Diffuse large B-cell non-Hodgkin's lymphoma and osteosclerotic myeloma with features of POEMS syndrome

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Multiple myeloma is a clonal hematopoietic neoplasm characterized by the proliferation of malignant plasma cells and associated end-organ damage, most notably lytic lesions in the bones. Osteosclerotic myeloma is an unusual variant of the disease in which the skeletal involvement is characterized by sclerotic lesions instead of classical lytic lesions. The disease can be associated with paraneoplastic symptoms, which have been given the acronym POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes). In addition to clonal plasma cell dyscrasias, some cases of POEMS syndrome are associated with Castleman's disease, and in 11% to 30% of the cases both Castleman's disease and clonal plasma cell proliferation are present. POEMS syndrome has rarely been described in patients with non-Hodgkin's lymphoma.

POEMS syndrome usually occurs in patients with osteosclerotic myeloma or Castleman's disease. We describe a patient with diffuse large B-cell non-Hodgkin's lymphoma and osteosclerotic myeloma who developed features of POEMS syndrome.

CASE REPORT

In 2008, a 59-year-old Hispanic woman presented with fever, drenching night sweats, and a 15-pound weight loss over 6 weeks. She previously had hypothyroidism and hypertension. She had no other complaints and had no neurological symptoms. Examination showed bilateral cervical and left axillary adenopathy measuring up to 2 cm in size. Lymph nodes were nontender and freely mobile. The spleen was palpable 3 cm below the costal margin. Computed tomography (CT) scans showed 3-cm paraaortic lymph nodes and multiple foci of sclerotic bone lesions in the pelvis and spine. A skeletal survey confirmed extensive sclerotic lesions (*Figure 1*). The leukocyte count was 5600/ μ L with 68% neutrophils and 30% lymphocytes, the hemoglobin level was 11.8 g/dL, the platelet count was 320,000/ μ L, and creatinine and alanine aminotransferase were normal. Lactate dehydrogenase was elevated at 520 U/L. Serum immune electrophoresis showed a 2.1 g/dL monoclonal protein, which was IgG lambda on immunofixation. A 24-hour urine protein excretion showed 85 mg of protein, most of which was lambda light chains. An excisional biopsy of a lymph node showed sheets of large atypical lymphoid cells

Figure 1. A skeletal survey showing a large sclerotic lesion in the right iliac bone extending into the right acetabulum.

with vesicular chromatin and irregular nuclei with prominent nucleoli and frequent mitoses (*Figure 2a*). The lymphoid cells expressed CD-20, PAX 5, and BCL-6. They did not express CD-10 or BCL-2. The Ki-67 index was 90%. Immunohistochemical staining for kappa and lambda light chains showed polyclonal plasma cells and no staining of the malignant B cells. Polymerase chain reaction showed a clonal rearrangement of the immunoglobulin heavy chain gene. Bone marrow aspirate

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Figure 2. (a) An excisional biopsy of a lymph node showing sheets of large atypical lymphoid cells with vesicular chromatin, irregular nuclei with prominent nucleoli, and frequent mitoses. (b) Bone marrow biopsy showing sheets of atypical plasma cells in a fibrotic background and surrounding osteosclerosis.

showed normal trilineage hematopoiesis with no infiltration by lymphoma; the core biopsy showed sheets of atypical plasma cells in a fibrotic background and surrounding osteosclerosis (Figure 2b). Overall, 80% of the core was infiltrated by plasma cells that showed lambda light chain restriction.

The patient was diagnosed with stage III diffuse large B-cell lymphoma with an international prognostic index score of 2 and osteosclerotic myeloma. She then received six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. At the end of chemotherapy, she had resolution of all palpable adenopathy and symptoms. She continued to have a palpable spleen, and serum electrophoresis continued to show a 2.1 g/dL of monoclonal IgG lambda. A free light chain assay showed a normal kappa: lambda ratio (0.84; normal, 0.26–1.65). CT/positron emission tomography (PET) scans showed no metabolically active lesions. Sclerotic bone lesions were noted and were not PET avid.

