use is tempered by high incidence of peripheral neuropathy.[11,12] We describe here a case of POEMS syndrome that showed significant clinical improvement after treatment with lenalidomide. Of note is that even though polyneuropathy is a known side effect of IMiDs, lenalidomide is an immune modulator that has the advantage of being cytotoxic to malignant plasma cells but has a much lower risk of peripheral neuropathy.[13]

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Case presentation

A 48-year-old African American woman with diabetes mellitus type 2 presented with a 5-month course of progressive peripheral neuropathy, weight loss, fatigue, and skin hyperpigmentation. She denied any urine or bowel complaints, back pain, trauma, fever, recent infection. Bilateral lower extremity power was poor (2/5) with complete foot drop and diminished pain, touch, and vibration sensation. There was marked hyperpigmentation and sclerodermoid changes of upper and lower extremities. Cranial nerves were intact as well as the findings in the remainder of the physical exam.

Laboratory findings revealed normal hemoglobin and white blood cell and platelet counts. Electromyography and nerve conduction analysis confirmed severe neuro-axonal degeneration. CSF analysis showed elevated protein level of 89 mg/dL. The patient was diagnosed with chronic inflammatory demyelinating polyneuropathy (CIDP) and treated with intravenous immunoglobulin without significant improvement. Bone survey and CT chest/abdomen/pelvis were performed and showed bilateral axillary lymphadenopathy, destructive left scapular lesion with multiple tiny osseous densities and lytic lesions, shotty para-aortic and inguinal lymphadenopathy (Figures 1 and 2).

Further work-up suggested the presence of 2 monoclonal proteins predominantly lambda chain on urine immunofixation and more than 10% plasma cells on bone marrow biopsy (Figure 3) all consistent with POEMS syndrome. The patient was started on treatment with lenalidomide 15 mg daily for 21 days of a 28-day cycle with once weekly dexamethasone (40 mg). By the second cycle of treatment, the patient was able to perform more activities of daily living and walk with assistance. The patient continued to improve after additional cycles of therapy; this was correlated with

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TABLE Clinical manifestations of POEMS syndrome

Peripheral neuropathy	Distal, symmetric, and progressive with a gradual proximal spread, predominantly motor. Subclinical to very symptomatic respiratory compromise from neuromuscular weakness also occurs.
Castleman disease	Giant lymph node hyperplasia, angiofollicular lymph node hyperplasia with no clonal plasma cell disorder, and typically little to no peripheral neuropathy but has several of the minor diagnostic criteria for POEMS syndrome.
Osteosclerotic bone lesions	95% of patients have solitary or multiple sclerotic lesions in pelvis, spine, ribs, and proximal extremities.
Monoclonal plasma proliferative disorder	Monoclonal protein (almost always lambda) is not large and is missed on serum protein electrophoresis in nearly one-third of patients if immunofixation(urine/serum) and serum immunoglobulin free light chain is not performed.
Organomegaly	Hepatomegaly, splenomegaly, lymphadenopathy
Endocrinopathy	Adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic
Skin changes	Hyperpigmentation, hypertrichosis, plethora, hemangiomata, white nails
Other features	Thrombocytosis, papilledema, pulmonary hypertension, restrictive lung disease, Cardiomyopathy (systolic dysfunction) ,arterial and venous thrombosis

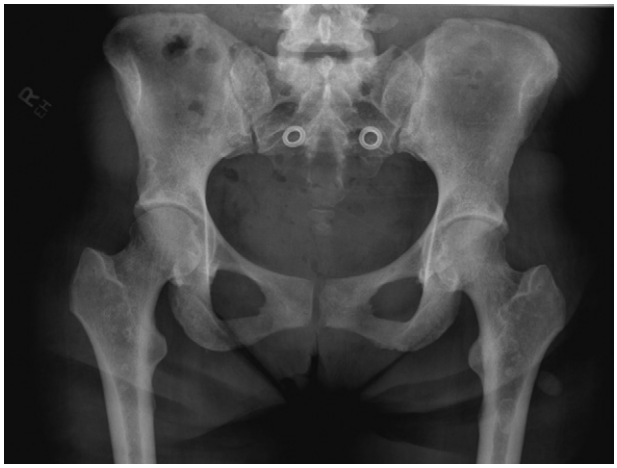

FIGURE 1 Bone survey showing multiple circular lucencies and focal densities in pelvis and proximal femur.

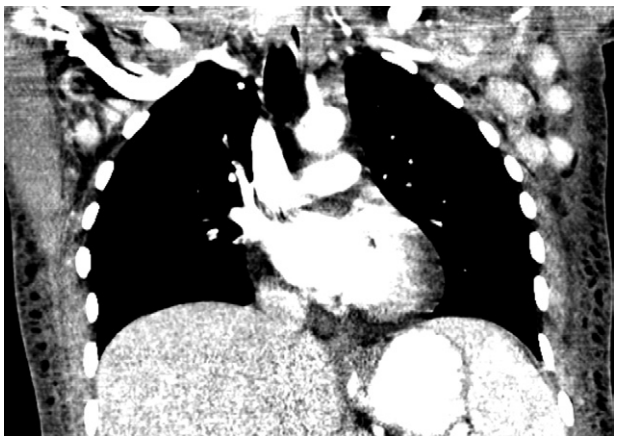

FIGURE 2 Bilateral axillary lymph nodes with destructive left scapular lesion.

a significant improvement in electromyography, nerve conduction studies, and serum light chain assay.

Discussion

Lenalidomide is a synthetic compound that is derived using structural modification of the chemical structure of thalidomide to improve potency and reduce side effects. It is known to be efficacious in the treatment of relapsed multiple myeloma, chronic lymphocytic leukemia, and myelodysplastic syndromes with deletion of chromosome 5q.[14] It possesses immunomodulatory and antiangiogenic properties, and although the exact mechanism of action has not been fully characterized, it exerts its actions on cytokines, inhibiting the secretion of pro-inflammatory cytokines (TNF-α, IL-1, IL-6, IL-12) and increasing the secretion of anti-inflammatory cytokines (IL-10) from peripheral blood mononuclear cells. The downregulation of TNF-α secretion is particularly striking and is up to 50,000 times more when compared with thalidomide.[15,16]

Elevated TNF-α production is implicated in the pathogenesis of various hematologic malignancies including chronic lymphocytic leukemia and myelodysplastic syndromes.[17,18] Similarly reduction in IL-6 and TNF-α level could explain the action of lenalidomide in multiple myeloma[19] and POEMS syndrome. Recent studies also suggest that the concomitant use of dexamethasone may influence lenalidomide's direct and immunomodulatory effects.[20] A trial of lenalidomide therapy in 9 patients with POEMS syndrome in France showed marked improvement in performance and neurological syndrome.[21] Similar results were seen in a trial in Spain.[22] Controlled clinical trials are not feasible in POEMS syndrome because of the rarity of this disorder however, our patient's favorable response to lenalidomide further supports

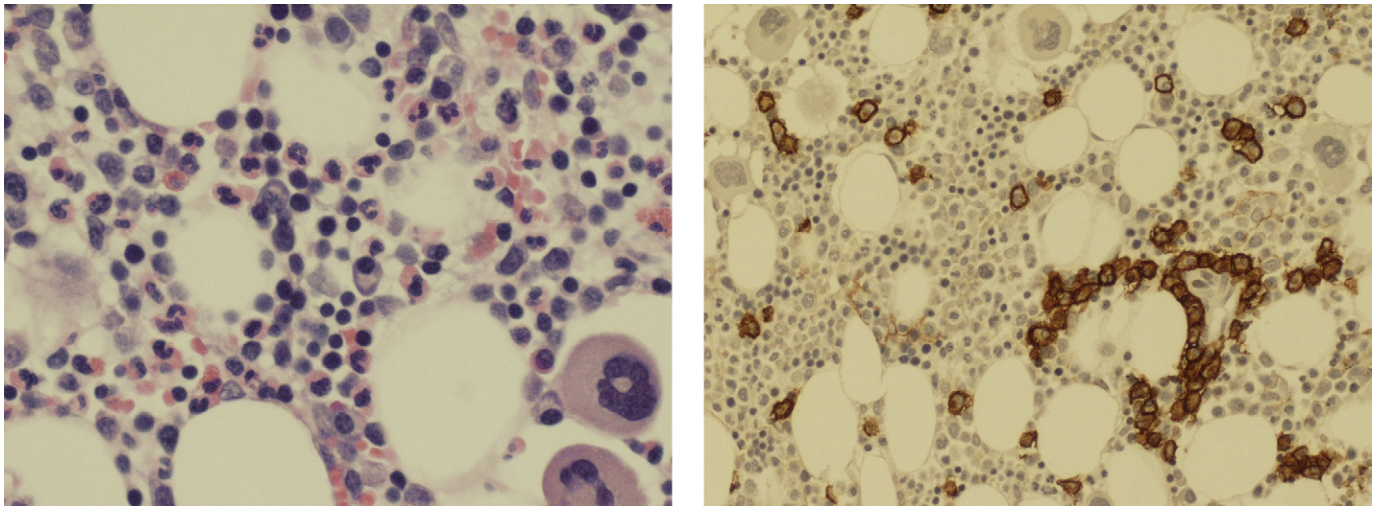

FIGURE 3 Normocellular bone marrow with trilineage hematopoiesis and scattered plasma cells (left), and immunostain for CD138 revealing clusters of plasma cells (> 10% of marrow components; right).

promising outcome with use of lenalidomide in treatment of POEMS syndrome.