She was then started on bortezomib and dexamethasone. In addition, zoledronic acid was administered every 4 weeks. At the end of 4 months, her spleen size remained stable and serum immune electrophoresis showed a decline in M protein to 0.5 g/dL. She subsequently received maintenance therapy with lenalidomide (10 mg daily) for 2 years. At the end of 2 years, her M spike remained stable at 0.6 g/dL, PET showed no PET-avid sites, and peripheral blood counts and chemistries were normal. Lenalidomide was discontinued, and the patient was placed on surveillance and did well.

At age 66, in March 2015, the patient was noted to have bilateral nonpitting edema in her lower extremities extending up to her knees. Her spleen remained palpable 2 to 3 cm below the costal margin. Blood counts continued to show no cytopenias (white blood counts, 5200/ μ L; hemoglobin, 13.8 g/dL; and platelets, 380,000/ μ L), renal function was normal, and immunoelectrophoresis showed a stable M spike of 0.6 g/dL. A free light chain assay continued to show a normal kappa: lambda ratio (0.77). A 24-hour urine protein excretion showed 80 mg of protein, most of which was lambda light chains. A

whole-body PET scan showed no signs of lymphoma relapse. A paraneoplastic phenomenon was suspected, and a plasma vascular endothelial growth factor (VEGF) level was noted to be elevated (1507 pg/mL; normal, 31–86 pg/mL). The patient was restarted on a regimen of bortezomib (1.3 mg/m²) and low-dose dexamethasone (20 mg weekly). Follow-up labs showed a decline in plasma VEGF levels, which correlated with resolution of her leg edema. Serum immune electrophoresis continued to show a stable M spike (Figure 3), and her spleen size did not regress with therapy.

DISCUSSION

POEMS syndrome is a paraneoplastic syndrome characterized by polyneuropathy, organomegaly, endocrinopathies, monoclonal protein, and skin changes. In addition, patients frequently have papilledema, extravascular volume overload (pleural effusions, ascites, peripheral edema), sclerotic bone lesions, and elevated plasma VEGF levels (1). Elevated circulating levels of various cytokines, including the plasma VEGF and

Figure 3. Serum immune electrophoresis and vascular endothelial growth factor levels.

interleukin-6, contribute to the clinical manifestations of the syndrome (2–4). Unlike multiple myeloma, serial measurements of M spike in the serum or urine do not correlate with disease activity in POEMS syndrome. Measurements of plasma VEGF levels correlate with treatment response.

The association of POEMS syndrome with diffuse large B-cell lymphoma is rare. A PubMed literature search showed only one prior report of a patient who presented with primary cutaneous large B-cell lymphoma, leg type, and associated features of the POEMS syndrome (5). The lymphoma cells expressed VEGF and interleukin-6 by immunohistochemistry, suggesting that the malignant B cells were the source of the cytokines producing POEMS syndrome.

Our patient had many features suggestive of POEMS syndrome (monoclonal plasma cells in the bone marrow, sclerotic bone lesions, IgG lambda monoclonal protein, splenomegaly, and a relatively indolent course without any cytopenias, hypercalcemia, or renal insufficiency). She developed symptoms of fluid overload and elevated plasma VEGF levels 7 years after being treated for the lymphoma and at a time when she had no clinical or PET evidence of lymphoma relapse. In addition, she had clinical improvement and a decline in VEGF levels upon receiving therapy directed against the plasma cells. This suggests that unlike the first case, the malignant B cells were not the source of plasma VEGF elevation in our patient; the source was most likely the plasma cells or adjoining stroma.

The simultaneous diagnosis of osteosclerotic myeloma and diffuse large B-cell lymphoma in our patient raises the interesting question whether these two malignancies were clonally related. Immunohistochemical staining showed that the malignant

lymphoma cells in our patient did not stain for lambda or kappa light chains, while the plasma cells were lambda restricted. Although not conclusive, this suggests that the two neoplasms might not be clonally related.

Diagnostic criteria have been proposed for POEMS syndrome (1). These require the mandatory presence of both polyneuropathy and monoclonal plasma cell proliferation, in addition to other major and minor criteria to establish the diagnosis. Despite being exposed to neurotoxic drugs over the past 8 years (bortezomib, vincristine), our patient did not have any symptoms of polyneuropathy. Yet, she had other unequivocal features of POEMS syndrome as described above. The other patient described by Nakayama et al did not have monoclonal plasma cell proliferation (5). Taken together, this suggests that POEMS syndrome may have an unusual presentation in patients with diffuse large B-cell lymphoma.

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