References

1. Dispenzieri A. POEMS syndrome. *Blood Rev*. 2007;21:285-99.
2. Soubrier MJ, Dubost JJ, Sauvezie BJ. POEMS syndrome: a study of 25 cases and a review of the literature. French Study Group on POEMS Syndrome. *Am J Med*. 1994;97:543-553.
3. Dispenzieri A. POEMS syndrome: 2011 update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2011;86: 591-601.
4. Dispenzieri A, Kyle RA, Lacy MQ, et al. POEMS syndrome: definitions and long-term outcome. *Blood*. 2003;101:2496-2506.
5. Gherardi RK, Belec L, Soubrier M, et al. Overproduction of proinflammatory cytokines imbalanced by their antagonists in POEMS syndrome. *Blood*. 1996;87:1458-1465.
6. Hashiguchi T, Arimura K, Matsumuro K, et al. Highly concentrated vascular endothelial growth factor in platelets in Crow-Fukase syndrome. *Muscle Nerve*. 2000;23:1051-1056.
7. Watanabe O, Maruyama I, Arimura K, et al. Overproduction of vascular endothelial growth factor/vascular permeability factor is causative in Crow-Fukase (POEMS) syndrome. *Muscle Nerve*. 1998;21:1390-1397.
8. Dispenzieri A, Moreno-Aspitia A, Suarez GA, et al. Peripheral blood stem cell transplantation in 16 patients with POEMS syndrome, and a review of the literature. *Blood*. 2004;104:3400-3407.
9. Li J, Zhang W, Li J, et al. Combination of mephalan and dexamethasone for patient with newly diagnosed POEMS syndrome. *Blood*. 2011;117:6445-6449.
10. Kanai K, Kuwabar S, Misawa S, et al. Failure of treatment with anti-VGEF monoclonal antibody for long-standing POEMS syndrome. *Intern Med*. 2007;46:311-313.
11. Tang X, Shi X. Successful bortezomib-based treatment in POEMS syndrome. *Eur J Haematol*. 2009;83:609-610.
12. Tosi P, Zamangi E, Cellini C, et al. Neurological toxicity of long-term (>1 yr) thalidomide therapy in patients with multiple myeloma. *Eur J Haematol*. 2005;74:212-216.
13. Dispenzieri A, Klein CJ, Maunermann ML. Lenalidomide therapy in a patient with POEMS syndrome. *Blood*. 2007;110: 1075-1076.
14. Kotla V, Goel S, Nischal S, et al. Mechanism of action of lenalidomide in hematological malignancies. *J Hematol Oncol*. 2009;2:36.
15. Corral LG, Haslett PA, Muller GW, et al. Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF-alpha. *J Immunol*. 1999;163:380-386.
16. Muller GW, Chen R, Huang SY, et al. Amino-substituted thalidomide analogs: potent inhibitors of TNF-alpha production. *Bioorg Med Chem Lett*. 1999;9:1625-1630.
17. Symeonidis A, Kourakli A, Katevas P, et al. Immune function parameters at diagnosis in patients with myelodysplastic syndromes: correlation with the FAB classification and prognosis. *Eur J Haematol*. 1991;47:277-281.
18. Giagounidis AA, Germing U, Haase S, et al. Clinical, morphological, cytogenetic, and prognostic features of patients with myelodysplastic syndromes and del(5q) including band q31. *Leukemia*. 2004;18:113-119.
19. Lichtenstein A, Tu Y, Fady C, Vescio R, Berenson J. Interleukin-6 inhibits apoptosis of malignant plasma cells. *Cell Immunol*. 1995; 162:248-255.
20. Gandhi AK, Kang J, Capone L, et al. Dexamethasone synergizes with lenalidomide to inhibit multiple myeloma tumor growth, but reduces lenalidomide-induced immunomodulation of T and NK cell function. *Curr Cancer Drug Targets*. 2010;10:155-167.
21. Jaccard A, Abraham J, Recher C, et al. Lenalidomide therapy in nine patients with POEMS syndrome [ASH 2009 abstract 3872].
22. Tomás JF, Giraldo P, Lecumberri R, Nistal S. POEMS syndrome with severe neurological damage clinically recovered with Lenalidomide. *Haematologica*. 2012;97:320-322.